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Advances in cardiac computed tomography: an update for primary care physicians

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Introduction

Coronary artery disease (CAD) remains the leading cause of mortality in the United Kingdom, causing a total of 120,000 deaths in 2003.[1] The lifetime risk of developing coronary heart disease (CHD) in the UK by the age of 40 has been estimated at 50% in men and 33% in women.[2] In addition to imposing a great burden, both economically and on the already stretched resources of the NHS, it is also the most important factor contributing to the number of years of life lost before the age of 65.[3]

Why screening for cardiovascular disease (CVD)?

There has been a tremendous improvement in our knowledge of the pathophysiology of cardiovascular disease (CVD), but the first presentation of a large proportion of patients is with sudden cardiac death and/or myocardial infarction (MI).[4] A recent statistical model of the effect of prevention of CAD and stroke in the US population showed that if every person received the preventive therapy they were eligible for, this would reduce the burden of CAD by 63% over a 30-year period.[5]

It has therefore become very important to identify the 'at risk' population and also to quantify their absolute risk. Available screening tests are aimed at estimating intermediate-term risk, i.e. the absolute risk of cardiovascular events in the next 10 years. A number of office-based risk stratification algorithms, based on patient demographics, clinical and social parameters are in existence, the most prominent of them being the Framingham risk score, PROspective Cardiovascular Münster study (PROCAM) and Systemic Cardiovascular Risk Evaluation (SCORE).

These office-based algorithms calculate a patient's 10-year global risk of CHD and classify them as low (<10%), intermediate (10-20%) or high risk (>20%).[6]

New imaging techniques are adding to the information available for assessing an individual's cardiovascular risk.

Coronary artery calcium (CAC)

It has been shown that calcium deposition occurs only within atherosclerotic plaque lesions and not in normal, healthy arteries.[7] It was widely believed that calcification of the arteries was an inevitable certainty of senescence. But that does not seem to be the case. It has been shown that calcium deposition occurs only within atherosclerotic plaque lesions and not in normal sections of arteries that are plaque free, irrespective of the age of the individual.[7] Recent evidence has suggested that arterial intimal calcification is a tightly regulated process very much akin to bone formation (see Table 1).[8,9]

Table 1. Classification of plaque lesions

I.	Isolated foam cells (macrophages laden with LDL)
II.	Multiple layers of foam cells
III.	Isolated pools of extra-cellular lipid formed
IV.	Isolated lipid pools become contiguous to form a lipid core
V.	Fibro-muscular tissue layers produced
VI.	Plaque rupture, plaque haemorrhage, thrombosis
VII.	Predominantly calcified plaque
VIII.	Fibrous tissue changes predominate

Key: LDL = low-density lipoprotein

CAC score

Since Agatston and co-workers standardised a coronary calcium imaging protocol by electron beam computed tomography (EBCT) in 1990,[10] a large body of evidence has accumlated on the incremental prognostic value of coronary artery calcium (CAC) over measured conventional risk factors in large series of patients.[11,12] Most of the studies assessing the prognostic significance of CAC scoring have been performed using EBCT, however, it has been shown that the CAC score measured using multi-slice computed tomography (MSCT) scanners correlates well with that measured with EBCT.[13]

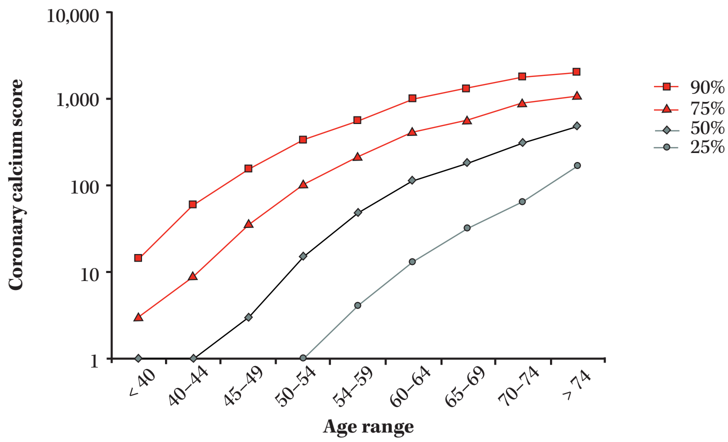
Clinical relevance of the CAC score

The amount of CAC correlates well with the segmental atherosclerotic plaque burden.[14] However, the presence of a calcified atherosclerotic plaque does not indicate a future risk of rupture. In fact, there are conflicting theories regarding the effect of calcium on plaque stability.[15,16]

Age and sex of a patient play an important role in determining the prevalence and extent of CAC. The prevalence of CAC increases with age in both sexes.[17]

As CAC scores vary greatly, even in subjects of similar age, a sex-age nomogram is required to assign a percentile rank to an individual patient against that of a matched population. In essence, this provides a measure of 'coronary age'.[18,19] For example, a

Figure 1. Sample of coronary calcium scores in asymptomatic men



An example of an age-sex nomogram with percentile ranges mapped out

60-year-old man with a CAC score of 20 agatston units (AU) is at a lower percentile rank, and hence at a lower 10-year risk of cardiovascular events, when compared to a 30-year-old man with the same CAC score because a younger man should have a lower score.

Hoff *et al.* analysed 35,246 self-referred, predominantly white, asymptomatic subjects between the ages of 30 and 90 years, and categorised them according to percentiles.[20] The sex-age nomogram generated from this study, despite its ethnic shortcomings, is particularly useful in the risk stratification of individuals in terms of their CAC scores and is extensively used to this day and is illustrated in a sample CAC score report (see Figure 1 and 2).

Unfortunately, most of the cohorts including large numbers of patients that have been used to generate the age-sex nomograms were not ethnically diverse.

The prevalence and progression of CAC in various ethnic groups is different, as demonstrated eloquently in the data from the Multi-Ethnic Study of Atherosclerosis (MESA).[21,22] An online calculator is available for the conversion of absolute CAC scores into a percentile rank and it is postulated that this percentile rank based on age, sex and ethnicity offers a greater predictive ability than the absolute CAC scores alone (see http://www.mesa-nhlbi.org/Calcium/input.aspx).

Clinical use of CAC score in relevant populations

Asymptomatic patients

Asymptomatic patients who are assigned to the high-risk group with office-based risk assessment algorithms such as the Framingham Risk Score (FRS) will benefit from intensive risk modification. Patients in the low-risk group are advised to follow a healthy lifestyle and their risk factors should be treated as and when diagnosed according to current guidelines. Patients in the intermediate-risk group pose a clinical dilemma and it is this group of patients that benefits most from CAC scoring.

In studies by Arad *et al.*[23] and Greenland *et al.*[12] of patients with intermediate FRS-estimated risk, progressive tertiles of CAC scores of <100 Au, 100-399 Au and >400 Au were associated with annualised CHD death and MI rates of 0.4%, 1.3% and 2.4%, respectively. This means that patients with intermediate FRS risk with a CAC score >400 Au have a 10-year CHD risk of >20%, putting them firmly in the high-risk group and on the path to intensive risk factor modification.

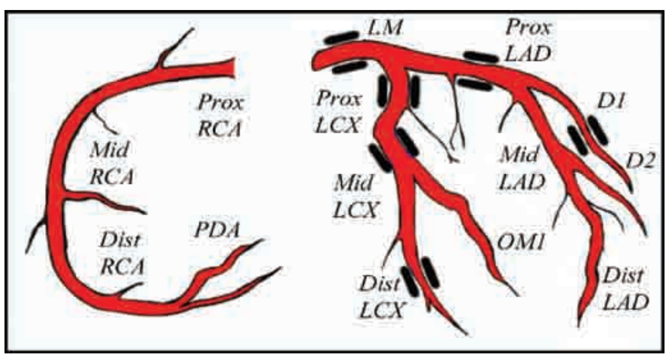
Figure 2. Sample CAC score report

A

	Lesions	Volume (mm^3)	Agatston score (Au)
Left main	1	1.21	0.92
Left anterior descending	4	39.79	37.61
Left circumflex	3	18.24	18.48
Right coronary artery	0	0.00	0.00
Total	**8**	**59.24**	**57.01**

Table showing the number of lesions, calcium volume and Agatston score in different coronary arteries

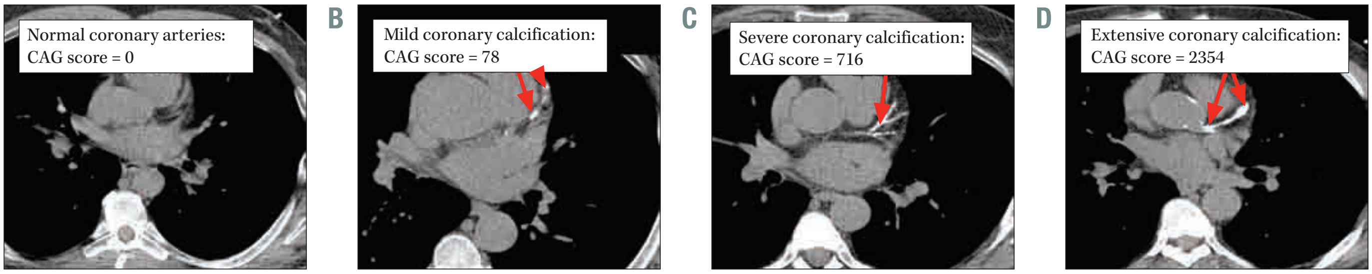
B



Diagramatic representation of coronary arteries with the calcified lesions marked

Key: RCA = right coronary artery; LCX = left circumflex artery; LAD = left anterior descending artery; D1 = first diagonal; D2 = second diagonal; OMI = obtuse marginal; CAC = coronary artery calcium

Figure 3. Scans illustrating different absolute CAC scores



A: Normal coronary arteries with a CAC score of 0 Au

B: Mildly calcified coronary arteries with plaque lesions seen in proximal and mid LAD. CAC score of 78 Au

C: Severe coronary artery calcification with a CAC score of 716 Au. Calcified plaque lesions seen in left main stem, proximal LAD, diagonal and proximal circumflex arteries

D: Extensive coronary artery calcification with a CAC score of 2,354 Au. Densely calcified plaque lesions seen in ascending aorta, left main stem and proximal LAD

Key: CAC = coronary artery calcium; LAD = left anterior descending artery

The ACC/AHA Expert Consensus Document on Coronary Artery Calcium Score[24] assessed six studies reporting the prognostic value of CAC scoring for CHD death and MI. In an asymptomatic cohort of 27,622 patients, it was shown that the 3-5 year risk of CHD was nearly four times higher in a patient with any detectable CAC compared with someone without any CAC (p<0.0001). In probably one of the largest studies of the prognostic significance of CAC,[25] which included 25,253 patients, twelve-year survival was 99.4% in people with a CAC score of 0 Au compared with 76.9% in those with a CAC score >1,000 Au, after adjusting for other risk factors.

The clinical role of CAC scoring was clearly illustrated by Anand *et al.*[26] in a high-risk asymptomatic diabetic population. They showed that pre-selection of patients with CAC score > 100 Au yielded far more significantly abnormal myocardial perfusion scans, confirming increased probability of significant CAD, than an unselected cohort of patients with diabetes.

Symptomatic patients

In a recent study by the Cooper Clinic in Dallas,[27] 664 patients underwent CAC scoring and computed tomography (CT) angiography with a 64-slice scanner. The prevalence of significant stenosis (>60%) was 7.9%, 8.3%, 14.5% and 27.2% for the successive quartiles of CAC scores of 1-100, 101-399, 400-1,000 and >1,000 Au (p<0.001 for the entire trend). Even after controlling for traditional risk factors, the odds ratio for detecting significant stenosis was 3.1 for people with CAC scores of 400-1,000, and 6.9 in those with a score >1,000 Au. Thus a CAC score of >400 Au was significantly associated with significant stenosis detected by CT angiography.

This finding was similar to the conclusions of a pooled analysis of 16 studies reported in the first ACCF/AHA expert consensus statement on CAC in 2000,[28] which reported that a higher calcium score was associated with an increased likelihood for the presence of significant coronary luminal stenosis (>50% stenosis). Figure 3 illustrates the scans for different absolute CAC scores, which are of relevance in symptomatic patients.

CT coronary angiography

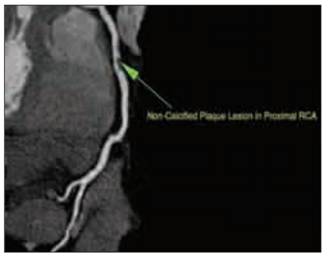
Conventional angiography is still widely regarded as the gold standard technique for imaging the coronary arteries. However, it is simply a two-dimensional lumenogram, providing very little information about the atherosclerotic plaque burden of the coronary tree. Intravascular ultrasonography (IVUS) is the current gold standard for assessment and characterisation of atherosclerotic plaque burden and morphology. As the mortality/serious morbidity rate associated with conventional coronary angiography is small yet tangible (0.1-0.2%), there has been a steady push to find a non-invasive imaging modality capable of visualising the coronary tree more effectively.

The technique

Coronary angiography requires the injection of 80-100 ml of iodine-based contrast agent (350-400 mg/ml of iodine) into the patient through a large antecubital vein at a rate of 4.5-6 ml/second. Images are acquired in a cranio-caudal direction using a retrospective ECG-gated technique. Retrospective

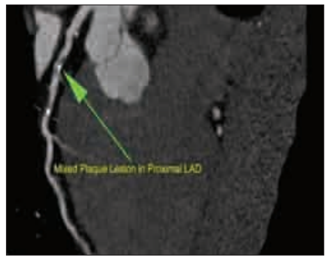
Figure 4. CT angiography showing the main types of plaque lesions (A, B) and a 3D image (C)

A



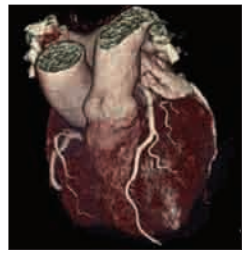
A curved multi-planar reconstruction (MPR) of an RCA vessel with a long non-calcified plaque lesion proximally causing 50-60% luminal stenosis

B



MPR of LAD showing two mixed plaque lesions in proximal and mid-LAD. The proximal lesion causing >70% luminal stenosis and the more distal lesion causing 50-60% luminal stenosis

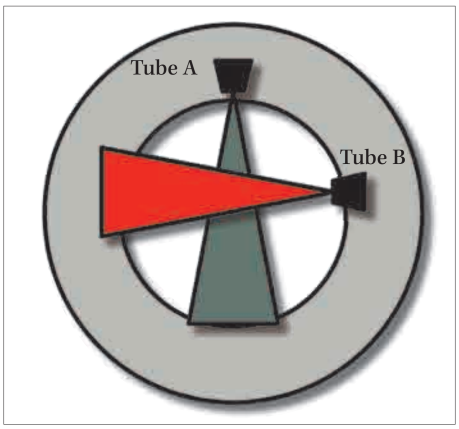
C



A volume rendered 3D image of a heart with normal coronary arteries

Key: CT = computed tomography

Figure 5. Dual source CT scanner: using two X-ray sources (A and B)



Diagramatic representation of dual source CT with two X-ray sources, A and B, offset at 90° to each other

Key: CT = computed tomography

gating is used because the images can be assessed post-acquisition and reconstructed for optimal image quality at different phases of the cardiac cycle if needed. The total breath-hold time needed for the newer MSCT scanners is around 20 seconds.

Image quality can also be improved with the use of sub-lingual glyceryl trinitrate (GTN) spray approximately five minutes prior to the scan and also beta-blockers (oral or intravenous) to get a heart rate ideally of <65 beats per minute, though a higher heart rate is not much of an issue with the DSCT scanners because of their higher temporal resolution.

Clinical role of CT angiography

Contrast-enhanced coronary angiography is a relatively new application for CT scanners, although there were early publications even with EBCT and 4-slice MSCT scanners.[29,30] Unlike the two-dimensional lumenogram of conventional angiography, this technique also allows visualisation of the vessel wall and the plaque itself, and has the potential for plaque characterisation, which brings us a step closer to identifying a vulnerable plaque, which is the 'holy grail' of cardiology.

The three main types of plaque lesions are classified according to their degree of calcification – namely, calcified, mixed and non-calcified plaque lesions. These are shown in Figure 4 together with a 3D image.

With each successive generation of CT scanners, starting with the four-slice scanners all the way through to dual-source CT (which uses two X-ray sources instead of one; see Figure 5) and 256/320 lice scanners, there has been a steady improvement in image quality. This is demonstrated in the percentage of segments evaluable per study, as shown in Table 2.

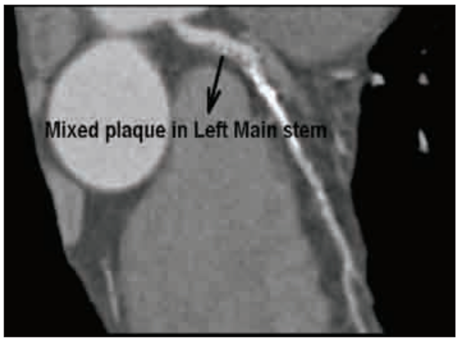
An important factor contributing to the

Table 2. Percentage of evaluable coronary segments

	Total number of segments	Number of evaluable segments	Percentage of evaluable segments
16-slice CT*	763	605	79.3%
64-slice CT**	1,065	935	88%
Dual source CT***	1,232	1,216	98%

*Kuettner *et al. JACC* 2004, **Raff *et al. JACC* 2005, ***Leber *et al. Eur Heart J* 2007

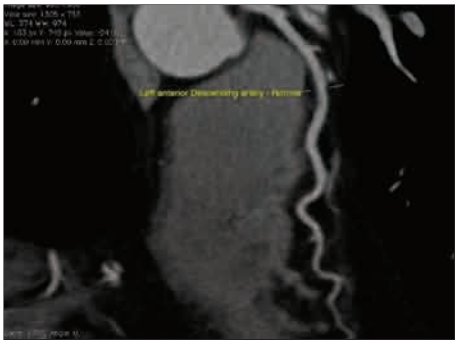
Figure 6. CT coronary angiography showing mixed plaque in left main stem



The arrow points to an irregular, mixed plaque lesion in the left main stem causing 30-40% luminal stenosis. Note also the heavily calcified proximal LAD just beyond the plaque in the left main stem

Key: CT = computed tomography

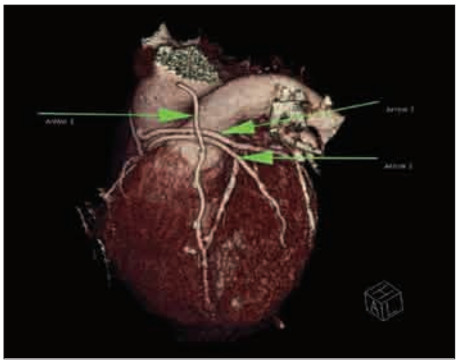
Figure 7. CT coronary angiography showing normal coronary artery



A curved MPR of a normal LAD artery

Key: CT = computed tomography

Figure 8. Imaging of coronary artery bypass grafts



1. Left internal mammary artery (LIMA) graft to LAD
2. Venous graft to diagonal
3. Venous graft to marginal

> **"In symptomatic patients, plaque lesions as assessed by CT coronary angiography have been shown to be of significant prognostic value"**

improvement in image quality is the improved temporal resolution of the newer scanners. For CT scanners, temporal resolution is dependent on the time taken for one rotation of the X-ray source around the region of interest, acquiring 360 degrees of data. For 16-, 64- and even the newer 256-slice scanners, the temporal resolution is approximately 165 ms and for the dual-source scanners, this is reduced to 83 ms.

Although the principle of contrast-enhanced CT coronary angiography has been around for at least a decade, its clinical utility has only recently been validated. This clinical role has been demonstrated in both symptomatic and asymptomatic patients.[31,32]

A recent meta-analysis of CT angiography studies using the 64-slice scanner[33] reported pooled data for nearly 2,500 patients. In a patient-based analysis reported by 18 of the studies, the sensitivity and negative predictive value (NPV) of this technique were 99% and 100%, respectively, while the specificity and positive predictive value (PPV) were 89% and 93%, respectively. The numbers are similar for the dual-source CT scanner, with an NPV of 99-100%, except that the percentage of evaluable segments was nearly 98% compared to 88% for 64-slice MDCT scanners.

Symptomatic patients

For patients with known risk factors for cardiovascular disease and presenting with classical symptoms of angina, CT coronary angiography offers no additional benefit. On the other hand, CT angiography is very useful in patients presenting with atypical symptoms. This is true irrespective of whether they were known to have had CAD previously or not.

In symptomatic patients, plaque lesions as assessed by CT coronary angiography have been shown to be of significant prognostic value.[32] Significant measures include the degree of luminal stenosis, the number of vessels with significant luminal stenosis and the presence of significant (>50%) plaque lesions, especially in the left main stem (see Figure 6) and in the proximal left anterior descending artery (Figure 7).

A study of 254 symptomatic patients who were divided according to their pre-test probability of having CAD showed that the post-test probability for the presence of significant CAD following negative coronary CT angiography was 17% for high-risk patients, but 0% for those with intermediate and low risk.[34]

Key points: cardiac computed tomography

- The coronary artery score correlates well with atherosclerotic plaque burden
- Patients with intermediate cardiovascular risk may benefit most from CAC scoring, as part of clarifying their risk status
- Contrast-enhaced coronary angiography may help to identify vulnerable plaques
- It can be used in asymptomatic patients with known risk factors

This highlights the role of CT coronary angiography in clinical decision-making for symptomatic patients with low and intermediate pre-test probability for significant CAD. Importantly, this study revealed that a negative CT coronary angiogram effectively rules out the presence of CAD in both native and bypass graft vessels (see Figure 8).

Asymptomatic patients

Few studies have looked at the prevalence of CAD in high-risk asymptomatic patients.[35,36] They have found an approximate prevalence of significant CAD of 20-25%. One study[36] looked at prevalence of any coronary plaque in asymptomatic diabetic patients compared with non-diabetic patients and showed a significant difference (67.7% *vs.* 91.4%; p<0.0001). But in a study of 1,000 consecutive asymptomatic patients,[31] the prevalence of any atherosclerotic plaque lesion was 22%, with only 5% having significant (>50% stenosis) CAD.

The debate about the use of CT coronary angiography as a screening tool is likely to continue until there is better evidence from large, prospective, randomised controlled trials. The negative aspects include the radiation dose to which patients are exposed and cost-effectiveness.

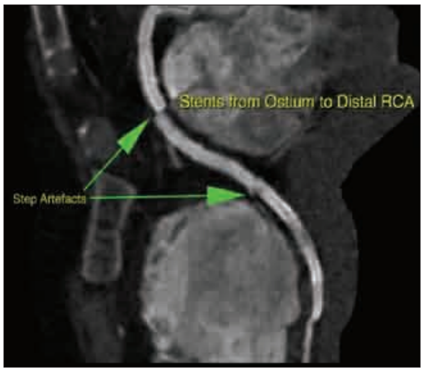
Pooled data from six studies included in a systematic review of CT angiography studies[29] reported gender-specific differences in radiation dose exposures, ranging from 7.5-15.2 mSv in men and 10.2-21.4 mSv in women. Two of the studies that used ECG-controlled dose modulation by reducing the tube current in systole reported effective radiation dose exposures of 7.5-8.6 mSv in men and 10.2-12.2 mSv in women. In the newer CT scanners using two X-ray sources, the effective radiation dose has been reported as 7.8-8.8 mSv. The cost-effectiveness should be demonstrated by a large prospective trial (RADICAL) comparing the standard chest pain unit model of care with a unit using CT angiography in symptomatic patients.

Factors affecting image quality

Some of the factors affecting the quality of CT angiography include:

1. Body mass index (BMI): the higher the BMI, the lower the contrast/noise ratio, which results in grainier images. This can be compensated for, to a certain extent, by increasing the tube current of the X-ray source, resulting in better images but with the trade-off of increased radiation dose.
2. Heart rate (HR) and movement (patient, respiratory): a slow, steady heart rate is desirable. Irregular HR, either as a result of ectopics or atrial fibrillation, causes step artefacts on the image, which makes analysis difficult. Movement also causes step artifacts.
3. Calcium and stents: metal in stents and calcium deposits in arteries cause 'blooming' artefacts. The denser the calcium, the harder it is to assess adjacent contrast-enhanced lumen, often resulting in over-estimation of the luminal stenosis caused by a plaque. It is anecdotally accepted that a CAC score of > 1,000 AU precludes CT coronary angiography. Some stents cause more artefacts than others. Assessment of coronary stents is dependent on their size, i.e. stents > 2.5 mm can be assessed for in-stent restenosis (see Figure 9).

Figure 9. Assessment of coronary stents



Multiple stents within the RCA. The right coronary artery (RCA) is stented from its ostium to the origin of the PDA. This was a result of patient movement during interventional coronary angiography causing dissection of the RCA

Summing up

CAC scoring is an appropriate test for patients predicted to be at intermediate 10-year risk as calculated by the FRS, with a view to reclassifying their risk status and modifying the intervention and management strategy. It is also a sensitive measure in symptomatic patients for predicting luminal stenosis.

In the absence of any National Institute for Health and Clinical Excellence (NICE) guidance on the use of CAC scoring, as well as its currently prohibitive cost, it is not yet readily available on the NHS. However, with mounting evidence for its clinical value and the growing availability of MSCT scanners in the UK, we hope that it will soon become an integral part of clinical risk stratification.

Available evidence shows that CT coronary angiography can be used in asymptomatic patients with known cardiovascular risk factors such as long-standing diabetes mellitus, hypertension, but cannot be recommended as a general screening tool for CAD. Cardiac CT is initiating a radical change in decision-making in CAD. Studies are also underway to evaluate the feasibility of using cardiac CT to quantify perfusion, function and wall motion with the hope that it will fulfil its early potential as a 'one-stop shop' for non-invasive cardiac imaging.

Conflict of interest

None declared.

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