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Computed tomographic coronary angiography – is it ready as a screening tool for coronary artery disease?

Joanna Melgies, Mark CK Hamilton and Nathan E Manghat

ABSTRACT – Currently, there are no formal screening programmes for coronary artery disease (CAD). Computed tomographic coronary angiography (CTCA) has been suggested as a non-invasive and reliable method of atherosclerotic plaque assessment, with the potential for use in screening programmes. In this article, we briefly present the current understanding of atherosclerotic plaque formation, explain key technological aspects of CTCA and critique this method in the light of World Health Organisation (WHO) criteria for devising a screening programme. Current evolving and future insights are also considered. Overall, in our view, there is currently insufficient evidence to support the formal use of CTCA in a screening programme for CAD, although this viewpoint will undoubtedly evolve.

KEY WORDS: Coronary artery disease, computed tomography, screening

Introduction

Coronary artery disease (CAD) affects approximately 2.6 million people in the UK, nearly 25% of whom do not experience any symptoms.[1] The most common cause of CAD is atherosclerosis.[2] Sudden rupture of a previously undiagnosed, usually shallow, non-calcified atherosclerotic plaque leads to acute thrombosis of coronary arteries, an acute coronary syndrome (ACS) and potentially sudden cardiac death. Therefore, early diagnosis of coronary atherosclerosis is desirable in patients at risk to prevent acute myocardial infarction (MI) (Box 1).

Currently, there are no devised screening programmes for CAD. The assessment of the degree of stenosis of coronary arteries only follows suspected symptomatic atherosclerosis. Computed tomographic coronary angiography (CTCA) has been shown to be a reliable, non-invasive method of coronary stenosis assessment that is now recommended for use in routine clinical practice in the UK.[3]

The referring physician must be aware of the implications of the recent guidelines on the indications for the use of calcium scoring and cardiac computed tomography (CT) in the assessment and management of patients with suspected cardiac chest pain.[4]

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Box 1. Fixed and potentially modifiable risk factors for coronary artery disease.

Fixed

- Age
- Male sex
- Positive family history
- Deletion polymorphism in the ACE gene (DD)

Potentially modifiable

- Hyperlipidaemia
- Cigarette smoking
- Hypertension
- Diabetes mellitus
- Lack of exercise
- Blood coagulation factors – high fibrinogen, factor VII
- CRP
- Homocysteinaemia
- Personality
- Obesity
- Gout
- Heavy alcohol consumption

ACE = angiotensin-converting enzyme; CRP = C-reactive protein.

Notably, CTCA is a powerful diagnostic tool for the exclusion of CAD. It is the only reliable non-invasive method to visualise coronary artery atheroma (significant and non-significant) where other imaging methods, such as stress perfusion imaging (with its various modalities) and invasive percutaneous catheter angiography (ICA), are 'normal'. Magnetic resonance coronary angiography (MRCA) has been used with some success but it is not currently recommended for coronary atheroma imaging in routine clinical practice; however, it can be used to delineate anomalous coronary arteries. Magnetic resonance imaging (MRI) is also not able to quantify coronary calcium burden.[5]

Ultimately, the use of CTCA as part of a screening programme in an appropriate population might contribute to the decrease in incidence of acute MI and sudden death, and facilitate optimal medical management.[6]

What is coronary atherosclerosis?

Formation of atherosclerotic plaques in the intimal layer of coronary arteries is a complex inflammatory process resulting in the accumulation of lipid, macrophages and smooth muscle cells. This process has been well described in the literature.[2,7]

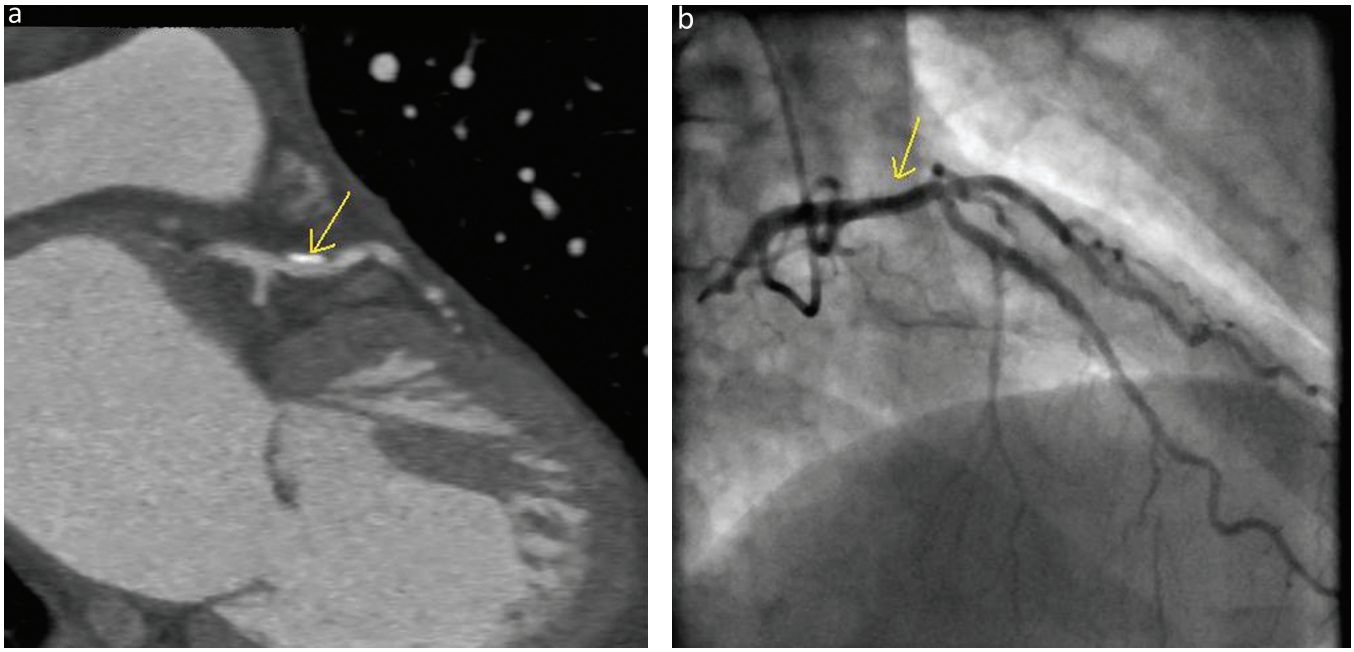

Fig 1. Left anterior descending artery atheroma. (a) CTCA of curved planar reformation showing mixed morphology plaque (arrow). (b) Catheter angiography showing mild irregularity but no significant stenosis (arrow). CTCA = computed tomographic coronary angiography.

An important mechanism of plaque proliferation is 'positive remodelling', which involves the outward spread of plaque volume within the arterial wall while preserving luminal calibre. Therefore, early, potentially vulnerable and subclinical atherosclerotic plaque can be overlooked on catheter angiography or myocardial perfusion imaging (Fig 1 and 2).

Electrocardiographic-gated computed tomographic coronary angiography

Some background understanding of the technique by the referring physician is important. CTCA is a rapid, reliable and non-invasive method of coronary artery imaging. It has the advantage of determining not only the dimensions of the arterial lumen (which might remain unaffected owing to positive remodelling), but also the evaluation of plaque composition.[8] However, imaging of the heart using CT is challenging. Isotropic (ie in all planes), submillimetre spatial resolution is required to reconstruct small, curvilinear branches of the coronary tree with clarity. Optimal temporal resolution is vital for the acquisition of motion-free images of a complex moving heart; this is especially difficult in patients with tachycardia or dysrhythmia.[9]

Multi-detector row computed tomography (MDCT) is in widespread clinical use with an effective spatial resolution of as little as 0.3 mm^3. The CT image data set is acquired using a high-flow (5–7 ml/s) bolus of iodinated contrast in a single, approximately 5-s breath-hold with the simultaneous use of electrocardiographic (ECG) gating. Images are processed in accordance with the patient's own heart beat. Although a full technical description of this process is beyond the scope of this article, it is important to note that there are two methods used: 'prospective' and 'retrospective' ECG gating.[9]

Prospective gating involves the scanning and reconstruction of a predetermined segment of the cardiac cycle, usually set at mid to late diastole, where cardiac motion is minimal. It was traditionally only used for 'calcium score' acquisition, but is now increasingly being used for CTCA following improvements in scanner temporal resolution. The main advantage is in the lower radiation dose afforded. The main disadvantage is the lack of any functional data and the potential for a non-diagnostic study if there is are significant motion reconstruction artefacts during image acquisition.[9]

Retrospective gating enables multiple phases of reconstruction of the entire scanned cardiac volume with the ability to generate cinematic movie loops of any structure of interest. Motion artefacts on one phase of reconstruction can be overcome by reconstruction of another phase; this is possible to a more limited degree with 'prospective' gating. The disadvantage of this method is the increased radiation dose owing to continuous scanning. However, methods of 'aggressive' ECG-gated dose modulation enable the X-ray tube current to be minimised during phases of greatest motion (ie ventricular systole) and maximised during ventricular diastole, which, in our experience, can still deliver radiation doses as low as ≤1 mSv in some patients (with attention to 'kilovoltage' reduction in slim individuals). Although image quality in systolic phases is inferior, it is mostly sufficient to enable assessment of ventricular function.[9]

The evolution of new 'iterative reconstruction' software algorithms effectively enables equivalent high-quality image reconstruction with the use of a lower radiation exposure (in the

order of 70% less). However, iterative reconstruction is associated with increased data reconstruction time.

To maximise the image quality, appropriate patient preparation is required. The use of high-flow iodine-based contrast warrants the usual precautions regarding allergies and renal insufficiency, and requires a high-flow cannula in the antecubital fossa. Ideally, the patient should have received a single dose of short-acting, cardioselective oral β-adrenoceptor blocker before the test, but heart rate reduction with intravenous metoprolol can be performed at the time of examination, although this can become time consuming. Vasodilation of the coronary arteries using sublingual nitroglycerin has been shown to improve image quality and stenosis evaluation; this might be contraindicated with concurrent phosphodiesterase inhibitor use. β-adrenoceptor blocker contraindications might necessitate the use of a rate-controlling calcium antagonist or sinus node blocker.[10]

However, can CTCA be used fully as a screening tool for CAD? In 1968, Wilson and Jungner devised a set of 10 criteria to validate a screening programme.[11] CTCA, in the context of screening, already fulfils some of these criteria, and three are further described here (Box 2).

'A suitable test should be devised for the early stage'

In some patients, ACS is the first clinical manifestation of coronary plaque.[12] Although ICA is able to detect luminal thrombosis, coronary calcification and plaque disruption, fissuring or ulceration, it is unable to demonstrate the qualitative features of the plaque without the combined use of intravascular ultrasound (IVUS)[12,13] (Box 3). CTCA can determine whether the plaque is calcified and, therefore, usually more stable or non-calcified and potentially more prone to rupture with subsequent thrombosis, or of mixed morphological composition.[8,14]

Currently and crucially, in our view, CTCA cannot yet predict the likelihood of plaque rupture with any certainty.[8]

Cyrus *et al* showed that 95% of plaques that are most vulnerable to rupture lie in proximal, large-sized coronary arteries and are non-occlusive but nonetheless fill more than 50% of the volume of lumen and vessel wall, with preservation of flow owing to positive remodelling and the formation of large lipid cores. They argued that the spatial resolution of the MDCT is still insufficient to visualise a thin fibrous cap; other features of plaque vulnerability are well determined on CTCA.[15]

There now exist robust prognostic data with respect to the degree of stenosis as determined by CTCA. A meta-analysis of large prospective studies by Hulten *et al* showed that absence of significant CAD on the CTCA provided an excellent 1-year prognosis.[16] This was further confirmed by a recent UK study that investigated patients at intermediate risk of CAD without a previous history of cardiovascular disease. It showed that no patients with normal or non-significantly stenosed coronary arteries underwent revascularisation in the follow-up period, as opposed to 36.4% of patients who tested positive on CTCA. The

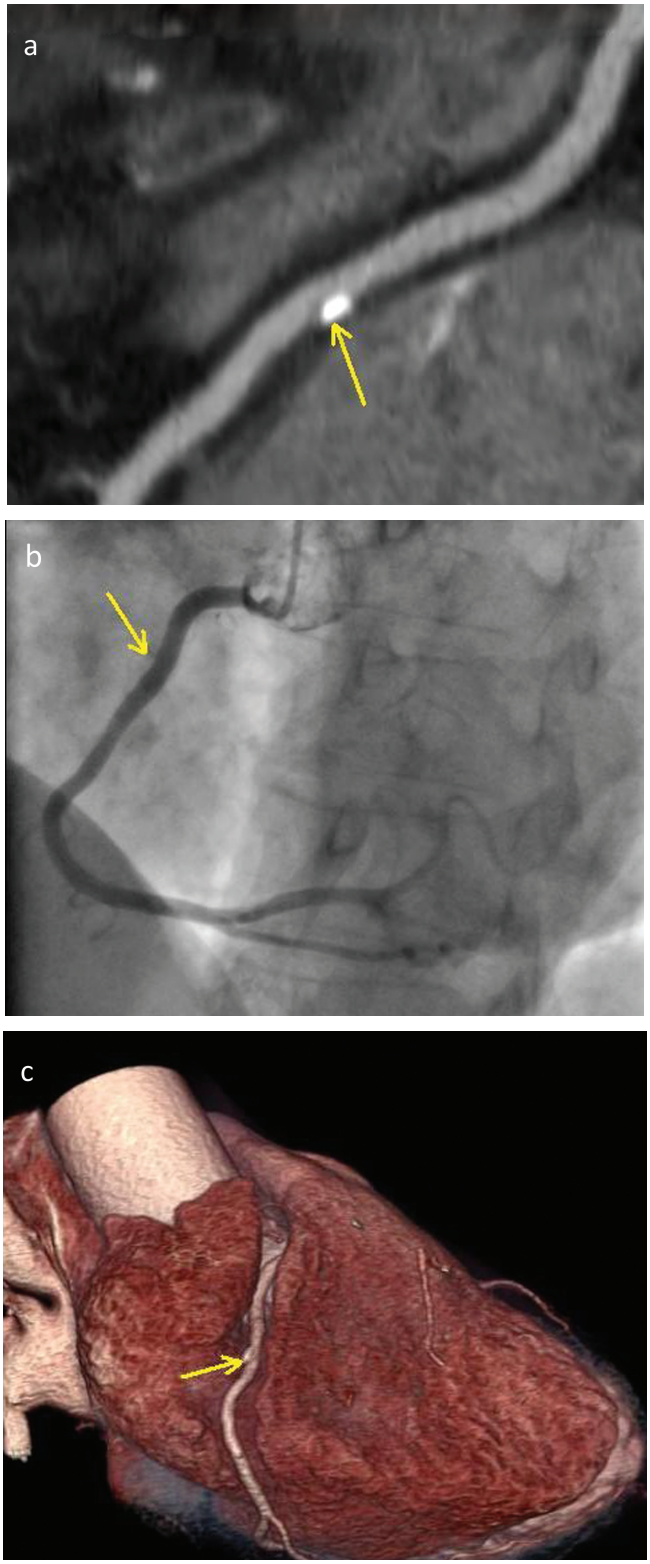

Fig 2. Right coronary artery atheroma. (a) CTCA of curved multiplanar reformation showing a focus of calcified plaque (arrow) with further diffuse, low attenuation non-calcified atheroma along the adjacent vessel wall not causing significant stenosis. (b) Catheter angiography showing a 'normal' vessel lumen. (c) Three-dimensional volume rendering showing the focal calcified plaque in the proximal RCA. CTCA = computed tomographic coronary angiography; RCA = right coronary artery.

Box 2. World Health Organisation Wilson–Jungner criteria (1968) for validity of a screening programme.

- ✓ The condition being screened for should be an important health problem
- ✓ The natural history of the condition should be well understood
- ✓ There should be a detectable early stage
- ✓ Treatment at an early stage should be of more benefit than at a later stage
- ? A suitable test should be devised for the early stage
- ✓ The test should be acceptable
- ? Intervals for repeating the test should be determined
- ? Adequate health service provision should be made for the extra clinical workload resulting from screening
- ? The risks, both physical and psychological, should be less than the benefits
- ? The costs should be balanced against the benefits

✓ = CCTA already fulfils this criterion in screening of CAD; ? = more evidence needed to establish whether CCTA fulfils this criterion; CAD = coronary artery disease; CCTA = computed tomography angiography.

Box 3. The features of atherosclerotic plaque that render it more prone to rupture.

Plaque features leading to higher rupture probability

- Positive remodelling
- Low calcification
- Poor fibrous cap formation
- Low plaque density
- Location in proximal vessels

researchers concluded that CTCA can confidently exclude significant CAD in an intermediate-risk population.[17]

By contrast, McEvoy *et al* performed a study on 1,000 asymptomatic patients and showed that screening with CTCA increased the incidence of invasive investigation and medication use in the screened group without any difference in the number of cardiovascular events between screened and unscreened patients at 18 months.[18] Although in low-risk populations, the likelihood of a cardiovascular event is likely to be low with such a short follow up and the researchers did not consider use of CTCA in screening justifiable.

However, Redberg *et al* noted that, in all of the recent studies, the pre-test probability of CAD was high, overestimating the diagnostic abilities of CTCA in asymptomatic CAD, and suggested clinical trials in this group before a screening programme is established.[19] However, it is well established that the accuracy of CTCA increases with decreasing calcium score, which should be lower in asymptomatic patients. Therefore, screening low-risk populations would potentially increase the sensitivity of the test because one of the confounding factors is now controlled for.[20,21] It should be argued that the most appropriate group with the greatest potential benefit for screening is identified, which in our view are the asymptomatic patients in the 'intermediate to high' risk groups.

Data derived from the large multinational CONFIRM registry (2012) have and will continue to provide key answers to many important topics regarding CTCA.[22]

In our opinion, a vital key to enhancing the diagnostic and indeed screening value of CTCA might lie with the use of nanotechnology and molecular imaging methods. Fluorescence molecular tomography involves radiolabelling of macrophage-derived protease activity in plaque, enabling higher positive predictive value of future ischaemic events.[15,23] Although currently in the research sphere, this is not yet in the domain of CT coronary imaging. Nuclear imaging techniques, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), have been shown to collect quantitative information non-invasively on the levels of expression of functional molecules and metabolic activities *in vivo* and thus provide functional diagnoses of unstable plaques with high sensitivity.[24]

The prospect of combined plaque characterisation, quantification and assessment of plaque activity is exciting and could drive a more aggressive medical or even interventional management strategy.

'The risks, both physical and psychological, should be less than the benefits'

Screening patients for CAD carries the potential benefit of cardiovascular event reduction. Although CTCA is considered to be a non-invasive technique, it arguably bears some physical and psychological risks. First, there is a radiation burden, which in the long term could have a low carcinogenic effect.[12] A multicentre cross-sectional study showed that estimated radiation dose of a single CTCA was 12.0 mSv; however, these results were highly variable among centres.[25]

With newer technologies and advancing CT techniques as mentioned previously, including high-pitch scanning and iterative reconstruction algorithm usage, radiation doses can be regularly decreased to <1–2mSv, thus further reducing the long-term risk[26–28] (Box 4). Such doses are comparable with, for example, a plain lumbar spine radiographic series, an investigation often performed for back pain with little clinical return with respect to radiation burden.

Additionally, the use of intravenous contrast in the investigation is associated with a small risk of anaphylaxis (incidence 0.004%).[29] Iodine-based contrast should be used with caution in patients with several comorbidities, such as asthma, renal impairment and diabetes mellitus.[30]

Redberg quoted a case of a woman with atypical chest pain, whose doctor requested CTCA just to 'reassure her' in one US centre.[19] The test showed multiple calcified and non-calcified plaques, which were (controversially) further investigated with catheter coronary angiography. During this examination, the patient had an iatrogenic left main stem coronary dissection and consequent infarction, requiring a bypass graft and, ultimately, a heart transplant.[31] The author concluded that the lower the pre-test risk probability, the higher the incidence of

false positive results and, hence, an increased action probability. This is an argument that holds true across any investigative pathway.[19]

Several subsequent studies have shown that performing CTCA leads to more invasive procedures and an increase in medical treatment.[18,32] However, Berti *et al* recently demonstrated that the use of CTCA had a greater impact on myocardial perfusion scintigraphy usage rates than on invasive coronary angiography.[33]

There is no investigation that can act as a substitute for a full and accurate clinical assessment with estimation of the pre-test probability when deciding upon the appropriateness of CTCA or other imaging test. As with any screening programme, using CTCA for early diagnosis might bear a risk of stress and anxiety connected with the procedure and the possibility of a false positive result. However, there are now several meta-analyses, including that of Budoff *et al*, that clearly show the high negative predictive value of CTCA to be 99%, which is of huge advantage in CAD exclusion and, thus, a powerful clinical tool in the most appropriate clinical setting.[21]

'The costs should be balanced against the benefits'

Currently, estimation of cardiovascular risk is done using cardiovascular risk prediction charts, commonly used in medical practice. Basing on the risk estimation, treatment guidelines have been established according to the severity of the cardiovascular risk.[34]

High incidence of cardiovascular risk in populations leads to greater triple therapy (aspirin, 3-hydroxy-3-methylglutaryl-coenzyme A [HMG-CoA] reductase and β-adrenoceptor blocker) prescription numbers. This poses the question of whether it is cost effective to treat based solely upon an empirical estimation.

Arguably, a CTCA screening programme could determine the actual cardiovascular risk, facilitating personalised treatment plans. At this point, it is important to note that the well-validated CT calcium score has been proven to be the most powerful independent marker to predict the relative risk of future coronary events.[35] It is of particular use in the 'intermediate' risk population groups, where its use can usefully modify the traditional Framingham Risk Assessment tool.

The use of CT coronary artery calcium scoring (CACS) alone as an adjunctive screening tool in the asymptomatic population is also controversial. Although it is of low radiation dose and does not involve the administration of intravenous contrast, it could be argued that medical therapy is unlikely to alter regardless of whether the patient has modifiable known risk factors. Equally, the question of whether triple therapy should start in the absence of known risk factors and in the presence of an intermediate calcium score should be posed. In addition, the presence of high coronary calcium in an asymptomatic individual does not warrant further investigation by perfusion imaging or catheter angiography according to current guidelines, but might pose, and indeed has posed, anxiety among attending physicians. A negative calcium score does not, of course, exclude the presence of non-calcified and potentially vulnerable atheroma.

In addition, the CONFIRM investigators recently reported the additional risk-predictive advantage by CTCA is not clinically meaningful compared with a risk model based on CACS.[36] Therefore, at present, the application of CTCA for the risk assessment of individuals without a chest pain syndrome should not be justified. Patients with hereditary hyperlipidaemia, especially low-density lipoprotein receptor-negative mutations, where the presence of subclinical plaque disease might be greater, could represent a subgroup that is likely to obtain greater current benefit from screening.

Attention to such strategies could contribute to the reduction in the cost of drug therapy and follow-up cardiology or general practitioner appointments. By contrast, drastically increasing the number of CTCA scans as part of a screening programme even in an appropriate cohort could prove far less cost effective.

Thus far, there is little evidence in the published literature as to the cost effectiveness of a CTCA scan in the context of assessment of asymptomatic individuals. National Institute for Health and Care Excellence (NICE) guidelines suggest the use of CTCA for the investigation of stable chest pain of new onset, where the estimated likelihood of CAD is 10–29% and calcium score is 1–400.[3] Although no UK centres have performed cost-effectiveness analysis of this method, some evidence comes from US-based researchers. Importantly, the cost-effectiveness calculation has to be tailored to the costs in local institutions and cannot be inferred from studies in another centre or country. Nonetheless, Min *et al* showed that CTCA-only approach is the most cost effective in the evaluation of patients with stable chest pain without known CAD and of intermediate risk.[37] However, another study by Miller *et al* identified no difference in total resource utilisation when CTCA was included in risk stratification.[38]

Finally, the analysis of cost effectiveness of a SPECT myocardial perfusion scan compared with that of CTCA performed by Shaw *et al* showed that, whereas cost reduction was observed in the evaluation of patients with suspected CAD, CTCA was less cost effective in patients with known CAD, mainly because subsequent coronary angiographies had to be performed in many cases.[6] This study in particular again stresses the importance of accurate pre-test clinical assessment to select appropriate individuals to undergo CTCA. The increased costs should nonetheless be viewed in the context of lifelong reduction of cardiovascular risks and balanced against empirical medical treatment.

Box 4. Techniques used to reduce radiation dose in CCTA.

- Patient positioning in the centre of gantry
- Adjustment of exposure to BMI
- Limiting the scan length and area
- Bowtie filters
- Cardiac noise reduction filter
- Iterative reconstruction
- ECG-gated dose modulation

BMI = body mass index; CCTA = computed tomographic coronary angiography; ECG = electrocardiographic.

Future directions

New techniques to more accurately quantify total plaque volume are also being developed that could enable follow up of plaque progression or regression. Interestingly, statin use has been associated with an increased prevalence and extent of coronary plaques containing calcium. This longitudinal effect of statins warrants further investigation.[39]

There is evolving research, using animal models, in the use of drug-eluting balloon angioplasty to plaques causing no significant stenosis, but being of a 'vulnerable' nature, whereby paclitaxel has been shown to cause plaque stabilisation.

Nanotechnology could enable the use of antiangiogenic particles to identify active plaque and attack atheroma. Recent studies strengthen the concept that intraplaque neovascularisation and bleeding are events that could have a major role in plaque progression and leukocyte infiltration, and might also serve as a measure of risk for the development of future events.[40] The development of vaccinations targeting atherosclerosis might also influence decisions to image preclinical disease.[41,42]

Concluding remarks

Asymptomatic coronary artery disease often results in sudden death from MI. Preventative methods, such as triple therapy, lifestyle advice and risk factor optimisation, have been implemented. A CTCA screening programme has also been suggested as a method of risk stratification.

Although the use of CT CACS alone might contribute to achieving a more precise relative risk assessment, it could be argued that this would not otherwise alter current medical practice regardless of the result. At the same time, it has to be remembered that there is no substitute for accurate preclinical assessment of patients at risk of CAD that will determine the most optimal investigative strategy.

The accuracy of CTCA is high (most notably a high negative predictive value) in determining the presence and severity of plaque. However, as yet, CTCA is unable to predict clearly the likelihood of plaque rupture in the context of non-significant stenosis. Additionally, it is argued that all research to date centres on subjects with known or suspected CAD and, therefore, the results of these studies do not necessarily apply to the general population.

It is our view that for such a screening programme to be successful, CTCA should not only be able to identify clearly preclinical disease in the most appropriate patient groups with cardiovascular risk factors, but also provide some assessment of plaque activity and, thus, potential vulnerability. Even if these criteria are achieved, there must be a proven effective therapy for plaque stabilisation and/or regression coupled with significant cost-effective reduction in cardiovascular mortality and morbidity that is either in addition to, or in place of, existing therapy that would otherwise not be given without the use of the screening test.

Continuous improvements in CT technology will continue to reduce radiation burden, improve diagnostic accuracy and might begin to provide the clinician with additional important insight into atherosclerotic disease activity that could guide future therapies.

Therefore, it is our opinion that there is currently insufficient evidence to support the use of CTCA in a screening programme for CAD. However, with continued technological advancement, this viewpoint will undoubtedly evolve.

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