

The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: systematic review

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The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: systematic review

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Abstract

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Objectives: To assess the clinical and cost-effectiveness of computed tomography (CT) screening for asymptomatic coronary artery disease; also to establish whether coronary artery calcification (CAC) predicts coronary events and adds anything to risk factor scores, and whether measuring CAC changes treatment.

Data sources: Main electronic databases were searched up to 2005, with a MEDLINE update in February 2006.

Methods: A systematic review of screening studies and economic evaluations was carried out. Studies were included in the review if screening for coronary heart disease was the principal theme of the study, and if data were provided that allowed comparison of CT screening with current practice, which was taken to be risk factor scoring. Mismatches between CAC scores and risk factor scoring were of particular interest. A review of the case for screening against the criteria used by the National Screening Committee (NSC) for assessing screening programmes was also undertaken.

Results: No randomised control trials (RCTs) were found that assessed the value of CT screening in reducing cardiac events. Seven studies were identified that assessed the association between CAC scores on CT and cardiac outcomes in asymptomatic people and included 30,599 people. Six used electron-beam CT. The relative risk of a cardiac event was 4.4 if CAC was present, compared to there being no CAC. As CAC score increased, so did the risk of cardiac events. The correlation between CAC and cardiac risk was consistent across studies. There was evidence that CAC scores varied among people with the same Framingham risk factor scores, and that within the same Framingham bands, people with higher CAC scores had significantly higher cardiac event rates. This

applied mainly when the CAC scores exceeded 300. There was little difference in event rates among the groups with no CAC, and scores of 1–100 and 101–300. In one study, CAC score was a better predictor of cardiac events than the Framingham risk scores. No studies were found that showed whether the addition of CAC scores to standard risk factor assessment would improve outcomes. There were reports from two observational studies that lowering of low-density lipoprotein cholesterol to about 3 mmol l⁻¹ or below with statin treatment modestly reduced CAC scores, but this was not confirmed in two RCTs. In three studies examining whether knowledge of CAC scores would affect compliance with lifestyle measures, perception of risk was affected, but it did not improve smoking cessation rates, although it did increase anxiety. There were a few economic studies of CT screening for heart disease, which provided useful data on costs of scans, other investigations and treatment, but relied on a number of assumptions, and were unable to provide definitive answers. One modelling study estimated that adding CT screening to risk factor scoring, and only giving statins to those with CAC score over 100, would save money, based on a cost per CT screen of US\$400 and statin costs of US\$1000 per annum per patient. However, the arrival of generic statins has reduced the price dramatically, and these savings no longer apply.

Conclusions: CT examination of the coronary arteries can detect calcification indicative of arterial disease in asymptomatic people, many of whom would be at low risk when assessed by traditional risk factors. The higher the CAC score, the higher the risk. Treatment with statins can reduce that risk. However, CT screening would miss many of the most dangerous

patches of arterial disease, because they are not yet calcified, and so there would be false-negative results: normal CT followed by a heart attack. There would also be false-positive results in that many calcified arteries will have normal blood flow and will not be affected by clinically apparent thrombosis: abnormal CT not followed by a heart attack. For CT screening to be cost-effective, it has to add value over risk factor scoring, by producing sufficient additional information to change treatment and hence cardiac outcomes, at an affordable cost per quality-adjusted life-year. There was

insufficient evidence to support this. Most of the NSC criteria were either not met or only partially met. It would be useful to have more data on the distributions of risk scores and CAC scores in asymptomatic people, and the level of concordance between risk factor and CAC scores, the risk of cardiac events per annum according to CAC score and risk factor scores, information on the acceptability of CT screening, after information about the radiation dose, and an RCT of adding CT screening to current risk factor-based practice.



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Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Coronary artery calcification (CAC) CAC positive means that calcium is present in the arteries; CAC negative means that it is not. (But beware of different definitions of positive.)

Cardiovascular disease Heart disease, stroke and peripheral vascular disease.

Echocardiography A form of ultrasound used to examine the heart.

Exercise testing on a treadmill A test for coronary heart disease, using ECG to show ischaemic changes on exercise.

General medical services Services provided by general practitioners in the UK; a term referring to the contract that the independent practitioners have.

Screening In epidemiological or public health usage, refers to applying a simple test to populations to distinguish those who probably have the disease or condition from those who probably do not. Those who screen positive are referred for a definite diagnosis by the gold-standard test. In imaging usage, screening is sometimes used to refer to radiological examinations.

Spiral computed tomography (CT) In spiral (sometimes called helical) CT, rather than taking one slice at a time as in standard CT, the X-ray tube rotates around the patient at the same time as the patient is moved through the scanner. This reduces the time taken to scan.

List of abbreviations

BFHS	British Family Heart Survey
CABG	coronary artery bypass grafting
CAC	coronary artery calcification
CAD	coronary artery disease
CHD	coronary heart disease
CI	confidence interval
CRD	Centre for Reviews and Dissemination
CT	computed tomography
CVD	cardiovascular disease
DARE	Database of Abstracts of Reviews of Effectiveness

EBCT	electron-beam computed tomography
ECG	electrocardiogram
ETT	exercise tolerance testing
FRI	Framingham Risk Index
FRS	Framingham risk score
GMS	general medical services
LDL	low-density lipoprotein
MI	myocardial infarction
MSCT	multislice computed tomography

continued

List of abbreviations *continued*

NCEP	National Cholesterol Education Program	QALY	quality-adjusted life-year
NHS EED	National Health Service Economic Evaluations Database	RCT	randomised controlled trial
NICE	National Institute for Health and Clinical Excellence	ROC	receiver operating characteristic
NSC	National Screening Committee	RR	relative risk
PTCA	percutaneous transluminal coronary angioplasty	SD	standard deviation
		SPECT	single-photon emission computed tomography
		UFCT	ultrafast computed tomography

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.



Executive summary

Background

Coronary heart disease (CHD) is one of the main causes of mortality and morbidity in the UK and other Western countries. The disease can be asymptomatic until the first event, which may be a fatal myocardial infarction (heart attack). Half of all heart attacks occur in people who have had no prior warning of coronary disease, and almost half will die from the first attack.

Risk scores based on well-known factors such as age, blood pressure, smoking, cholesterol and diabetes have been used to assess risk, but are imperfect: not all high-risk people develop heart disease, and many low-risk people do. Indeed, depending on which cut-off is used to define high risk, most heart attacks occur in low-risk people, because the number of people at low risk is much greater than the number at high risk. There is therefore a need for a better way of identifying those at risk so that they can treat themselves with lifestyle measures, or receive drug therapy such as statins and antihypertensive drugs as appropriate.

Computed tomography (CT) is a form of radiological imaging that can detect calcium deposits in the coronary arteries. This calcification is a marker for CHD, and so CT imaging could be a way of detecting asymptomatic but serious CHD. CT is quick and non-invasive, but does involve a relatively large radiation dose.

Objectives

The aim of the review was to assess the clinical and cost-effectiveness of CT screening for asymptomatic coronary artery disease (CAD). The first question was whether such screening would be worthwhile. If so, subsidiary questions included how to target screening, and which CT method should be used. Other questions included:

- Does coronary artery calcification (CAC) predict coronary events?
- Does CAC add anything to risk factor scores?
- Does measuring CAC change treatment?

Methods

A systematic review of screening studies and economic evaluations was carried out, along with a review of the case for screening against the criteria used by the National Screening Committee (NSC) for assessing screening programmes.

Search strategy and inclusion criteria

Searches were carried out for a broad range of evidence using a sensitive search strategy, using the bibliographic databases MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane CENTRAL Register of Clinical Trials, NHS EED, the HTA database, Science Citation Index, BIOSIS, Web of Science Proceedings and the National Research Register. There was no language restriction.

Preliminary searches showed that there had been no randomised controlled trials (RCTs) to evaluate screening for CAD using CT, and so no limitation on type of study was applied. Systematic reviews were sought for the period 1994–2005, and assessed for quality. Primary studies were sought only for the years subsequent to the dates of searches in the recent reviews. It was decided that information from observational studies such as case series or cohort studies may provide evidence of effectiveness and costs. Ideally, studies would include an intervention to reduce risk. The bibliographies of included studies were searched, but authors were not contacted for further information. Studies were included if screening for CHD was the principal theme of the study, and if data were provided that allowed comparison of CT screening with current practice, which was taken to be risk factor scoring. The study was particularly interested in whether there were mismatches between CAC scores and risk factor scoring, for example if some people with low risk factor scores had high CAC scores, and vice versa, since this might imply that CT detection of CAC provided added value to risk scoring alone.

Results

No RCTs were found that assessed the value of CT screening in reducing cardiac events. Seven studies

were identified that assessed the association between CAC scores on CT and cardiac outcomes in asymptomatic people and included 30,599 people. Six used electron-beam CT. The relative risk of a cardiac event was 4.4 if CAC was present, compared to there being no CAC. As CAC score increased, so did the risk of cardiac events. The correlation between CAC and cardiac risk was consistent across studies.

There was evidence that CAC scores varied among people with the same Framingham risk factor scores, and that within the same Framingham bands, people with higher CAC scores had significantly higher cardiac event rates. This applied mainly when the CAC scores exceeded 300. There was little difference in event rates among the groups with no CAC, and scores of 1–100 and 101–300. In one study, CAC score was a better predictor of cardiac events than the Framingham risk scores.

No studies were found that showed whether the addition of CAC scores to standard risk factor assessment would improve outcomes. There were reports from two observational studies that lowering of low-density lipoprotein cholesterol to about 3 mmol l⁻¹ or below with statin treatment modestly reduced CAC scores, but this was not confirmed in two RCTs. Three studies examined whether knowledge of CAC scores would affect compliance with lifestyle measures. The knowledge affected perception of risk, but did not improve smoking cessation rates. It did increase anxiety.

Summary of cost-effectiveness

There were few economic studies of CT screening for heart disease. These provided useful data on costs of scans, other investigations and treatment, but had to rely on a number of assumptions, and were unable to provide definitive answers. One modelling study estimated that adding CT screening to risk factor scoring, and only giving statins to those with a CAC score over 100, would save money, based on a cost per CT screen of US\$400 and statin costs of US\$1000 per annum per patient. However, the arrival of generic statins has reduced the price dramatically, and these savings no longer apply.

Conclusions

CT examination of the coronary arteries can detect calcification indicative of arterial disease in asymptomatic people, many of whom would be at low risk when assessed by traditional risk factors. The higher the CAC score, the higher the risk. Treatment with statins can reduce that risk. However, CT screening would miss many of the most dangerous patches of arterial disease, because they are not yet calcified, and so there would be false-negative results: normal CT followed by a heart attack. There would also be false-positive results in that many calcified arteries will have normal blood flow and will not be affected by clinically apparent thrombosis: abnormal CT not followed by a heart attack.

For CT screening to be cost-effective, it has to add value over risk factor scoring, by producing sufficient extra information to change treatment and hence cardiac outcomes, at an affordable cost per quality-adjusted life-year. There was insufficient evidence to support this. Most of the NSC criteria were either not met or only partially met.

Recommendations for future research

It remains unclear whether CT screening would provide sufficient extra information over risk factor scoring for it to be worthwhile.

- More data are needed, including from the UK, on the distributions of risk scores and CAC scores in asymptomatic people, and the level of concordance between risk factor and CAC scores.
- The risk of cardiac events per annum according to CAC score and risk factor scores should be assessed
- Information on the acceptability of CT screening, after information about the radiation dose, would be useful.
- An RCT could be conducted on adding CT screening to current risk factor-based practice.

Chapter I

Aim of the review

This review was commissioned by the UK HTA Programme on behalf of the National Screening Committee (NSC). The aim of the review was to examine the clinical effectiveness and cost-effectiveness of screening for heart disease using computed tomography (CT), taking into account the effect on mortality, detection of early disease and the impact on quality of life. One stimulus for the review was publicity about the use of whole-body CT screening, which is not currently provided by the NHS, but may be on offer in the private sector. This review did not consider the effectiveness of screening for conditions other than coronary heart disease (CHD). A separate review has considered the case for screening for lung cancer.

A previous review for the HTA Programme, covering evidence on spiral CT and electron-beam computed tomography (EBCT) published up to October 1997, included only two studies of its use in asymptomatic coronary artery disease (CAD) (compared with 15 in symptomatic disease).¹

The review is concerned with screening in people with no symptoms of heart disease at all, and not with those who have known coronary disease. The term 'screening' is used in the epidemiological sense, of a simple test used to distinguish those who probably have the disease (on definitive testing) from those who probably do not, rather than in any imaging sense.

Chapter 2

Background

Introduction

Coronary heart disease

CHD is one of three common manifestations of cardiovascular disease (CVD), along with cerebrovascular disease (transient ischaemic attacks and stroke) and peripheral vascular disease. CHD is the leading cause of death in the UK, accounting for more than one in five deaths in men and one in six deaths in women. It caused 117,000 deaths in the UK in 2002.

CHD is responsible for a substantial proportion of premature deaths (under 75 years); 22% of premature deaths in men and 13% of premature deaths in women, in 2002. It is also estimated to be the leading cause of disability in Europe. The cost of CHD to the UK economy was estimated to be approximately £5300 million in 1999.²

Several studies have considered the impact of CHD on quality of life. All demonstrate consistently that CHD has a negative impact on a wide variety of aspects of a person's life, including physical activity, sleep, fatigue, anxiety and work. (For a fuller review see the HTA monograph on the use of statins for the prevention of coronary events by Ward and colleagues.³)

Despite age-adjusted death rates from CHD falling over the past 30 years, CHD deaths in the UK remain high compared with European neighbours and the rate of decline is slower in the UK. There is geographical variation in the UK, with a general north-south trend, the highest rates being seen in the north.² Variations in CHD death rates are also found in association with socio-economic status and race. Age is one of the most important predictors of CHD. The prevalence of treated CHD has been estimated to be around 4.7% of men and 3.2% of women, but this ranges from 0.01% in those aged less than 35 years to more than 16% in those over 65 years.² With an ageing population, the number of deaths from CHD may increase.

CHD has been recognised as a leading public health priority across the UK.

CHD: the importance of asymptomatic disease

For people with symptoms of CHD, further investigation to assess cause, severity and risk factors is part of routine clinical practice in the UK. The most common presenting symptom for CHD is angina but, for many, the first manifestation is myocardial infarction (MI) or sudden death. From the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) project, data from Glasgow report that among approximately 4000 people with an MI, 51% had no history of CHD before presenting with their MI, and about half died from their first event.⁴ Similar data have been presented from the Framingham study.⁵

Because such a high proportion experience their first symptoms in the form of an MI or death, there is a strong case for primary prevention or early detection strategies to be considered.

In the absence of warning symptoms, ways to identify people at risk of CHD before an event have been sought for many years. Risk factors for CHD include older age, male gender, smoking, hypertension, abnormal lipid profiles, diabetes, obesity and sedentary lifestyle, and these have been used to develop risk scoring systems such as the Sheffield system.⁶

Natural history of coronary artery calcification

All of the risk factors above, with the exception of age, are considered to be causal in, or contributory to, the development of atheromatous plaques, the pathological abnormality underlying CHD. Individual variability in plaque development is thought to be a combination of genetic susceptibility and combination/duration effects of the risk factors.⁷

A variety of presymptomatic markers for early disease has been considered. Although coronary angiography can detect atheromatous disease in asymptomatic individuals, the risks and costs associated with such invasive investigations makes them unsuitable as potential screening tools.⁸

Electrocardiography, exercise tolerance testing (ETT), exercise echocardiography (ECHO), exercise single-photon emission computed tomography (SPECT), EBCT and multidetector helical CT have all been used to detect abnormalities that might correlate with early CHD. All have been shown to correlate with the presence of CHD, but with variable sensitivity and specificity. A systematic review by the US Preventive Services Task Force of the most studied methods of screening [electrocardiogram (ECG), ETT and EBCT] was published in December 2003.⁹ Their findings in relation to ECG and ETT are discussed briefly here. Findings in relation to EBCT are discussed later.

The US task force review found that many observational studies had examined the role of resting ECG and of ETT in predicting the risk of future CHD events. For resting ECG, abnormal test results (a variety of ECG changes have been studied) were associated with an increased risk of future CHD event. The increase in risk depended on type of abnormality and race. However, the high false-positive rate causes substantial problems in terms of follow-up investigation and ECG was a relatively insensitive test for CHD, so there were many false negatives as well.⁹ Patients with a normal ECG may suffer a heart attack shortly afterwards.

Cohort studies evaluating the predictive value of ETT in asymptomatic populations found that 5–25% of people had abnormal test results with depression of the ST segment on the ECG, and that abnormal results were associated with cardiac events in the future. Again, sensitivity was relatively low (10–62% depending on the length of study) and the positive predictive value ranged from 6 to 48%. In addition, in a UK study, approximately 0.5% of the male population went on to receive urgent triple vessel bypass surgery after screening with ETT. However, to achieve this detection rate, all people with positive ETT had to undergo cardiac catheterisation. Given that most asymptomatic people with abnormal ETT will not go on to have cardiac events within the follow-up time of most of the cohort studies (3–8 years), the risks of cardiac catheterisation were not insubstantial for this low-risk group.⁹

At the time of the review, the US task force authors identified no literature about the effect of screening on health outcomes. They noted one subgroup analysis of the Multiple Risk Factor Intervention Trial that reported that asymptomatic people with abnormal treadmill tests who received

risk factor modification advice had a lower risk of CHD mortality than those who received usual care.⁹

Calcification of plaques

In the natural history of CHD, atherosclerotic plaques develop within the coronary arteries. It has therefore seemed attractive to detect asymptomatic people at risk of future cardiac events by imaging these plaques in the coronary arteries. Coronary artery angiography has been the gold standard for detecting narrowing of arteries, and for a long time, the only method that enabled assessment of coronary artery plaques. However, atherosclerotic plaques in coronary arteries continually accumulate calcium in an age-related manner in pre-existing lesions.¹⁰ With advances in non-invasive imaging techniques, it is possible to measure coronary artery calcification (CAC) using CT. Pathological studies at autopsy have shown a strong correlation between the amount of calcium deposited and the severity and extent of the CHD.¹¹ Similarly, correlations have been demonstrated between the amount of CAC visualised by CT and the extent of atherosclerosis on coronary angiography. However, not all plaques are calcified and the most vulnerable plaques, in terms of risk of rupture leading to thrombosis and occlusion, are lipid laden and non-calcified. It also appears that vulnerable plaques can occur in isolation and in the absence of CAC elsewhere in the vascular tree.^{7,10,11} Coronary angiography encounters the same limitations as vulnerable plaques may not result in any significant luminal narrowing, and hence is not a perfect gold standard. CAC is therefore seen as much as a marker of a person's burden of atheroma, as a marker of specific lesions. There is some evidence that coronary atherosclerosis is reversible and studies of statins in CHD have shown that, in some individuals, atheroma (as visualised by angiography) can regress with treatment.^{12–16} How this regression relates to survival is not well reported.^{7,10,11}

Current service provision

There is no screening service for CHD using CT in the UK, but some private healthcare providers may offer it.

In an attempt to identify people at the highest risk of developing CHD, the various risk factors noted above have been combined in a variety of scoring systems. These are in wide clinical use in the UK as risk calculators used to predict the likelihood of

a future cardiac event in people who are currently symptom free, and are usually used for making decisions about whether to start statin therapy.^{3,9}

In the past it has been the consensus that only those with an absolute risk per annum of 3% or more for heart attacks should be treated, but the evidence from intervention trials, along with the marked drop in the cost of statins following the arrival of generic forms, has supported a trend towards lowering the threshold.^{3,9,17}

The risk factor assessment of greater than 30% absolute risk of CHD in the next 10 years triggers interventions to modify risk factors: blood pressure, lipids, smoking and lifestyle, if current UK guidelines are followed. It is estimated that 3% of men (aged 30–74 years) and 0.3% of women fall into this risk band (*Table 1*).

In 2006, National Institute for Health and Clinical Excellence (NICE) guidance lowered the recommended threshold to a risk of 2% per annum for CVD (10-year risk of CVD event of 20%).¹⁸ Once over 50 years of age, other risk factors play a lesser role in predicting risk, and identification of low-risk individuals is particularly difficult using current risk calculators.

As mentioned, NICE, the British Hypertension Society and the Joint British Societies have recently recommended a shift from CHD to all CVD risk estimation as this better reflects clinical practice and the pathology of the conditions.

So, there are two groups in whom screening may be beneficial: people in whom disease is already present but is asymptomatic, and people who are at a higher risk of developing CHD in the future. CT screening for CAC is detecting those in the

first group, who already have evidence of pathological change. Risk factor scores identify those at high risk of developing disease. The two groups will overlap, and management may be similar, except that marked CAC may trigger referral to cardiological assessment (angiography with a view to revascularisation), in addition to other treatments such as statins.

Imaging technology for CHD screening

Continuous cardiac movement has always made imaging the heart technically challenging. Currently, there are two non-invasive methods for the visualisation and quantification of coronary artery calcification: EBCT and multislice computed tomography (MSCT). Successful imaging of the coronary arteries requires sufficient acquisition speeds to suppress cardiac motion artefact and high spatial resolution. The early work in non-invasive cardiac imaging used EBCT, as images from conventional CT at that time were limited by motion artefact.

In EBCT, an electron beam is directed towards four tungsten targets to generate X-rays that pass through the patient to detectors. Unlike conventional CT, mechanical motion in the gantry is eliminated and short exposure times of 50–100 ms are possible. Image acquisition can be synchronised with the patient's ECG and triggered during diastole, a period of relative cardiac standstill. In the UK, the availability of EBCT is limited and the greater cost of these scanners would be a significant factor in considering their use in a screening programme.

In 1998 MSCT systems were introduced and the combination of fast rotation time and multidetector row acquisition became of particular importance for cardiac applications. Coronary arteries are complex, small structures. The average diameter of the left main coronary artery is 4 mm and to image these structures properly, in-plane and through-plane spatial resolutions of 1 mm are necessary. Through-plane (z) resolution of 0.6 mm is now possible with 16-slice CT systems, and this has improved the visualisation of calcification along the course of the coronary artery tree. These systems have also improved acquisition speeds by nearly 40-fold compared with those of single-slice CT. Newer systems using 64-slice CT coupled with intravenous contrast media may be able to detect non-calcified plaques, but are not relevant to any population screening programme.

TABLE 1 Percentages of men and women in England and Scotland at different levels of risk of CHD events in next 10 years

Absolute risk of CHD (%)	England		Scotland	
	Men	Women	Men	Women
≥30	3	–	2	0.3
25–29	5	2	3	1
20–24	8	2	6	1
15–19	12	5	10	4

Adapted from Joint British recommendations on prevention of CHD in clinical practice.¹⁷

As with EBCT, motion artefact is reduced by prospective ECG triggering or retrospective ECG gating. However, the prospectively ECG-triggered technique depends on a regular heart rate, and misregistration can occur in the presence of a cardiac arrhythmia. The ability to perform retrospective ECG overcomes the limitations of prospective ECG triggering in patients with cardiac arrhythmia.

In retrospective ECG gating, raw data are acquired in the conventional spiral acquisition mode, using a constant table-feed speed while simultaneously recording the ECG. The table-feed speed is slower than in routine spiral CT to allow for an over-sampling of image data. On the basis of the recorded ECG, only the data acquired during diastole are used for image reconstruction. To improve temporal resolution further, special postprocessing reconstruction algorithms are used, and the fan beam angle is reduced to a minimum to reduce the exposure time to about 250 ms. In the presence of arrhythmia, the reconstruction interval for each individual image stack can be shifted arbitrarily within the cardiac cycle, so that reconstruction always coincides with the same interval during diastole at each level of the cardiac volume.

An unenhanced MSCT technique has been described by many groups for the sensitive detection and quantification of CAC, which has been shown to correlate accurately with the presence of coronary atherosclerosis.¹⁹ A tube voltage of 120 kV is routinely applied and for most MSCT, a 100-mA tube current is used to achieve sufficient signal-to-noise levels to detect even small calcified lesions. CAC has been defined as a high-attenuation lesion above the threshold of 130 Hounsfield units (the linear attenuation coefficient) in an area of at least 1 mm².

Quantification of the amount of calcified tissue in the coronary arterial tree has traditionally been based on a semi-quantitative score described by Agatston and colleagues.²⁰ However, more recent quantitative measures (Ca²⁺ volume, Ca²⁺ mass) have resulted in better results for repeatability and inter- and intra-observer variability. The greatest potential to increase accuracy, consistency and reproducibility lies in advanced software platforms that allow assessment of equivalent volume and total calcified plaque burden in terms of absolute calcium mass, based on actual scanner-specific calibration.

Until definitive results on the usefulness of coronary calcium scoring from cohort trials are

available, the current role of CT coronary artery calcium measurements was summarised as follows, in the American College of Cardiology and American Heart Association expert consensus:⁷

- “(a) A negative CT test makes the presence of atherosclerotic plaque, including unstable plaque, very unlikely.
- (b) A negative test is highly unlikely in the presence of significant luminal obstructive disease.
- (c) Negative tests occur in the majority of patients who have angiographically normal coronary arteries.
- (d) A negative test may be consistent with a low risk of a cardiovascular event in the next 2–5 years.
- (e) A positive CT confirms the presence of a coronary atherosclerotic plaque.
- (f) The greater the amount of calcium, the greater the likelihood of occlusive CAD, but there is not a 1-to-1 relationship, and findings may not be site specific.
- (g) The total amount of calcium correlates best with the total amount of atherosclerotic plaque, although the true ‘plaque burden’ is underestimated.
- (h) A high calcium score may be consistent with moderate to high risk of a cardiovascular event within the next 2–5 years.”

The first statement could be challenged on the grounds that a negative CT result does not exclude the presence of vulnerable plaques; it depends on how one defines ‘very unlikely.’”

A screening programme using MSCT technique would be relatively simple and convenient for the patient, who needs only to lie in the CT scanner for approximately 10 minutes. No special preparation is required before the test, and there is no restriction on the types of medication taken before or during the test. The patient is asked to hold his or her breath for 10–30 seconds, depending on heart rate and the CT scanner type. The total door-to-door time is approximately 15 minutes.

Radiation dose

The quoted radiation dose during cardiac CT varies considerably in the literature, as a result of variations in imaging parameters and the lack of standardised protocols. It has been estimated that the lifetime risk of developing cancer attributable to all diagnostic X-rays is 0.6–1.8%.²¹ In the UK this equates to up to 700 cancers per year. It is imperative to obtain a radiological diagnosis with the lowest radiation dose that is reasonably achievable [the ‘as low as reasonably achievable’ (ALARA) principle].²² Compared with chest X-ray, CT results in exposure to higher radiation doses.

In a screening programme the balance between image quality and radiation dose is particularly important. An effective radiation dose of approximately 1 mSv has been suggested for a prospectively ECG-triggered four-slice CT using a tube voltage of 120 kV, which compares favourably with a catheter-based coronary angiogram at 4–5 mSv (chest X-ray is approximately 0.1 mSv; mammogram 0.4 mSv).

However, retrospective ECG-gated imaging is associated with a higher radiation exposure owing to continuous X-ray exposure and overlapping of data acquisition. New techniques are being developed to reduce the amount of redundant radiation that does not contribute to image generation.

Screening programme requirements

Further investigation of those who screen positive

If CT screening for heart disease was added to the assessment of risk of CHD by standard risk factor scoring, then there could be two approaches.

- The presence of CAC would be taken simply as a marker of significant arterial disease and treatment started without further investigation.
- The presence of CAC, or perhaps of more severe levels of it, might be taken as an indication for further investigations, which might be angiography with a view to revascularisation, or possibly less invasive tests such as exercise ECG. However, it is likely that screening for CAC would lead to an increase in the numbers referred for invasive angiography.

Interventions for those screened positive

Primary preventive interventions for CHD focus on modifying risk factors by lifestyle modification (diet, exercise, smoking cessation). However, there is good evidence for the use of medications to modify some of the risk factors, in particular statins for lowering lipids.

Hyperlipidaemia

Lifestyle change

Lifestyle change has been demonstrated to be effective in reducing cholesterol under the strict conditions of an RCT. The difficulty has been to sustain change in the general population. A review by Tang and colleagues²³ showed that in free-living populations, dietary adherence was poor and total cholesterol was lowered by only a few

per cent. An HTA monograph²⁴ reviewing the role of statins noted that dietary change could sustain cholesterol reductions of 0.05–0.3 mmol l⁻¹. The authors estimated that this reflects a reduction in mortality of 200–6000 deaths, but recognised that the gains may only be for those who are motivated and achieve significant cholesterol change.

Drug treatment

Trials of primary prevention support the effectiveness of therapies to reduce lipids, with no evidence of a lower threshold below which no additional benefit is gained. The difference is that the absolute risk of a cardiac event is low in those with lower lipid levels.^{3,9,17} Substantially more people fall into the lower risk categories and cost-effectiveness and safety then become issues.

Current UK guidance from NICE on the use of statins¹⁸ is to target those with greater than 20% absolute 10-year CVD risk with treatment and lifestyle advice to modify risk factors, a recent change that has been reflected in the guidelines for treatment issued by a variety of UK organisations.

Hypertension

Blood pressure reduction in hypertension reduces cardiovascular and all-cause mortality in the primary preventive setting. The important role of hypertension in cardiovascular disease mortality has recently been summarised in “Easing the pressure: tackling hypertension”, produced jointly by the Faculty of Public Health and the National Heart Forum.²⁵

Lifestyle change

A review by NICE for its hypertension guideline (2004) supported the role for lifestyle interventions in the reduction of blood pressure, recommending lifestyle advice as an initial step in the care of people with hypertension²⁶ (Table 2).

Drug treatment

In the UK, guidelines from both NICE and the UK Hypertension Society support two categories of hypertensive patient who should be treated with drug therapy:

- those with blood pressure 160/100 mmHg or higher
- those with blood pressure 140/90 mmHg or higher and who have a raised cardiovascular risk (10-year risk of CVD event of 20% or more).

The target of therapy is to reduce blood pressure to below 140/90 mmHg, increasing or adding treatments as necessary.

TABLE 2 Effects of lifestyle interventions in hypertension (aggregated trial results)²⁶

Lifestyle intervention	Average reduction in systolic and diastolic blood pressure (mmHg)	Percentage who achieve a reduction in systolic blood pressure of 10 mmHg or more
Healthy, weight-reducing diet	5–6	40
Regular aerobic exercise	2–3	30
Combined diet and exercise	4–5	25
Relaxation techniques	3–4	33
Alcohol within recommended limits	3–4	30
Salt reduction	2–3	25

Source: Management of hypertension in adult in primary care (NICE guideline), (2004).²⁶

Other drug interventions

Even among hypertensive patients, the benefits of aspirin did not outweigh the harms from haemorrhage, and showed no evidence of reduction in all-cause or cardiovascular mortality. Evidence for warfarin or clopidogrel is even less robust in the setting of primary prevention.²⁷

General lifestyle modification

The Cochrane Collaboration has published a series of reviews examining the evidence for primary preventive actions in CHD.^{28–32} Interventions to increase physical activity show some moderate success in sustaining activity and modifying risk factors, although no review has been conducted to assess the impact on cardiovascular outcomes. A review of the recently popular diet trend of ‘low glycaemic index’ diets showed only weak evidence of impact on risk factors for CHD including cholesterol. Most of the trials were short term and none considered long-term cardiovascular end-points. Dietary advice to reduce or modify fat and cholesterol intake, in studies of over 24 months, does support a small but potentially important reduction in cardiovascular events.³⁰ This supports the role of lifestyle advice in groups where pharmacological intervention is not recommended or economically viable. A review of the role of omega 3 fats in preventing CHD did not find any evidence to support a cardioprotective effect.³¹

Multiple risk factor modification strategies

A Cochrane review in 2005²⁸ examined the role of multiple risk factor modification in primary prevention of CHD and found 18 trials of greater than 6 months’ duration. Various educational and counselling interventions were included, and in some studies these were used in combination with pharmacological interventions. Changes in blood

pressure, cholesterol and smoking were observed in the groups receiving multiple risk factor modification interventions. However, total and cardiac mortality were not reduced. In hypertensive patients, there was some evidence of an impact on mortality.²⁸

Current uptake of interventions for primary prevention

The level of uptake of guidelines and the degree to which treatment of the appropriate clinical groups is achieved in current practice have been poorly studied. There is little evidence about uptake of risk factor modification in clinical practice. Even the uptake and use of drug treatments are not well documented in the literature. There is some evidence that even in the highest risk groups (with known CHD, hypertension, diabetes) UK clinicians are not treating all those in whom the guidance would support statin therapy.^{3,33–35} Despite the evidence for active secondary prevention in people with known CHD, a study by the Cardiac Society in 1996 [Action on Secondary Prevention through Intervention to Reduce Events (ASPIRE)] found that GP recording of risk factors was poor even in this high-risk group.³⁶

Treatment of hypertension is known to suffer from three challenges:

- recognition of those with the condition [now subject to incentives as part of the new general medical services (GMS) contract]
- adequate treatment of those who are recognised (around 10% of people with hypertension in the UK estimated to have attained a treated blood pressure of less than 140/90 mmHg)
- adherence to treatment among those who are treated (an estimated 50–80% of those prescribed treatment for hypertension do not take all of their medication).²⁵

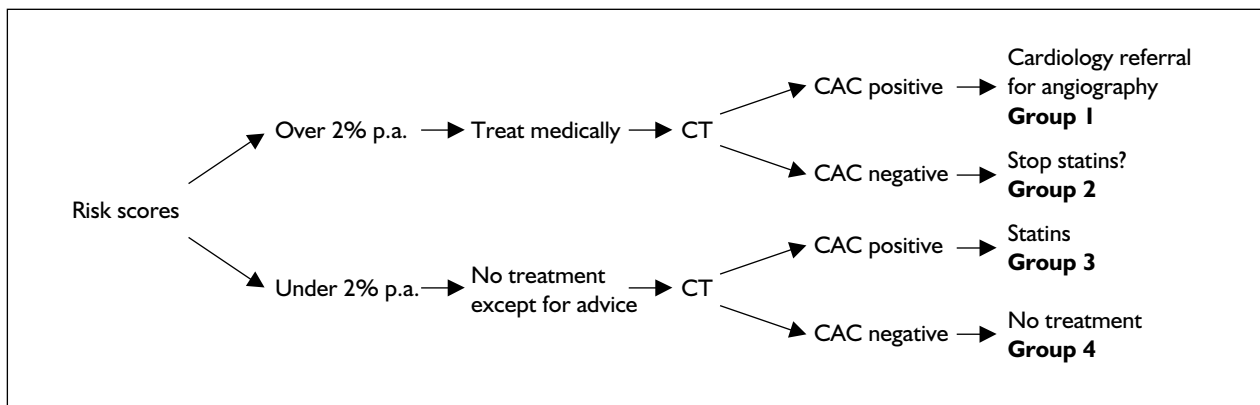


FIGURE 1 Flow diagram of the potential role of CT screening for heart disease

There do not appear to have been any studies in the published literature about the implementation of risk factor modifications in people who are at increased risk of CHD (i.e. over 20 or 30% 10-year risk).³

Conclusion

In theory, CT screening for CAC could be used in different ways. It could be additional to risk factor scoring, with the aims being:

- to identify those with high scores who require further cardiological investigation
- to identify those with high risk scores who have no CAC and who might therefore not be treated. However, some patients with no CAC have high-risk, low-attenuation plaques and so a negative CAC score would probably not be grounds for not treating those with high risk scores. A normal CT scan can be followed by a heart attack
- to identify those with low risk scores but who might have CAC; but in that case, there would be no point in risk scoring.

A possible flowchart is illustrated in *Figure 1*.

- In group 1, who are at higher risk and are CAC positive, there may be a case for angiography to identify patients with prognostically significant disease, such as proximal (e.g. left main stem)

stenosis, whereby coronary artery bypass grafting (CABG) would be recommended even in asymptomatic patients as it improves life expectancy. There is no good evidence that percutaneous transluminal coronary angioplasty (PTCA) has prognostic benefits in stable CHD. Rather than going directly to angiography, there may be a role for exercise testing or similar non-invasive investigation; patients who do very well on ETT are unlikely to have significant proximal coronary narrowing. However, such approaches have little in the way of an evidence base.

- In group 2, there may be a reluctance to stop statins without evidence that it is safe to do so in a group that is CAC negative but currently regarded as high risk; especially as early vulnerable plaques can be especially dangerous.
- In group 3, it would seem reasonable to prescribe statins, on the grounds that CAC is an indicator of arterial disease, and that there seems to be no lower threshold below which statins are not of benefit; but other factors may be causing the atherosclerosis, and would need to be addressed.
- Group 4 would not be treated.

So, screening may affect group 1, perhaps adversely through invasive investigations, perhaps beneficially through correction of critical stenoses by angioplasty or CABG; would probably not affect group 2; may benefit group 3; and would have no effect on group 4.

Chapter 3

Evidence of clinical effectiveness

Methods of the literature review

Literature search

Preliminary searches showed that no randomised controlled trials (RCTs) had been conducted to evaluate screening for CHD using CT. The search was therefore not restricted by study design. All primary studies evaluating CT screening for CHD were sought. To be included, the study had to include an intervention to modify risk in those who were found to have CHD.

Systematic reviews were also sought and assessed for quality. The conclusions of the systematic reviews are reported under a separate section in this chapter. A sensitive search strategy (described in full in Appendix 1), including the keywords for CHD, CT examination and mass screening, was constructed to search MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane CENTRAL Register of Controlled Clinical Trials, NHS EED, HTA database, DARE, Bandolier, Health Management Information Consortium, Research Findings Register, National Horizon Scanning Centre, Science Citation Index, Web of Science Proceedings and National Research Register. The register of projects held by the International Network of Agencies for Health Technology Assessment (INAHTA) was also checked. For completeness, the search strategy was not restricted by language; where non-English-language reports were identified, they were noted but translations were not sought. The searches were from 1994 to 2005 (unless otherwise stated in Appendix 1). A MEDLINE update was undertaken in February 2006. The bibliographies of included studies were also searched, but authors of included studies were not contacted for further information.

Selection of papers

The sensitive search identified a large number of potential titles. Each title and abstract was reviewed by one of the authors (CB) to assess the relevance to this review. Two categories of titles were included for data extraction:

- for inclusion in the clinical effectiveness review
- for inclusion in the cost-effectiveness review.

The inclusion and exclusion criteria were as follows:

- screening for CHD was the principal theme of the paper
- primary research (RCT, cohort or case-control, economic analysis) or systematic review
- CT screening compared with current practice, which was taken to be risk factor scoring.

Studies evaluating the use of methods for screening for CHD other than CT were not included, nor were studies that evaluated the use of CT for other conditions, including other cardiac conditions (e.g. whole-body screening).

Relevant papers were retrieved and reviewed by two members of the review team, independently. Data extraction included details of the screening protocol, follow-up, diagnosis and participants. Information was sought about test characteristics including sensitivity and specificity. The checklists and methods described in Centre for Reviews and Dissemination (CRD) Report 4 were used for the quality assessment of studies.³⁷ Papers meeting the criteria for the review of cost-effectiveness studies are dealt with separately in Chapter 5.

Summary of included studies

This review was looking for evidence that, when used as part of a screening programme, CT had an impact on CHD outcomes.

Therefore, a sensitive search strategy was used to look initially for systematic reviews from 1994 to 2005. The most recent good-quality reviews had search strategies that covered up until 2003, and therefore the search for primary research was restricted to the period from January 2004 to June 2005.

Two reviewers (CB, LB) examined the list of titles and abstracts to identify studies that would fit the criteria for inclusion. The reviewers were in agreement (kappa score 1.0) that there were no studies that met the inclusion criteria. This was consistent with the findings of the systematic

TABLE 3 Included studies

Study	Number of participants	Method of recruitment
Kondos, 2003 ⁴³	5,635 (8,855 had CT, but not all had full clinical details)	Self-referral
Shaw, 2003 ⁴⁴	10,377	Referral by primary care physician because of risk factors
Arad, 2000 ³⁹	1,177	Self-referral or referred by physician in response to adverts
Greenland, 2004 ⁴¹	1,461	Recruited by advertising then selected because have more than one risk factor
Wong, 2000 ⁴⁶	926	Self-referral or referred by physician
Itani, 2004 ⁴²	6,120	Opportunistic use of CT imaging conducted for lung cancer screening
Arad, 2005 ⁴⁰	4,903	Population volunteers

reviews identified for inclusion, where no relevant studies were identified for the period before 2004.

There seem to be no trials examining reduction of CHD risk in people identified to be at high risk by CT screening. Therefore, the following questions were addressed to examine the current evidence base for CT screening for heart disease.

- Does CAC predict coronary outcomes?
- Does CAC add anything to risk factor scores?
- Does measuring CAC change the treatment?

Results of additional searching

Predicting coronary outcomes

EBCT has been shown to be a sensitive test for detecting coronary calcium, with reported sensitivity of around 80% compared with coronary angiography.⁹ In symptomatic patients, O'Rourke and colleagues⁷ found sensitivities of 68–100% and specificities of 21–100% with pooled data of 91% sensitivity and 49% specificity for EBCT (if one assumes that the gold standard is coronary angiography). This setting is more straightforward because coronary angiography can be legitimately performed as the standard investigation as there is a clinical indication.

The systematic literature review outlined above, and bibliographic searching of relevant published reviews, identified seven studies that assessed the association between CAC scores on CT and cardiac outcomes in asymptomatic people (Appendix 2).^{38–46} One study was excluded⁴⁵ because it was limited to the diagnosis of cardiac disease in people with atypical chest pain. A further study was not available to the review team and has only been published in abstract form.³⁸

Of the seven studies included in this review, two principal routes of recruitment were used (*Table 3*). Three^{39,43,46} used adverts to obtain self-referrals of participants with no restriction as to risk factor profiles. Greenland and colleagues also sought self-referrals, but excluded those with a risk score lower than 10% over 8 years based on Framingham scores.⁴¹ One study⁴⁴ restricted the study population to those referred by their physician and with a risk score lower than 10% over 8 years or “above average risk of CHD”. One study used CT images obtained for lung cancer screening to assess CAC scores.⁴² The last study recruited volunteers without symptoms from a general population.⁴⁰

A total of 30,599 people participated in the included studies. *Table 4* summarises their characteristics and risk factors for CHD. All except for one study⁴² used EBCT imagers. The study by Itani and colleagues used images from a mobile helical CT imager that had been obtained originally for the purpose of screening for lung cancer.⁴²

Reporting of CAC

Six studies reported sufficient information to be able to compare outcomes for those with any CAC versus those with no CAC.^{39–43,46} In the other study,⁴⁴ the lowest CAC score group comprised those with a score below 10. Five studies reported CAC scores by ranges (interquartile and others); none used the same cut-offs.^{39–41,44,46}

Outcome measures

To estimate the relative risk of coronary events for different levels of CAC, information was sought that would enable absolute numbers of people in the various risk categories to be calculated.

TABLE 4 Characteristics of patients included in trials

Study	Age, mean \pm SD (years)	Hypertension ^a (%)	Hypercholesterolaemia ^a (%)	Smokers (current/past) ^a (%)	Diabetes mellitus ^a (%)	Family history of CHD (%)
Kondos, 2003 ⁴³	50 \pm 9 (men), 54 \pm 9 (women)	20	39	48	3.4	NR
Shaw, 2003 ⁴⁴	53 \pm 10.4	44	62	40	6	69
Arad, 2000 ³⁹	53 \pm 11	25	42	10	5	44
Greenland, 2004 ⁴¹	65.7 \pm 7.8	29	18	12	NR	NR
Wong, 2000 ⁴⁶	54 \pm 10	26	55	24	5	NR
Itani, 2004 ⁴²	61.4 \pm 11.3	NR	NR	NR	NR	NR
Arad, 2005 ⁴⁰	59 \pm 6	34	Cholesterol, mean \pm SD: 224 \pm 33 mg dl ⁻¹	10	6	21

^a Percentage of participants reporting the presence of the risk factor plus appropriate medication (Greenland directly checked blood pressure and cholesterol).
NR, not reported in published study.

Two studies reported sufficient information for all-cause mortality.^{42,44} Three reported cardiac death plus MI^{41,43,46} and one³⁹ included revascularisation events only if they related to new-onset symptoms. *Table 5* summarises the CAC scores and outcomes.

The relative risk of cardiac events for each study was estimated first by comparing any CAC to no CAC (*Figure 2*). All five studies showed an increased risk of cardiac events among people in whom CT had identified CAC, and statistical testing for heterogeneity was not significant ($p = 0.348$). The overall relative risk of a cardiac event if CAC is present was estimated to be 3.5 [95% confidence interval (CI) 2.5 to 5.0]. However, there was substantial heterogeneity in the study populations, particularly in terms of risk factors assessed (*Table 4*). Sensitivity analysis, removing the one study not using EBCT, did not substantially alter the results.⁴²

For all-cause mortality, using the largest study, by Shaw and colleagues⁴⁴ the relative risk was estimated to be 4.0 (95% CI 3.0 to 5.4), comparing CAC of 10 or below versus greater than 10.

Insufficient information was provided in the published studies to allow adjustment for age or other cardiac risk factors in the pooled analysis. However, adjusted data were presented in the published articles in a number of different formats.

Kondos and colleagues⁴³ reported a model incorporating the five risk factors measured (age,

smoking, hypercholesterolaemia, diabetes and hypertension) plus the presence of CAC, and found CAC to be an independent predictor of 'hard' cardiac outcomes (MI and cardiac death) with a relative risk (RR) of 10.46 (95% CI 3.85 to 28.4) after adjustment for the other five factors. The Kondos study is noteworthy for the much stronger relationship in men than in women.

Shaw and colleagues⁴⁴ incorporated age, gender, diabetes, family history, hyperlipidaemia, hypertension and smoking with four raised CAC levels. They demonstrated an independent association between CAC and all-cause mortality, and showed a trend towards increasing events with increasing CAC score (CAC score 11–100: RR 1.64, 95% CI 1.12 to 2.41; CAC score 101–400: RR 1.74, 95% CI 1.16 to 2.61; CAC score 401–1000: RR 2.54, 95% CI 1.62 to 3.99; CAC score >1000: RR 4.03, 95% CI 2.52 to 6.40).

Arad and colleagues' first study³⁹ looked at three different cut-offs for CAC (>80, >160, >600) in a model adjusting for hypercholesterolaemia, hypertension, diabetes and age. Again, an independent association with CAC was found and there was a trend towards an increased risk of MI or cardiac death with increasing CAC score (CAC score >80: RR 14.3, 95% CI 4.9 to 42.3; CAC score >160: RR 19.7, 95% CI 6.9 to 56.4; CAC score >600: RR 20.2, 95% CI 7.3 to 55.8).

Greenland and colleagues⁴¹ found that within each stratum of the Framingham risk score (FRS) there was a gradient of association between risk of

TABLE 5 CAC scores and outcomes

Study	Subgroups	Number screened	CAC score	Number with CAC	events	Event definition
Kondos, 2003 ⁴³	Men	4,151	None	1,086	3	MI, cardiac death (excluded non-cardiac death)
			Any	3,065	49	
	Women	1,484	None	730	2	
			Any	754	4	
Shaw, 2003 ⁴⁴		10,377	≤ 10	5,946	62	All-cause mortality
			11–100	2,044	53	
			101–400	1,432	54	
			401–1000	623	39	
			> 1000	332	41	
Arad, 2000 ³⁹	All	1,172	0	293	2	MI, CABG/stent (only if for new pain), cardiac death
			1–4	293	1	
			5–97	293	4	
			>97	293	32	
Greenland, 2004 ⁴¹	All	1,461	None	316	14	MI, cardiac death
			1–100	321	21	
			101–300	171	15	
			>300	221	34	
Wong, 2000 ⁴⁶		926	None	392	0	MI (no deaths occurred)
			1–15	131	0	
			16–80	131	2	
			81–270	127	3	
			>270	122	1	
Itani, 2004 ⁴²	Men	3,377	None	2,546	3	Cardiac death
			Any	831	9	
	Women	2,743	None	2,367	1	
		Any	376	3		
	All	6,120	None	4,913	33	All-cause mortality
			Any	1,207	31	
Arad, 2005 ⁴⁰	All	4,903	None	1,504	0.54%	Fatal and non-fatal MI (40 events), CABG and percutaneous coronary intervention (PCI) (59 events), stroke (7) and peripheral vascular disease surgery (13)
		1–99	1,973	1.00%		
		100–399	686	5.50%		
		>399	450	14.00%		

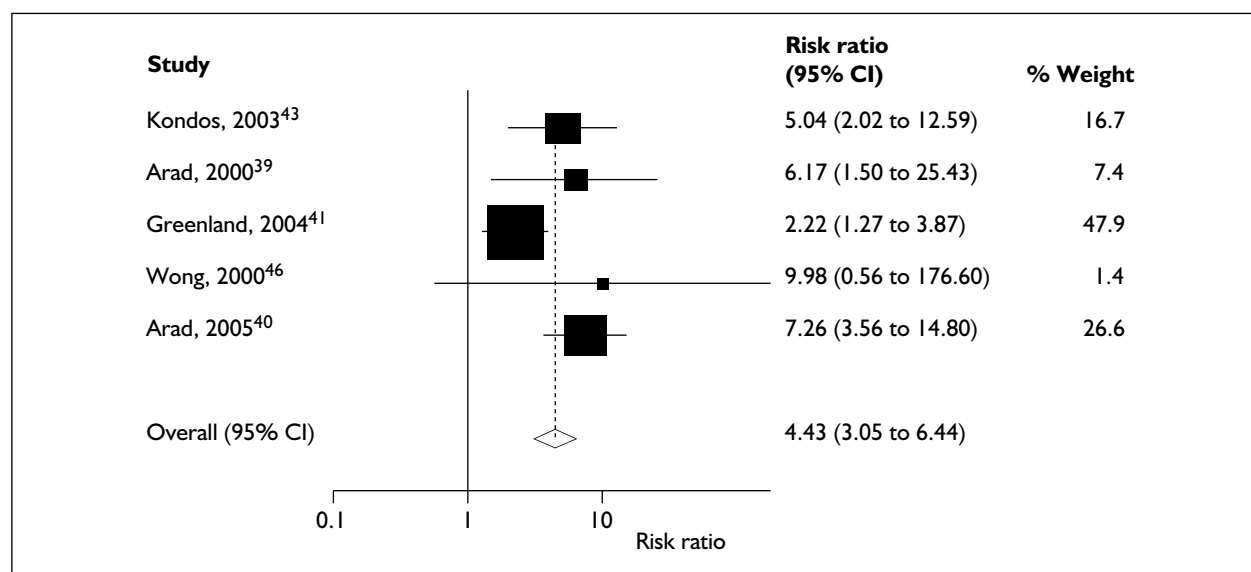


FIGURE 2 Relative risk of cardiac death or MI (both Arad studies include revascularisation) comparing any CAC with no CAC

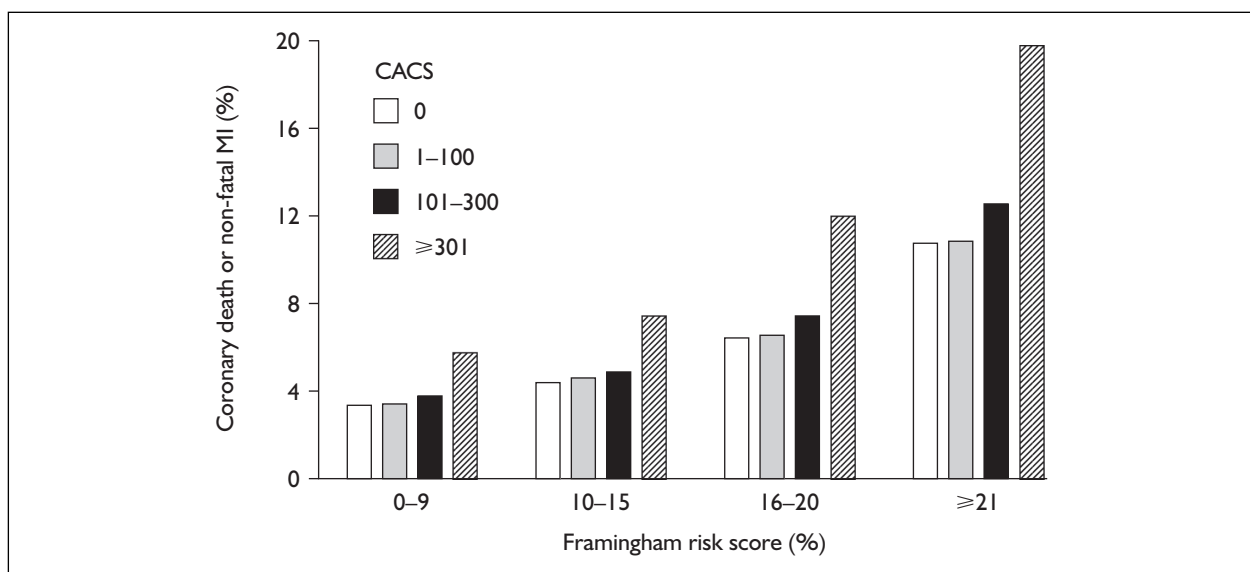


FIGURE 3 Predicted event rates for CHD death or non-fatal MI for Framingham risk scores.

“Predicted 7-year event rates from Cox regression model for CHD death or nonfatal myocardial infarction for categories of FRS or CACS

The rates are stratified by 4 levels of Framingham Risk Score (FRS) and 4 levels of the coronary artery calcium score (CACS). Pairwise analyses compared the highest CACS level (>300) with each of the lower levels of CACS within each FRS group. Analysis of variance with pairwise comparisons revealed a statistically significant difference between a CACS of >300 and each of the other 3 CACS groups for an FRS of >10% ($p < 0.001$) and between a CACS of >300 and a CACS of zero for an FRS of <10% ($p = 0.01$).”

Copyright © 2004, American Medical Association. All rights reserved. Reproduced with permission from Greenland and colleagues (2004).⁴¹

cardiac death and MI and CAC score (*Figure 3*). Although they report an association between FRS and all-cause mortality, no association was identified between CAC score and all-cause mortality.

Wong and colleagues⁴⁶ adjusted for age, gender, hypertension, hypercholesterolaemia, smoking and diabetes, and found a similar correlation as described above between CAC score and cardiovascular events (death, MI, revascularisation).

Itani and colleagues⁴² did not present data regarding risk scores.

Arad and colleagues⁴⁰ reported that CAC predicted coronary events more accurately than the FRS; the area under the receiver operating characteristic (ROC) curve was 0.79 for CAC and 0.68 for FRS. They also report that CAC added value to FRS. In the lowest FRS risk group (low = expected event rate < 10% in 10 years), there were no coronary events in the first and second quintiles of CAC. In the intermediate FRS group (expected 10–20% event rate in 10 years), the event rates per year in ascending tertiles of CAC were (estimated from graph) 0.2%, 0.5% and 2.4%.

In the highest FRS group (expected event rate over 20% in 10 years) the rates in the CAC tertiles were (again from graph) 2%, 1% and 3.9%.

Two weaknesses of this study were that the composite indicator was made up about half by CABG and PTCA, and that the event rate was much lower than expected from the FRS, thereby reducing the power.

In an accompanying editorial, Grundy⁴⁷ comments that in the first FRS group, CAC carries more weight than FRS. He suggests that if CAC is over 100, patients could be classed as high risk; if under 50 as low risk.

Therefore, there appears to be consistent evidence that CAC correlates with risk of cardiac outcomes and that this association is independent of other recognised cardiac risk factors, in particular, age. It is less clear whether CAC score correlates with all-cause mortality.

Adding to risk factor scores

Figure 3 illustrates that CAC scores reveal different levels of risk of cardiac events within groups of people with the same Framingham or risk factor score, particularly where CAC is greater than 300.⁴¹

There was no significant difference with increasing CAC score among those in the lowest Framingham score categories of 0–9%, although the number of participants with CAC above 300 was small.

Current guidance supports the treatment of people whose risk of cardiac events is greater than 20% over 10 years or 2% per annum. Raggi,⁴⁸ using a prospective cohort, compared individuals' CAC scores with scores obtained from a large asymptomatic population used to generate age- and gender-specific CAC score percentiles based on those people with a CAC score above 0. The study found that CAC score percentile was a strong independent predictor of cardiac outcomes, and that used alone, or in combination with standard risk factors and age, it provided incremental prognostic information (ROC area under the curve values: age = 0.61; age + risk factors = 0.71; CAC score percentile + risk factors + age = 0.84; CAC score alone = 0.82). The study also estimated that the annual risk of a cardiac event for someone over the 50th centile of CAC score for their age and gender was approximately 2%. Hence, using that score would identify a similar proportion to currently used risk score, but they would not be exactly the same people.

Becker and colleagues⁴⁹ also used a cohort to estimate age- and gender-specific percentiles of CAC based on calcium mass rather than Agatston score. However, at the time of publishing the authors had not reported outcome data that enabled them to assess the advantage of replacing age with CAC in the Framingham risk factor score. They identified two groups where CAC could potentially help in changing care, those where traditional risk scores result in an intermediate risk, and those over the age of 50 years. Age is a strong predictor of cardiac events, but among people over 50 years there is a wide variation in CAC scores or mass. Therefore, the authors argued that there was the potential to permit more accurate risk prediction by placing more emphasis on CAC than on age.

Hoff and colleagues⁵⁰ compared CAC scores with overall risk score based on traditional risk factors using a large cohort of over 30,000 asymptomatic people referred to a single medical centre for CT, to assess the correlation between risk factors and CAC score. When compared to risk scores, CAC was significantly different in each risk factor score category except between zero and one risk factor. Again, no information was available on the cardiac outcomes among the participants studied.

Changing treatment

No studies were found that considered whether the addition of CT to measure CAC would change the management of people, compared with the use of standard risk factor assessment. Three studies have examined the impact of assessing CAC using CT on the motivation of participants to change behaviours such as smoking and modification of other cardiac risk factor.^{51–53} First, O'Malley and colleagues⁵¹ surveyed a consecutive sample of asymptomatic people who had undergone EBCT for CAC. Forty-two per cent of the sample had CAC and these people were more likely to consider themselves at increased cardiac risk. However, they found no difference in the motivation to stop smoking, or change in smoking behaviour, between those with CAC and those without.

Wong and colleagues⁵³ surveyed 560 people undergoing EBCT. They reported a change in physician-led interventions such as prescribing aspirin (RR 1.86 for being prescribed aspirin if CAC present versus no CAC) and hypercholesterolaemia medications (RR 3.45) among those with CAC. However, statistically significantly more of those people with CAC reported losing weight (RR 1.67) and decreasing fatty intake (RR 1.58). There was no significant difference in smoking cessation. Those who had CAC on CT reported increased anxiety (RR 2.73).

In an RCT by O'Malley and colleagues,⁵² 450 people were randomised to one of four trial arms:

- to receive CT results plus intensive case management of risk factors
- to receive CT results with normal care
- not to receive CT results plus intensive case management
- not to receive CT results and receive standard care.

Groups were similar at baseline for Framingham risk factor scores. Comparing intensive case management with usual care, O'Malley identified a statistically significant improvement in Framingham risk among those receiving intensive case management [10-year FRS mean change: -0.06% (SD 0.19) versus 0.74% (SD 0.18), $p = 0.003$]. When adjusting for knowledge of CAC score, along with a variety of other psychological factors, only the number of risk factors present and intensive case management had an effect on improving or stabilising projected risk. The knowledge of CAC results did not affect the ability of participants to achieve a reduction in or stabilisation of risk factors.

TABLE 6 Summary of systematic reviews

Review	Methods	Conclusions
Pignone, 2003 ⁹	Adequately described in report	No trials with intervention Evidence of association between CAC and cardiac outcomes EBCT not recommended for screening
O'Malley, 2000 ⁵⁴	Adequately described in report	No trials with intervention Evidence of association between CAC and cardiac outcomes EBCT not recommended for screening
O'Rourke, 2000 ⁷	Adequately described elsewhere	No trials with intervention Evidence of association between CAC and cardiac outcomes
Pletcher, 2004 ⁵⁵	Adequately described in report	CT vs prognosis Meta-analysis supports independent predictive value of CAC scores but heterogeneity of studies
ICSI, 2004 ⁵⁶	Adequately described elsewhere	Narrative reporting of studies CT vs prognosis: supports association between CAC and cardiac events
CCOHTA, 2003 ⁵⁷	Adequately described elsewhere	Evidence for MSCT: one study supports similarity between EBCT and MSCT No evidence to support role in screening asymptomatic people

Service implications of screening

In some areas in the UK, there is insufficient CT capacity, and some patients already have to wait for non-urgent CT examinations. Were screening to be introduced, more CT machines would be needed.

Summary of systematic reviews and planned trials

Systematic reviews

Six systematic literature reviews were identified and are summarised in *Table 6*. All of the reviews were consistent with the findings that no trials could be found where CT (in combination with risk factor scores or alone) was used to target people to interventions with a view to assessing the impact on cardiac outcomes and all-cause mortality.

Additional trial information

Three studies have explored whether CAC can be modified by statin or other drug therapies.

Raggi⁴⁸ describes the Beyond Endorsed Lipid Lowering with EBCT Scanning (BELLES) trial (an RCT), which assessed the effect of aggressive (atorvastatin 80 mg per day) versus moderate

(pravastatin 40 mg) statin therapy on the progression of coronary atherosclerosis measured by EBCT in postmenopausal women. The results⁵⁸ showed that the more aggressive arm had lower cholesterol, but there was no difference in CAC progression. It was a trial but not one of screening.

Arad and colleagues⁵⁹ also report a trial in which one group was given atorvastatin plus vitamins C and E, and the other matching placebo. The results on total and low-density lipoprotein (LDL) cholesterol were as expected, but there was no effect on CAC progression at a mean follow-up of 4 years. Oddly, there was no significant difference in cardiac outcomes, perhaps because of relatively small numbers and a low MI (fatal and non-fatal) rate of 0.8% a year; it was the volunteer group mentioned earlier.

Ongoing trials

Schmermund and colleagues⁶⁰ report another trial of different statin doses, this time 80 mg versus 10 mg of atorvastatin. As expected, lipid levels fell with the larger dose, but there was no difference in CAC scores at 12 months.

There appear to be ethnic differences in CAC prevalence that could affect its value as a screening tool in different populations. In a comparison of

two (relatively small; numbers 100 and 98) groups of American (Pittsburgh) and Japanese (Kusatsu) men by Sekikawa and colleagues,⁶¹ the Japanese had less CAC despite having higher prevalences of the classical risk factors for ischaemic heart disease, including smoking, hypertension, total cholesterol and LDL levels.

The Multi-Ethnic Study of Atherosclerosis⁶² trial, due to report in 2008, will provide additional information about the association between CAC, other cardiac risk factors and risk of cardiac events. The studies by Arad and colleagues were mainly in Caucasians.

Summary

EBCT (and probably other forms of CT) can detect and quantify CAC. CAC predicts coronary artery events, and there is a dose-response relationship, with higher levels of CAC being associated with a higher event rate. CAC can add to the information from clinical risk scores such as the Framingham score, and could be used to shift people from intermediate to high or low risk. However, there is no evidence that knowledge of risk scores has affected outcomes. Statin treatment trials show reductions in cholesterol, but not in CAC.

Chapter 4

Economic review of CT screening for heart disease

As an introduction to the potential for cost-effective screening for and treatment of CHD, Liu⁶³ presents an analysis of the economic burden of CHD within the UK. CHD is the leading single cause of death and one of the most important causes of years of life lost before the age of 65. A societal perspective is adopted, using data from 1999. Unit-cost data were derived from the Personal Social Services Research Unit (PSSRU), NHS reference costs, the study by Gray and colleagues⁶⁴ of cardiac rehabilitation, and Department of Health estimates of drug costs. Health service costs included were:

- NHS preventive activities £12.6 million
- GP preventive care costs £48.2 million
- community health care and £74.8 million
 social services costs
- outpatient care £33.3 million
- A&E attendances £16.5 million
- inpatient and day-patient care £933.3 million
- cardiac rehabilitation services in £28.4 million
 hospital and community facilities
- drug treatment £582.4 million

This gives a total direct NHS cost for CHD in 1999 of £1.73 billion.

Productivity losses were estimated through average annual earnings coupled with the economic activity rate, the unemployment rate, retirement ages, the number of coronary deaths and the certified incapacity days arising from CHD. The productivity losses were estimated as £2.91 billion for 1999. Informal care costs were estimated at £2.42 billion by the application of the average net hourly wage of £8.32 to informal carers below the age of 65, while the average net wage for caring services of £5.73 was applied to informal carers above the age of 65.

While the estimates of productivity losses and informal care costs would not typically be included in NHS estimates of cost-effectiveness, the estimate of the direct costs to the NHS is considerable.

Standford⁶⁵ presents a relatively simple analysis of the direct screening cost per individual identified with CHD, this being simulated for screening with exercise ECG, stress thallium, stress echocardiogram,

positron emission tomography (PET), ultrafast computed tomography (UFCT) and cardiac catheterisation. However, he does not consider CT screening. Sensitivities and specificities for these tests are drawn from Patterson,⁶⁶ which given the lack of a gold standard for the detection of CHD in asymptomatic individuals suggests that Standford is probably in effect modelling the cost-effectiveness of screening for CHD in symptomatic individuals, with sensitivity analyses for 100%, 70% and 20% prevalence of CHD. The greater the prevalence, the greater the willingness to pay for more expensive technologies with better sensitivities. However, the analysis is of limited relevance to this review. It serves as a reminder of the importance of the prevalence of CHD within the population being tested, or rather, as it would be unethical to apply a gold standard of angiography within the asymptomatic population, the importance of follow-up data as to the likelihood of a cardiac event. The costs reported in Standford⁶⁵ that are relevant to this review are: exercise ECG US\$292, stress echocardiography \$687, UFCT \$395 and catheterisation \$2694.

A similar approach is provided in the review article by Marwick.⁶⁷ This attempts to assess the cost-effectiveness of testing for CAD with stress echocardiography as opposed to exercise ECG. Tests accuracies are given in terms of sensitivities and specificities through a meta-analysis of other studies, while cost-effectiveness in terms of the cost per quality-adjusted life-year (QALY) is simulated for prevalences of CAD ranging between 20 and 100%. Similar criticisms to those made of the paper by Standford apply and the results are of limited relevance to this review. Medicare costs derived from the information provided by Marwick are exercise ECG US\$125, stress echocardiography \$286 and angiography \$2469. Note that the costs for exercise ECG and stress echocardiography are somewhat lower than those reported in Standford.

O'Malley and colleagues⁶⁸ present an estimate of the cost-effectiveness of screening for CHD with CT, by determining the marginal cost per additional at-risk patient identified through the addition of CT to assessment through the Framingham Risk Index (FRI). Data were obtained

from 1000 participants in the Prospective Army Coronary Calcification Project, which screened army personnel between the ages of 39 and 45. Patients with known CHD or angina were excluded. 'At risk' was defined as having a greater than 1% annual risk of a cardiac event as determined by the FRI. However, the effectiveness of adding CT to the FRI was by assumption; a CAC score of 0 did not modify the patient FRI risk, while the presence of calcification was assumed to multiply the FRI risk four-fold, this applying to 17.6% of those screened. It appears that the cost per additional at-risk patient identified is based on the number of those with an FRI risk of up to 1% being identified as having calcification by CT.

The assumption of a four-fold increase in risk from calcification appears largely arbitrary, and renders the results of the modelling of hypothetical rather than of real-world interest. It also appears likely that the model will predict too many cardiac events, given that there is no offsetting reduction in the risk of an event in those identified as having no calcification. Clinical effectiveness estimates for treatment and quality of life estimates are also largely by assumption. The cost per additional at-risk individual identified is stated as \$9789, this being most sensitive to the cost of the CT and the cost of medication. The cost per QALY is stated as \$86,752. But as already noted, these values are largely hypothetical. More concrete results concern the cost of the CT examination (\$400), the cost of exercise ECG (\$400), the cost of catheterisation (\$1200) and the cost of medication (\$300 per annum). The CT cost is much higher than in the UK reference costs, where it ranges from £49 to £104.

Shaw and colleagues⁶⁹ synthesise much of the existing evidence, although noting that few published economic evaluations exist. To be cost-effective, an imaging screening tool would be required to provide additional information over and above that of conventional risk scoring. There is also the possibility of low-cost laboratory markers emerging, such as highly sensitive C-reactive protein. Shaw and colleagues outline the elements that would contribute to the cost-effectiveness of screening in terms of the detection of true positives; that is, the patient benefits and induced costs of appropriate further testing and treatment, while also drawing attention to the potential harm from false positives. For CT, there may also be a safety issue around repeated testing. These adverse impacts will be of greater importance in populations with a lower prevalence of disease.

Shaw⁶⁹ anticipates that any screening test will, if positive, be followed up by at least one additional diagnostic test, this possibly reflecting likely American practice; that is, a screening test does not lead to a definite diagnosis itself. Shaw asserts that these downstream diagnostic tests are likely to account for a greater cost burden than the direct costs of screening. The cost per screen for EBCT, including labour, consumables and capital costs (details not supplied), is estimated to be similar to that for exercise ECG at around \$100 (all test costs were read from a graph; the year was not stated), each with relatively tight confidence intervals. Within this, it should be noted that the estimate for echocardiography is not greatly higher at perhaps \$140, although the upper confidence interval stretches up to perhaps \$400, which may reflect uncertainty as to the amount of specialist input required for its interpretation. Catheterisation is estimated to cost around \$2000, with upper and lower confidence limits of \$1000 and \$4750.

Intermediate outcome measures are likely to be required in any evaluation of screening for CHD, as survival and quality of life are not directly affected by the test. Extrapolating short-term proxy outcome data to changes in life expectancy presents something of a challenge. From this, Shaw and colleagues⁶⁹ suggest that intermediate outcome measures such as the cost to identify coronary disease or cardiac event may be appropriate. They define an intermediate outcome model using the change in death or MI rate at 3–5 years' follow-up as the outcome measure. The difference in test accuracy is projected at between 0.1 and 10%, which the authors state as appearing consistent with the range of possible outcomes noted for non-invasive imaging. Test costs were varied between \$20 and \$1000, while induced costs were varied between two and 100 times these amounts. These are combined with annual risks of MI or death for people with intermediate risk of between 0.6 and 2.0%. A cut-off for cost-effectiveness of between \$250,000 and \$500,000 is stated as being reasonable, presumably because a number of life-years would be saved.

The main result of this hypothetical modelling is that tests that induce a more than 100-fold downstream cost compared with test cost appear unlikely to be cost-effective. Tests costing \$250–1000 are also stated as having to be decidedly more accurate to be cost-effective, detecting between six and ten more 'events'. Shaw and colleagues note that this is a largely hypothetical exercise that requires validation with real-world

TABLE 7 Estimated 10-year risk of cardiac events in asymptomatic men

NCEP group	10-year risk of cardiac event (%)				
	FRI	CAC = 0	CAC = 1–100	CAC = 100–400	CAC >400
1	13.1	2.8	12.1	22.2	27.4
2	9.6	2.7	11.5	21.2	26.1
3	17.8	3.7	16.0	29.3	36.2
4–5	21.9	4.6	19.7	36.1	44.6

data. However, it appears that Shaw and colleagues confuse detecting 'events' with the detection of individuals with probable CHD that leads to the likelihood of events within the group deemed positive, even in the context of an intermediate outcomes model. Given the hypothetical nature of the modelling and the concern around the detection of 'events', the results of the modelling appear to be of questionable applicability.

Shaw and colleagues⁶⁹ also review the cost-effectiveness literature of screening for CHD, citing the Rumberger study reviewed below and another paper by Shaw and colleagues.⁷⁰ This undertook a costing study of CT screening in 676 low- and intermediate-risk asymptomatic individuals.

This is reported as incurring screening costs of \$37,620 and \$23,220 in low- and intermediate-risk patients, respectively. The cost-effectiveness of screening is reported as approaching \$500,000 per life-year in low-risk individuals, with an annual risk below 0.6%. However, cost-effectiveness ratios of \$42,339 per life-year and \$30,742 per life-year are reported for individuals with an annualised risk of 1.0% and 2.0%, respectively. The model structure and basis for these calculations is not clear.

Rumberger⁷¹ evaluates the cost-effectiveness of using CT to guide statin therapy in intermediate- and high-risk groups. CT is seen as potentially adjudicating in issues of risk stratification. In this study, 214 asymptomatic American men with known lipid levels and no previous history of CHD were evaluated with the FRI and placed in one of four groups according to the National Cholesterol Education Program (NCEP) scoring system (1, 2, 3 and 4–5), this yielding the 10-year risk of a cardiac event for each group according to the FRI. The 214 men were subsequently examined by CT.

Associating the CT data from the 214 asymptomatic men with the 10-year risk of a cardiac event used a two-stage process. CAC scores were related to

maximum stenosis severity in a study of 214 patients undergoing clinically indicated arteriography. Maximum stenosis severity was related to the 10–15-year incidence of cardiac events in a study of 2400 patients undergoing clinically indicated arteriography. This linkage was used to estimate the 10-year risk of a cardiac event in the 214 asymptomatic men (*Table 7*).

The critical assumption with this is that the likelihood of a 10-year risk of a cardiac event in the asymptomatic men is the same as that in patients with clinically indicated arteriography, for a given CAC score. While this is an understandable assumption to make given the difficulties around a gold standard for tests in the asymptomatic men, it may not be warranted. Intuition suggests that the average likelihood of a cardiac event will be somewhat lower in asymptomatic than in symptomatic people for whom arteriography is indicated. Perhaps more problematic for the study, there is no obvious *a priori* reason to believe that this will affect the matrix of probabilities in *Table 7* for the different CAC scores in a predictable or symmetric manner.

Given the above risks, the only additional clinical data required are on the effectiveness of treatment. This is taken to be a 35% reduction in relative risk. The source for this is unclear, but it is similar to reductions seen in statin studies. A sensitivity analysis of 'aggressive' treatment with additional lifestyle improvements, oral aspirin and possibly antioxidant therapy is presented as yielding a 50% relative risk reduction.

The costs that are needed to populate the model are those of the CT (\$400), the costs of medication (\$1000 per annum) and the costs of cardiac events. A weighted average of the 5-year cost of stable angina (\$52,800 at 35%), MI (\$97,400 at 52%) and non-sudden cardiac death (\$27,400 at 13%) taken from the literature yields an average cost per event of \$72,600. Discounting does not appear to have been applied.

The presentation of cost-effectiveness results concentrates on NCEP groups 3 and 4–5. The total cost of testing and treatment for each of these groups is presented on the basis of:

- none being given statins:
NCEP 3 \$1,292,280
NCEP 4–5 \$1,589,940
- all being given statins:
NCEP 3 \$1,839,982
NCEP 4–5 \$2,033,461
- only CAC > 100 being given statins:
NCEP 3 \$1,385,105
NCEP 4–5 \$1,631,106.

Unfortunately, it is not entirely clear whether the above costs are for a cohort of 100 men across the NCEP groupings 1, 2, 3 and 4–5, or for a cohort of 100 men in each NCEP group. As Rumberger does not present the overall distribution of patients between groups and categories, again it is not possible to check this. It is also not entirely clear whether Rumberger has applied the cost of CT to all scenarios, or only the last where it is used to determine the subgroups receiving statins.

For NCEP group 3, the cost-effectiveness of all being given statins versus no treatment is stated as \$8640 per event avoided per year. The parallel figure for the cost-effectiveness of only those with a CAC score over 100 being given statins versus no treatment is stated as \$2249 per event avoided per year. It is not clear within these figures whether the FRI-derived 10-year risk of an event is used for the scenarios under which all are given statin treatment, with the CAC-derived risks being used for the scenario under which only the subgroup with a CAC score above 100 is given statins. It would be possible to apply only the CAC-derived 10-year risk of an event under all three scenarios, although the question remains as to how this relates to the FRI 10-year risk.

Rumberger⁷¹ does not present the cost-effectiveness of all being given statins versus only those with a CAC score over 100 being given statins. Giving all patients statins will prevent more events, at a net cost of \$454,877 within the NCEP 3 group. Unfortunately, as Rumberger does not state the additional number of events that will be avoided by giving all statins, the cost-effectiveness of this relative to only those with a CAC score over 100 being given statins cannot be calculated.

The parallel figures for all receiving statins and only those with CAC score over 100 in NCEP group 4–5 are \$7028 and \$1686. Again, the cost-

effectiveness of giving all NCEP 4–5 statins relative to only those with a CAC score over 100 being given statins cannot be calculated.

Rumberger⁷¹ represents a brave attempt to assess the cost-effectiveness of CT screening for CHD. The principal difficulty with the results of Rumberger is that they rest on the relationship between the CAC score and the 10-year risk of an event in symptomatic patients in whom arteriography is indicated. The likelihood of this relationship applying in the asymptomatic population is unclear. The 10-year risk derived from these scores within NCEP subgroups is also not demonstrated to be the same as or close to that derived from the FRI, upon which the NCEP groups are defined.

Wonderling and colleagues⁷² provide an analysis of the British Family Heart Study (BFHS). In an interesting study design, in each of 13 towns across the UK a matched pair of willing GP practices was selected for participation. One of each pair of GP practices was randomly selected for screening, and within this GP practice the male patients aged 40–59 years and their partners were randomly allocated to screening or to no screening. Those patients allocated for screening were invited to attend and their risk factor was calculated on the basis of previous medical history, smoking history, body mass index, blood pressure, cholesterol concentration and glucose concentration. Where indicated, appropriate lifestyle advice and medication were given. After 1 year the intervention group was rescreened and the comparison group invited for screening. The external comparison group, comprising all patients in GP practices not selected for the screening intervention, was viewed as the appropriate group for clinical comparisons. The internal comparison group, comprising those patients not selected for screening within the GP practices selected for the screening intervention, was viewed as the appropriate group for cost comparisons. The outcomes were the mean cost and the mean cost per 1% reduction in risk, based on the Dundee score.

Detailed resource use is provided within the paper. An average-sized four-partner practice of 7500 patients would have 11.8% eligible men which, with two-thirds having partners, would give 1500 eligible for screening per practice. For the screening, fixed costs per individual amounted to £25.84, with screening and follow-up amounting to £37.30 to give a total of £63.14. This is sensitive to assumptions as to throughput. Nursing time

amounted to 66% of this total, consumables 17%, equipment 10%, and secretarial and other support 7%.

Those in the intervention group were prescribed five more drugs per 100 individuals, but received fewer non-intervention health checks and consultations. Outpatient visits were slightly higher in the intervention group, but inpatient visits were slightly lower. These differences largely cancelled each other out, with the screened group on average costing £275 as against £216 for the unscreened group, a difference in cost of roughly the cost of the initial screen.

Cost-effectiveness was estimated as the cost per 1% reduction in coronary risk score as calculated by the Dundee score. For men, the average difference

in coronary risk between the intervention group and the comparison group was 13%. For women, the parallel difference was 10%. The direct programme costs were reasonably tightly estimated, being £66 and £57 for men and women, respectively. However, much greater heterogeneity was observed in the overall cost differences between groups, being £77 (95% CI £29 to 124) for men and £13 (–£48 to £73) for women. This yields a cost-effectiveness in terms of direct programme costs of £5–6 for a 1% reduction in coronary risk, with an average of £5.26 across men and women. Given the difference in downstream cost estimates between men and women, the overall cost per 1% reduction in risk for men is around £6 for men, but only a little over £1 for women, to give an average of £4.30.

Chapter 5

Cost-effectiveness considerations and the ideal data set

CT screening is not the only means of ensuring that more patients receive care for suspected but asymptomatic CHD. The simplest means of achieving this is to lower the risk score required for treatment, as NICE appears likely to recommend and as is incorporated in the above. This ensures that more people receive appropriate medical treatment, but also necessarily means that more people receive possibly inappropriate medical treatment as there will be a higher number of false positives. However, given the lack of a gold standard for the detection of CHD in asymptomatic individuals, this lowering of the index of suspicion is more with regard to the likelihood of patients deemed positive benefiting from treatment than with regard to the actual diagnosis of CHD.

This underlines that any trial aiming to assess the cost-effectiveness of screening for CHD in asymptomatic individuals with whatever technology will be a joint test of:

- the screening technology
- current protocols for treatment
- the effectiveness of treatment.

In the absence of a gold standard it is not possible to assess the cost-effectiveness of screening for CHD in asymptomatic individuals in isolation.

CT may detect CHD that is associated with calcification at an early stage, long before symptoms develop, or can be provoked by, for example, exercise ECG testing. However, the cost-effectiveness of medication in early asymptomatic CHD is unclear. The West of Scotland Coronary Prevention Study (WOSCOPS)⁷³ showed that statins are effective in primary prevention, but at a cost per life-year gained that was probably not affordable then. Even with statin prices dropping, it is unlikely that treating a risk of 1.5% per annum would be approved by NICE.

CT may miss CHD that is not associated with calcification. As noted in the clinical effectiveness section, lipid-laden, non-calcified plaques can occur in isolation and in the absence of CAC

elsewhere in the vascular tree. These plaques are noted as the most vulnerable in terms of the risk of rupture leading to thrombosis. The progression of calcification in asymptomatic individuals to either an event or symptomatic CHD that would be picked up within the healthcare system and treated is not clear. Similarly, the cost-effectiveness of treating asymptomatic individuals with calcification is also not clear. A similar effect within CT screening may be possible through the raising of the CAC score required for treatment.

It could be envisaged that for a screening programme, CT examination could replace the conventional risk system. Instead of being called to primary care for risk assessment, people at a certain age could be invited to secondary care for CT. Those with high CAC levels would then be referred for cardiological investigation to determine whether angioplasty or CABG was indicated (although since there are no trials in asymptomatic people, such interventions would be based on reasonable extrapolation rather than evidence). The investigative pathway might involve exercise ECG or other non-invasive investigation to detect stenosis or otherwise prioritise people for angiography, but this would require further research. Exercise testing is only positive when arterial disease restricts blood flow, and hence is not suitable as a screening tool for early disease. Those with medium CAC could be given statins; those with low CAC would be given lifestyle advice. *Figure 4* shows the possible pathways.

However, rather than abandon risk scoring, current thinking appears to be to retain this but possibly add CT to this risk scoring, to risk stratify patients more accurately for follow-up treatment. The risk scoring of the Joint British Societies Risk Prediction Chart splits patients into three groups: high, medium and low risk of an event. The costs and potential effects of adding CT or ECG testing in these groups will differ.

- In the high-risk group, CT could be used as part of a work-up, with or without other tests such as exercise ECG, as a prior test to

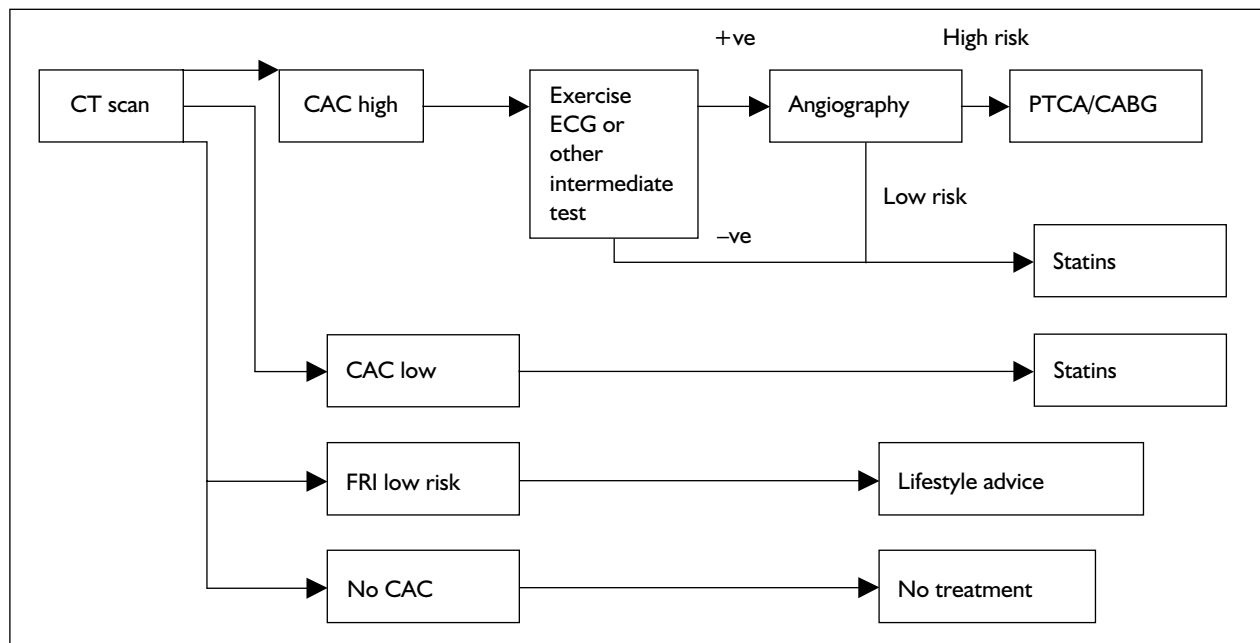


FIGURE 4 Possible pathways of care based on CAC

angiography and possible revascularisation by PTCA or CABG; that is, as an additional test to rule out the expense and possible risk associated with angiography. However, in some patients there may be restrictions in the vessels without calcification, in which case CT may wrongly rule out those in whom PTCA is appropriate, and who may be picked up by exercise ECG. Conversely, there would be a danger of this group having invasive procedures and revascularisation despite being asymptomatic.

- In the intermediate-risk group, current practice is likely to be to recommend medical treatment. CT could be used to confirm the need for this medical treatment; that is, to rule it out in those with low CAC scores. However, since CAC scoring may be negative in people with non-calcified but vulnerable plaques, absence of CAC may not change management in this group. It is also possible that the results of CT may indicate a worse prognosis than originally suspected from the simple risk scoring. In this case, the CT result could be used to rule in further testing with a view to possible angiography. Intuition suggests that this may be the main impact of additional testing within a screening programme: identifying those at medium risk who are really at higher risk, and would otherwise be missed and may go on to an unsuspected event.
- In the low-risk group, CT could be used to confirm that medical treatment is currently not

appropriate, but this would probably not be cost-effective. However, they will be low risk and large numbers would need to be studied for many years to be sure that it was safe to have no treatment.

Figure 5 outlines the pathways of care based on the FRI.

The main point to note is if the current risk scoring system stratifies patients reasonably accurately, the likely costs and benefits from adding CT will differ between those deemed to be at high, medium and low risk. For instance, if the current thinking is to add CT assessment to risk scoring, this may be cost-effective in the intermediate-risk group but not in the low-risk group.

To assess the cost-effectiveness of screening with combined risk scoring and CT, the ideal data set would be similar to that of the Rumberger study:

- the association between the risk score and the CAC score (i.e. initial patient distribution)
- the likelihood of a patient within each cell being identified as symptomatic CHD before an unforeseen event, and treated for CHD
- the likelihood of an event within each cell of the patient distribution if left untreated (events would ideally be differentiated by severity, type of event and its effect on quality of life)
- the effectiveness of treatment within each cell of the patient distribution.

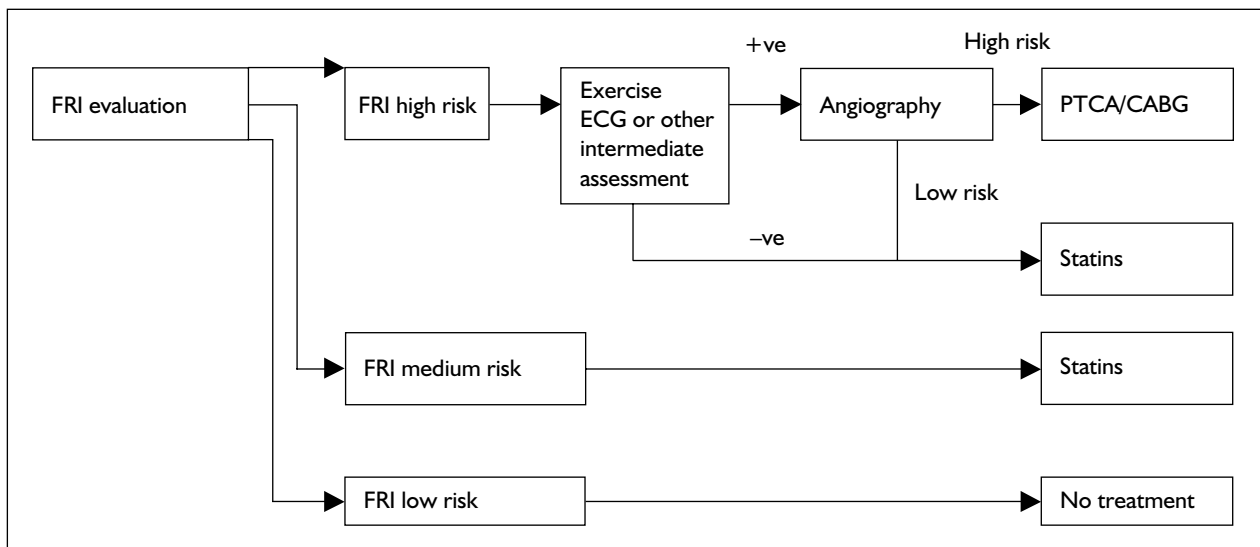


FIGURE 5 Pathways of care based on the FRI

An RCT could be envisaged with one arm being risk scored, while the other arm would be risk scored and have CT. This would yield the initial patient distribution. Follow-up of the arm that was only risk scored and treated accordingly could be used to yield the likelihood of a risk-scored patient deemed not to be at risk and not treated medically having an unforeseen event.

A difficulty may arise in estimating the likelihood of an event for patients left untreated within each cell of the CT-scanned arm of the trial. Ethical considerations are likely to mean that treatment cannot be withheld from certain higher risk cells of patients, or placebo given. Within these cells of the patient distribution in the CT arm of the trial, only the likelihood of an event with treatment would be available. The likelihood of an event without treatment would probably have to be inferred from this and estimates of treatment effectiveness from patients in clinical trials that were not differentiated by CAC score.

For the remaining cells of the patient distribution within the CT arm of the trial, it may be ethical to withhold treatment. But to evaluate the value of CAC scoring on treatment options, these would need to be split into treatment and no-treatment arms. Again, to the extent that long-term treatment of the asymptomatic individual has possible side-effects, ethical problems in treating these patients may also arise. If so, further assumptions as to the effectiveness of treatment in these treatments would have to be made from patients in clinical trials that were not differentiated by CAC score. However, if CAC

scoring cannot be used to differentiate treatment within a trial, there would be no value or point to such a trial. It seems less likely that ethical considerations would bar the treatment of these individuals.

As a consequence, a trial similar to that of the BFHS could be envisaged. The BFHS split GP practices into those not performing screening and those performing screening, and further split the patients within the practices performing screening into those invited and those not. A parallel trial could be envisaged, but with all practices involved performing screening based on risk scoring. CT scanning could be added to all practices, or it could be the additional element differentiating practices and patients within these practices. The critical point is that patients would have to be split between current practice based on the risk scoring and treatment options as permitted by CAC scores, with treatment according to CAC scores being similarly split.

This again underlines the difficulties that arise from the lack of a gold standard in the asymptomatic patient. There is no formal testing of the accuracy of testing. Any trial will be a joint test of the test accuracy, the patient pathway and the effectiveness of treatment. There are various possible permutations of tests. This also applies to the possible treatment routes, given that a new test is being applied. Not all permutations could be explored, and decisions would have to be made as to the patient testing, referral and treatment pathways that would be examined.

A further difficulty arises in terms of the outcome measure. Estimating the impact on the likelihood of adverse events would require a long-term trial. The BFHS survey circumvented this by measuring the impact on the risk score. This was appropriate for the BFHS survey, but would not be appropriate in a trial aiming to assess the value of the CAC score relative to the more traditional risk scoring.

If risk stratification affects patient management and patient behaviour, this will affect patient outcomes and costs. To the extent that a screening test increases the sensitivity of diagnosis, this may potentially:

- increase the costs and potential adverse events arising from appropriate further testing of higher risk asymptomatic individuals
- slow CHD progression through the appropriate early treatment of higher risk asymptomatic individuals, avoiding possibly more costly and risky treatment as symptoms develop and these individuals are picked up in the healthcare system
- reduce the incidence of unforeseen events associated with CHD through the appropriate treatment of higher risk asymptomatic individuals, and avoid the costs associated with these adverse events.

If a screening test increases the specificity of diagnosis, this may potentially:

- reduce the costs and potential adverse events arising from inappropriate further testing of lower risk asymptomatic individuals
- reduce the adverse events associated with the inappropriate treatment of lower risk

asymptomatic individuals, and avoiding the costs associated with these adverse events.

The relative importance of the sensitivity and specificity of the test will depend on the prevalence of CHD in the group or groups being tested. Although this is not directly observable in the testing of asymptomatic patients, to the extent that risk stratification is meaningfully separating patients it would be anticipated that the prevalence of CHD in those deemed at lower risk would be similarly low. This may increase the importance of having a high specificity within this group, and so altering the index of suspicion to require a higher CAC score for further referral or treatment.

Patients currently present to their GP and may be assessed on an ad hoc basis according to their risk factors. CT could be added to the risk assessment currently undertaken, as a diagnostic tool available to the GP. It is not immediately apparent that this group of patients necessarily parallels that which would be called in a formal population-based screening programme. As a consequence, the appropriate index of suspicion for testing in the population-based screening programme may not parallel that which should be applied by GPs in testing presenting patients. Similarly, within the group(s) called for screening, the relative importance of better sensitivity over better specificity will be dependent on the prevalence of CHD in the group(s) in question, in addition to the quality of life and cost aspects of the above bulleted points. In terms of cost-effectiveness, the significance of the safety of repeated CT will also depend on the prevalence of CHD in the group(s) screened; that is, the number of people exposed to CT scanning with its small associated radiological risks who are CHD free.

Chapter 6

Discussion

Summary of findings

CT can detect calcification of the coronary arteries in people with no symptoms at all, many of whom would be at low risk when assessed by traditional scoring systems. So CT can add value to risk scoring. The more extensive the calcification, and the higher the CAC score, the higher the risk. Treatment, most notably with statins, can reduce the risk.

However, CT will miss many of the most dangerous patches of arterial disease (dangerous in the sense of being liable to rupture and lead to a coronary thrombosis and MI) because they are not calcified. Calcification takes time to appear and in effect represents stabilisation of the plaque. However, calcification is indicative of arterial disease and hence of the presence of unstable plaques elsewhere. The converse also applies: arteries with calcified plaques may have normal blood flow with little risk of thrombosis.

The value of the additional information is uncertain. It would depend on how much better CAC score was than a clinical risk score such as Framingham or Sheffield, and then on how many patients would be treated who would not otherwise have been, and then on how successful that treatment was in reducing events. Success would depend on both efficacy (known) and compliance. It might be thought that seeing disease in one's artery would improve compliance, but this was not the case in the studies reported in Chapter 2.

In the highest risk group, it is unlikely that a low CAC score would lead to the stopping of statins. So CT screening would not affect treatment and would not be worthwhile, except that a high CAC score may lead to further investigation that may or may not be of benefit. All of the patients being investigated would have had their risk reduced by statins (and other treatments, such as antihypertensive agents, when appropriate).

In lower risk groups, when the risk score is lower than the 'statin threshold', then the value of CAC would be that a high score could lead to treatment. So the greatest value of CT may be in triage of those at intermediate risk by conventional scores.

Discussion

CT screening for asymptomatic heart disease has understandable appeal because risk-scoring systems are unsatisfactory, as they cannot identify all those who are going to have cardiac events. They can identify those at high risk, but such people represent a small proportion of the population, and most heart attacks occur in the much larger low-risk group.

Ramachandran and colleagues showed that while mean scores showed good correlations with events, there was wide overlap in scores between those who had events and those who did not.⁷⁴

The appeal of screening to the public is not restricted to heart disease. Schwartz and colleagues carried out a survey of the American public's views on cancer screening, including whole-body CT screening. Only 27% thought there might be any disadvantages, and most of those thought only of discomfort during the procedure or anxiety.⁷⁵ The public enthusiasm for CT screening may reflect the marketing of CT by commercial organisations. Concern has been raised in the USA about the ethics of providing CT screening in response to public demand.⁷⁶ Picano⁷⁷ reported that,

"Informed consent for radiological examinations is often not sought, and even when it is, patients are often not fully informed, even for considerable levels of radiation exposure and long-term risk."

The article notes that "radiological examinations confer a definite (albeit low) risk of cancer", and Picano provides a diagram indicating that CT of the chest gives a radiation dose equivalent to about 400 chest X-rays and an additional lifetime cancer risk of about (estimated from graph) 1 in 4000. Admittedly, this may be low compared to the risk of heart disease.

Does screening for heart disease using CT meet the NSC criteria?

The UK NSC criteria for evaluating screening programmes were adapted from the WHO criteria

published in 1966. The criteria are published on the NSC website.⁷⁸

This section applies the 22 criteria to CT screening for heart disease and summarises the evidence presented in the previous chapters. The criteria are numbered, and the reviewers' view on the extent to which the criteria are satisfied is appended after each criterion. Not all are applicable.

The condition

1. *The condition should be an important health problem*

Fully met.

2. *The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage*

Partially met. The presence of CAC represents a detectable sign of disease in people who are asymptomatic, and who are at higher risk. But some people at high risk will be CAC negative.

3. *All the cost-effective primary prevention interventions should have been implemented as far as practicable*

Primary prevention requiring lifestyle changes, particularly to diet and smoking, are inadequately implemented, but largely because of widespread non-compliance among the population. Statins are being used, but mainly for secondary prevention, although increasingly they may be used for primary prevention among those at higher risk.

Partially met.

4. *If the carriers of a mutation are identified as a result of screening, the natural history of people with this status should be understood, including the psychological implications*

Not applicable.

The test

5. *There should be a simple, safe, precise and validated screening test*

CT screening is not simple; the radiation dose is high enough to cause concern and measurement of CAC is imprecise. However, the test is validated in the sense that high levels correlate well with risk of events. Partially met.

6. *The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed*

Not yet met. A suitable cut-off level remains to be agreed.

7. *The test should be acceptable to the population*

Not yet known. The concept of screening may be attractive, but once people have been warned of the possible risk from radiation, it may be less acceptable.

8. *There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals*

Not met. There is no consensus as yet on what to do with people who have no symptoms but who are CAC positive; whether to treat all with statins, and so on, and to refer none, or whether those with an as yet undefined CAC threshold should be referred for angiography.

9. *If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out*

Not applicable.

The treatment

10. *There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment*

Partially met. There are effective treatments for early stage CHD, notably the statins. Since some first events are fatal, reduction of those by earlier treatment will give better outcomes than late treatment. However, we do not have data on treatment based on CAC.

11. *There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered*

There are not currently any evidence-based policies on what level of CAC should be treated. It could be argued that the presence of CAC proves that disease is present, and that all should be treated. However, this may not be approved on cost-effectiveness grounds, because those with CAC will represent a wide spectrum of risk.

Not met.

12. *Clinical management of the condition and patient outcomes should be optimised in all healthcare providers prior to participation in a screening programme*

The answer here depends on how 'condition' is defined. If it refers to all ischaemic heart

disease, then one could point to suboptimal care. For example, community thrombolysis is under-used in rural areas, and few hospitals can provide immediate angioplasty for MI.⁷⁹ If it refers to early asymptomatic disease, then it can be argued that care will not be optimised until all people above, say, 35 have had their risk scores checked and been given appropriate advice and treatment. Not met.

The screening programme

13. *There should be evidence from high-quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity*

Not met; there are no trials.

14. *There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public*

Not met; it might well be, but there is no such evidence.

15. *The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)*

Not met. There is a lack of evidence on the psychosocial effects of widespread screening; concerns over the impact of the radiation dosage, uncertainty about whom to refer for angiography and the adverse consequences of that in large numbers of asymptomatic people. One consequence of screening the coronary arteries is the incidental finding of non-cardiac lesions such as lung nodules, and liver, bone and kidney lesions.⁸⁰

16. *The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money)*

Not met, given lack of evidence on cost-effectiveness.

17. *There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards*

Not applicable at this stage.

18. *Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme*

If detection of CAC by screening resulted in more patients being referred for cardiological assessment, it is unlikely that the extra workload would be manageable. More angiograms would be required. If detection was followed only by statin treatment in primary care, the workload would be manageable. Uncertain whether met or not.

19. *All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available*

In theory, much of the asymptomatic coronary disease is preventable by healthier lifestyles. Not met.

20. *Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice*

Not yet applicable.

21. *Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public*

Not yet applicable.

22. *If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members*

Not applicable.

Summary

Using the criteria of the NSC, CT screening for heart disease in asymptomatic populations cannot be justified at present.

Research needs

Better ways of identifying which asymptomatic people are at high risk of heart disease are needed.

The research needs regarding CT screening include:

- Which form of CT should be used? Most studies have used EBCT, but recent developments include the multislice devices.
- Which measure to use: most studies use CAC scores based on the Agatston method, but others use measures of volume of calcium. There are also different software packages for quantifying calcification, which may give different results.⁸¹
- How should selection for CT be done? As suggested above, one possibility is that it might be used for those at intermediate risk by conventional scoring systems.
- What are the distributions of risk scores and CAC scores in asymptomatic people at different ages? What level of concordance is there between risk scores and CAC? What are the risks of cardiac events per annum for each level?
- What cut-offs should be used, first for selection for CT; and secondly, which CAC score should trigger treatment and/or further investigation such as angiography?
- Would CT screening be cost-effective, even if only for certain groups?
- Would CT screening be acceptable to fully informed people?
- A randomised trial of adding CT screening to current practice would be useful, but it might be preceded by economic modelling to estimate in which groups it would be most likely to be cost-effective. For example, people with type 1 diabetes are at increased risk of ischaemic heart disease, and within the diabetes group, those with increased amounts of protein in the urine (microalbuminuria) are at highest risk. However, it might be argued that CT would not change treatment because those with diabetes should already be considered for statin therapy. A trial could be done by providing some practices with a CT screening service, and having control practices without, to see whether the additional risk stratification data influenced clinical management.

Anand and colleagues,⁸² from London, report CAC results in 864 patients referred for EBCT on the grounds of high risk scores, by GPs or cardiologists. From this group, 220 consecutive patients with Agatston scores over 100 were further investigated using SPECT. Abnormal SPECT findings indicating silent ischaemia from reduced flow in the coronary arteries were found in 18% of those with Agatston scores of 100–400 and in 45% of those with scores of over 400.

- Other means of selection include the metabolic syndrome as defined by WHO.⁸³ The information that is most needed is whether the use of CT screening would reduce mortality and morbidity.
- Newer forms of CT such as the multislice scanner may have a place in the assessment of symptomatic CAD. It is possible that the presence of calcification would make detection of obstruction difficult, and one role of EBCT may be to select out those not suitable for MSCT examination; but that is not really a screening issue.
- Pilot studies could also provide information on the underlying prevalences among different groups (by age, ethnicity, and co-morbidities such as diabetes), which may help to target any future screening programme.

One issue for the NSC to consider is whether RCTs are always essential. It could be argued that the value of diagnostic tests can be determined by other study designs. However, the value of screening depends not only on the information obtained from the tests, but also on whether that information leads to improved outcomes.

Another issue that would have to be addressed is how people would be selected for screening. The population to be screened would need to be defined, starting with an age threshold, and based on primary care records. The question could be expressed in a two-fold way: is there an asymptomatic group that should be screened for CAD, and if so, what role does CT have in screening?



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Contribution of authors

Corri Black (Clinical Lecturer in Public Health) drafted the protocol, conducted the review of effectiveness, undertook data extraction and contributed to the preparation of the manuscript for publication. Ewen Cummins (Health Economist) conducted the economic appraisal and the economic literature review, with input from Norman Waugh (Professor of Public Health). Shonagh Walker (Specialist Registrar in Radiology) provided expert input, summarising the technology, reading and commenting on drafts. Lynda McIntyre (Systematic Reviewer) undertook the data extraction. Graham Hillis (Senior Lecturer in Cardiology) provided methodological and expert advice throughout, reading and commenting on drafts. Norman Waugh coordinated the review and prepared the final manuscript. All authors assisted in preparing the manuscript, reading and commenting on drafts, and reading the final draft.



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Appendix I

Search strategy

The following search terms were used to identify relevant articles.

MEDLINE search strategy 1966–2005

Updated to 8 June 2005.

- 1 MESH - exp myocardial ischemia or exp coronary disease or exp angina pectoris or exp exp coronary arteriosclerosis or exp coronary stenosis or exp coronary thrombosis or exp coronary vasospasm or exp myocardial infarction or exp myocardial stunning or exp ischemic preconditioning, myocardial
- 2 OR Textwords coronary heart disease OR coronary artery disease OR coronary disease
- 3 AND MESH exp Mass Screening OR Textwords screen\$
- 4 AND MESH exp computed tomography, x-ray computed or exp colonography, computed tomographic or exp tomography, spiral computed
- 5 OR CT scan\$ in title OR CT Screen in title OR comput\$ adj1 tomography in title
- 6 OR electron beam computed tomography as a keyword
- 7 Also used above CT terms with Textwords Full body screen\$ OR full-body screen\$ or whole body Screen\$ or body screen\$ or total body screen\$
 - a Above all limited to Reviews 1994–2005.
 - b Above then limited to all papers 2003–2005 inclusive.
6. coronary.tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Mass Screening/
9. screen\$.tw.
10. exp tomography/ or exp magnetic resonance imaging/ or exp tomography, emission-computed/ or exp tomography, optical/ or exp tomography, x-ray/
11. (ebct or ebt or ct or msct).tw.
12. (electron adj3 tomograph\$).tw.
13. (computed adj3 tomograph\$).tw.
14. (coronary adj10 tomograph\$).tw.
15. 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 7 and 15
17. randomized controlled trial.pt.
18. random\$.tw.
19. 17 or 18
20. 16 and 19
21. limit 20 to yr="2005 - 2006"
22. limit 21 to english language

Update of MEDLINE (OVID) search strategy Run 1 February 2006

1. exp Myocardial Ischemia/
2. exp Coronary Disease/
3. exp Angina Pectoris/
4. coronary aneurysm/ or coronary arteriosclerosis/ or coronary stenosis/ or coronary thrombosis/ or myocardial infarction/ or myocardial stunning/
5. exp Ischemic Preconditioning/

EMBASE search strategy 1980–2005

Updated to 8 June 2005.

- 1 MESH exp ischemic heart disease or exp angina pectoris or exp coronary artery constriction or exp heart infarction or exp myocardial disease or exp coronary artery disease or exp coronary artery anomaly or exp coronary artery constriction
- 2 OR coronary heart disease OR coronary artery disease or coronary disease
- 3 AND MESH exp screening or mass screening OR textwords screen\$
- 4 AND MESH exp computer assisted tomography or exp computer assisted emission tomography or exp computer assisted impedance tomography or exp electron beam tomography or exp high resolution computer tomography or exp optical coherence tomography or exp single photon emission emission computer tomography or exp spiral computer assisted tomography
- 5 OR CT scan\$ in title or CT screen in Title or comput\$ adj1 tomography in title
- 6 Also used above with MESH exp whole body tomography

- 7 Exp Cardiovascular risk AND Screen\$ AND tomography\$ OR CT sc\$
 - a Above all limited to Reviews 1994–2005.
 - b Above then limited to all papers 2003–2005 inclusive.

The Cochrane Library Issue 3 2004 (including CRD databases DARE, NHS EED, HTA)

Last updated February 2005.

- 1 All fields Coronary Artery Disease or Coronary Heart Disease or Coronary Disease
- 2 OR MESH heart diseases exp all trees
- 3 OR Ischemia exp all trees
- 4 AND all field CT screen* or CT scan* or computer assisted tomography
- 5 OR MESH Tomography, X-ray computed exp
- 6 OR MESH Tomography,X-Ray exp
- 7 OR Tomography Scanners Xray computed
- 8 OR computer next assisted abstract or CT abstract
- 9 AND MESH Mass screening
- 10 OR screen*

All fields full next body next screen* OR
All fields whole next body next screen* OR
All fields body next screen*

All fields full next body next scan*
All fields whole next body next scan*

Searched The Cochrane Heart Group all
categories

Science Citation Index and Social Science Citation Index 1990–2004 ISI Proceedings

Updated weekly to 8 June 2005.

- 1 TS=(coronary SAME disease) OR (coronary SAME calc*) OR (heart SAME disease*) OR atherosclerosis OR (artery SAME calcification*) OR (ischemic heart disease*) OR (myocardial infarction*) OR (preventive cardiology) OR (coronary risk*) OR (artery disease*)

- 2 AND TS=screen* OR mass screening
- 3 AND TS=CT screen* OR computer assisted tomography OR CT scan* OR computed-tomography OR electron SAME tomography OR CT SAME tomography
- 4 TS=whole body screen* OR whole body scan* OR full body screen* OR whole body scan* OR complete body screen* or complete body scan*
- 5 AND TS=CT screen* OR computer assisted tomography OR CT scan* OR computed-tomography OR electron SAME tomography OR CT SAME tomography

EMB Reviews

Last updated February 2005.

- 1 Coronary disease\$ OR coronary heart disease\$ OR coronary artery disease\$ OR heart disease\$ OR calcification
- 2 AND screen\$
- 3 AND CT Screen\$ OR CT scan\$ OR computed tomography

National Research Register

Last updated March 2005.

- 1 coronary next disease OR coronary next heart next disease OR coronary next artery next disease OR calcification AND screen* OR computed next tomography OR CT sc*

TRIP database 1999–2005

Last updated March 2005.

- 1 coronary AND screening
- 2 (evidence based)

British Heart Foundation

Last updated June 2005.

Coronary heart disease AND statistics

Appendix 2

Summary of studies reviewed

Study	Associated publications	Number of participants	Inclusion status
CAC versus outcomes			
Kondos, 2003 ⁴³	Sullivan, 1998 ⁸⁴	5,635 ^a	Included
Shaw, 2003 ⁴⁴	Raggi, 2000; ⁸⁵ Raggi, 2001 ⁸⁶	10,377	Included
Arad, 2000 ³⁹		1,177	Included
Greenland, 2004 ⁴¹	Yang, 1999 ⁸⁷	1,461	Included
Wong, 2000 ⁴⁶		926	Included
Itani, 2004 ⁴²		6,120	Included
Arad, 2005 ⁴⁰		4,903	Included
<i>Total</i>		30,599	
Shivalkar, 2004 ⁴⁵			Excluded: atypical chest pain
Agatston, 1996 ³⁸			Excluded: not available
CAC adding to risk factor scores			
Greenland, 2004 ⁴¹	Yang, 1999 ⁸⁷	1,461	Included
Raggi, 2001 ⁸⁶	Shaw, 2003 ⁴⁴	10,122	Included
Becker, 2005 ⁴⁹		1,473	Included
Hoff, 2003 ⁵⁰		30,908	Included
CAC changing treatment			
O'Malley, 2002 ⁵¹		144	Included
Wong, 1996 ⁵³		703	Included
O'Malley, 2003 ⁵²		450	Included
^a 8855 had CT, but not all reported.			



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