EDITORIAL COMMENT

Coronary artery calcification: does it predict obstructive coronary artery disease?

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Calcification of the coronary arteries plays a key role in the pathophysiology of atherosclerosis. Coronary calcification is an active process culminating in extracellular matrix deposition of calcium by osteoblast-like cells that has some resemblance to bone formation [1]. Subintimal coronary calcification is almost exclusively associated with the presence of coronary atherosclerosis and is considered the hallmark of coronary atherosclerosis. Coronary calcific lesions are considered advanced lesions and calcification following plaque rupture of a high-risk plaque is thought to be part of the healing process [2].

The presence of coronary calcification is a surrogate marker of the overall plaque burden. Not all plaques are calcified and histological studies have revealed that the total calcium area was approximately 20 % of the total atherosclerotic plaque burden area [3].

There is no generally accepted relationship between plaque calcification and plaque stability. Traditionally calcific plaques are considered to be stable but plaques with spotty calcification (small amount of calcification in a spotty distribution) have been associated with plaque instability and acceleration to progression of CAD [4, 5]. However, the extent of calcification is a marker of instability somewhere in the coronary tree rather than a marker of local plaque instability [4].

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Coronary calcification can be easily detected by computed tomography (CT). The epicardial vessels can be readily identified on a non-contrast enhanced CT scan (calcium scan), because the density of the coronary wall and blood is higher than the surrounding peri-coronary fat. Coronary calcium deposits have a 2 to 10 fold higher density than surrounding tissues and coronary calcium is identified as a hyper-attenuating coronary lesion above a threshold of 130 Hounsfield units (HU). The amount of calcium is quantified using the Agatston score (calcium score) which is derived from the product of the area of calcification (mm^2) and a factor determined by the maximal density (HU) within that area. The factor is 1,2,3,4 with a density of 130 to 199, 200 to 299, 300 to 399 or >400 HU respectively [6].

The calcium scan does not require contrast medium and can be acquired with a low radiation dose of less than 1.0 mSv [7]. This is associated with a lifetime attributable risk of cancer that for men and women at 50 years of age at 8 and 20 per 100,000 persons per year, respectively.

The calcium score is a significant predictor of risk of adverse cardiovascular events that has independent incremental value of risk prediction beyond the traditional risk prediction scores such as the Framingham risk score or the Euro risk score. Increasingly higher calcium scores are associated with increasingly higher risk of adverse cardiovascular events and all-cause mortality.

The calcium score can also be used to predict the presence of obstructive coronary artery disease (CAD).

Calcium score to predict obstructive CAD

The non-enhanced calcium scan represents an anatomic measure of the coronary plaque burden. The degree of a coronary obstruction is weakly correlated with the amount of calcium on a segment-by-segment basis, which is caused

by the often occurring positive coronary wall remodelling at the site of the calcific plaque to preserve the coronary lumen size. Calcification is associated with both non-obstructive and obstructive coronary lesions and thus the calcium score is not specific for the presence of an obstructive lesion.

However, the total coronary calcium score is correlated with the presence of an obstructive angiographic coronary lesion [8].

A meta-analysis was performed from 16 studies of patients who were symptomatic and referred to invasive coronary angiography [8]. The sensitivity and specificity was 80 % and 40 % respectively (Table 1). The odds of calcium for detecting minimal CAD (<50 %) with no calcium present as reference was 6.8 (95 % CI 3.0–5.6), for >50 % obstruction 16.4 (95 % CI 5.1–53.1) and for >70 % obstruction 50 (95 % CI 24.1–103.0).

A positive calcium score moderately predicts the presence of significant coronary obstruction. Higher calcium scores, taking into account gender and age, are more predictive of obstructive CAD [9, 10]. This is illustrated in Figs. 1 and 2 which are taken from a study by Haberl et al. [9].

A calcium score of zero is associated with a very low prevalence of any coronary atherosclerotic plaque and is almost exclusively associated with the absence of an obstructive (≥50 %) lesion, although in young patients and in patients presenting with acute coronary syndrome a significant noncalcific plaque may be present, albeit that its presence is very low [11]. Patients with zero calcium have an excellent prognosis [11].

Predictive value of calcium score in patients with moderate CKD

Patients with end-stage chronic kidney disease (CKD) have (very) high coronary calcium scores and increased cardiovascular mortality which is mainly related to progressive

**Table 1** Calcium score to predict >50 % coronary obstruction [8]

Subjects	3683
Male %	67
Mean age (years)	55.3
Prevalence calcium %	66
Prevalence of significant CAD[a] %	57
Sensitivity (weighted) %	80 range 68–100
Specificity (weighted) %	40 range 21–100
Predictive accuracy (weighted) %	59 range 41–95

[a] significant CAD was defined as luminal irregularities in 2 reports, >50 % or ≥50 % stenosis in 11 reports and ≥70 % or ≥75 % stenosis in 3 reports
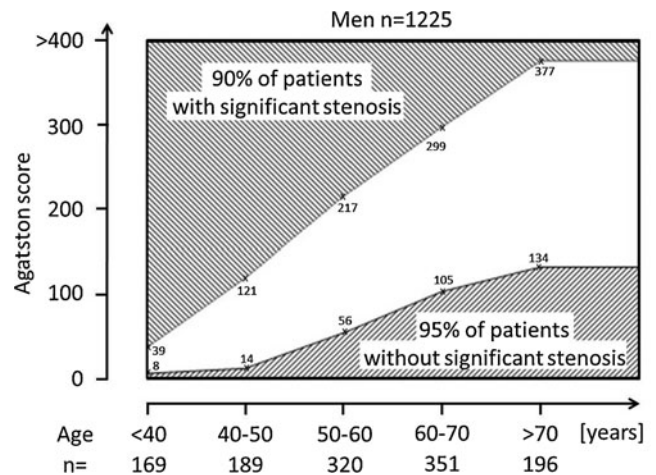
Fig. 1 Coronary calcium score prediction of the obstructive CAD in different age groups in men referred for coronary angiography. The lower scores define the thresholds for the 95 % of patients without obstructive CAD. The higher scores represent the thresholds for the 90 % of patients with obstructive CAD. The prediction is uncertain within the orange area. Adapted from Haberl et al. J Am Coll Cardiol 2001; 37:451–7

coronary atherosclerosis with associated higher calcium scores, but the presence of other risk factors, hypertension or diabetes, also play a role. But also patients in earlier stages of CKD have a higher prevalence of calcium score and CAD than patients without CKD [12, 13]. Reports about the predictive value of the coronary calcium score in patients with end-stage CKD to identify obstructive CAD are conflicting and studies in patients with moderate CKD are lacking [14–16]. In this issue of the journal Yiu et al. compared the value of the calcium score to predict obstructive CAD in patients with moderate CKD (n=69) with patients without CKD (n=635) [17]. They demonstrated that the calcium score was almost equally predictive in both patient groups, with the caveat that the optimal cut-off value of the score is
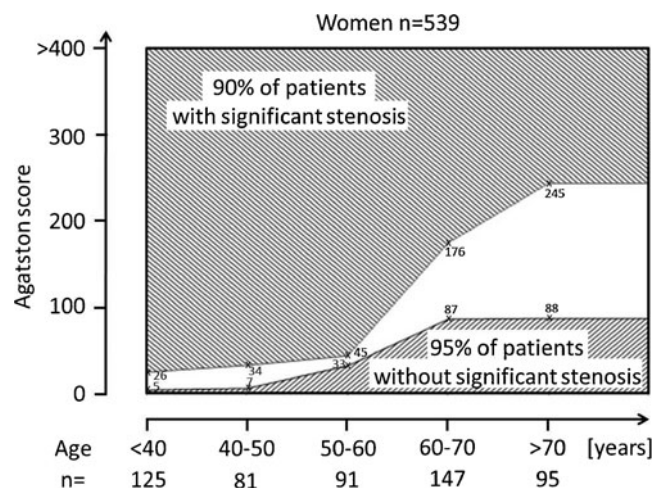
Fig. 2 Coronary calcium score prediction in women. See legend Fig. 1

higher in patients with moderate CKD. This may be expected because in CKD patients coronary calcification not only takes place in the sub-intima (as is the case in coronary atherosclerosis) but in addition also in the media of the coronary wall (media-sclerosis or Moenckeberg-type atherosclerosis) [18].

CT imaging cannot distinguish between subintimal calcification and medial calcification. Nevertheless, the authors demonstrated that the calcium score is moderately predictive to identify obstructive CAD in patients with moderate CKD with a sensitivity of 73 % and a specificity of 70 %. The role of medial calcification as a marker of cardiovascular risk or as a predictor of obstructive CAD is not well defined due to the lack of an adequate imaging modality.

Coronary calcium scanning is appealing because it is more than a risk factor, it is the disease in itself. The question remains: should we use the coronary calcium score as a predictor of obstructive CAD in a general population or in this case in patients with moderate CKD? Arguments in favour of its use are the convenience, no use of contrast medium, low radiation exposure and low costs. A significant argument against is the low specificity and high false-positive rate of the calcium scan to predict obstructive CAD in the general population and the moderate sensitivity and specificity in patients with moderate CKD. One may argue that instead CT coronary angiography is performed to directly identify obstructive CAD which nowadays can be acquired with a very low radiation dose (<1 mSv) and high diagnostic accuracy, although it is less convenient, requires the supervision of a radiologist, use of contrast medium, and is more costly.

In any case, further studies are needed to demonstrate that either a calcium scan or CT coronary angiography affects patients' management and improves prognosis.

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