REVIEW

Role of computed tomography in risk assessment for coronary heart disease

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Coronary heart disease is the most common cause of death in Western countries, with a rising incidence in developing countries. It is part of the spectrum of cardiovascular diseases that have common end points of myocardial infarction, stroke and death. As these end points often occur suddenly and often in those with no known disease, identification of those people at high risk is important. Besides the known traditional risk factors, direct imaging of the calcified plaque as a marker for atherosclerotic disease has been extensively studied with electron beam computed tomography and now with multislice computed tomography. This review discusses the role of computed tomography in assessment of cardiovascular risk in both people with or without symptoms.

Coronary heart disease (CHD) remains one of the main causes of morbidity and mortality in the world, particularly in Western countries,¹ despite its declining trend. In the UK, it is the most common cause of death,² and its incidence along with other cardiovascular causes is predicted to double by 2020.³ Moreover, the death rate from CHD has been proportionately increasing in eastern European and other developing countries.²

RATIONALE FOR PREVENTION OF CARDIOVASCULAR DISEASES

It is now well recognised that CHD is part of the spectrum of cardiovascular diseases (CVDs) that have common underlying risk factors and may manifest as myocardial infarction, stroke or death.⁴ The underlying pathology is usually atherosclerosis, which develops insidiously over several years and is usually advanced by the time symptoms occur. The end points of infarction, stroke and death often occur suddenly and before medical care is available, by which time therapeutic interventions are either inapplicable or are only palliative. The prevalence of CVD is strongly related to lifestyle and physiological factors, some of which can be modified by lifestyle changes and drugs. This may lead to prevention of and reduction in CHD, and a consequent decrease in cardiovascular morbidity and mortality.

RISK ASSESSMENT AND RATIONALE FOR DEMONSTRATION OF ATHEROSCLEROSIS

The Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention highlighted the priorities in clinical

practice for prevention of CVDs on the basis that preventive efforts are most efficient and cost effective when directed to those at most risk.⁴ They recommended targeting patients with established CVD and those asymptomatic people at high risk of developing CVD. Various multifactorial risk assessment methods, such as Framingham Risk Score (FRS) and PROspective Cardiovascular Münster,⁵ and more recently Systematic COronary Risk Evaluation,⁴ have been developed and recommended to assess the risk. These models are based on a combination of risk factors including age, sex, total cholesterol, high-density lipoprotein, smoking, hypertension, diabetes and family history of premature CHD. However, limitations of using the risk factors alone to predict occurrence of cardiovascular events are well known. Data from the Framingham Heart Study suggest that after adjustment for other factors, only 27% of CHD events among men and 34% of events among women were attributable to raised cholesterol⁶ (fig 1). Moreover, large trials in primary and secondary prevention⁷ have shown that lipid-lowering drugs decrease cardiovascular mortality in all patients irrespective of their cholesterol levels, indicating that other factors may influence the disease.

To improve the assessment of cardiovascular risk by traditional risk factors, methods that directly show atherosclerotic plaque and the arterial wall have been described. This is especially important, as established obstructive coronary atherosclerosis does not often occur at the site of acute thrombotic occlusion,^{8–10} but rather at the site of non-obstructive plaque. Thus, techniques such as exercise testing to diagnose ischaemia or pharmacological means to diagnose severity of the coronary stenosis will fail to identify many asymptomatic people who are at risk. The atherosclerotic plaque or thickening of the vessel wall may be directly demonstrated by various imaging techniques such as carotid ultrasound, computed tomography and magnetic resonance imaging.¹¹ Computed tomography has been widely and intensively studied, and is the topic of this review.

WHY USE COMPUTED TOMOGRAPHY?

Cardiovascular risk stratification by computed tomography has primarily been carried out by

Abbreviations: CAC, coronary artery calcification; CAD, coronary artery disease; CHD, coronary heart disease; EBCT, electron beam computed tomography; MSCT, multislice computed tomography; CVD, cardiovascular disease

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Box 1: Rationale for risk assessment

- Coronary heart disease (CHD) is a leading cause of morbidity and mortality worldwide.
- CHD forms a part of the spectrum of cardiovascular diseases, with common end points of myocardial infarction, stroke and death.
- Prevalence of CHD is related to lifestyle and physiological factors, most of which can be modified to reduce the risk.
- Efforts to reduce risk are best directed to those at most risk.

detecting and quantifying calcified atherosclerotic plaque in the coronary arteries, as it is highly sensitive for imaging calcification in the body. It is well established that calcification in the coronary arteries is a specific marker for atherosclerotic coronary artery disease (CAD), and is absent in the normal arterial vessel wall.^{12–13} This has been substantiated by various studies comparing calcification detected by computed tomography with histopathology.^{14–15} However, it is also recognised that non-calcified plaque and lipid-laden vulnerable plaque could be present in the absence of calcium.¹⁶ Non-calcified plaque can now also be imaged with contrast-enhanced computed tomography (described later in Future developments).

High calcium scores increase the probability of vulnerable plaques, but do not identify specific vulnerable lesions. Calcification in the coronary arteries as seen on fluoroscopy has long been known to predict the degree of CAD and hence the prognosis.^{17–18} This knowledge led to the use of coronary artery calcification (CAC) as detected by computed tomography in the assessment of cardiovascular risk.

COMPUTED TOMOGRAPHY TECHNOLOGIES

Two different types of computed tomography scanners are currently being used for estimation of calcium in the coronary arteries—namely, the electron beam computed tomography (EBCT) scanner and, more recently, the multi-slice computed tomography (MSCT) scanner (table 1). For the purpose of assessment of calcium in coronary arteries,

Box 2: Methods of risk assessment**Risk factors**

- Advancing age
- Male sex
- Hypertension
- Smoking
- Raised total cholesterol or reduced high-density lipoprotein cholesterol
- Diabetes mellitus
- Family history of premature coronary heart disease
- Obesity

Risk markers

- Direct evidence of arterial wall thickness or plaque by any of the following:
 - B-mode ultrasound: measures the intima-media thickness
 - Computed tomography: measures the calcified plaque (now demonstration of soft plaque is also possible with contrast-enhanced computed tomographic angiography)
 - Magnetic resonance imaging: demonstration of vessel wall thickness and plaque
- Indirect evidence of atherosclerotic disease by any of the following:
 - Ankle-Brachial Pressure Index
 - Exercise electrocardiography testing
 - Stress nuclear perfusion test
 - Stress echocardiography

Novel serum markers

- C reactive protein and homocysteine

computed tomography scanning is carried out with electrocardiography gating, irrespective of the type of scanner.

EBCT scanner

The EBCT scanner was specifically designed to image the heart, as conventional computed tomography scanners were

Figure 1 Case 1: A 77-year-old man who presented with acute coronary syndrome (non-ST elevation myocardial infarction) underwent CT coronary calcification as part of a research study. Scan showed extensive calcification in the left main stem (LMS) and left anterior descending artery (A, arrowheads), with Agatston score 580. Angiogram showed a tight stenosis in the distal LMS (B, arrow). This patient had no conventional risk factors apart from his age.

Box 3: Rationale for use of computed tomography in cardiovascular risk assessment

- Computed tomography is highly sensitive in detecting calcification in the body
- Calcification in the coronary arteries is a specific marker for atherosclerotic disease
- Traditional risk factors have known limitations in assessment of individual risk
- Computed tomography permits direct visualisation and quantification of calcified plaque non-invasively
- Demonstration of coronary calcification and thus atherosclerotic disease by computed tomography
 - is not limited by exercise capacity of the patient
 - does not depend on the presence of inducible ischaemia and thus obstructive coronary artery disease

too slow to image the beating heart. This technology was first suggested in 1979.¹⁹ The gantry design of these scanners did not use any moving parts and were therefore much faster, with shorter scan times compared with conventional computed tomography scanners. In the early years, the EBCT scanners (also called cine computed tomography or ultrafast computed tomography scanners) were used to evaluate myocardial thickening, wall motion and regional blood flow.²⁰ However, it was not until 1989 that the first use of EBCT scanner in the detection of CAC was described.²¹

The EBCT scanner, unlike conventional computed tomography scanners, uses electromagnetically focused electrons to sweep stationary tungsten target rings to produce x rays. There have been various models of EBCT scanners, from the original C-100 to the latest e-Speed (General Electric) introduced in 2003, which is capable of 33 ms true temporal resolution per slice.²² In this evolution, the basic technical principle has remained unchanged, but improvements have occurred in spatial resolution, and manipulation, management display and storage of data. Coronary artery calcium scoring with EBCT yields effective radiation doses of 1.0 and 1.3 mSv for male and female patients, respectively.²³

MSCT scanner

These scanners are the natural successors to conventional computed tomography scanners and have been developed by the slip-ring technology, which allows continuous helical scanning, faster rotation of the tube-detector assembly and multiple rows of detectors in the direction of the table movement (ie, the z axis). First to be introduced was a two-slice scanner in 1994, followed by a four-slice scanner in 1999, which, for the first time, showed the real potential of non-EBCT scanning in imaging the heart, particularly for calcium scoring and computed tomographic angiography of bypass grafts. Since then, 16-slice, 32-slice and 40-slice scanners have been introduced, with the latest being a 64-slice scanner in 2004.

As the MSCT scanners cost substantially lesser than the EBCT scanners, they have become more widespread in use. This has led to their evaluation in CAC. Although the initial studies with two-slice computed tomography scanners were not satisfactory, more recent studies with four-slice and higher scanners have shown higher correlation with phantom measurements of calcium and improved interscan variability.²⁴ This has been made possible by increased temporal resolution of the MSCT scanners and their ability to reconstruct overlapping images. However, it is to be understood that most of the published prognostic data

available today were acquired using EBCT scanners. The radiation dose with MSCT is 1.5 and 1.8 mSv in male and female patients, respectively,²³ for a protocol similar to that with EBCT.

CALCIUM SCORING

Standardised methods for imaging, identification and quantification of coronary artery calcium using EBCT have been published.^{16, 25} Similar methods have been developed for imaging with MSCT scanners, attempting to reconstruct the images in a way similar to that by EBCT, so that the same methods of scoring and interpretation can be applied. On images obtained with either scanner, coronary arteries are identified as soft-tissue structures, usually surrounded by fat, in the cardiac grooves, whereas calcified coronary deposits are seen as bright white areas along their course (fig 2A–D). For detection and scoring of calcium, an arbitrary value of +130 Hounsfield units (HU), which is a measurement of x ray attenuation on computed tomography, and an area >1.0 mm² are often used. The threshold of +130 HU was selected as it is 2 standard deviations (SD) greater than the attenuation of normal soft tissues. Regions of interest are placed manually around the pixels thought to have calcium, and the scanner software calculates the various scores. The Agatston score²⁶ is the oldest and most commonly used calcium scoring system. It is derived by summing the number of pixels above the threshold, and includes a weighting factor for the maximum density in each plaque. More recently described scoring methods are a volume score (the total volume of voxels above the threshold)²⁷ and mass score (the total mineral content in an identified plaque).²⁸ These are said to be more accurate, with less interscan variability than the Agatston score, and comparable between different scanners.

The prevalence of coronary calcium normally increases with age, with women lagging by about 10 years compared with men. Although the total calcium score reflects the total plaque burden, the age and sex of the person has to be taken into account to understand the relevance of a particular score. Instead of absolute calcium scores, the centile scores for a given age and sex are more helpful in predicting the risk.²⁹ In these groups, the absolute CAC score can be very low at the time of a cardiovascular event; yet the centile (comparing the index patient with a large cohort of asymptomatic people matched for age and sex) can be very high (>75th or >90th centile). Hence, the “vascular age” of the patient who has had a cardiovascular event is substantially more than that of a person who has had no such event, and may matter more than the biological age of the person as

Table 1 Comparison of electron beam computed tomography and multislice computed tomography scanners

EBCT scanner	MSCT scanner
<i>Advantages</i>	
Images the heart very rapidly (high temporal resolution, 33–100 ms)	More widely available owing to lower cost
Has been in use for a long time, and thus is the source of most of the prognostic data	Temporal resolution is fast approaching that of EBCT
Lower radiation dose	Studies now show similar accuracy to EBCT
<i>Limitations</i>	
High costs and thus very limited availability	Higher radiation dose than EBCT, but can be reduced by certain techniques

EBCT, electron beam computed tomography; MSCT, multislice computed tomography.

Figure 2 Morphology of coronary arteries with calcium. (A) Left main stem (arrowhead) with calcium in its bifurcation extending into the left anterior descending artery (LAD; arrow). (B) Further calcium is seen in the LAD and its diagonal branch (arrowheads), with origin of the circumflex artery (CXA; arrow) posteriorly. (C) Origin of right coronary artery (RCA; arrow) with complex calcification (arrowhead). (D) Further calcified plaques are seen in mid-RCA (arrow) and in the CXA (arrowhead).

a risk for cardiovascular events.³⁰ This has led to development of sets of nomograms for calcium scores based on age and sex, and grouped by centile ranking. The largest of these is the Kondos database,³¹ which gives the Agatston calcium scores on 35 246 asymptomatic people with EBCT and on 2030 asymptomatic people with MSCT.³²

RISK ASSESSMENT WITH COMPUTED TOMOGRAPHY IN PEOPLE WITH SYMPTOMS

People with known CVD are already at high risk of developing subsequent events and are thus candidates for aggressive lifestyle modification and treatment with suitable drugs.⁴ Regarding further management, additional imaging of the calcified plaque with computed tomography may have a limited role in these patients. However, several studies have shown the prognostic role of CAC in patients presenting with chest pain for assessment with coronary angiography.

A multicentre study on 491 patients³³ undergoing coronary angiography and EBCT found that higher calcium scores were associated with an increased risk of coronary events over a period of 30 months as compared with patients in the lowest quartile of score (odds ratio 10.8, 95% confidence interval (CI) 1.4 to 85.6). In multivariate analysis, the only predictor of a hard cardiac event was log calcium score and not the number of angiographically diseased vessels.

Keelan *et al*³⁴ carried out EBCT in 288 patients with symptoms undergoing angiography, and followed them for a mean of 6.9 years. Using a stepwise multivariate model, they

found age and CAC score to be the only independent predictors for future hard coronary events (risk ratios 1.72 and 1.88, respectively; $p < 0.05$), and not angiographic stenosis or other conventional risk factors. This study confirms the findings of an earlier study that it is the extent of plaque burden as determined with the extent of CAC that provides more prognostic information than angiography or risk factors in patients with symptoms.

Georgiou *et al*³⁵ followed 192 patients presenting with chest pain to the emergency department for a mean of 50 (SD 10) months. They found that the presence of CAC (calcium score > 0) and increasing absolute calcium score values were strongly related to the occurrence of hard events ($p < 0.001$) and all cardiovascular events ($p < 0.001$). The patients with absolute calcium scores in the top two quartiles had a relative risk of 12.1 for new cardiovascular events as compared with the patients in the lower two quartiles. The annualised rate of cardiovascular events was 0.6% for patients with CAC score 0 compared with 13.9% for those with CAC score > 400 ($p < 0.001$). Furthermore, absence of CAC was associated with a very low risk of future cardiac events in this population over the subsequent 7 years (annual event rate $< 1\%$).

Mohlenkamp *et al*³⁶ recently studied the prognostic value of very high calcium scores in male patients with symptoms and those who were undergoing coronary angiography. They followed 150 patients for 5 years and found that events occurred early and more often in those with CAC score > 1000 . Only left main disease (hazard ratio 4.3; 95% CI 1.4 to

13.0) and CAC score (hazard ratio 1.7; 95% CI 1.1 to 2.5) independently predicted overall hard events, whereas only CAC score >90th centile independently predicted all events (hazard ratio 2.5; 95% CI 1.3 to 4.8) including stroke and revascularisation. These data show that extensive calcium deposits are not associated with a more "stable coronary environment", as we would be tempted to surmise if CAC were taken to indicate a healed vessel wall damage. On the contrary, extensive calcification may indicate that the atherosclerotic process is far advanced, with several non-calcified plaques prone to rupture admixed with calcified and more stable areas.

RISK ASSESSMENT WITH COMPUTED TOMOGRAPHY IN ASYMPTOMATIC PEOPLE

It is well known that acute myocardial infarction (some of which present as sudden death) occurs as the first manifestation of CHD in as many as 50–60% of people without any prior symptoms of disease. For this and other reasons discussed earlier, identification of people who may be at high risk for developing the disease becomes vital, and it is this group that is likely to benefit most from primary prevention measures. Numerous large studies have been carried out to explain the role of CAC in assessing cardiovascular risk in asymptomatic people.

Until 1999 three large studies^{37–39} were published, which were subjected to critical review by the American College of Cardiology/American Heart Association Expert Consensus Document on use of EBCT for diagnosis and prognosis of CAD.¹⁶ The studies, totalling <3000 asymptomatic people, although showing increased risk of high calcium scores with combined end points of both hard and soft cardiovascular events (odds ratio 20–35), failed to convincingly show predictive ability for hard events alone. For a test to be most valuable when asymptomatic patients are screened, it should increase the likelihood of CHD above the probability determined by standard and readily available assessments based on traditional risk factors. This incremental value of EBCT over traditional multivariate risk assessment models was not satisfactorily established. The report concluded that the use of EBCT in selected asymptomatic patients can be justified only when carried out in the context of a medical assessment, only after the more standard cardiac risk assessment is considered insufficient by the doctors to direct further treatment plans.

Since then, further large studies have been published.^{29 40–46} These publications, most of which are prospective, total about

35 000 asymptomatic people, with a follow-up ranging from 3 to 7 years. Among the most recent studies, the St Francis Study⁴⁵ followed 4613 asymptomatic people aged 50–70 years for a mean of 4.3 years. For coronary calcium score threshold ≥ 100 versus score ≤ 100 , the relative risk was 9.6 (95% CI 6.7 to 13.9) for all atherosclerotic cardiovascular events, 11.1 (95% CI 7.3 to 16.7) for all CAD events, and 9.2 (95% CI 4.9 to 17.3) for non-fatal myocardial infarctions and death. The coronary calcium score predicted CAD events independently of standard risk factors and was superior to the FRS in the prediction of events (mean area under the receiver–operating characteristic curve 0.79 (SD 0.03) v 0.69 (SD 0.03), $p < 0.001$), and improved the stratification of those falling into the FRS categories of low, intermediate and high risk ($p < 0.001$).

In their study on 10 746 asymptomatic adults (64% men) known to have no CAD, Lamonte *et al*⁴⁶ quantified the CAC with EBCT. During a mean follow-up of 3.5 years, 81 hard events (non-fatal myocardial infarction and death due to CAD) and 287 total events (hard events and coronary revascularisation) were recorded. Age-adjusted rates (per 1000 person-years) of hard events were computed according to four CAC categories: no detectable CAC and incremental sex-specific thirds of detectable CAC; these rates were, respectively, 0.4, 1.5, 4.8 and 8.7 (trend $p < 0.001$) for men and 0.7, 2.3, 3.1 and 6.3 (trend $p = 0.02$) for women. CAC levels also were positively associated with rates of total CHD events for women and men (trend $p < 0.001$ each). The association between CAC and CHD events remained significant after adjustment for CHD risk factors.

Women are known to have a lower prevalence of coronary calcification and smaller calcification scores than men. Until recently, there was paucity of sufficient data regarding the role of CAC in risk assessment in women. Apart from the previous study,⁴⁶ Raggi *et al*⁴⁷ followed 10 377 asymptomatic people (of whom 40% were women) for a mean of 5 years after EBCT, and showed 3-fold, 5.5-fold and 5.5-fold increased relative risk ratios for women compared with men with coronary calcification scores of 101–399, 400–1000 and >1000 ($p < 0.001$), respectively. Receiver–operating characteristic curve analyses to assess coronary calcification added incremental prognostic value to FRS values ($p < 0.001$). The authors thus showed that EBCT may be a useful tool for risk stratification in women, where the early diagnosis of CHD remains a strong challenge.

The role of CAC assessment in the elderly (>70 years) and the young (40–50 years for both men and women) has also been recently considered. Vliegenthart *et al*⁴⁸ assessed 1795

Figure 3 Case 2: A 44-year-old asymptomatic man with intermediate risk (12% according to the Joint British Societies Risk prediction chart) underwent a calculated computed tomography scan, which showed calcified plaques in the proximal left anterior descending artery (LAD), its diagonal branches and circumflex artery (fig 1A,B; all arrowheads). The total Agatston score was very high at 469 for the patient's age, thus changing his risk category to high. Angiography was carried out, which showed a 70% stenosis in the proximal LAD (fig 2C; arrowhead).

asymptomatic participants aged 62–85 years (mean 71 years) with EBCT screening and a mean follow-up of 3.3 years. The risk of CHD increased with increasing calcium score. Compared with calcium scores of 0–100, the multivariate-adjusted relative risk of coronary events was 3.1 (95% CI 1.2 to 7.9) for calcium scores 101–400, 4.6 (95% CI 1.8 to 11.8) for scores 401–1000 and 8.3 (95% CI 3.3 to 21.1) for scores >1000. The predictive value in people aged >70 years was similar. Also, the risk prediction based on the cardiovascular risk factors improved when coronary calcification was added. On the other hand, the Prospective Army Coronary Calcium Project,⁴⁹ with 2000 healthy men and women aged 40–50 years and a mean follow-up of 3 years, showed an 11.8-fold increased risk for incident CHD ($p = 0.002$) with any degree of calcium in a Cox model controlling for the FRS in men. This study, however, was underpowered to evaluate a similar relationship in young women.

Increasing data now show the independent and incremental value of CAC in predicting the risk for CHD and mortality in different age groups and both sexes. CAC may be a superior tool for risk stratification than the conventional risk factors, as CAC reflects the overall effect of risk factors, both known and unknown, on the arterial wall.⁵⁰

ASSESSMENT OF CHANGE IN CALCIFIED PLAQUE WITH PHARMACOLOGICAL INTERVENTION

Attempts have been made to assess the change in size or volume of the calcified plaque with pharmacological intervention.⁵¹ A reduced rate of progression of the plaque is seen in patients receiving statins as primary prevention compared with those not treated. More recently, in the St Francis Heart Study randomised clinical trial on 1005 asymptomatic men and women with calcium score >80th centile, Arad *et al*⁵² failed to show any change in progression of CAC or any marked reduction in atherosclerotic cardiovascular events with 20 mg atorvastatin, and vitamins C and E in the study group. However, according to the authors, the study was underpowered and the study population undertreated. Further randomised studies will be required to recommend the clinical use of computed tomography coronary calcium for this purpose. Moreover, the effect of any lifestyle modification or pharmacological intervention will be not only on calcified but also on non-calcified plaques that will be challenging to image, quantify and assess over time. Limitations in assessment of change in plaque progression do not negate the risk stratification and prognostic value of calcium scoring.

HOW TO USE COMPUTED TOMOGRAPHY CAC IN RISK ASSESSMENT?

Current evidence suggests that to be most cost effective, CAC can be assessed with computed tomography, in conjunction with traditional risk assessment techniques, in men aged >40 years and women aged >55 years.⁴⁹ FRS and other similar office-based methods should still be used as the first step to screen people for potential risk. In those with low risk (FRS <10% in 10 years) CAC was not effective,⁴⁴ whereas for those who fall in the highest risk category (FRS >20% in 10 years) CAC measurement will add little predictive information of value. The greatest contribution of CAC estimation is in asymptomatic people with intermediate risk (FRS 10–20% per year), in whom CAC score >100 Agatston units or >75th centile can raise the risk to a higher level^{43 44 53} (fig 3). With this approach, a low CAC score in the intermediate-risk category will move a person to lower risk because of paucity of events in those with lower scores. Some researchers have attempted to construct models to determine the benefit of CAC score (post-test risk estimate) from the conventional risk factors⁵⁴ for implementation in clinical practice.

It has to be emphasised that coronary calcification for cardiovascular risk stratification by computed tomography can be best used as a referral by a general practitioner or a doctor well versed with traditional risk assessment and treatment. This is important as the preventive efforts are most efficient when targeted to those at highest risk.⁴ Moreover, when patients undergo computed tomography, they are also exposed to a small but definite dose of radiation, which for the purpose discussed is equivalent to a half a year's natural background radiation. Although there is considerable debate about the risk associated with such dose levels, "as low as reasonably achievable" principles mandate that such procedures be used in a responsible manner.²³

FUTURE DEVELOPMENTS

Although the above studies on asymptomatic people provide powerful data for risk stratification, most are based on selected self-referred or doctor-referred asymptomatic people. Two large population-based studies (NHHLI-sponsored Multi-Ethnic Study of Atherosclerosis⁵⁵ and the Heinz Nixdorf-RECALL study⁵⁶) are well under way to evaluate the use of CAC in a multiethnic, population-based cohort of asymptomatic people representing all socioeconomic strata.

Demonstration of non-calcified soft plaque has also now become possible using contrast-enhanced MSCT, and attempts made for its quantification^{57 58} show a good correlation with intravascular ultrasound. However, this has been carried out on symptomatic people for assessment of obstructive coronary disease. It has yet to be seen how this can be used for risk stratification in asymptomatic people. A major hurdle will be the high radiation dose with MSCT coronary angiography (ranging between 7 and 13 mSv) for screening purposes compared with the much smaller dose with coronary calcium computed tomography.²³

CONCLUSION

This review represents a summary of the most current evidence supporting the use of CAC quantification for risk prediction. The evidence presented suggests that this tool may improve our ability to risk stratify asymptomatic people, particularly those with an intermediate pre-test probability of the disease. It may also be more cost effective if used in selected populations. This is the position endorsed by both The European Society of Cardiology⁴ and the American College of Cardiology.¹⁶ Additionally, as recommended by the Society of Atherosclerosis Imaging,⁵⁹ screening for CAC could be carried out as the initial test in older people with atypical chest pain and no risk factors for atherosclerosis—

Key references

- Poulter N. Global risk of cardiovascular disease. *Heart* 2003;**89**(Suppl II):ii2–5.
- Backer GD, Ambrosioni E, Borch-Johnsen K, *et al*. European guidelines on cardiovascular disease prevention in clinical practice. *Eur J Cardiovasc Prev Rehabil* 2003;**10**(Suppl 1):S1–78.
- Pearson TA. New tools for coronary risk assessment. What are their advantages and limitations? *Circulation* 2002;**105**:886–92.
- Rumberger JA. Tomographic plaque imaging with CT: technical considerations and capabilities. *Prog Cardiovasc Dis* 2003;**46**:123–34.
- Grundy SM. The changing face of cardiovascular risk. *Am Coll Cardiol* 2005;**46**:173–5.

absent or low CAC scores would exclude CAD with a high degree of probability. Moreover, MSCT can potentially be applied more widely without compromising on the accuracy.

Thus, currently, CAC screening seems to be a useful and reasonable approach to better risk stratify selected patients, although a definitive answer will depend on the results of ongoing longitudinal studies.

Further reading

- **Naghavi M**, Falk E, Hecht HS, *et al.* From Vulnerable Plaque to Vulnerable Patient-Part III - A New Paradigm for the Prevention of Heart Attack: Identification and Treatment of the Asymptomatic Vulnerable Patient: Executive Summary of the Screening for Heart Attack Prevention and Education (SHAPE) Task Force Report. *Am J of Cardiol* 2006;**98**(suppl 1):2-15.
- **Clouse ME**. Noninvasive screening for coronary artery disease with computed tomography is useful in Controversies in Cardiovascular medicine. *Circulation* 2006;**113**:125-146.
- **McClelland RL**, Chung H, Detrano R, *et al.* Distribution of coronary artery calcium by race, gender, and age. Results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2006;**113**:30-37.
- **Achmermund A**, Mohlenkamp S, Berenbein S, *et al.* Population-based assessment of subclinical coronary atherosclerosis using electron-beam computed tomography (from Heinz Nixdorf Recall Study). *Atherosclerosis* 2006;**185**:177-182.

SELF-ASSESSMENT QUESTIONS (TRUE (T)/FALSE (F)); ANSWERS AT THE END OF REFERENCES

1. Epidemiology of coronary heart disease (CHD)

- It is the most common cause of death in developed countries.
- Death rates from CHD in developed countries are increasing.
- Incidence of CHD in developing countries is reducing.
- CHD is part of the spectrum of cardiovascular diseases.
- Common end points of myocardial infarction, stroke and death take time to develop and manifest.

2. Risk assessment in CHD

- It is unnecessary as most risk factors cannot be modified.
- Traditional risk factors of advanced age, hypercholesterolaemia, hypertension, diabetes or smoking truly reflect the total risk of a person.
- Direct demonstration of arterial plaque can be used to determine the individual risk.
- Methods inducing ischaemia can reliably show the risk in an asymptomatic person.
- Methods such as ultrasound, computed tomography and magnetic resonance imaging for risk assessment should be used only in conjunction with traditional risk assessment methods.

3. Electrocardiography-gated computed tomography scan can be used for risk assessment because of the following

- It is the most sensitive non-invasive technique to demonstrate the calcified plaque directly.

- It depends on the exercise capacity of a person.
- It does not depend on the presence of obstructive disease in the coronary arteries.
- It demonstrates both calcified and non-calcified plaques without any intravenous contrast.
- It is a risk-free technique.

4. Use of computed tomography in risk assessment in people with symptoms

- Computed tomography has no role in risk assessment in people with symptoms.
- The extent of calcified plaque is related to future events.
- Degree of angiographic stenosis is a better prognostic indicator than the extent of calcified plaque.
- Absence of calcium in the coronary arteries is associated with a very low future risk of cardiovascular events.
- Very high calcium scores indicate a stable coronary disease.

5. Use of computed tomography in risk assessment in asymptomatic people

- It provides a direct measure of calcified plaque in the coronary arteries.
- Large amounts of data are available, showing the prognostic value of the extent of calcium that is independent of the risk by traditional methods.
- The incremental prognostic value of the degree of calcification has not yet been shown.
- It should not be used for this purpose in women of any age as they do not exhibit calcium in their arteries.
- It should be used in conjunction with the traditional risk assessment methods, and people with intermediate risk benefit the most from calcium tomography calcium assessment.

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REFERENCES

- World Health Organization**. The atlas of heart disease and stroke. 2005. http://www.who.int/cardiovascular_diseases/resources/atlas/en/index.html (accessed 25 Aug 2006).
- Petersen S**, Peto V, Rayner M. *Coronary heart disease statistics*. London: BHF, 2004.
- Poulter N**. Global risk of cardiovascular disease. *Heart* 2003;**89**(Suppl 1):ii2-5.
- Backer GD**, Ambrosioni E, Borch-Johnsen K, *et al.* European guidelines on cardiovascular disease prevention in clinical practice. *Eur J Cardiovasc Prev Rehabil* 2003;**10**(Suppl 1):S1-78.
- Assmann G**, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10 year follow up of the prospective cardiovascular Munster (PROCAM) study. *Circulation* 2002;**105**:310-15.
- Wilson PWF**, D'Agostino RBP, Levy D, *et al.* Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;**97**:1837-947.
- Heart Protection Study Collaborative Group**. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7-22.
- Giroud D**, Li JM, Urban P, *et al.* Relation of the site of acute myocardial infarction to the most severe coronary arterial stenosis at prior angiography. *Am J Cardiol* 1992;**69**:729-32.
- Little WC**, Constantinescu M, Applegate RJ, *et al.* Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? *Circulation* 1988;**78**:1157-66.
- Tousoulis D**, Davies G, Stefanadis C, *et al.* Can angiography predict the vulnerable lesion that progresses to myocardial infarction? *J Am Coll Cardiol* 2000;**35**:261-2.

- 11 Pearson TA. New tools for coronary risk assessment. What are their advantages and limitations? *Circulation* 2002;**105**:886–92.
- 12 Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* 1993;**362**:801–9.
- 13 Stary HC, Chandler AB, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis: a report from the Committee on Vascular Lesions of the Council of Arteriosclerosis, American Heart Association. *Circulation* 1995;**92**:1355–74.
- 14 Mautner GC, Mautner SL, Froehlich J, et al. Coronary artery calcification: assessment with electron beam CT and histomorphometric correlation. *Radiology* 1994;**192**:619–23.
- 15 Sangiorgi G, Srivatsa SS, Rumberger JA, et al. Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histological study of 723 coronary artery segments using nondecalcifying methodology. *J Am Coll Cardiol* 1998;**31**:126–33.
- 16 O'Rourke RA, Brundage BH, Froelicher VF, et al. American College of Cardiology/American Heart Association expert consensus document on electron beam computed tomography for the diagnosis and prognosis of coronary artery disease. *Circulation* 2000;**102**:126–40.
- 17 Lieber A, Jorgens J. Cinefluorography of coronary artery calcification: correlation with clinical arteriosclerotic heart disease and autopsy findings. *Am J Roentgenol* 1961;**86**:103.
- 18 Hamby RI, Tabrah F, Wisoff BG, et al. Coronary artery calcification: clinical implications and angiographic correlations. *Am Heart J* 1974;**87**:565–70.
- 19 Boyd DP, Gould RG, Quinn JR, et al. A proposed dynamic cardiac 3-D densitometer for early detection and evaluation of heart disease. *IEEE Trans Nucl Sci* 1979;**26**:2724–7.
- 20 Lipton MJ, Higgins CB, Farmer D, et al. Cardiac imaging with a high-speed Cine-CT scanner: preliminary results. *Radiology* 1984;**152**:579–82.
- 21 Tanenbaum SR, Kondos GT, Veselik KE, et al. Detection of calcific deposits in coronary arteries by ultrafast computed tomography and correlation with angiography. *Am J Cardiol* 1989;**63**:870–2.
- 22 Rumberger JA. Tomographic plaque imaging with CT: technical considerations and capabilities. *Prog Cardiovasc Dis* 2003;**46**:123–34.
- 23 Hunold P, Vogt FM, Schmermund A, et al. Radiation exposure during cardiac CT: effective doses at multi-detector row CT and electron-beam CT. *Radiology* 2003;**226**:145–55.
- 24 Detrano RC, Anderson M, Nelson J, et al. Coronary calcium measurements: effects of CT scanner type and calcium measure on rescanned reproducibility—MESA study. *Radiology* 2005;**236**:477–84.
- 25 Wexler L, Brundage B, Crouse J, et al. Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications—a statement for health professionals from the American Heart Association. *Circulation* 1996;**94**:1175–92.
- 26 Agatston AS, Janowitz W, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;**15**:827–32.
- 27 Callister TQ, Coall B, Raya SP, et al. Coronary artery disease: improved reproducibility of calcium scoring with an electron-beam CT volumetric method. *Radiology* 1998;**208**:807–14.
- 28 Rumberger JA, Kaufman L. A Rosetta stone for coronary calcium risk stratification: agatston, volume, and mass scores in 11,490 individuals. *Am J Roentgenol* 2003;**181**:743–8.
- 29 Raggi P, Coall B, Callister TQ. Use of electron beam tomography data to develop models for prediction of hard coronary events. *Am Heart J* 2001;**141**:375–82.
- 30 Bellasi A, Raggi P. Diagnostic and prognostic value of coronary artery calcium screening. *Curr Opin Cardiol* 2005;**20**:375–80.
- 31 Hoff JA, Chomka EV, Krainik AJ, et al. Age and gender distributions of coronary artery calcium detected by electron beam tomography in 35,246 adults. *Am J Cardiol* 2001;**87**:1335–9.
- 32 Schmermund A, Erbel R, Silber S, et al. Age and gender distribution of coronary artery calcium measured by four-slice computed tomography in 2,030 persons with no symptoms of coronary artery disease. *Am J Cardiol* 2002;**90**:168–73.
- 33 Detrano R, Hsiai T, Wang S, et al. Prognostic value of coronary calcification and angiographic stenoses in patients undergoing coronary angiography. *J Am Coll Cardiol* 1996;**27**:285–90.
- 34 Keelan PC, Bielak LF, Ashai K, et al. Long-term prognostic value of coronary calcification detected by electron-beam computed tomography in patients undergoing coronary angiography. *Circulation* 2001;**104**:412–17.
- 35 Georgiou D, Budoff MJ, Kaufer E, et al. Screening patients with chest pain in the emergency department using electron beam tomography: a follow-up study. *J Am Coll Cardiol* 2001;**38**:105–10.
- 36 Mohlenkamp S, Lehmann N, Schmermund A, et al. Prognostic value of extensive coronary calcium quantifies in symptomatic males—a 5-year follow-up study. *Eur Heart J* 2003;**24**:845–54.
- 37 Arad Y, Spadaro LA, Goodman K, et al. Predictive value of electron beam computed tomography of the coronary arteries. 19-month follow-up of 1173 asymptomatic subjects. *Circulation* 1996;**93**:1951–3.
- 38 Secci A, Wong N, Tang W, et al. Electron beam computed tomographic coronary calcium as a predictor of coronary events: comparison of two protocols. *Circulation* 1997;**96**:1122–9.
- 39 Detrano R, Wong ND, Doherty T, et al. Coronary calcium does not accurately predict near-term future coronary events in high-risk adults. *Circulation* 1999;**99**:2633–8.
- 40 Arad Y, Spadaro LA, Goodman K, et al. Prediction of coronary events with electron beam computed tomography. *J Am Coll Cardiol* 2000;**36**:1253–60.
- 41 Wong ND, Hsu JC, Detrano RC, et al. Coronary artery calcium evaluation by electron beam computed tomography and its relation to new cardiovascular events. *Am J Cardiol* 2000;**86**:495–8.
- 42 Kondos GT, Hoff JA, Sevrakov A, et al. Electron beam tomography coronary artery calcium and cardiac events. A 37-month follow-up of 5635 initially asymptomatic low-to intermediate-risk adults. *Circulation* 2003;**107**:2571–6.
- 43 Shaw LJ, Raggi P, Schisterman E, et al. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. *Radiology* 2003;**228**:826–33.
- 44 Greenland P, LaBree L, Azen SP, et al. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA* 2004;**291**:210–15.
- 45 Arad Y, Goodman KJ, Roth M, et al. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study. *J Am Coll Cardiol* 2005;**46**:158–65.
- 46 Lamonte MJ, Fitzgerald SJ, Church TS, et al. Coronary artery calcium score and coronary heart disease events in a large cohort of asymptomatic men and women. *Am J Epidemiol* 2005;**162**:421–9.
- 47 Raggi P, Shaw LJ, Berman DS, et al. Gender-based differences in the prognostic value of coronary calcification. *J Womens Health* 2004;**13**:273–83.
- 48 Vliegenthart R, Oudkerk M, Hofman A, et al. Coronary calcification improves cardiovascular risk prediction in the elderly. *Circulation* 2005;**112**:572–7.
- 49 Taylor AJ, Bindeman J, Feuerstein I, et al. Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors mean three-year outcomes in the Prospective Army Coronary Calcium (PACC) Project. *J Am Coll Cardiol* 2005;**46**:807–14.
- 50 Thompson GR, Partridge J. Coronary calcification score: the coronary-risk impact factor. *Lancet* 2004;**363**:557–60.
- 51 Hecht HS. Translating tomographic plaque imaging into treatment: interventional lipidology. *Prog Cardiovasc Dis* 2003;**46**:149–70.
- 52 Arad Y, Spadaro LA, Roth M, et al. Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C, and vitamin E: the St. Francis Heart Study randomized clinical trial. *J Am Coll Cardiol* 2005;**46**:166–72.
- 53 Grundy SM. The changing face of cardiovascular risk. *J Am Coll Cardiol*, 2005;**46**:173–5.
- 54 Pletcher MJ, Tice JA, Pignone M, et al. What does my patient's coronary artery calcium score mean? Combining information from the coronary artery calcium score with information from conventional risk factors to estimate coronary heart disease risk. *BMC Med* 2004;**2**:31.
- 55 Bild D, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol* 2002;**156**:871–81.
- 56 Schmermund A, Mohlenkamp S, Stang, et al. Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: rationale and design of the Heinz Nixdorf RECALL Study. Risk factors, evaluation of coronary calcium and lifestyle. *Am Heart J* 2002;**144**:212–18.
- 57 Leber AW, Knez A, Becker A, et al. Visualising noncalcified coronary plaques by CT. *Int J Cardiovasc Imaging* 2005;**21**:55–61.
- 58 Mollet NR, Cademartiri F, Nieman K, et al. Noninvasive assessment of coronary plaque burden using multislice computed tomography. *Am J Cardiol* 2005;**95**:1165–9.
- 59 Hecht HS. Practice guidelines for electron beam tomography: a report of the Society of Atherosclerosis Imaging. *Am J Cardiol* 2000;**86**:705–6, A709.

ANSWERS

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