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IVUS in bifurcation stenting: what have we learned?

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Intravascular ultrasound (IVUS) has dramatically changed our understanding of coronary atherosclerotic disease and the response to percutaneous coronary intervention (PCI). Indeed, angiography has limitations in assessing the extent of plaque burden and distribution, true luminal size and may provide only very modest information regarding the composition of the coronary lesion. On the contrary, these parameters can be easily obtained by the tomographic cross-sectional format provided by IVUS. In particular, IVUS has revealed that the extent of atherosclerotic disease is significantly more diffuse and localised calcifications are present much more commonly than is appreciated by angiography, occurring in 70-80% of lesions treated. Superficial calcium deposits are among the most important IVUS predictors of lesion response to PCI. The information from IVUS has also led to a dramatic change in the stent-deployment algorithm, ushering in the "high pressure deployment era" with dual antiplatelet therapy. Currently, concerns regarding drug-eluting stent (DES) thrombosis and the associated high morbidity and mortality have led to resurgence of IVUS use. Indeed, this imaging modality is being utilised on a day-to-day basis in an increasing number of catheterisation laboratories to monitor and optimise PCI. In the process, interventional cardiologists are able to view the procedure they are performing with an increased level of insight and understanding. The additional value of IVUS application can be particularly appreciated in the treatment of complex coronary lesions, such as those located at bifurcation sites. Determining anatomic configuration, selecting treatment strategy and assessing final result are key factors in bifurcation lesion treatment that may have a significant impact on acute and long-term outcomes.

Coronary bifurcation lesion assessment with IVUS

Pre-intervention assessment of coronary bifurcation disease with IVUS has provided important insights on the non-uniform extent and distribution of the atherosclerotic plaque burden. Plaques are located opposite the side branch take-off, are more concentric proximal to the side branch, and more eccentric just distal to the side branch. Moreover, they typically spare the flow divider, maintain eccentricity across a wide range of vessel stenoses, and are influenced by the angle of the side branch take-off, such that plaque is also deposited preferentially toward an acute angle (toward an inner radius of curvature) and away from an obtuse angle (toward the outer radius of curvature)[1,2]. Main vessel stenting may enhance carina displacement and atheroma shift across the side branch ostium leading to side branch ostium narrowing (often referred to as "snow-ploughing" or "carinal shift")[3]. This has been associated with an increased risk of transient or permanent branch closure. Angiographic evidence of ostial side branch stenosis has been found to be a strong predictor of side branch occlusion[4]. However, it is difficult to distinguish which side branches are most likely to occlude after PCI solely on the basis of angiographic evaluation. Furukawa et al demonstrated that side branches showing at IVUS diffuse plaque around the ostium with >50% stenosis were at higher risk for occlusion[5]. On the contrary, side branch occlusion was uncommon (<10%) after PCI if no plaque was present at the side branch ostium.

The angiographic assessment of intermediate lesions of left main coronary artery (LMCA) continues to be problematic. Use of IVUS has shown to be of particular value in characterising distal LMCA lesion morphology and to ensure the lesion is "real" and truly requires treatment (Figure 1). It has been demonstrated that when

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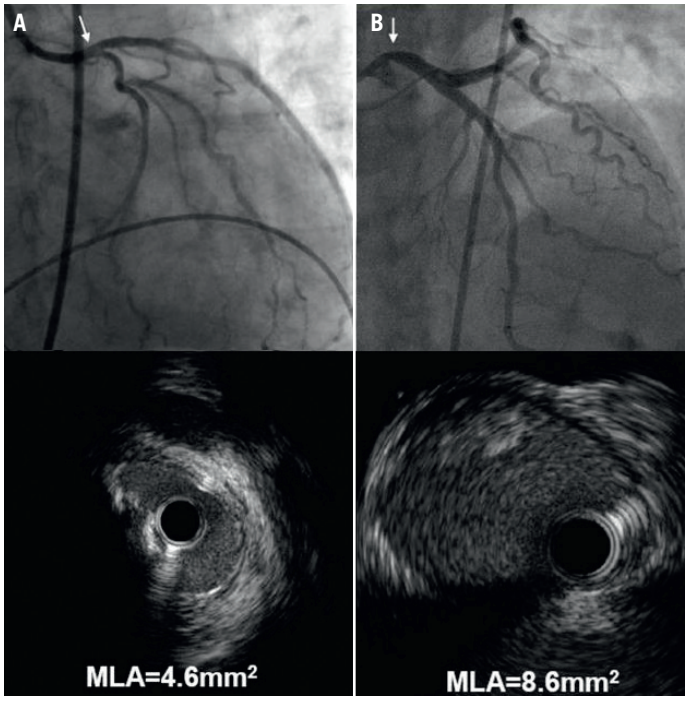

Figure 1. Discrepancy between angiography and IVUS for left main coronary artery evaluation. A) Angiography shows a normal appearance (top, arrow), whereas IVUS demonstrates a significant plaque burden with a corresponding MLA of 4.6 mm² (bottom). B) Severe ostial stenosis is detected by angiography (top, arrow) and not confirmed by IVUS evaluation (bottom).

decision-making about revascularisation is based on physiological data, a significant number of patients can be spared from unnecessary coronary artery bypass surgery or PCI. Similarly, in a study by Sano et al there were no correlations between angiographic assessment of intermediate LMCA lesions, IVUS and quantitative coronary angiography (Figure 2)[6]. Additionally, Abizaid et al demonstrated that IVUS-determined minimal lumen diameter (MLD) was the most important quantitative predictor of cardiac events at one year in 122 patients who underwent angiographic and IVUS assessment of LMCA disease severity[7]. Moreover, another IVUS study showed that plaque extension from the LMCA to the left anterior descending coronary artery (LAD) is present in about 90% of lesions[8]. These findings have an important role in the decision-making process when treating a distal LMCA bifurcation stenosis. For example, minimal plaque burden in the left circumflex coronary artery (LCX) ostium by IVUS may provide reliable guidance for selection of a specific stent strategy, e.g., provisional stenting. Indeed, no previous study has shown the benefit of systematic two stenting over the provisional strategy[9-11]. The Sano et al study indicated also that a precise assessment of distal LMCA bifurcation, including the LAD and LCX ostia, requires wiring and imaging of both daughter vessels back to the LMCA[6]. They demonstrated that the oblique/tangential IVUS imaging findings of the side branch from the main vessel may introduce errors in IVUS measurements due to angulations, eccentricity or non-coaxial transducer location[12,13]. Furthermore, the minimal lumen diameter (MLD) of the LMCA may differ when imaged from a pullback beginning in the LAD vs. a pullback beginning in the LCX (Figure 3). However, since IVUS can artificially increase, but not decrease lumen dimensions, the smallest minimal lumen area (MLA) is always the most accurate. Use of IVUS may also provide a criterion that can be useful in defining a "critical" LMCA stenosis. It has been demonstrated that IVUS-determined MLD and MLA cut-off values of 2.8 mm and 5.9 mm², respectively, provide the best sensitivity and specificity to predict the physiological significance of a LMCA stenosis and are well correlated with a fractional flow reserve cut point of 0.75. Additionally, these data are aligned with the Murray's law (LMr3=LADr3+LCXr3) and do not depend on finding a disease-free reference segment[14].

IVUS guidance for bifurcation lesion PCI

The use of IVUS imaging may have an impact on PCI strategy. First, IVUS can select the appropriate stent size and length as well as guiding the most appropriate technique for coronary bifurcation lesion treatment. Second, it may be helpful in optimally expand the stent avoiding stent under-expansion, malapposition, incomplete lesion coverage and overstretch of the stent diameter[15]. Indeed, IVUS studies have shown that stent dimensions are important predictors of restenosis even in the DES era[16]. Regardless of the angiographic result, IVUS imaging of main and side branch often reveals inadequate stent expansion in at least one branch. Costa et al studied 40 patients with coronary bifurcation lesions who underwent crush stenting, a technique originally developed to overcome stent under-expansion and incomplete coverage of the side branch ostium. Interestingly, they demonstrated that the minimum stent area (MSA) was at the crush zone[17]. Specifically, when both branches were considered the MSA was found at the side branch ostium in 68% of lesions. Furthermore, "incomplete

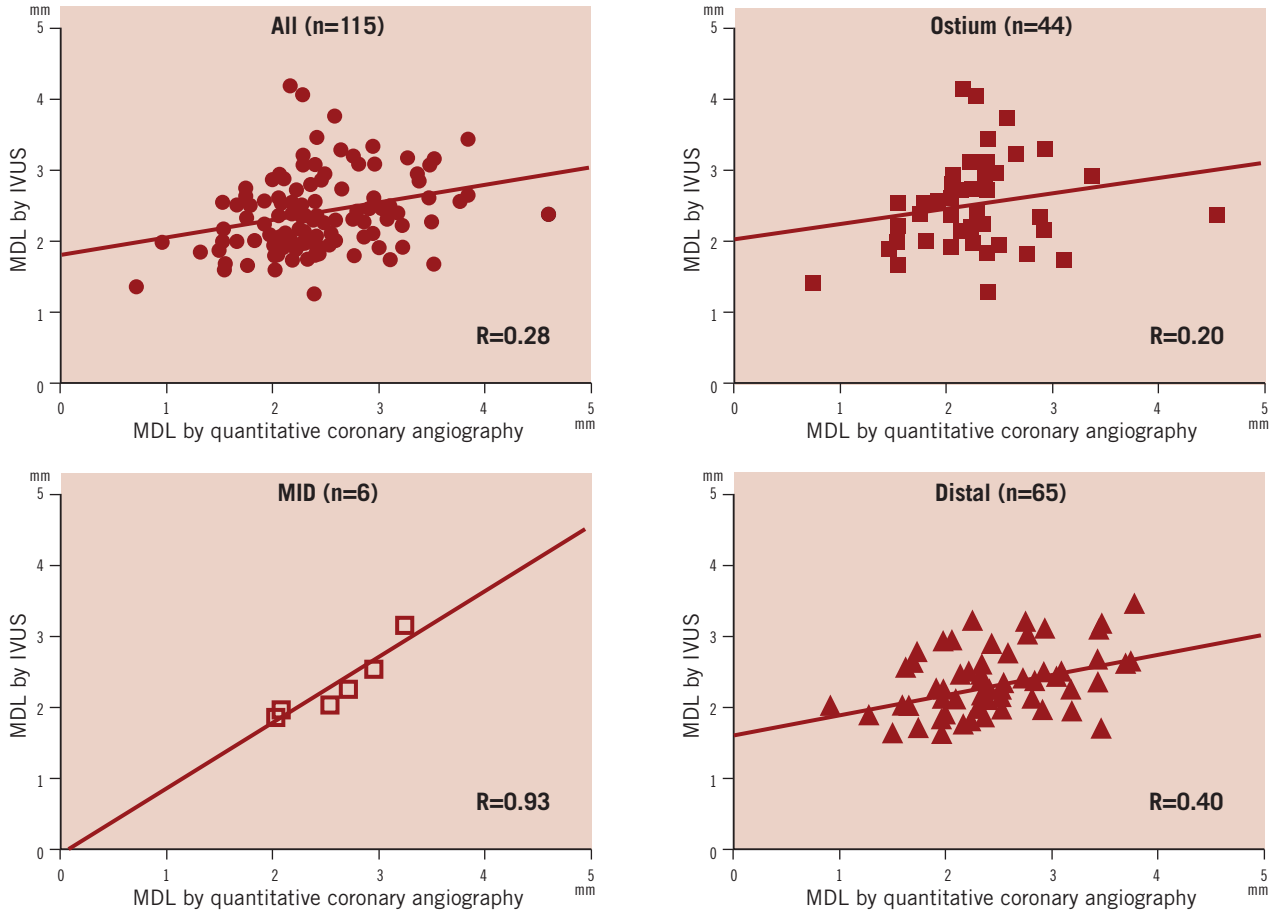

Figure 2. Correlations between minimal lumen diameter by IVUS and QCA for all, ostial, mid and distal left main coronary artery lesions (modified from Ref. 6).

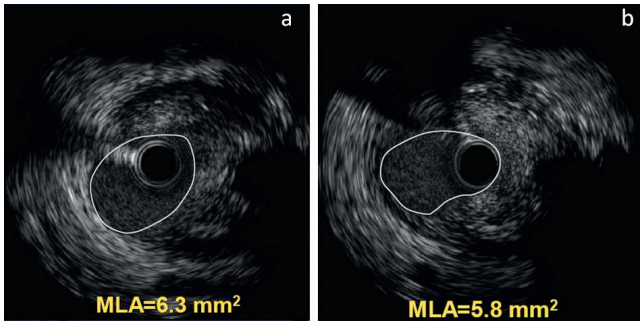

Figure 3. Left main coronary artery evaluation by IVUS pullback from the left anterior descending coronary artery (a) and the left circumflex artery coronary artery (b) showing a minimal lumen area discrepancy of 0.5 mm².

crushing", defined as incomplete apposition of side branch or main vessel stent struts against the main vessel wall proximal to the carina, was found in more than 60% of lesions (Figure 4a). This could be one of the main mechanisms of the higher restenosis rate occurring at this location, because even a small amount of intimal hyperplasia superimposed on a significant stent under-expansion can result in restenosis. Therefore, optimisation of the result in the side branch is still the goal even in the DES era and new strategies are needed to achieve an adequate result without compromising the main vessel.

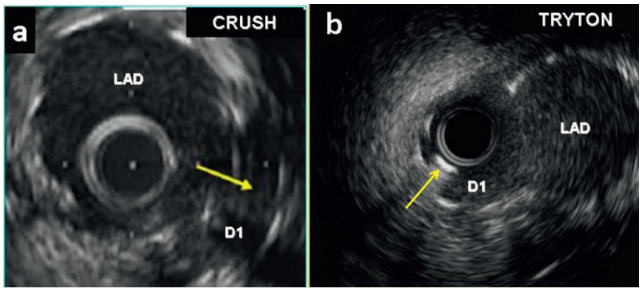

Figure 4. (a) IVUS evaluation after crush-stenting of a true bifurcation lesion in the proximal left anterior descending coronary artery/first diagonal branch showing incomplete apposition of the side branch stent struts and stent underexpansion of the side branch ostium (arrow). (b) IVUS evaluation after treatment with a Tryton stent of a true bifurcation lesion in the proximal left anterior descending coronary artery/first diagonal branch. Note the optimal carina reconstruction and the well-apposed stent with full and symmetric expansion at the side branch ostium. The arrow indicates the guidewire. LAD: left anterior descending coronary artery; D1: first diagonal branch

The mechanism of restenosis after distal LMCA treatment with DES using the T-stent technique and the predictive value of post-procedural MSA in the side branch were evaluated in another study in which 73 bifurcation lesions were examined with post-procedural and 9-month follow-up IVUS images for both main

vessel and side branch[18]. At post-procedural IVUS evaluation, stent expansion was significantly less in the side branch than in the main vessel. Moreover, the MSA site was most frequently observed at the distal main vessel stent and side branch ostium. At follow-up, there was a significant correlation between post-procedural MSA and MLA in the corresponding segments. In addition, the percentage of neointimal area was significantly higher in the side branch ostium compared with the proximal, mid and distal main vessel. Of note, the optimal cut-off values of post-procedural MSA at the side branch ostium and at the main vessel middle area were predictive of MLA at follow-up (side branch ostium 4.83 mm^2, main vessel middle area 6.14 mm^2). The larger MSA observed in the main vessel as compared to the side branch ostium provides an explanation for the increased restenosis observed at the side branch ostium. Increased neointimal hyperplasia may also play a role in the higher rate of restenosis in bifurcation lesions compared with non-bifurcation lesions despite use of DES.

Impact of IVUS guidance on outcome

A large cohort study reported that IVUS guidance during DES implantation significantly reduced the thrombosis rate and showed a favourable trend for repeat revascularisation[19]. The effect of IVUS guidance may prove to be even more useful in complex bifurcation lesion treatment. The long-term effect of IVUS guidance was assessed for the first time by Park et al in 758 patients with *de novo* non-LMCA bifurcation lesions who were assigned to IVUS (473 patients) or angiographic (285 patients) guidance. Comparison of adverse outcomes (death, stent thrombosis and target lesion revascularisation) between the two groups at 4-year follow-up showed that IVUS-guided stenting significantly reduced all-cause mortality in patients receiving DES. Conversely, no significant impact of IVUS on stent thrombosis rate was observed both in patients receiving DES or bare-metal stents. However, IVUS-guided stenting significantly reduced very late stent thrombosis in the DES group, while it did not have any effect on the target lesion revascularisation rate[20]. In this study, the long-term survival benefit of IVUS guidance in patients receiving DES was mainly driven by a reduction in very late stent thrombosis. Indeed, it has been demonstrated that late stent thrombosis is an important contributor to long-term mortality after DES treatment. Thus, the difference in mortality observed by Park et al might be explained by reduced rate of thrombotic events when the procedures were performed under IVUS guidance. Stent under-expansion, incomplete lesion coverage, edge dissections and longitudinal plaque shifting, which likely contribute to DES thrombosis are often missed by angiography and are detected by IVUS.

A retrospective study showed that IVUS-guided treatment of LMCA lesions with DES was not associated with a significant clinical long-term benefit compared with an angiography-guided procedure[21]. However, this finding may be due to the underpowered nature of this retrospective study. The large MAIN-COMPARE (revascularisation for unprotected left MAIN coronary artery stenosis: COMparison of Percutaneous coronary Angioplasty versus surgical REvascularization) multicentre registry assessed long-term outcomes of unprotected LMCA stenosis treated by either coronary artery bypass surgery or PCI[22]. Among 975 patients undergoing PCI of the LMCA, 77.5% were treated with IVUS guidance, while angiography only was used in the remaining 22.5%. The comparison of the 3-year outcome between the two groups showed a strong trend towards a lower mortality risk with IVUS guidance (6% vs. 13.6%, log-rank P=0.063; Hazard ratio 0.54; 95% CI, 0.28 to 1.03; Cox-model p=0.061).

Dedicated bifurcation stents

The need for dedicated bifurcation stents (DBS) stems from the limitations of the different stenting techniques even in the DES era, including failure to maintain side branch access, difficult re-wiring and balloon or stent tracking into the side branch, distortion of the main vessel stent by side branch stent dilation, and inability to fully cover, scaffold and expand the side branch ostium. The main need for a DBS is to provide interventional cardiologists with the ability to stent bifurcation lesions is a manner similar to lesions located in straight coronary segments, i.e., a straightforward technique with reliable deployment achieving complete lesion coverage and scaffolding. Valuable insights into our understanding of DBS may be derived from IVUS. We evaluated with IVUS a novel DBS, the Tryton Side-Branch Stent™, (Tryton Medical, Inc., Durham, NC, USA). Tryton is a balloon-expandable cobalt-chromium bare-metal stent with a distal zone that scaffolds the side branch, a transition zone designed to accommodate the wide range of ostial anatomy and a proximal zone designed to accommodate a standard stent. The Tryton is deployed with the transition zone at the side branch origin with the distal end in the side branch and proximal zone in the main vessel proximal to the side branch origin. The Tryton I, first-in-man (FIM) study demonstrated feasibility and safety of the Tryton stent when used in conjunction with a DES in the treatment of complex bifurcation lesions with excellent long-term results (6-month late loss=0.17 mm, TLR=1%, TVR=3%, and no side branch failures)[23]. The low late loss and restenosis rate observed in this study were somewhat surprising for a BMS. Two distinct mechanisms might provide an explanation for these results: 1) radial diffusion of the lipophylic antiproliferative drug from the DES implanted in the MV; 2) complete coverage and better expansion of the side branch ostium. While the first mechanism remains speculative, the second could be investigated by an IVUS study. For this reason, we designed the IUVANT (Intravascular Ultrasound eVAluatioN of Tryton stent) study to evaluate with IVUS imaging the post-procedural and 9-month follow-up results of the Tryton stent implanted in 33 non-LMCA *de novo* coronary bifurcation lesions of 32 consecutive patients. Appropriately sized Xience V (Abbott Vascular, Santa Clara, CA, USA) stents were positioned in the main vessel with the proximal portion covering the Tryton stent and the distal portion extending beyond the side branch ostium into the distal main vessel. Preliminary analysis of IVUS images demonstrated complete coverage of side branch ostium with full stent expansion, high symmetry and large final area at the carina site (Figure 4b)[24]. Of note, mean stent expansion at

the side branch ostium, defined as minimum stent area/average lumen area, was 88%. At follow-up, IVUS showed a very low neointimal hyperplasia cross sectional area at MLA site both in the main vessel and in the side branch stent.

Lessons learned

First, IVUS should be considered in the assessment of patients with coronary bifurcation lesions, particularly in those with angiographically ambiguous LMCA disease. The accurate evaluation of the bifurcation lesion, including the ostia of the main and of the side branch, requires wiring and imaging of both arteries and cannot be accomplished by imaging just one of these two daughters vessels back to the proximal main vessel. This technique is specifically required when LMCA disease is under evaluation. Second, a better insight into plaque configuration with IVUS can diminish the unnecessary use of the two-stent procedure by distinguishing "true stenosis" from "pseudostenosis" caused by artefacts, including coronary spasm or calcification at the side branch. This may play a role in improving outcomes allowing an appropriate selection of stenting strategy. In fact, it has been demonstrated that the systemic use of a single-stent strategy compared to a two-stent strategy may reduce the risk of stent thrombosis as well as repeat revascularisation in bifurcation lesions. Third, IVUS taught us that different stenting techniques (e.g., crush, T-stenting) leave small ostial side branch diameters and frequent incomplete stent apposition and carina coverage, findings that may explain the high rate of side branch restenosis. Fourth, IVUS guidance may reduce the long-term mortality rate of PCI, especially when DES are used, for unprotected LMCA stenosis when compared with conventional angiographic guidance. Fifth, imaging assessment by IVUS of DBS may improve our understanding of different technologies and the knowledge of the steps needed for proper implantation. This may offer a superior evaluation of procedural results and has the potential to improve the long-term outcome of new devices specifically designed for coronary bifurcation lesions.

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