

## CAC score vs IVUS MLA: is this the right comparison?

Commentary on

Prevalence of a minimal luminal cross sectional area of coronary arteries < 4 mm<sup>2</sup> determined by intravascular ultrasound in patients with coronary artery calcium scores of 0-100, 100-200, 200-300, 300-400, and > 400 determined by cardiac computer tomography

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Shao *et al.* report that coronary artery calcium (CAC) scores determined by computed tomography (CT) do not accurately predict significant obstructive coronary artery disease (CAD) determined by intravascular ultrasound (IVUS) [1]. Besides the fact that the study contains too few observations for meaningful comparison, is this finding surprising; and did this study ask the right question?

The authors used an IVUS minimum lumen area (MLA) < 4 mm<sup>2</sup> as an index of stenosis severity. While this has been correlated with intracoronary Doppler FloWire measured coronary flow reserve [2], myocardial perfusion imaging [3], and intracoronary pressure wire measured fractional flow reserve (FFR) [4], an MLA cut-off ≥ 4 mm<sup>2</sup> is more indicative of a lesion that is not hemodynamically significant and in which intervention can be safely deferred [5] than of the converse – i.e., an MLA < 4 mm<sup>2</sup> indicating hemodynamic significance necessitating intervention. Second, these validation studies were all done in > 3 mm major epicardial arteries excluding the left main coronary artery. Even in their small study (*n* = 25) the authors included one patient with a lesion in a diagonal branch and three patients with lesions in the left main coronary artery in which an equivalent IVUS threshold cut-off would be 6.0 mm<sup>2</sup> [6]; furthermore, the authors do not report vessel sizes or even proximal, mid, or distal lesion location. Third, it is not clear from this study why the particular arteries were studied by IVUS; lesions are widely distributed in all three arteries of patients with coronary artery disease. The baseline data from PROSPECT (Providing Regional Observations to Study Predictions of Events in the Coronary Tree) shows that high risk patients have, on average, approximately 4.0-4.5 non-culprit lesions with a plaque burden > 40%, but only one of them has an MLA < 4 mm<sup>2</sup>. A better gold standard would have been FFR to determine the presence of a hemodynamically significant lesion. Such a study would, ideally, include FFR of all three coronary arteries or, at least, of the coronary artery with the worst angiographic disease.

What does CAC score actually measure? Previous studies have reported a strong relationship between CAC score and the subsequent risk of acute coronary events [7, 8]. The conventional explanation is that the CAC score correlates with overall plaque burden and the greater the overall plaque burden the more likely the presence of a vulnerable plaque whose rupture and thrombosis would lead to an event. While IVUS MLA is a more accurate measure of lumen compromise than is angiographic diameter stenosis, both are anatomic measures of stenosis severity; they do not measure plaque burden and cannot indicate the presence of a vulnerable plaque. A better comparison would have been CAC score vs IVUS plaque burden or CAC score as a predictor of the presence of one or more vulnerable plaques. While greyscale IVUS cannot detect a thin-capped fibroatheroma (TCFA) – the most common type of vulnerable plaque, newer radio-frequency algorithms – integrated backscatter (IB)-IVUS [9] or virtual histology (VH)-IVUS or optical coherence tomography (OCT) [10] – have shown promise as TCFA detectors. There are other vulnerable plaque types as well – plaque erosions that can only be detected in vivo using OCT or calcific nodules that can be detected by greyscale IVUS. However, a study of CAC score to predict an IB-IVUS, VH-IVUS, or OCT-detected TCFA would have required a three vessel imaging study since it is now clear that TCFAs are relatively infrequent even in high risk patients [11, 12]. Finally, while there have been reported associations between CAC scores and angiographic lesion severity, those studies [1] have involved hundreds of patients [13], not the small number in the study by Shao *et al.* (1) and (2) suggest that only the highest calcium score may actually be predictive of an angiographically significant lesion [14].

When performing any scientific study, it is important to first ask the right question and second to select the best analytic modalities to answer that question – or, as reviewers are fond to emphasize, to formulate a correct hypothesis.

## References

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