Managing Patients With Intermediate In-Stent Restenotic Lesions
Is It “Prime Time” for Intravascular Ultrasound Imaging?

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The importance of intravascular ultrasound (IVUS) as an adjunctive technology facilitating optimal coronary interventional procedural technique has become increasingly evident over the past decade. IVUS is currently appreciated as an invaluable tool enabling better assessment of reference vessel size and coronary lesion morphology, including gross plaque characteristics and lesion length. Accordingly, the adjunctive use of IVUS with angiography offers distinct advantages in the setting of performing coronary interventions. The structural information acquired by ultrasound imaging has helped us plan and better execute the optimal coronary interventional procedures to achieve improved procedural efficiency and outcomes. These benefits have become more critical as we progressively approach more complex coronary lesions with catheter-based therapies. In addition, IVUS has shown to be a useful tool to investigate other possible structural causes relating to adverse events, including stent thrombosis. Late-acquired stent malapposition, stent fracture, inadequate lesion coverage, and excessive stent overlap are all readily detected by IVUS.

Once the decision to perform reintervention has been made, IVUS may be useful to better understand the mechanism of in-stent restenosis (inadequate expansion versus neointimal proliferation). This facilitates our decision-making process regarding the most appropriate treatment strategy when approaching these patients. The role of IVUS in helping to determine whether to treat a lesion with indeterminate clinical and functional data remains unclear. This potential contribution is even more questionable in the setting of the challenging “intermediate” angiographic lesion.

This issue of Circulation: Cardiovascular Interventions, Doi et al examines the potential value of 9-month IVUS measurements as a predictor of late target lesion revascularization (TLR) up to 3 years. The investigators report on 635 patients enrolled in the IVUS substudies of the TAXUS IV, V, and VI trials that did not require reintervention at the time of 9-month angiography. Overall, 36 late TLR events occurred during the 9-month to 3-year follow-up period. By using receiver operating characteristics analysis, they found that the best predictor for TLR was a minimal lumen area (MLA) value of 4.2 mm² (c statistic, 0.74) for paclitaxel-eluting stents (PES) and 4.0 mm² (c statistic, 0.73) for bare-metal stents (BMS). The rate of late TLR in PES-treated patients with a 9-month MLA ≥4 mm² was significantly lower as compared with those with an MLA <4 mm² (2.9% versus 11.6%, respectively). Similar differences were also observed in BMS-treated patients (3.5% in patients with a 9-month MLA ≥4 mm² versus 11.1% in those with an MLA <4 mm²). Noting this low rate of late TLR in the group of patients with an MLA ≥4 mm², the authors question the practice of intervening on such lesions at routine follow-up in the absence of symptoms. Therefore, they conclude that IVUS may be a useful adjunctive modality for decision-making in this scenario.

Several important messages can be derived from this report. First, earlier experience using brachytherapy as an antiproliferative agent in treating restenosis raised concerns regarding a possible late catch-up phenomenon. Animal studies have suggested that the antiproliferative agents used in currently available drug-eluting stents delay, rather than permanently suppress, neointimal proliferation. Although 3-year angiographic and IVUS results are not available, the findings of this report suggest that an eventual late catch-up phenomenon does not clinically manifest more often in PES versus BMS. This finding is pertinent to practicing interventional cardiologists and our patients. Second, the concept that IVUS-derived quantitative measurements might facilitate clinical decision-making at follow-up in post-PCI patients is...
also an attractive suggestion. Indeed, providing a definitive target that would better discriminate intermediate lesions requiring reintervention from those who do not would be very useful. Physiological measurements such as fractional flow reserve have been shown to be of value in these situations. It is not unreasonable that anatomic measurements such as those determined by IVUS might provide similar guidance. However, it is critical to confirm the correlation of this assessment with functional or clinical data.

Although the present study by Doi et al provides some insight on the role of IVUS in the setting of intermediate lesions, several concerns need to be considered. This predictive analysis is based on only 36 events occurring during the late follow-up period. The relatively low number of events has an impact on the power of an index such as MLA to predict future events. Notably, the sensitivity and specificity curves from which the cutoff values are derived show that MLA for both PES and BMS are only modest predictors of curves from which the cutoff values are derived show that MLA for both PES and BMS are only modest predictors of future events. Notably, the sensitivity and specificity has an impact on the power of an index such as MLA to predict future events. Therefore, the ability of an MLA <4 mm² to predict late TLR was low. For this reason, we agree and share the author’s prudent advice to not take these data as a prescription to intervene in all in-stent restenosis lesions <4 mm². Therefore, this study, although showing a low late-TLR rate in the group with an MLA ≥4 mm², leaves the issue regarding the treatment of asymptomatic patients with an MLA <4 mm² unanswered. The lack of this information makes this IVUS target of limited value when trying to make the correct therapeutic decision of whether to intervene.

Our challenge involves what to do with the angiographic intermediate lesion (40% to 70% stenosis) in the absence of functional and clinical imperatives to treat. Doi et al offer no convincing message to help us address this dilemma in our clinical practice. This study does not really deal with intermediate lesions; rather, it analyzes a more broadly defined lesion population (<70% angiographic stenosis). Therefore, this analysis includes a significant number of lesions that are quite mild; 50% of the PES group had <23% stenosis and 50% of the BMS group had <33% stenosis. Excluding these patients with minimal disease, the TLR rate in the group with an MLA ≥4 mm² would be higher, and we suspect that the MLA cutoff value might be different. An analysis focused only on patients with intermediate lesion may provide results that are more clinically applicable.

Historically, cardiologists have been uncomfortable making clinical decisions based on anatomic assessments of intermediate lesions. An ideal signal that would help physicians to best determine whether to intervene in this challenging setting should have several important features. This signal should be easily and safely accessible, simple to interpret, and cost effective, with compelling positive or negative predictive value. Currently, when stress test imaging is not available to guide the decision to intervene in asymptomatic patients, FFR is considered the preferable “in-cath lab” tool. Several studies have shown that the functional assessment by FFR provides a reliable signal predicting future clinical events. Whether one of the numerous ultrasound-derived anatomic measurements might serve this purpose remains unclear. Several investigations have assessed the correlation between anatomic ultrasound measurements and functional ischemic testing, providing inconclusive results.

IVUS-derived anatomic measurements might provide similar guidance, as suggested by this and a previous report. Further support of this concept would require a prospective clinical trial testing the application of an IVUS-dictated clinical strategy similar to the DEFER trial’s investigation using FFR.

Management of our post-PCI patients continues to be best dictated by clinical symptom status and stress imaging. When an intermediate in-stent restenosis lesion is serendipitously found in the catheterization laboratory, FFR continues to be the preferred method to evaluate whether to revascularize. The use of IVUS alone to dictate the decision to intervene is still not ready for “prime time.”

Disclosures

Dr Bass is on the speaker’s bureaus for Eli Lilly and Daiichi Sankyo and has received research support from Baxter. Dr Capranzano has no conflicts to disclose.

References


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