Clinical Utility of Intravascular Imaging and Physiology in Coronary Artery Disease

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ABSTRACT

Intravascular imaging and physiology techniques and technologies are moving beyond the framework of research to inform clinical decision making. Currently available technologies and techniques include fractional flow reserve; grayscale intravascular ultrasound (IVUS); IVUS radiofrequency tissue characterization; optical coherence tomography, the light analogue of IVUS; and near-infrared spectroscopy that detects lipid within the vessel wall and that has recently been combined with grayscale IVUS in a single catheter as the first combined imaging device. These tools can be used to answer questions that occur during daily practice, including: Is this stenosis significant? Where is the culprit lesion? Is this a vulnerable plaque? What is the likelihood of distal embolization or periprocedural myocardial infarction during stent implantation? How do I optimize acute stent results? Why did thrombosis or restenosis occur in this stent? One of the legacies of coronary angiography is to presume that one technique will answer all of these questions; however, that often has been proved inaccurate in contemporary practice. (J Am Coll Cardiol 2014;64:207–22) © 2014 by the American College of Cardiology Foundation

More than 2 decades have passed since Drs. Nico Pijls and Bernard DeBruyne introduced fractional flow reserve (FFR) as a method of assessing coronary stenosis severity and since Dr. Paul Yock invented grayscale intravascular ultrasound (IVUS) that spawned second-generation intravascular imaging techniques such as: 1) IVUS radiofrequency tissue characterization, including virtual histology (VH)-IVUS, integrated backscatter IVUS, and iMap; 2) optical coherence tomography (OCT), the light analogue of IVUS; and 3) near-infrared spectroscopy that detects lipid within the vessel wall and that has recently been combined with grayscale IVUS in a single catheter as the first combined imaging device. These tools have moved beyond the research setting. They are useful for answering questions that occur during daily practice including: Is this stenosis significant? Where is the culprit lesion? Is this a vulnerable plaque? What is the likelihood of distal embolization or periprocedural myocardial infarction (MI) during stent implantation? How do I optimize acute stent results? Why did thrombosis or restenosis occur in this stent?

The subspecialty of interventional cardiology is data driven. Although correlations with histopathology are important, the ultimate benefit will be determined if these techniques improve clinical diagnosis, treatment, outcomes, and whether patients benefit, irrespective of technical or histopathological accuracy.

IS THIS STENOSIS SIGNIFICANT?

Three randomized trials (DEFER [Deferral Versus Performance of PTCA in Patients Without Documented Ischemia], FAME [Fractional Flow Reserve Versus Angiography for Multivessel Evaluation]-I, and FAME-II) established FFR (the ratio of distal to proximal pressure at maximum hyperemia) as the...
gold standard for assessing the significance of a non-left main coronary artery (LMCA) lesion. DEFER showed it was safe to defer percutaneous coronary intervention of lesions with an FFR >0.75 (1,2). The FAME-I trial found that treating lesions with an FFR >0.80 by using mostly first-generation drug-eluting stents (DES) was harmful, whereas not treating such lesions was cost-saving (3,4). The FAME-II trial found that treating lesions with an FFR <0.80 with the use of optimal medical therapy alone was deleterious compared with optimal medical therapy plus DES implantation (5). Although initially more expensive, the increased cost of “optimal medical therapy plus DES implantation” was decreased by one-half 1 year later (6).

Its predecessor, coronary flow reserve (CFR), measures the relative increase in coronary flow velocity during maximal hyperemia, reflecting both epicardial stenoses and the microcirculation, and is influenced by many factors affecting the microcirculation, such as diabetes, ventricular hypertrophy, and prior myocardial infarction. Unlike CFR, FFR is able to measure the actual volume of blood flow through a stenotic coronary artery as a percentage of normal hyperemic flow, because at maximum hyperemia, flow into a myocardial territory is proportional to pressure since the resistance is minimal and constant. FFR is independent of pressure, heart rate, contractility, and the status of the microcirculation and takes into account both antegrade and retrograde collateral blood flow, as well as the amount of viable myocardium.

There has been a recent renewal of interest in resting indices, such as iFR (instantaneous wave free ratio) or a hybrid approach combining iFR and FFR. However, the validity of these alternative physiologic approaches will depend on the clinical outcomes of randomized iFR vs. FFR trials, such as DEFINE-FLAIR or SwedeHeart.

Many studies have attempted to identify invasive imaging criteria that are equivalent to FFR or noninvasive testing. Although the IVUS minimum lumen area (MLA) in non-LMCA lesions is the parameter that best correlates with physiology, reported IVUS MLA cutoff thresholds range from 2.1 to 4.4 mm² (Table 1) (7-25) and are smaller in Asian patients than in studies of Western populations, the “most common” cutoff is approximately 3.0 mm². Most IVUS studies show a relatively high negative predictive value but a low positive predictive value, indicating that using IVUS to justify the need for percutaneous intervention is wrong approximately one-half of the time. There have been no randomized IVUS trials comparable to DEFER, FAME-I, or FAME-II or randomized trials of IVUS deferral compared with FFR deferral. However, a recent propensity-matched study by de la Torre Hernandez et al. (26) suggests that clinical outcomes are similar whether IVUS or FFR is used to decide which lesions to stent or which to leave alone, although a greater number of lesions are stented with IVUS compared with FFR (72% vs. 51.2%; p < 0.0001).

Anatomic assessment of lesion severity is not improved with OCT, although OCT-derived MLA cutoffs are smaller than with IVUS (19,27-29). Some studies have “corrected” for vessel size (12,13,16,17), but none has factored in subtended viable myocardium.

In a recent substudy from the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) Study, non-fibroatheromas were associated with very few events at 3 years of follow-up, suggesting that tissue characterization and plaque composition may be an alternate method to predict lesion stability and defer intervention (30).

LMCA LESIONS

Four angiographic studies (2 historic [31,32] and 2 contemporary [33,34]) indicated that agreement among experts regarding the significance of an LMCA lesion can be as low as 30% (Fig. 1). There have been 2 equivalent FFR and IVUS registry studies in patients with intermediate LMCA lesions in which an FFR >0.80 or an IVUS MLA >6.0 mm² was used to defer revascularization, with similar long-term results compared with patients with an FFR <0.80 or an MLA <6.0 mm² treated with revascularization (33,35). A study by Jasti et al. (36) in Western patients indicated that an IVUS MLA <6 mm² in the LMCA best correlated with an FFR <0.80, while a study in Korean patients suggested that 4.8 mm² was the preferred IVUS MLA cutoff (37), which is again consistent with the smaller MLA cutoffs found in Asian patients compared with Western patients.

Both IVUS and FFR have limitations in assessing LMCA disease. Ideally, when clinically indicated, IVUS should be performed from both the left anterior descending and left circumflex coronary arteries to define the MLA within the LMCA and to accurately assess disease at the left anterior descending and left circumflex ostia (38,39). Patients with LMCA disease have not typically been included in the many FFR
validation studies, and FFR may have limitations in the setting of a significant concomitant LAD stenosis (40,41).

WHERE IS THE CULPRIT LESION?

In patients with acute coronary syndrome, plaque rupture occurs in 60% to 65% of cases, plaque erosion in 30% to 35%, and a calcified nodule in 5%. The final common pathway is thrombus formation (42). Sometimes, the culprit lesion is evident clinically, but as seen in the VANQWISH (Veterans Affairs Non-Q-Wave Infarction Strategies in-Hospital) trial, nearly 50% of these patients either have no identifiable culprit or have multiple potential culprits (43).

This 47-year-old male patient was admitted to a coronary care unit because of chest pain, initially underwent diagnostic angiography followed by bypass surgery (left internal mammary artery to the left anterior descending and saphenous vein graft to the left circumflex artery) for an ostial left main stenosis similar to the one shown by the white arrow in this angiogram. He did well for approximately 1 month, developed recurrent pain. He was readmitted to the coronary care unit, underwent repeat angiography (which showed closure of both the internal mammary artery and saphenous vein grafts), and had repeat bypass surgery, this time using saphenous vein grafts to both the left anterior descending and left circumflex arteries. He again did well for about 1 month before developing recurrent chest pain. At this time, the patient was referred for an intravascular ultrasound (IVUS) study of the ostial left main stenosis. IVUS of the ostial stenosis (white arrow) showed no left main disease or lumen compromise. There was at most mild intimal thickening (a). Note the shadowing caused by the aortic wall (b). The guiding catheter had been retracted and was out of view. Adapted with permission of CRF Press from Intracoronary Ultrasound by Gary S. Mintz.
Previous studies have shown that positive remodeling is more common in culprit lesions of patients presenting with acute coronary syndrome and is seen in association with plaque rupture, yellow plaque color, and thrombus formation. Conversely, negative remodeling is more common in target lesions of patients presenting with stable symptoms (44-47). IVUS detects plaque ruptures in approximately one-half of ST-segment elevation MI culprit lesions (48-50). However, the superior resolution and the
obligatory flushing with OCT sharply outline the plaque rupture cavity and residual fibrous cap fragment to optimize ruptured plaque identification (48); OCT can detect erosions (although there is some disagreement regarding the definition [48,51–53]); and OCT can identify and differentiate between red and white thrombus (54). However, red thrombus, which is almost universal in these patients, can shadow and obscure underlying plaque morphology (Fig. 2). Recent near-infrared spectroscopy data indicate that a maximum lipid core burden index >400 within a 4-mm segment is a signature of plaques causing an ST-segment elevation MI (55).

Other unusual culprit lesion morphologies that can be detected by using both IVUS and OCT include calcific nodules (53,56) and spontaneous coronary artery dissections (Fig. 3) (57,58).

IS THIS A VULNERABLE PLAQUE?

The precursor of the ruptured, thrombotic plaque is the thin-cap fibroatheroma (TCFA), the most common type of vulnerable plaque (42). Although an early, small, grayscale IVUS study suggested that a large eccentric plaque containing a shallow echoluent zone is at increased risk for instability (59), to date only VH-IVUS has been shown to predict future nonculprit events. In the PROSPECT study, predictors of nonculprit events at 3 years were a VH-TCFA, an IVUS MLA <4.0 mm², and an IVUS plaque burden >70% (60). These findings, especially the importance of a large plaque burden, were supported by the VIVA (VH-IVUS in Vulnerable Atherosclerosis) and ATHEROREMO-IVUS (European Collaborative Project on Inflammation and Vascular Wall Remodeling)
Although VH-IVUS can only infer the presence of a TCFA by the presence of a necrotic core abutting the lumen, OCT is able to identify many features of a TCFA, including fibrous cap thickness <65 μm, macrophages in the fibrous cap, and an underlying lipid core (51). However, only 1 small OCT study has found that lesions with rapid progression (angiographic lumen loss >0.4 mm within 7 months) have an increased frequency of intimal laceration, microvessels (which may be a source of blood extravasation and intraplaque hemorrhage), lipid pools, TCFA, macrophages, and intraluminal thrombi (63).

IVUS substudies of the PROSPECT study have highlighted the paradox between plaque ruptures or calcified nodules that cause acute coronary syndrome events versus the benign nature of secondary, non-culprit plaque ruptures or calcified nodules that are detected incidentally (64,65). Although positive remodeling was not an independent predictor of events in the PROSPECT, VIVA, or ATHEREMO-IVUS studies, a substudy from the PROSPECT study found that it is not just positive remodeling, but also the extremes of positive and negative remodeling that predicted events (66).

The appropriateness of using routine invasive imaging to screen for vulnerable plaques as part of primary or secondary prevention is the subject of debate and depends on the prevalence of vulnerable plaques, as well as how often and how rapidly they develop spontaneously, remain unstable, or stabilize (67,68); the impact of contemporary medical therapy on clinical events; and complications associated with routine 3-vessel invasive imaging (60). PROSPECT, VIVA, and ATHEREMO-IVUS studies demonstrated that contemporary medical therapy mostly impacted revascularization and not hard events of death or MI (60–62). Currently, we cannot predict which plaques carry a risk of complications high enough to warrant prophylactic therapy, although a randomized substudy within the PROSPECT-II study will attempt to address this issue.

**WHAT IS THE LIKELIHOOD OF DISTAL EMBOLIZATION OR PERIPROCEDURAL MI DURING STENT IMPLANTATION?**

Predictors of myonecrosis during stent implantation are a large, grayscale IVUS attenuated plaque (“shadowing” in the absence of calcification), especially when shadowing begins closer to the lumen.
than to the adventitia (69–73) (Fig. 4); a large VH-IVUS necrotic core, VH-T DFA (74), or similar findings using integrated backscatter IVUS (75,76) or iMap (77); a large amount of OCT lipid or an OCT-T DFA (78–83); a large lipid-rich plaque detected by using near-infrared spectroscopy (84–86); and the presence of plaque rupture, whether detected by IVUS or OCT (79,87–90). The common denominator is the presence of a T DFA, with or without plaque rupture, that is responsible both for the imaging findings and for periprocedural MI during stent implantation (91–94). Conversely, the absence of these findings indicates a low probability of a periprocedural MI.

**FIGURE 5 Very Late Stent Thrombosis With Aneurysm and Stent Fracture**

The left anterior descending artery has been treated using 2 Cypher stents (Cordis Corporation, Miami Lakes, Florida) 1.5 years ago. (A and B) Coronary angiogram shows stent thrombosis (white arrow in A) with stent fracture (white arrow in B). (C to E) Intravascular ultrasound imaging reveals aneurysm formation (a), that was better seen in the longitudinal reconstruction (b in F), and (E) absence of stent struts confirming stent fracture. The external elastic membrane area in the proximal reference (C) measures 14.1 mm², and the external elastic membrane area at the site of the aneurysm (D) measures 31.4 mm².

**HOW DO I OPTIMIZE ACUTE STENT RESULTS?**

In both bare-metal stents and DES, the IVUS predictors of early stent thrombosis or in-stent restenosis (ISR) are underexpanded stent (Fig. 5) (95–112) and inflow/outflow track disease (e.g., dissections, significant plaque burden, edge stenosis) (99,104,105,107,108,113–116), but not acute stent malapposition (108,110,117–119) as long as the stent is well expanded. Underexpansion refers to the size of the stent, whereas malapposition refers to the contact of the stent with the vessel wall. The 2 terms and concepts are not interchangeable, and the term
“underdeployment” is imprecise and unclear (Fig. 6). Although bigger is better regarding stent expansion and less is more with respect to stent edge plaque burden, acceptable procedural endpoints are a minimum stent area (98,101,104,106,111,112) and stent-edge plaque burden (113,115,116) that maximize the probability of long-term stent patency while minimizing the risk of stent failure (Table 2).

Four meta-analyses of the randomized IVUS versus angiographic-guided bare-metal stent implantation trials showed that IVUS guidance reduced restenosis, repeat revascularization, and major adverse cardiac events but not death or MI (120-123). Four meta-analyses of IVUS versus angiographic-guided DES studies (the most recent of which involving 3 randomized trials and 14 observational studies with 26,503 patients) found that IVUS guidance reduced stent thrombosis (124-127), MI (125-127), repeat re-vascularization (126,127), and mortality (124-127) despite using more stents and/or longer stents in
IVUS-guided patients. A propensity score-matched analysis was possible in 9 studies (124,126), and there was no evidence of heterogeneity or publication bias. IVUS guidance was associated with a larger post-procedure angiographic minimum lumen diameter with no evidence of increased periprocedural MI (127). Two studies questioned the value of IVUS guidance in MI patients undergoing primary percutaneous intervention (128,129), but the ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) study suggested the opposite: that IVUS guidance had its greatest impact in MI patients (130). Most recently, a study reporting patient-level data from 4 Spanish registries showed that IVUS guidance reduced cardiac death, MI, and repeat revascularization in patients undergoing DES implantation for unprotected LMCA disease (131).

### TABLE 2

<table>
<thead>
<tr>
<th>Ref. #</th>
<th>N</th>
<th>Follow-Up</th>
<th>Stent</th>
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<th>MSA Location</th>
<th>Cutoff</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<td>(98)</td>
<td>543</td>
<td>TLR</td>
<td>BMS</td>
<td>MSA</td>
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<td>PPV = 17%, NPV = 94%</td>
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<td>MSA</td>
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<td></td>
<td>SES</td>
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<td>5.0 mm²</td>
<td>76%</td>
<td>83%</td>
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<td>(104)</td>
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<td>Angiographic in-stent restenosis</td>
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<td>MSA</td>
<td>5.5 mm²</td>
<td>67%</td>
<td>67%</td>
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<td>40 mm</td>
<td>Stent length</td>
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<td>81%</td>
<td>78%</td>
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<td>482</td>
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<td>BMS</td>
<td>MSA</td>
<td>6.4 mm²</td>
<td>c statistic = 0.64</td>
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<td>1,098</td>
<td></td>
<td></td>
<td>PES</td>
<td>MSA</td>
<td>5.7 mm²</td>
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<td>403</td>
<td>Angiographic in-stent restenosis</td>
<td>SES</td>
<td>MSA</td>
<td>8.2 mm²</td>
<td>80%</td>
<td>81%</td>
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<td></td>
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<tr>
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<tr>
<td></td>
<td>LAD ostium</td>
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<td>73%</td>
<td>85%</td>
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<tr>
<td></td>
<td>LCX ostium</td>
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<td></td>
<td>78%</td>
<td>78%</td>
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<tr>
<td>(111)</td>
<td>541</td>
<td>Angiographic in-stent restenosis</td>
<td>SES</td>
<td>MSA</td>
<td>5.5 mm²</td>
<td>72%</td>
<td>66%</td>
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<tr>
<td>229</td>
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<td>EES</td>
<td>MSA</td>
<td>5.4 mm²</td>
<td>60%</td>
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<td>ZES</td>
<td>MSA</td>
<td>5.3 mm²</td>
<td>57%</td>
<td>62%</td>
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<tr>
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<td>106</td>
<td>IVUS MLA &lt;4 mm²</td>
<td>DES</td>
<td>MSA</td>
<td>6.1 mm²</td>
<td>PPV = 91%</td>
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<td></td>
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<tr>
<td>1,098</td>
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<td></td>
<td></td>
<td></td>
<td>PPV = 70%</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Side branch</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>(115)</td>
<td>255</td>
<td>Angiographic edge restenosis</td>
<td>BMS</td>
<td>Edge plaque burden</td>
<td>48%</td>
<td>c statistic = 0.70</td>
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<td>276</td>
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<td></td>
<td>PES</td>
<td>Edge plaque burden</td>
<td>47%</td>
<td>c statistic = 0.69</td>
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<td>(116)</td>
<td>433</td>
<td>Angiographic edge restenosis</td>
<td>E-ZES</td>
<td>Edge plaque burden</td>
<td>56.3%</td>
<td>67%</td>
<td>86%</td>
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<tr>
<td>422</td>
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<td></td>
<td>R-ZES</td>
<td>Edge plaque burden</td>
<td>57.3%</td>
<td>80%</td>
<td>87%</td>
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<tr>
<td>813</td>
<td></td>
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<td>EES</td>
<td>Edge plaque burden</td>
<td>54.2%</td>
<td>86%</td>
<td>80%</td>
<td></td>
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</tbody>
</table>

BMS = bare-metal stent(s); DES = drug-eluting stent(s); EES = everolimus-eluting stent(s); IVUS = intravascular ultrasound; LCX = left circumflex; LM = left main; MSA = minimum stent area; NPV = negative predictive value; PES = paclitaxel-eluting stent(s); POC = polygon of confluence; PPV = positive predictive value; SES = sirolimus-eluting stent(s); TLR = target lesion revascularization; ZES = zotarolimus-eluting stent(s).

### TABLE 3

<table>
<thead>
<tr>
<th>Causes of Stent Failure (Thrombosis or Restenosis)</th>
<th>Bare-Metal Stents</th>
<th>Drug-Eluting Stents</th>
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<tr>
<td></td>
<td>&lt;30 days</td>
<td>&gt;1 yr</td>
</tr>
<tr>
<td>Procedure-related complications including underexpansion, edge plaque burden or dissection, geographic miss</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Intimal hyperplasia</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Neoatherosclerosis</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Late malapposition or aneurysm formation</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Stent fracture</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Uncovered stent struts</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

IVUS-guided patients. A propensity score-matched analysis was possible in 9 studies (124,126), and there was no evidence of heterogeneity or publication bias. IVUS guidance was associated with a larger post-procedure angiographic minimum lumen diameter with no evidence of increased periprocedural MI (127). Two studies questioned the value of IVUS guidance in MI patients undergoing primary percutaneous intervention (128,129), but the ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) study suggested the opposite: that IVUS guidance had its greatest impact in MI patients (130). Most recently, a study reporting patient-level data from 4 Spanish registries showed that IVUS guidance reduced cardiac death, MI, and repeat revascularization in patients undergoing DES implantation for unprotected LMCA disease (131).
beneficial but the increased information provided compared with angiography alone (132). Advocates of OCT have cited superior resolution, enhanced imaging during flushing, ease of image interpretation, and detection of dissections, tissue protrusion, and malapposition not seen on IVUS (133–135). However, unlike IVUS, there are no established concepts regarding stent sizing by using OCT, and there are little data on OCT criteria for optimal stent implantation or predictors of adverse events. For example, there is no agreement whether an OCT-measured minimum stent area is larger, smaller, or the same as IVUS (133–136). Enhanced OCT detection of stent edge dissections, tissue prolapse, thrombus, or stent-vessel wall malapposition is not associated with predicting adverse events (137–140). One small, randomized, blinded study comparing IVUS- versus OCT-guided DES implantation found that, because of its limited penetration, less aggressive OCT stent sizing is associated with more stent underexpansion and a larger reference segment plaque burden compared with IVUS (136).

Although FFR has a limited role in stent optimization, it is probably the best technique to determine whether a jailed side branch is compromised after provisional bifurcation stenting (141–145). Most of the
time, the angiographic appearance of side branch ostial lumen compromise is an artifact, and FFR is >0.80 because lumen compromise is due to carina shift that is eccentric and focal and not due to plaque shift.

**WHY DID THROMBOSIS OR RESTENOSIS OCCUR IN THIS STENT?**

While most causes of stent thrombosis and ISR (Table 3) have been elucidated with IVUS, they can also be detected with OCT. The emergence of neatherosclerosis as an important cause of late stent failure (146-156), and observations regarding the relationship between lack of stent strut tissue coverage and late/very late stent thrombosis (157,158), neither of which can be identified by using IVUS (148), indicate that OCT may be the imaging technology of choice in this clinical setting.

OCT studies have shown that neatherosclerosis occurs earlier after DES than bare-metal stents, occurs with greater frequency with many types of DES versus bare-metal stents, can present as either ISR or very late stent thrombosis, and may be responsible for the majority of very late stent thrombosis; it is associated with greater clinical instability at the time of presentation (ACS in ISR and STEMI in very late stent thrombosis) and periprocedural MI at the time of treatment of ISR or stent thrombosis (146-156). However, it should be noted that OCT findings in stent thrombosis may depend on whether aspiration thrombectomy is performed before (154) or after (157) OCT imaging, because aspiration will remove not only thrombus but also fragments of neatherosclerotic plaques such as foamy macrophages, cholesterol crystals, and a thin fibrous cap (159). Other than neatherosclerosis, the clinical impact of OCT patterns on neointimal tissue (i.e., heterogeneous vs. homogeneous vs. layered vs. peri-strut low-intensity areas [160-169]) are not clear.

**SUMMARY AND BARRIERS TO IMPLEMENTATION**

There are 3 main barriers to implementing an intravascular imaging and physiology program: cost, expertise, and convincing interventional cardiologists of the limitations of relying on coronary angiography alone. In some countries, the cost of these techniques can dwarf that of the other materials used during percutaneous intervention. Education is problematic; interpretation is not intuitive, not even with OCT (170); and requires an understanding of artifacts, limitations, and confounders, like all medical imaging techniques. One of the legacies of coronary angiography is to presume that one technique will answer all of these questions; however, that often has been proved inaccurate in contemporary practice. Although there may be few randomized trials, the utility of these techniques to answer routine clinical questions is undeniable (Central Illustration).

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