

## Is a Minimum Stent Area of 5.7 mm<sup>2</sup> Good Enough?

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In this issue of **Revista Brasileira de Cardiologia Invasiva**, Brito et al.<sup>1</sup> report the impact of the final post-procedure intravascular ultrasound (IVUS) stent dimensions on mid-term outcomes after implanting the Endeavor drug-eluting stent (DES). Using an IVUS minimum lumen area (MLA) of 4.0 mm<sup>2</sup> at 6 months of follow-up as the primary endpoint in their analysis, the authors report that the post-intervention minimum stent area (MSA) of > 5.7 mm<sup>2</sup> best predicts a 6-month MLA > 4.0 mm<sup>2</sup> (area under curve = 0.815; 95% CI 0.68-0.95; p < 0.001, with a sensitivity and specificity of 80%).

Why an IVUS MLA of 4.0 mm<sup>2</sup> as an endpoint? As Sonoda et al.<sup>2</sup> did before them, the authors used an IVUS MLA < 4.0 mm<sup>2</sup> as a measure of restenosis. Where does this number come from? In 1998, Abizaid et al.<sup>3</sup> showed that an IVUS MLA < 4.0 mm<sup>2</sup> predicted a coronary flow reserve (CFR) < 2.0 measured by the Doppler FloWire with a diagnostic accuracy of 92%. Next in 1999, Nishioka et al.<sup>4</sup> compared IVUS minimum lumen dimensions to stress myocardial perfusion imaging with almost identical findings. Third, also in 1999, Takagi et al.<sup>5</sup> compared IVUS minimum lumen dimensions with fractional flow reserve (FFR) measured using the intracoronary pressure wire; the MLA correlated with FFR, and an MLA 4.0 mm<sup>2</sup> correlated well with a FFR of 0.8. Finally, Abizaid et al.<sup>6</sup> reported that the 1-year event rate of 248 lesions with an MLA ≥ 4.0 mm<sup>2</sup> was only 4.4% with a target lesion revascularization (TLR) rate of only 2.8%.

It is worthwhile to take a minute to critically examine these studies since they are often taken a bit out of context. First, these analyses were in lesions in non-left main major epicardial vessels > 3 mm in size and not in branches or mid to distal segments of major arteries. Second, these studies indicated that it was safe to defer intervention if the MLA was ≥ 4.0 mm<sup>2</sup>; these studies did not indicate that intervention was indicated if the MLA was < 4.0 mm<sup>2</sup>. Third, the CFR study by Abizaid et al.<sup>3</sup> as well as a subsequent FFR study by Takayama and Hodgson indicated that lesion length

was also important<sup>7</sup>. Finally, diabetics always had more events for the same MLA compared to non-diabetics.

In the context of the study of Brito et al.<sup>1</sup>, can an IVUS MLA measurement be used as a criterion for in-stent restenosis (ISR)? Nishioka et al.<sup>8</sup> studied 150 intermediate ISR lesions in 142 patients. Repeat intervention was deferred if the MLA measured by IVUS was > 3.5 mm<sup>2</sup> even if the patients had symptoms; in patients with an IVUS MLA > 3.5 mm<sup>2</sup>, the 2-year event-free survival rate was high (96.5%). More recently, Doi et al.<sup>9</sup> showed, in an analysis of 331 patients treated with Taxus stents who did not require TLR in the first 9 months post-intervention and who were followed for 3 years, that the optimal thresholds of MLA at 9-months that best predicted subsequent TLR-free survival at 3 years was 4.2 mm<sup>2</sup> (c = 0.7448). Thus, yes, an IVUS MLA < 4.0 mm<sup>2</sup> seems to be a reasonable surrogate for angiographic and clinical restenosis independent of the amount of intimal hyperplasia in the proper patient and vessel size subset.

Why is the post-intervention MSA so important? Numerous studies in both the bare metal stent and DES eras have shown that the IVUS MSA is the strongest predictor of stent thrombosis or restenosis. The study by Brito et al.<sup>1</sup> using an IVUS endpoint, previous studies by Sonoda et al.<sup>2</sup> (IVUS endpoint) and Hong et al.<sup>10</sup> (angiographic endpoint), and unpublished data from the combined TAXUS IV, V, and VI and TAXUS ATLAS WH, LL, and DS trials (angiographic endpoint) all seem to indicate the same thing – that an IVUS MSA of 5.0-5.7 mm<sup>2</sup> best separated subsequent restenosis from non-restenosis. In the first of these studies by Sonoda et al.<sup>2</sup> from the SIRIUS trial, a post-intervention Cypher MSA < 5.0 mm<sup>2</sup> best predicted an 8-month MLA < 4.0 mm<sup>2</sup>. In the second of these studies by Hong et al.<sup>10</sup> from the single-center Asan Medical Center experience, the final post-intervention Cypher MSA that best predicted 6-month angiographic restenosis was < 5.5 mm<sup>2</sup>. In addition, the IVUS-measured stent length that best separated restenosis from non-restenosis was > 40 mm;

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lesions with final MSA < 5.5 mm<sup>2</sup> and stent length > 40 mm had the highest rate of angiographic restenosis. Another IVUS study of 169 lesions in 138 patients treated with Cypher stents showed that a post-intervention MSA of < 5.0 mm<sup>2</sup> and a stent length of > 30 mm were independent predictors for angiographic restenosis<sup>11</sup>. Finally, in the combined TAXUS studies experience the optimal thresholds of post-intervention IVUS MSA that best predicted freedom from angiographic restenosis at 9 months was  $\geq 5.7$  mm<sup>2</sup> (Doi et al., unpublished findings).

What else is important? While stent underexpansion is the strongest predictor of early and late DES failures, clinicians continue to focus on malapposition often confusing and using interchangeably the concepts of underexpansion and malapposition or using the imprecise term underdeployment. Yet, there is little data linking acute malapposition with adverse events. Although acute stent vessel wall malapposition is technique related and dependent on device sizing, post-implantation and follow-up IVUS have demonstrated that early stent malapposition has no bearing on either restenosis or thrombosis regardless of whether the malapposition is resolved or persistent<sup>12-15</sup>. Instead, edge problems, inflow/outflow tract disease, geographic miss, or the plaque burden at the stent edge is an important and consistent predictor of edge restenosis after DES implantation<sup>16-18</sup>; and these are underappreciated and often overlooked.

Is an IVUS MSA of 5.0-5.7 mm<sup>2</sup> large enough in all DES treatments? Probably not and for many reasons.

First, the SIRIUS trial (Sonoda et al.<sup>2</sup>) and some of the TAXUS trials (Doi et al.<sup>9</sup>) enrolled relatively low-risk patients compared with real-world cohorts (Hong et al.<sup>10</sup>). Studies have consistently showed a relationship between increasing patient and lesion complexity and increased risk of restenosis.

Second, cut-points are accurate in predicting stent patency, but are not good in predicting restenosis. If the MSA is larger than the cut-point, then the chance of not developing restenosis is high. If the MSA is less than the cut-point, then restenosis may or may not occur. In addition, other factors – strut fracture, non-homogeneous stent-strut distribution, etc – must be taken into account.

Third, in all of the studies there was a stepwise relation between the post-intervention MSA and the likelihood of restenosis. A post-intervention MSA larger than the cut-point was associated with a greater chance of long-term patency, and the smaller the MSA the greater the likelihood of restenosis.

Finally, if “one size fit all”, an MSA of 5.0-5.7 mm<sup>2</sup> would be achieved by 100% expansion of any 2.5-2.75 mm DES. Thus, manufacturers would only have to make one size stent for all vessels with a reference

diameter  $\geq 2.5$  mm (even up to 4mm!), and one size would fit all situations. This was not the case in the early Cypher stent experience when shortages in larger stent sizes lead to the use of undersized stents in larger vessels with a high rate of adverse events.

So, is an MSA of 5.7 mm<sup>2</sup> good enough? No, not in larger vessels. But it will also be hard to achieve in small vessels just like an MLA of 4.0 mm<sup>2</sup> would be less appropriate as a criterion for significant lumen compromise in a small vessel. Finally, it should be noted that little measurement difference in MSA measurements in the 5.0-5.7 mm<sup>2</sup> range.

## CONFLICT OF INTEREST

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