Old test: New twist

The primary use of coronary artery calcium scoring has been in its ability to predict coronary artery disease (CAD) events in generally asymptomatic patients and to provide incremental risk stratification beyond the use of traditional clinical risk factor assessment.1 Thresholds of calcium burden, as determined by the area-density scoring or Agatston scoring method, on the basis of age, sex, and race, provide a reference for physicians in regard to risk, with more extensive coronary artery calcium (CAC) associated with increased risk of subsequent future events. This prognostic value of CAC has been well established and can be incorporated into the overall risk assessment to modify clinical management.1–3

There is no doubt that cardiac CT can detect subclinical atheroma. CAC is almost 100% indicative of the presence of some degree of atherosclerosis, either non-obstructive or obstructive. For obstructive CAD, the sensitivity of any coronary artery calcium is high.3 However, CAC has not been widely used as the sole test to diagnose obstructive CAD in that a tradeoff exists for the test sensitivity and specificity on the basis of the threshold used for defining the presence or absence of disease. Indeed, the presence of calcium is not 100% specific for identification of a significant, flow-limiting coronary artery lesion, and overall specificities and the positive predictive values are low. Reasons for this limited predictive accuracy include limitations of prior studies by biases such as verification bias and referral bias. Importantly, the lesion calcification can be influenced by many factors, including prior plaque instability and healing, age, and inflammation such that, although the extent of total calcium in a patient is generally related to the atherosclerotic burden, there can be significant variability between arteries and within any given individual plaque. It is important to recognize that a positive calcium score (score > 0) is most often not associated with significant obstructive CAD. However, a calcium score of 0 does not exclude the presence of atherosclerotic plaques or obstructive disease, particularly in symptomatic persons.4

In this issue of the Journal, Qian et al5 report on vessel and lesion calcium score in comparison to total CAC score for the diagnosis of obstructive CAD. In this small retrospective study of patients undergoing calcium scoring and invasive coronary angiography, the authors found that, among patients who had positive calcium scores, the amount of vessel-specific calcium or lesion-specific calcium had a greater degree of association with significant obstructive CAD than the total calcium score. In other words, the extent of calcium within a lesion or vessel was a more accurate predictor of an obstructive lesion than the total calcium score. The use of vessel-level calcium is potentially a new twist on an old test.

The natural progression of atherosclerosis entails compensatory vessel enlargement (positive or outward vessel remodeling) to accommodate plaque progression and to maintain the lumen area. Once the progressive atherosclerotic process overcomes the compensatory remodeling process, luminal obstruction occurs. Plaque calcification can occur at any time point within this dynamic process, but it is most often associated with plaque age. Therefore, at some level, the findings of Qian et al5 are in part expected: the greater the degree of calcium, the higher the likelihood of obstructive disease. But before we become enthusiastic about such a finding, it is important to point out a number of potential limitations that may influence the way we interpret small diagnostic accuracy studies.

The study population size determines the applicability of the new diagnostic technique as well as its generalizability to various other populations. The description of the patients’ clinical presentation and characteristics is important to assess generalizability, particularly when these variables (such as symptoms, age, and prior events) can modify the utility of the test (study population bias). In addition, as with most studies examining the diagnosis of obstructive CAD, only patients referred for coronary angiography were included in the study by Qian et al,5 representing a common but unavoidable limitation (verification bias). In this regard, because patients included in this study were already referred to the catheterization laboratory, the disease prevalence due to patient referral bias was significantly higher than that seen in a general population in which calcium scoring is typically used. Most importantly, only patients with measurable CAC were included in the study, and only vessels with positive calcium were included in the vessel-based analysis (noncalcified vessels were excluded). This raises the severity of the disease
in the study population which can directly influence the test’s performance characteristics. In addition, the exclusion of any patient without calcium (or any noncalcified vessels) from the analysis of diagnostic accuracy virtually invalidates any estimates of specificity and predictive values. Therefore, it is impossible to determine what the diagnostic performance of the test would be in an unselected population or when all coronary vessels are included. Moreover, the clinical presentation and many baseline characteristics (and risk factors) of patients were not included, limiting our ability to interpret the results. Finally, the prognosis and subsequent clinical events of patients were not reported in the study.

An unintended interpretation of the study could be that patients without calcification do not have obstructive CAD. Because patients without coronary calcium were excluded from the analysis, as well as vessels without calcium (even when another vessel in the same patient had calcium present), no conclusions can be made for the diagnostic accuracy of vessel calcium in patients with suspected CAD. Furthermore, the authors did not compare specific lesion-versus-lesion stenosis, only general patient and vessel-level calcium. In addition, because only calcium was measured, the true “lesion” extent remains unknown. Note that symptomatic patients with a zero calcium score are at some measurable risk of obstructive and clinically significant CAD.4

Finally, compared with CAC scoring, multidetector computed tomography angiography (MDCTA) has the ability to directly diagnose the presence or absence of obstructive and nonobstructive CAD. MDCTA has been tested and has established diagnostic performance characteristics.6–8 Therefore, the use of vessel calcium score alone to replace MDCTA or to prompt referral for diagnostic angiography is unlikely. However, further refinement of calcium score on a vessel or lesion level may indeed assist in assessing the prognosis of patients with atherosclerosis or assist in assessing heavily calcified vessels in patients who cannot undergo MDCTA. This new twist on an old test does indeed warrant further study.

References