Chest pain of recent onset:

Assessment and investigation of recent onset chest pain or discomfort of suspected cardiac origin

Section 2

Full Guideline - Consultation Version

May 2009

National Clinical Guidelines Centre for Acute and Chronic Conditions

Make all comments on this version putting the page number and line number for each comment

Table of contents

Recommendations for presentation with stable chest pain

Note: The numbering is consistent to follow on from the other recommendations

When people present with stable chest pain of suspected cardiac origin, healthcare professionals should consider a diagnosis of angina caused by myocardial ischaemia. Angina can be diagnosed based on:

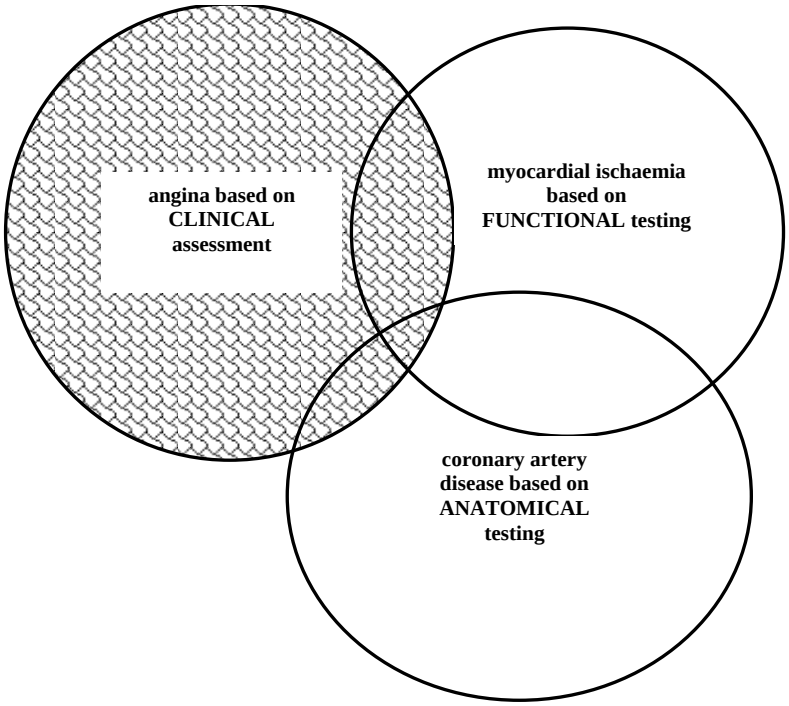
- the clinical history alone (a typical history is sufficient for a diagnosis)
- the clinical history and functional testing which demonstrates myocardial ischaemia
- the clinical history combined with anatomical testing which demonstrates significant obstructive CAD.

The endpoint for diagnosing angina in people who present with stable chest pain may be any of these individually or in combination.

In addition, tests in asymptomatic people may find the presence of obstructive CAD and/or myocardial ischaemia, but in the absence of chest pain or discomfort these people are not diagnosed with angina.

This is demonstrated diagrammatically below.

Making a diagnosis of angina in people presenting with chest pain



The shaded area shows the scope of this guideline

Table 1 Diagnosis of angina: Typicality, age, sex, risk factors and presence of CAD

	Non-specific chest pain				Atypical angina				Typical angina			
	Men		*Women*		*Men*		*Women*		*Men*		*Women*	
Age (years)	*Lo*	*Hi*	*Lo*	*Hi*	*Lo*	*Hi*	*Lo*	*Hi*	*Lo*	*Hi*	*Lo*	*Hi*
35	3	35	1	19	8	59	2	39	30	88	10	78
45	9	47	2	22	21	70	5	43	51	92	20	79
55	23	59	4	25	45	79	10	47	80	95	38	82
65	49	69	9	29	71	86	20	51	93	97	56	84

Values are per cent with CAD[1]
Hi = High risk = smoking, hypertensive, diabetic
Lo = Low risk = none of these three. If there are resting ECG ST-T changes or Q waves, the likelihood of CAD is higher in each cell of the table.

The shaded areas are those with a very low likelihood of CAD (< 10%) or very high likelihood of CAD (> 90%)

N.B. These results are likely to overestimate CAD in primary care populations

1 Adapted from Gibbons RJ, Abrams J, Chatterjee K, Daley J et al. ACC/AHA 2002 Guideline Update for the Management of Patients With Chronic Stable Angina: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for the Management of Patients With Chronic Stable Angina). American College of Cardiology, American Heart Foundation. 2002

3.1 Clinical assessment

Hyperlink to evidence statements for history, risk factors and physical examination

3.1.1.1 Be aware that angina can be diagnosed based on one or more of the following:

- clinical assessment alone
- clinical assessment combined with either obstructive CAD found on anatomical testing, or myocardial ischaemia, found on functional testing, or
- all three.

3.1.2 History, risk factors and physical examination

3.1.2.1 Take a detailed clinical history documenting:

- the age and sex of the person
- the characteristics of the pain, including its location, radiation, severity, duration and frequency, and factors that provoke and relieve the pain
- any associated symptoms
- any history of angina, MI, coronary revascularisation, or other cardiovascular disease
- any coronary risk factors.

3.1.2.2 Be aware that the following factors make a diagnosis of angina more likely:

- increasing age
- male
- typical angina symptoms (see recommendation 3.2.2.4)
- cardiovascular risk factors including:
  - a history of smoking
  - diabetes
  - hypertension
  - hyperlipidaemia
  - family history of premature CAD

  - history of established coronary heart disease, for example previous MI, coronary revascularisation
  - other cardiovascular disease.

3.1.2.3 Carry out a physical examination in all people with a history of chest pain or discomfort to:

- identify risk factors for cardiovascular disease
- identify signs of other cardiovascular disease
- exclude non-coronary causes of angina (for example, severe aortic stenosis, cardiomyopathy)
- exclude other causes of chest pain or discomfort.

3.1.2.4 Be aware that a diagnosis of angina is less likely when the pain is:

- continuous or very prolonged
- unrelated to activity
- brought on by breathing in
- associated with symptoms such as dizziness, palpitations, tingling or dysphagia.

3.1.2.5 Be aware that:

- typical angina symptoms are:
  - constricting discomfort in the front of the chest, or in the neck, shoulders, jaw, or arms
  - precipitated by physical exertion or psychological stress
  - relieved by rest or GTN within about 5 minutes
- atypical angina symptoms are two of the three features above
- non-anginal chest pain symptoms are fewer than two of the features above.

3.1.3 Gender differences in symptoms of stable angina

Hyperlink to evidence statements for gender differences

3.1.3.1 Be aware that central chest pain is not always the main symptom in people with stable angina. The diagnostic pathway is determined by the likelihood of CAD, which itself is influenced by gender and age. However, the actual differences in presenting symptoms between men and women are small.

3.1.4 Ethnic differences in symptoms of stable angina

Hyperlink to evidence statements for ethnic differences

3.1.4.1 Be aware that there are no major differences in symptoms of stable angina among different ethnic groups.

3.1.5 Resting 12-lead ECG

Hyperlink to evidence statements for ECG

3.1.5.1 Take a resting 12-lead ECG as soon as possible.

3.1.5.2 Be aware that a normal resting 12-lead ECG does not rule out a diagnosis of stable angina.

3.1.5.3 Be aware that a number of changes on a resting 12-lead ECG are consistent with CAD and may indicate previous infarction. These include:

- pathological Q waves in particular,
- LBBB
- ST-segment and T wave abnormalities (for example, flattening or inversion).

Consider these changes along with the person's clinical history and risk factors.

3.1.6 Making a diagnosis based on clinical assessment

3.1.6.1 Before considering diagnostic investigations, estimate the likelihood of CAD (see table 1) in people without confirmed CAD. Base the estimate on the initial clinical assessment and the ECG.

3.1.6.2 If angina is very likely based on clinical assessment (greater than 90%, see tTable 1), treat for angina.

3.1.6.3 Follow local protocols for angina[2] for people who are diagnosed with angina on the basis of clinical assessment and a resting 12-lead ECG. No further diagnostic investigations for angina are needed.

3.1.6.4 Do not carry out further diagnostic investigations to exclude angina in people who are diagnosed with non-cardiac chest pain based on clinical assessment and a resting 12-lead ECG.

3.1.6.5 Do not carry out a chest X-ray to help diagnose angina. Consider carrying out a chest X-ray if other conditions such as lung cancer or pulmonary oedema are suspected.

3.1.6.6 If angina is very unlikely based on clinical assessment (less than 10%, see tTable 1), consider other diagnoses.

3.1.6.7 If a cardiac cause for chest pain has been ruled out, but people have risk factors for cardiovascular disease, follow the appropriate guidance, for example 'Lipid modification' (NICE clinical guideline 67), 'Hypertension' (NICE clinical guideline 34).

3.1.6.8 Consider alternative causes of chest pain (such as gastrointestinal or musculoskeletal pain) in people who are unlikely to have angina or if diagnostic investigations exclude CAD.

3.1.6.9 Do not routinely offer aspirin if the person's chest pain is unlikely to be angina.

3.1.6.10 Carry out further investigations if there is no firm diagnosis of angina, based on clinical assessment and a resting 12-lead ECG, and offer aspirin.

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[2] NICE is developing a clinical guideline on stable angina. Publication is expected in July 2011.

3.2 Diagnostic testing

3.2.1.1 Include the estimate of the likelihood of angina (see recommendation 3.1.6.1) in all requests for diagnostic investigations and in the person's notes.

3.2.1.2 Offer information about the risks of diagnostic testing, including any radiation exposure.

3.2.2 First-line diagnostic investigations

For people with a high pre-test likelihood that chest pain is caused by angina (more than 60%) and an uncertain diagnosis

Hyperlink to evidence statements for anatomical tests

3.2.2.1 Offer invasive coronary angiography after clinical assessment and a resting 12-lead ECG if:

- coronary revascularisation is being considered, and
- it is clinically appropriate and acceptable to the person.

3.2.2.2 Consider either 64-slice (or above) CT coronary angiography or non-invasive functional imaging after clinical assessment and a resting 12-lead ECG if:

- coronary revascularisation is not being considered, or
- invasive coronary angiography is not clinically appropriate or acceptable to the person.

3.2.2.3 Follow local protocols for angina[3] while waiting for the results of investigations if the pre-test likelihood of angina is greater than 60%.

3.2.2.4 Exclude CAD as the cause of symptoms and investigate other causes if no significant CAD is found during invasive coronary angiography or 64-slice (or above) CT coronary angiography.

[3] NICE is developing a clinical guideline on stable angina. Publication is expected in July 2011.

For people with a moderate pre-test likelihood that chest pain is caused by angina (30–60%) and an uncertain diagnosis

Hyperlink to evidence statements for non-invasive stress tests

3.2.2.5 After clinical assessment and a resting 12-lead ECG, offer non-invasive functional imaging for myocardial ischaemia. Use:

- myocardial perfusion scintigraphy with single photon emission computed tomography (MPS with SPECT)
- stress echocardiography
- first-pass contrast-enhanced magnetic resonance (MR) perfusion, or
- MR imaging for stress-induced wall motion abnormalities.

The choice of imaging method should take account of locally available technology and expertise, and the person and their preferences, including any contraindications.

3.2.2.6 MPS using SPECT is recommended for the diagnosis of suspected CAD in the following circumstances[4].

- As the initial diagnostic tool for people with suspected CAD for whom stress electrocardiography poses particular problems of poor sensitivity or difficulties in interpretation, including women, patients with cardiac conduction defects (for example, left bundle branch block), and people with diabetes, and for people for whom treadmill exercise is difficult or impossible.
- As part of an investigational strategy for the diagnosis of suspected CAD in people with lower likelihood of CAD and of future cardiac events. The likelihood of CAD will be based on the assessment of a number of risk factors including age, gender, ethnic group, family history, associated comorbidities, clinical presentation, physical examination, and results from other investigations (for example, blood cholesterol levels or resting electrocardiogram).

[4] This recommendation is taken from NICE technology appraisal 73 (www.nice.org.uk/TA73)

3.2.2.7 Use adenosine or dipyridamole as stress agents for MPS with SPECT and first-pass contrast-enhanced MR perfusion.

3.2.2.8 Use exercise or dobutamine for stress echocardiography or MR imaging for stress-induced wall motion abnormalities.

3.2.2.9 Confirm a diagnosis of angina if reversible ischaemia is found during non-invasive functional imaging. Follow local guidelines for angina[5] .

3.2.2.10 When reversible myocardial ischaemia is not found during non-invasive functional imaging, consider other causes for chest pain.

3.2.2.11 Offer invasive coronary angiography when the results of non-invasive functional imaging are inconclusive (see recommendation 3.2.2.1).

For people with a low pre-test likelihood that chest pain is caused by angina (less than 30%) and an uncertain diagnosis

Hyperlink to evidence statements for calcium scoring

3.2.2.12 After clinical assessment and a resting 12-lead ECG, offer CT calcium scoring.

3.2.2.13 Following calcium scoring, if the score is

- zero, investigate other causes of chest pain
- 1–400, offer 64-slice (or above) CT coronary angiography
- greater than 400, offer invasive coronary angiography. If this is not clinically appropriate or acceptable to the person and revascularisation is not being considered, offer non-invasive functional imaging. See recommendation 3.2.2.5 about the choice of method.

[5] NICE is developing a clinical guideline on stable angina. Publication is expected in July 2011.

For people with confirmed CAD (for example, previous MI, revascularisation, previous angiography)

Hyperlink to evidence statements for non-invasive stress tests

3.2.2.14 Offer non-invasive functional testing to people with confirmed CAD when there is uncertainty about whether chest pain is caused by myocardial ischaemia. An exercise ECG may be used instead of functional imaging.

3.2.3 Further investigations

3.2.3.1 Offer non-invasive functional imaging (see recommendation 3.2.2.5) for myocardial ischaemia if invasive coronary angiography or 64-slice (or above) CT coronary angiography has shown CAD of uncertain functional significance.

3.2.4 If uncertainty remains following further investigations

3.2.4.1 Consider investigating other causes of angina, such as cardiomyopathy or small vessel disease in people with typical angina-like chest pain who, on initial assessment, either have:

- an extremely low likelihood of CAD, or
- investigation excludes flow-limiting disease in the epicardial coronary arteries.

3.2.4.2 Consider alternative causes for chest pain when diagnostic investigations exclude angina as the cause of the pain.

3.2.5 Investigations that are generally not helpful in the diagnosis of stable angina

Hyperlink to evidence statements for non-invasive stress tests

3.2.5.1 Do not use MR coronary angiography for diagnosing CAD.

3.2.5.2 Do not use exercise ECG as the primary diagnostic test for myocardial ischaemia in people without known CAD.

5 People Presenting with Stable Chest Pain Chapter

5.1 Assessment

Introduction

A universal definition for stable angina has not been agreed internationally, in contrast to that which has been developed for MI (Thygesen, K., Alpert, J. S., and White, H. D., 2007).

There are inherent difficulties in the use of the term angina (shortened from the more precise angina pectoris) because it is used to describe two different concepts. The first is the use of the term angina as a symptom, and the second is the use of angina as a description for CAD (angina is the commonest consequence of symptomatic CAD in Western society). The GDG recognized the differences in the usage of the word.

When the term angina is used to describe a symptom, it is characteristically due to myocardial ischaemia. The symptom, when typical, is recognized by most people as of cardiac origin. A typical description would be of sub-sternal pain, or discomfort, perhaps with radiation to the throat, the shoulders or the arm(s). The symptom is described variously as for example heavy, dull, pressing, burning, usually a visceral sensation (although sometimes the word ‘sharp’ meaning ‘severe’, may be used). Some patients deny the use of the word ‘pain’, emphasizing the variable nature of the symptom. When associated with chronic stable heart disease, the symptom is typically triggered by exertion or other causes of increased cardiac work, is worsened by cold air, or a recent meal, and is relieved rapidly by rest.

Most would use the term angina to describe these typical symptoms. However, where does the typical symptom become less than typical? Many people with CAD have symptoms which appear to be related to their CAD, but these symptoms would not be considered to be typical angina. Clearly there is a spectrum of typicality, ranging from the description given briefly above, to a pain which is non-central, long lasting, coming with no provocation, and being

worsened by chest wall movement. Such a symptom would be very unlikely to be due to CAD, and few clinicians would use the term ‘angina’ to describe such a symptom. It is unlikely that there would be a clear consensus as to where along the spectrum the symptom would no longer warrant the term ‘angina’.

Angina the symptom when more typical, is usually due to a cardiac condition. Although usually due to CAD, other cardiac conditions may be responsible. The list characteristically includes aortic valve disease and hypertrophic cardiomyopathy. However, the experienced clinician has seen patients in whom a symptom very similar to that described above has been due to hypertension, overweight, anxiety or dysfunctional breathing. The confusion is particularly marked when the symptom occurs outside the context of exercise and further investigation of a patient with suspected angina (the symptom) may reveal that the heart is not responsible, and the patient is considered as ‘not having angina’. Further confusion may arise when an ACS may be responsible for non-exertional symptoms, which occurs when myocardial ischaemia is triggered by a reduction in myocardial oxygen supply due to a change in a coronary artery, rather than an increase in myocardial oxygen demand due to increased myocardial work as in stable angina.

The association of the term angina for the symptom associated with CAD has led to angina often being used synonymously with CAD. Generally however, the diagnosis of CAD is only fully confirmed by imaging the arteries, usually by invasive or CT coronary angiography. However the epidemiological association of typical symptoms reflecting myocardial ischaemia with CAD often allows a confident diagnosis to be made even short of imaging the arteries, and the GDG recognized that in most cases, the association of the typical symptom with pathology was straightforward, and that treating the pathology would relieve the symptom. However, in patients with less typical symptoms how can we know that the symptom of that the patient describes is actually due to CAD even if this can be demonstrated?

There is a difficulty in knowing at which point along the spectrum of symptom typicality the term angina may sensibly be applied. The same applies to the

spectrum of severity of coronary obstruction and the relation of this obstruction to myocardial ischaemia. The artery with mild atheromatous changes in the wall is not usually capable of producing ischaemia. The severe sub-totally obstructed artery is usually associated with ischaemia under conditions of increased myocardial work. The impact of intermediate degrees of obstruction on coronary flow may not be clear and other measures than simply determining the degree of coronary obstruction may be needed in order to define whether such a narrowing is causing ischaemia. Non-invasive functional testing may show ischaemia associated with a lesion, but has inherent limitations in terms of sensitivity and specificity. So for example it is possible for a patient to have symptoms typical of myocardial ischaemia, but normal non-invasive functional testing, yet have severe coronary obstruction the relief of which cures the symptom. Studies using invasive measures of maximal flow suggest that even the visual severity of stenoses may not always relate well to functional impact.

Fortunately in many cases such considerations do not impact on clinical decision-making. However they need to be borne in mind when considering less typical presentations. The GDG was aware of these issues, and made strenuous attempts to ensure that the deliberations took them into account when interpreting the evidence regarding the role of the diagnostic strategies. The GDG also recognised that this guideline was to make a diagnosis in patients with chest pain of suspected cardiac origin, not to determine their definitive management, including the need for any additional testing for prognostic assessment, in those diagnosed with angina.

The GDG considered that the diagnosis of angina, the symptom due to coronary obstruction, might be made from a typical history consistent with myocardial ischaemia alone, the history in combination with functional testing demonstrating myocardial ischaemia, the history consistent with myocardial ischaemia in combination with the finding of significant obstructive CAD, or all three.

5.1.1 History, risk factors, physical examination

5.1.1.1 Evidence statements for history, risk factors, physical examination

1 One systematic review (search date 2003) in patients with stable chest pain of suspected cardiac origin found that the presence of typical angina symptoms, serum cholesterol > 300 mg/dl, age > 70 years, and a prior history of MI were the most useful components of the clinical assessment for ruling in a diagnosis of CAD. The most useful characteristics for ruling out a diagnosis of CAD were non-anginal chest pain, pain duration > 30 minutes, and intermittent dysphagia. The physical examination gave little additional information for the diagnosis of CAD. The physical examination gave little additional diagnostic information to the clinical history and the assessment of risk factors. (Chun, Andrea Akita and McGee, Steven R., 2004)

2 A study that assessed whether the information available from the clinical evaluation of a given patient could determine the probability of CAD prior to testing (using Bayes' theorem) found that in 4952 symptomatic patients referred for coronary angiography the prevalence of angiograhically-confirmed CAD was greater in patients with typical angina (90%) compared with patients with atypical angina (50%), and the prevalence of CAD in patients with atypical angina was greater than in those with non-anginal chest pain (6%). The prevalence of CAD in 23 996 unselected subjects at autopsy was 4.5%, the prevalence increased with increasing age, and women at all ages had a lower prevalence compared with men. Results of conditional-probability analysis found that the pre-test likelihood of CAD, varied widely according to sex, gender and symptoms, for example, a woman aged 30 to 39 years with atypical symptoms had a pre-test likelihood of 4% compared with 92% for a man aged 50 to 59 years with typical symptoms. (Diamond, G. A. and Forrester, J. S., 1979)

3 A study in 170 patients with stable chest pain that were referred for coronary angiography considered patients to have typical angina if they had substernal discomfort brought on by physical exertion and was relieved within 10 minutes through rest or nitroglycerin. Patients were considered to have atypical angina if they had only 2 of the defined factors for typical angina. Patients were considered to have non-anginal discomfort if they had 1 of the defined characteristics of typical angina. (Diamond, G. A., Staniloff, H. M., Forrester, J. S. et al , 1983)

4 A study that used Bayes' theorem to calculate probability of CAD in 170 patients with stable chest pain without prior MI or coronary artery bypass surgery referred for coronary angiography found that there was no significant difference between the predicted probability and the angiographic findings when the predicated probability was based on the age and gender of the patient within each symptom class (non-anginal, atypical, typical). (Diamond, G. A., Staniloff, H. M., Forrester, J. S. et al , 1983)

5 A study in patients with stable chest pain that developed a stepwise logistic regression model for predicting the probability of significant CAD (3627 patients) found that in 1811 patients the type of chest pain (typical, atypical or non-anginal) was the most important characteristic for the prediction of CAD (≥ 75% coronary stenosis), followed by prior MI, sex, age, smoking, hyperlipidaemia, ST-T wave changes on ECG, and diabetes. In men the effect of an increasing age was more important than in women for prediction of CAD, in women smoking was more important than men, and smoking and hyperlipidaemia were more important for the prediction of CAD at younger ages. (Pryor, D. B., Harrell, F. E., Jr., Lee, K. L. et al , 1983)

6 A study in 168 patients with stable chest pain that were referred for coronary angiography found that the following variables were significant predictors of CAD (≥ 75% stenosis in a least one

coronary artery); age, gender, chest pain (type), diabetes, smoking, hyperlipidaemia, prior MI, and significant Q waves and ST-T wave changes. For severe disease (≥ 75% stenosis in all three major arteries or of the left main coronary artery obstruction) the following variables were significant predictors; age, gender, chest pain (type, frequency, course, nocturnal, length of time present), diabetes, smoking, hyperlipidaemia, hypertension, peripheral or cerebral artery disease, carotid bruit, prior MI, and significant Q waves and ST-T wave changes. For the presence of significant left main artery obstruction, the following variables were significant predictors; age, gender, chest pain (type), diabetes, peripheral or cerebral artery disease and carotid bruit. For survival at 3 years, the following variables were significant predictors; age, gender, chest pain (frequency, course, nocturnal), peripheral or cerebral artery disease, carotid bruit, ventricular gallop, prior MI, significant Q waves and ST-T wave changes, conduction abnormalities, premature ventricular contractions and cardiomegaly on chest X ray. (Pryor, D. B., Shaw, L., McCants, C. B. et al , 1993)

7 A study that developed a logistic regression model to predict CAD (> 70% coronary stenosis) in 211 patients with episodic chest pain (at least 2 episodes) admitted to hospital for elective coronary angiography found that the following were independent predictors of significant CAD; age > 60 years, pain brought on by exertion, patient having to stop all activities when pain occurs, history of MI, pain relieved within 3 minutes of taking nitroglycerin, at least 20 pack years of smoking, and male gender. The following were not independent predictors; location and radiation of pain, character of pain, hypertension, hypercholesterolaemia, history of angina, worsened by cough, deep breathing or movement of torso or arm. (Sox, H. C., Jr., Hickam, D. H., Marton, K., I et al , 1990)

8 A study in patients with stable episodic chest pain (at least 2 episodes) presenting to two primary healthcare settings (793

patients in total) and one secondary healthcare setting (170 patients) found that although patients in the primary and secondary settings had similar chest pain scores derived from the clinical history (pain, age, gender and smoking), the prevalence of CAD in the primary care patients was lower than the angiography patients across the first four scores bands compared with the angiography patients, while the prevalence at the highest score band was similar in both the primary and secondary healthcare settings. (Sox, H. C., Jr., Hickam, D. H., Marton, K., I et al , 1990)

9 A study in patients with stable episodic chest pain (at least 2 episodes) presenting to primary and secondary healthcare setting found that for older men with typical angina symptoms and who smoked the likelihood of CAD was similar in those presenting to primary care compared to in those referred for invasive coronary angiography. (Sox, H. C., Jr., Hickam, D. H., Marton, K., I et al , 1990)

10 A study in 405 patients with stable chest pain > 1 month and without a prior history of MI, coronary angiography, angioplasty or coronary artery bypass grafting found that the following predicted the likelihood of significant CAD (≥ 50% coronary stenosis); male gender, age, relief with rest, dizziness, smoking, hypertension, diabetes and a chest pain score. The physical examination gave little additional diagnostic information to the clinical history and the assessment of risk factors. (Wu, E. B., Hodson, F., and Chambers, J. B., 2005)

11 A study that selected patients from a registry representative of men in the primary healthcare setting (7735 patients) found that increased prevalence of CAD was associated with increasing severity of breathlessness. Breathlessness was more common in men with angina across all categories of breathlessness (none, mild, moderate, severe) compared with men with no chest pain or non exertional chest pain. (Cook, D. G. and Shaper, A. G., 1989)

12 No health economics evidence was found for history, risk factors and physical examination.

Back to recommendations

5.1.1.2 Clinical evidence for clinical history

What is the incremental benefit and cost-effectiveness of a clinical history, in evaluation of individuals with stable chest pain of suspected cardiac origin?

What is the incremental benefit and cost-effectiveness of assessment of cardiovascular risk factors in evaluation of individuals with stable chest pain of suspected cardiac origin?

What is the incremental benefit and cost-effectiveness of a physical examination in evaluation of individuals with stable chest pain of suspected cardiac origin?

One systematic review (Chun, Andrea Akita and McGee, Steven R., 2004) and seven cohort studies (Diamond, G. A. and Forrester, J. S., 1979) (Diamond, G. A., Staniloff, H. M., Forrester, J. S. et al , 1983) (Pryor, D. B., Harrell, F. E., Jr., Lee, K. L. et al , 1983) (Pryor, D. B., Shaw, L., McCants, C. B. et al , 1993) (Wu, E. B., Hodson, F., and Chambers, J. B., 2005) (Sox, H. C., Jr., Hickam, D. H., Marton, K., I et al , 1990) (Cook, D. G. and Shaper, A. G., 1989) were reviewed. For the purposes of our summary of the evidence, clinical history is defined as the information that the patient gives the health care professional at the time of presentation with chest pain. Cardiovascular risk factors are defined as known components of the medical history that increase the risk of developing or having CAD such as family history of premature CAD and prior history of MI, in addition to other factors such as age and gender. Physical examination is defined as that which elicits the patient's signs when they present with chest pain.

The systematic review (search date 2003) examined the use of the clinical history, risk factors and the physical examination in the assessment of patients presenting to outpatient clinics with stable intermittent chest pain that were subsequently referred for coronary angiography (Chun, Andrea Akita

and McGee, Steven R., 2004). The majority of studies excluded patients with valvular heart disease or non-ischemic cardiomyopathy. The diagnostic standard for diagnosing CAD was cardiac catheterization revealing substantial stenosis of any major epicardial vessel. The diagnostic standard in some studies was > 50% stenosis of any epicardial vessel, while in others it was > 70% to 75% stenosis. A total of 64 papers were identified. Likelihood ratios (LR for the presence (positive LR (PLR)) and absence (negative LT (NLR)) of CAD were calculated for the individual components of the clinical history, risk factors and physical examination (Chun, Andrea Akita and McGee, Steven R., 2004).

A summary of the main findings is shown in Table 2. Typical angina chest pain was defined as substernal discomfort precipitated by exertion, improved with rest or nitroglycerin (or both) in less than 10 minutes. Atypical angina chest pain was defined as substernal discomfort with atypical features; nitroglcerin not always effective, inconsistent precipitating factors, relieved after 15 to 20 minutes of rest. Non-anginal chest pain was defined as pain unrelated to activity, unrelieved by nitroglycerin and otherwise not suggestive of angina. Based on LR the most useful predictor of CAD was the presence of typical angina chest pain (7 studies; sensitivity range 50% to 91%, specificity range 78% to 94%, positive LR (PLR) 5.8 (95%CI 4.2 to 7.8)). The following risk factors were the most useful predictors of CAD; serum cholesterol > 300 mg/dl (2 studies; sensitivity range 24% to 29%, specificity range 93% to 94%, PLR 4.0 (95%CI 2.5 to 6.3)), prior history of MI (7 studies; sensitivity range 42% to 69%, specificity range 66% to 99%, PLR 3.8 (95%CI 2.1 to 6.8), NLR 0.6 (95%CI 2.1 to 0.6)), and age > 70 years (4 studies; sensitivity range 2% to 52%, specificity range 67% to 99%, PLR 2.6 (95%CI 1.8 to 4.0)). Hypertension, diabetes, smoking, moderate hypercholesterolaemia, family history of CAD and obesity were not helpful for diagnosis. For ruling out a diagnosis of CAD the most important component of the chest pain assessment were the presence of non-anginal chest pain (5 studies; sensitivity range 4% to 22%, specificity range 14% to 50%, PLR 0.1 (95%CI 0.1 to 0.2)), chest pain duration > 30 minutes (1 study: sensitivity 1%, specificity 86%, PLR 0.1 (95%CI 0.0 to 0.9)) and intermittent dysphagia (1

study: sensitivity 5%, specificity 80%, PLR 0.2 (95%CI 0.1 to 0.8)) (Table 1). The presence of atypical chest pain was less helpful compared with non-anginal chest pain respect to the PLR, although the specificity range was greater than that found for non-anginal pain (5 studies, sensitivity range 8% to 44%, specificity range 62% to 94%, PLR 1.2 (95%CI 1.1 to 1.3).The physical examination gave little additional diagnostic information for the diagnosis of CAD (Table 2) (Chun, Andrea Akita and McGee, Steven R., 2004).

1

Table 2

Diagnosing CAD in Patients with Stable, Intermittent Chest Pain					
If Finding is:					
Finding (number of studies)	Patient number	Sensitivity Range (%)	Specificity	Present Likelihood Ratio* (95% Confidence Interval)	Absent
Classification of chest pain					
Typical angina	11,544	50-91	78-94	5.8 (4.2-7.8)	-
Atypical angina	11,182	8-44	62-94	1.2 (1.1-1.3)	-
Non-anginal chest pain	11,182	4-22	14-50	0.1 (0.1-0.2)	-
Alleviating factors					
Nitroglycerin	380	60-74	29-56	1.2 (0.9-1.6)	0.7 (0.6-0.9)
Nitroglycerin within 5 minutes	380	53-63	69-71	1.9 (1.4-2.4)	0.6 (0.5-0.8)
Associated symptoms					
Dizziness	250	18	64	0.5 (0.3-0.8)	1.3 (1.1-1.5)
Dyspnea	250	63	30	0.9 (0.8-1.1)	1.2 (0.8-1.8)
Heart burn	130	38	63	1.0 (0.7-1.6)	1.0 (0.7-1.3)
Dysphagia	130	5	80	0.2 (0.1-0.8)	1.2 (1.0-1.4)
Duration of chest pain					
<5 minutes	130	86	65	2.4 (1.7-3.4)	0.2 (0.1-0.4)
>30 minutes	130	1	86	0.1 (0.0-0.9)	1.2 (1.0-1.3)
Frequency of chest pain					
>1/day	100	50	69	1.6 (0.9-3.0)	-
<1/day and >1/wk	100	19	81	1.0 (0.9-3.0)	-

<1/wk	100	31	50	0.6 (0.4-1.0)	-
Radiation					
Left arm	250	35	58	0.8 (0.6-1.2)	1.1 (0.9-1.4)
Right arm	250	21	86	1.5 (0.8-2.8)	0.9 (0.8-1.0)
Neck	250	19	80	1.0 (0.6-1.6)	1.0 (0.9-1.1)
Risk factors					
Male sex	17,593	72-88	36-58	1.6 (1.5-1.7)	0.3 (0.3-0.4)
Age (years)					
<30	14,569	0-1	97-98	0.1 (0-1.1)	-
30-49 †	15,681	16-38	47-57	0.6 (0.5-0.7)	-
50-70	15,481	62-73	44-56	1.3 (1.3-1.4)	-
>70	15,266	2-52	67-99	2.6 (1.8-4.0)	-
Hypertension	1478	36-60	55-78	1.2 (1.0-1.6)	0.9 (0.7-1.0)
Diabetes	1478	10-29	86-97	2.3 (1.7-3.1)	0.9 (0.8-0.9)
Current/past tobacco use	1478	42-77	47-68	1.5 (1.3-1.6)	0.7 (0.6-0.8)
Cholesterol (mg/dL)					
<200					
201-250	1585	10-11	58-71	0.3 (0.2-0.4)	-
251-300	1585	27-31	60-65	0.8 (0.7-0.9)	-
>300	1585	34-35	76-83	1.7 (1.2-2.3)	-
	1585	24-29	93-94	4.0 (2.5-6.3)	-
Family history of CAD	1003	41-65	33-57	1.0 (0.9-1.1)	1.0 (0.9-1.1)
Prior myocardial infarction	8216	42-69	66-99	3.8 (2.1-6.8)	0.6 (2.1-0.6)
Obesity	387	43-45	54-74	1.3 (0.8-2.1)	0.9 (0.7-1.1)
Number of Risk Factors ‡					

None	6434	7	78	0.3 (0.3-0.4)	-
Any 1	6434	35	57	0.8 (0.8-0.9)	-
Any 2	6434	39	73	1.4 (1.3-1.6)	-
3 or more	6434	18	92	2.2 (1.9-2.6)	-
Physical examination					
Earlobe crease	1338	26-80	33-96	2.3 (1.3-4.1)	0.6 (0.4-0.8)
Chest wall tenderness	442	1-25	69-97	0.7 (0.4-1.1)	1.0 (1.0-1.1)
Ankle-brachial index <0.9	165	20	95	4.1 (1.0-17)	0.8 (0.8-0.9)
Arcus senilis	200	40	86	3.0 (1.0-8.6)	0.7 (0.6-0.8)

*Likelihood ratio if finding is present = positive; ratio if finding is absent = negative.

†Pooled estimate for age 30-49 includes two studies that combined age <30 yrs and age 30-49yrs

‡Risk factors in this study included smoking (>25 pack-years or more than half pack per day within 5 years of catheterization) diabetes mellitus, hypertension (systolic >140 mm Hg) and hyperlipidemia (fasting cholesterol level > 250 mg/dL).

Permission requested from original source (Chun, Andrea Akita and McGee, Steven R., 2004).

Comparison of studies that used a diagnostic standard of > 50% coronary stenosis versus > 70% to 75% coronary stenosis found that the pooled PLRs were comparable. In studies using > 50% stenosis, the pooled PLR were 5.6 for typical angina chest pain, 1.1 for atypical chest pain, and 0.1 for non-anginal chest pain. In studies using > 70 to 75% stenosis, the PLR were 5.6 for typical angina chest pain, 1.3 for atypical chest pain, and 0.1 for non-anginal chest (Chun, Andrea Akita and McGee, Steven R., 2004).

The first cohort study assessed the use of analysis of probability as an aid in the clinical diagnosis of CAD according to concepts included in Bayes' theorem of conditional probability (Diamond, G. A. and Forrester, J. S., 1979). The aim of the study was to demonstrate that using information available from the clinical evaluation of a given patient could determine the probability of CAD prior to testing. The study examined the prevalence of CAD in 4952 symptomatic patients referred for coronary angiography identified from a

review of the literature that classified the patients as having 'typical angina', 'atypical angina' or non-anginal chest pain'. The study also examined the mean prevalence of CAD in an unselected population of 23 996 persons at autopsies (Diamond, G. A. and Forrester, J. S., 1979).

Typical angina was defined as (1) constricting discomfort in the anterior chest, neck, shoulders, jaw or arms, (2) precipitated by physical exertion or psychological stress, and (3) relieved by rest or nitroglycerin within minutes. Atypical angina was defined as 2 out of 3 of these symptoms, and non-anginal chest pain was defined as less than 2 of these features. Table 3 summarises the prevalence of angiographically confirmed CAD in the 4953 patients; the prevalence of disease in patients with typical angina symptoms was about 90%, whereas for atypical angina patients the prevalence was 50% ($P < 0.001$), and for non-anginal patients was 16% ($P < 0.001$) (Diamond, G. A. and Forrester, J. S., 1979).

Table 3

Prevalence of angiographic CAD in symptomatic patients

Symptom	Proportion of Patients affected	Pooled mean ± SEP* (%)
Non-anginal chest pain	146/913	16.0±1.2
Atypical angina	963/1931	49.9±1.1
Typical angina	1874/2108	88.9±0.7

*Standard error of the per cent. These values establish statistical levels of error but do not include errors due to sampling bias and other factors, which are probably of greater magnitude.

Permission requested from source (Diamond, G. A. and Forrester, J. S., 1979).

Table 4 details the results of the prevalence of coronary artery stenosis at autopsy from 23 996 unselected persons. The mean prevalence of CAD in

this population was 4.5%. Significant differences in disease prevalence occurred when subjects were classified according to age and sex. Differences ranged from 1.9% for men aged 30 to 39 years of age, to 12.3% for men aged 60 to 69 years. For women the differences ranged from 0.3% for women aged 30 to 39 years of age, to 7.5% for women aged 60 to 69 years. Women in all age groups had a lower prevalence of coronary artery stenosis compared with the respective age groups in men (Diamond, G. A. and Forrester, J. S., 1979).

Table 4

Prevalence of coronary artery stenosis at autopsy

Age	Men		Women	
Year	Proportion affected	Pooled mean ± SEP* (%)	Proportion affected	Pooled mean ± SEP (%)
30 -39	57/2954	1.9±0.3	5/1545	0.3±0.1
40-49	234/4407	5.5±0.3	18/1778	1.0±0.2
50-59	488/5011	9.7±0.4	62/1934	3.2±0.4
60-69	569/4641	12.3±0.5	130/1726	7.5±0.6
Totals	1348/17 013		215/6983	
Population-weighted mean †		6.4±0.2		2.6±0.2

*Standard error of the per cent

† Population weighting was performed by use of the 1970 US Census figures.

Permission requested from source (Diamond, G. A. and Forrester, J. S., 1979).

An estimate of disease likelihood was made based on the patient's age and gender from data detailed in Table 5, and a second estimate of disease likelihood was determined using data on the presence or absence of

symptoms detailed in Table 3. A pre-test likelihood of CAD was estimated for any patient (according to any combination of age, sex and symptoms) as determined by conditional-probability analysis. The results of the analysis are shown in Table 5. There was a wide range of pre-test likelihoods according to sex, gender and symptoms. For example the analysis found that a woman in the age range 30 to 39 years with atypical symptoms had a pre-test likelihood of 4% compared with 92% for a man in the age range 50 to 59 years with typical symptoms (Diamond, G. A. and Forrester, J. S., 1979).

Table 5

Pre-test likelihood of CAD in symptomatic patients according to age and sex.*

Age	Non-anginal chest pain		Atypical angina		Typical angina	
Year	Men	Women	Men	Women	Men	Women
30-39	5.2±0.8	0.8±0.3	21.8±2.4	4.2±1.3	69.7±3.2	25.8±6.6
40-49	14.1±1.3	2.8±0.7	46.1±1.8	13.3±2.9	87.3±1.0	55.2±6.5
50-59	21.5±1.7	8.4±1.2	58.9±1.5	32.4±3.0	92.0±0.6	79.4±2.4
60-69	28.1±1.9	18.6±1.9	67.1±1.3	54.4±2.4	94.3±0.4	90.6±1.0

*Each value represents the percent ±1 standard error of the per cent, calculated from the data in Tables and 3.

Permission requested from source (Diamond, G. A. and Forrester, J. S., 1979).

The second cohort study evaluated the use of a micro computer software programme (CADENZA, which utilized Bayes' theorem of conditional probability) to analyse and report the results of various clinical variables relative to the diagnosis of CAD (Diamond, G. A., Staniloff, H. M., Forrester, J. S. et al , 1983). The study comprised 1097 consecutive patients evaluated by noninvasive testing for suspected CAD without prior MI or coronary artery bypass surgery. The majority of the patients were referred for testing due to

symptoms or findings consistent with possible myocardial ischaemia, the remaining were a heterogeneous asymptomatic group referred from various settings. The mean age of the patients was 56±11 years, and 70% were male. Each patient was evaluated for risk factors according to Framingham criteria (Salel, A. F., Fong, A., Zelis, B. S. et al , 1977) each patient had a clinical evaluation, underwent an exercise ECG, and subsequently underwent at least one additional diagnostic test (cardiokymography, cardiac fluoroscopy for coronary calcium, thallium perfusion scintigraphy, and technetium-gated blood pool scintigraphy) (Diamond, G. A., Staniloff, H. M., Forrester, J. S. et al , 1983).

Patients were considered to have typical angina if they had substernal discomfort brought on by physical exertion and was relieved within 10 minutes through rest or nitroglycerin. Patients were considered to have atypical angina if they had only 2 of the defined factors for typical angina. Patients were considered to have non-anginal discomfort if they had 1 of the defined characteristics of typical angina (Diamond, G. A., Staniloff, H. M., Forrester, J. S. et al , 1983).

A total of 170 patients from 1097 outpatients were subsequently referred for diagnostic coronary angiography (15%). CAD was defined as luminal narrowing ≥ 50%. Outcomes were; predicted probability of CAD from the CADENZA software programme compared with the prevalence of CAD according to the number of diseased vessels, and cardiac events at 1 year follow up (Diamond, G. A., Staniloff, H. M., Forrester, J. S. et al , 1983).

There was no significant difference between the predicted probability and the angiographic findings when the predicated probability was based on the age and sex of the patient within each symptom class (asymptomatic, non-anginal discomfort, atypical angina and typical angina). In each symptom class, the probability of CAD was consistently slightly higher in the 124 patients found to have CAD compared with the 46 patients that were found not to have CAD, but this was not significant. When the predicted probability findings were compared with the initial Framingham risk scores there was a reasonable correlation independent of the factor of symptom class. These findings

indicated that the Framingham risk factors were modest discriminators for CAD independent of symptom classification. All 170 patients underwent exercise ECG, 93 patients had cardiokymography, 82 patients had cardiac fluoroscopy for coronary calcium, 115 patients had thallium perfusion scintigraphy, and 102 patients had technetium-gated blood pool scintigraphy. Table 6 details the probability of disease according to the number of diseased vessels found at coronary angiography. These data were assessed in 3 ways; (1) based on age, sex, symptom class and risk factors prior to diagnostic test, (2) based on all available data prior to catheterization, (1), stress ECG plus at least one other noninvasive test and (3) based on every combination of the tests performed on each patient; (1) (2) and coronary angiography. For each case, the probability of disease tended to increase in proportion to the number of diseased vessels however the standard deviations were large (Diamond, G. A., Staniloff, H. M., Forrester, J. S. et al , 1983).

Table 6

CAD Probability and Angiography					
Number of Diseased Vessels					
	0	**1**	**2**	**3**	**1+2+3**
Patients (no.)	46	21	46	57	124
Estimates before testing; age, sex, symptom class and risk factors					
Mean Probability	0.291	0.595	0.623	0.660	0.635
Standard deviation	0.259	0.342	0.334	0.327	0.332
Estimates before angiography; age, sex, symptom class and risk factors stress ECG plus at least one other non-invasive test					
Mean Probability	0.253	0.745	0.772	0.843	0.800
Standard deviation	0.322	0.387	0.321	0.284	0.315
All estimates; age, sex, symptom class and risk factors, stress ECG plus at least one other non-invasive test, coronary angiography					
Test combination	500	316	640	724	1680
Mean probability	0.304	0.557	0.730	0.746	0.704

Standard deviation	0.321	0.377	0.323	0.331	0.322
Test Combination refers to the following accumulated tests; age, sex, symptom class and risk factors prior to diagnostic test, stress ECG plus at least one other noninvasive test, coronary angiography. Permission requested from source (Diamond, G. A., Staniloff, H. M., Forrester, J. S. et al , 1983).					

The study found that the mean predicted probability for CAD increased from 30% for the patients without angiographic disease to 56% for patients with 1 vessel disease, 73% for those with 2 vessel disease and 75% for patients with 3 vessel disease. There was overlap between the distribution of the data sets especially for those with 2 and 3 vessel disease, which were not significantly different. Eight percent of the probability estimates for patients without angiographic disease were in excess of 90%, while 9.7% of the probability estimates for the patients with angiographic disease were under 10%. The average difference between the observed prevalence of disease and that predicted by the probability of CAD was 3.4% for estimates based on sex, age, symptoms and risk factors (Diamond, G. A., Staniloff, H. M., Forrester, J. S. et al , 1983).

The study also assessed the predicted probability of CAD and the observed extent of disease. It was found that if the patient had a probability of below 25% when disease was present, single vessel disease was slightly more prevalent than multi-vessel disease. Above a probability of 75%, multi-vessel disease predominated. At a probability of 100%, multi-vessel disease accounted for 89% of all angiographic disease. These findings indicated that disease probability was a reasonable quantitative measure of anatomic severity (Diamond, G. A., Staniloff, H. M., Forrester, J. S. et al , 1983).

Table 7 details the results of probability of CAD and future coronary events. Data were available in 969 of the 1097 outpatients initially recruited. Five patients were excluded due to non cardiac death and follow up was interrupted by referral for coronary artery bypass surgery in 47 patients. There were 15 (1.6%) cardiac events (7 non fatal MIs and 8 cardiac deaths) in the 922 patients who did not undergo coronary angiography or cardiac bypass surgery during the 1 year follow-up. As stated each of the initial outpatients

had a clinical history taken and a risk determination performed, and underwent from 2 to 5 non-invasive events (average 3.3 per patient) providing from 4 to 32 different test combinations per patient. Thus a total of 9628 test combinations were analysed; 8900 estimates in the 970 patients without morbid events, 592 in the 47 surgical and 136 in the 15 patients with cardiac events. The event rates for MI and for cardiac death were similar in magnitude. When the data from the patients lost to follow up were included, and the data normalized the event rates were predicted to be; 3.1% for total events, 1.7% for MI, and 1.4% for cardiac death. It was stated that these findings were consistent with other studies of prevalence in stable chest pain patients with suspected CAD (Diamond, G. A., Staniloff, H. M., Forrester, J. S. et al , 1983).

Table 7

One Year Follow-Up for Coronary Events

Class	No. of patients	No. of estimates	CAD probability	Standard Deviation
Observed (patients)				
No events	907		0.486	0.403
Bypass surgery	47		0.898	0.251
Myocardial infarction	7		0.874	0.308
Cardiac Death	8		0.795	0.333
Observed (estimates)				
No events		8900	0.527	0.381
Bypass surgery		592	0.858	0.252
Myocardial infarction		72	0.816	0.282
Cardiac Death		64	0.746	0.301
Predicted (estimates)				
No events		5250*	0.547	0.375
Myocardial infarction		92¶	0.825	0.276
Cardiac Death		76†	0.763	0.294

*Includes 4690 estimates from posterior probability to have disease but no event, and 560 surgical estimates predicted from figure 7 not to have an event: (8900 x 0.527) + (592-20-12) = 5250. ¶Includes 20 surgical estimates predicted from figure 7 to have infarction. †Includes 12 surgical estimates predicted from figure 7 to have a cardiac death.

Permission requested from source (Diamond, G. A., Staniloff, H. M., Forrester, J. S. et al , 1983).

The third study aimed to determine which characteristics from the initial clinical assessment of patients with stable chest pain were important for estimating the likelihood of significant CAD (Pryor, D. B., Harrell, F. E., Jr., Lee, K. L. et al , 1983). A total of 5438 patients were included in the study. This patient population was divided into two groups; a 'training' sample of 3627 patients that were used to develop a model for predicting the probability of significant CAD using stepwise logistic regression analysis, and a 'test' population of 1811 patients. The model was used in the test population to predict the probability of significant CAD for each patient. The model was validated in a separate population giving an estimate of prevalence of CAD (Chaitman, B. R., Bourassa, M. G., Davis, K. et al , 1981).

The model used variables taken from the clinical history, risk factors and physical examination, and results of the chest X ray and ECG. Patients were considered to have typical angina if they had substernal discomfort brought on by physical exertion and was relieved within 10 minutes through rest or nitroglycerin. Patients were considered to have atypical angina if they had only 2 of the defined factors for typical angina. Patients were considered to have non-anginal discomfort if they had 1 of the defined characteristics of typical angina (Diamond, G. A., Staniloff, H. M., Forrester, J. S. et al , 1983). Progressive chest pain was defined as an increasing frequency, duration or severity in the previous 6 weeks before catheterization. Preinfarction pain was defined as a very unstable chest pain pattern that resulted in admission of the patient to the coronary care unit for evaluation of possible MI. Duration of chest pain was determined either from the time chest pain first developed in the patient, or from when the patient experienced a MI. For a determination of prior MI, only diagnostic Q waves were accepted as ECG evidence.

Significant CAD was defined as ≥ 70% luminal narrowing (Pryor, D. B., Harrell, F. E., Jr., Lee, K. L. et al , 1983).

Of the 5438 patients that were referred, 3645 patients had significant CAD. In training group of 3627 patients, 2379 patients had CAD and 1266 patients did not. In the 'test group' of 1811, 1266 patients had CAD and 545 did not. The results of the clinically important characteristics which determined the presence of CAD are detailed in Table 8 and the poor clinical predictors in Table 9. The results from the training population found the type of chest pain (typical, atypical or non-anginal) was the most important characteristic followed by previous MI, sex, age, smoking, hyperlipidaemia, ST-T wave changes on ECG, and diabetes. The study also found that in men the effect of an increasing age was more important than in women, smoking was more important for women than men, and that smoking and hyperlipidaemia were more important at younger ages (Pryor, D. B., Harrell, F. E., Jr., Lee, K. L. et al , 1983).

Table 8

Clinically Important Characteristics	
Chi-Square*	
Pain Type (typical, atypical, nonanginal)	1,091
Previous Myocardial Infarction (history only, electrocardiographic evidence only, both, none)	511
Sex	187
Age	119
Smoking	79
Hyperlipidemia	26
ST-T wave changes	28
Diabetes	12

Interactions Age x sex Age x smoking Age x hyperlipidemia Sex x smoking
* Chi-square added to the model, adjusted for the characteristics that precede it. Permission requested from source (Pryor, D. B., Harrell, F. E., Jr., Lee, K. L. et al , 1983).

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Table 9

Poor Clinical Predictors of Significant CAD	
	Chi-Square*
Chest Pain Severity	0.96
Chest Pain Frequency	8.57
Nocturnal Chest Pain	2.22
Progressive Chest Pain	2.54
Preinfarctional Angina	9.70
Vascular Disease	0.40
Duration of CAD	9.16
Congestive Heart Failure	0.59
Hypertension	5.19
Family History	6.39
Ventricular Gallop	1.06
Cardiomegaly	1.41
Electrocardiographic Premature Ventricular Contractions	0.46
* Adjusted for model variables. Chi-Square greater than 3.84, $P < 0.05$.	
Permission requested from source (Pryor, D. B., Harrell, F. E., Jr., Lee, K. L. et al , 1983).	

2

Validation of the logistic regression model developed from the clinically important characteristics found that the predicted probability of disease was nearly identical to that observed in the test population. The median prediction for a patient with significant CAD was 94% compared with 33% for patients without disease. A predicted disease probability of greater than 0.83 was found in 75% of patients with CAD, and in less than 10% for patents without disease. Conversely a probability of significant disease of less than 0.33 was found in nearly 50% of patients without disease, and in less than 5% with disease. Comparison of the model with an external population (Chaitman, B. R., Bourassa, M. G., Davis, K. et al , 1981) found that the predicted estimates from the model were nearly equal to the observed prevalence of disease (Pryor, D. B., Harrell, F. E., Jr., Lee, K. L. et al , 1983).

The fourth study examined a regression model based on clinical history and risk factors for the diagnosis of CAD in a stable chest pain population with suspected CAD (Pryor, D. B., Shaw, L., McCants, C. B. et al , 1993). The predictive regression model applied to the study population had previously been developed and tested (Pryor, D. B., Harrell, F. E., Jr., Lee, K. L. et al , 1983). One thousand and thirty consecutive patients referred to an outpatient department for coronary angiography were considered. One hundred and sixty eight of these were the final study population and were subsequently referred for cardiac catheterization within 90 days. The study had three diagnostic outcomes of; presence of significant CAD (≥ 75% luminal diameter narrowing of at least one major coronary artery), the presence severe CAD (presence of significant obstruction of all three major arteries or the left main coronary artery), and the presence of significant left main coronary artery obstruction. There was one prognostic outcome of survival at 3 years (Pryor, D. B., Shaw, L., McCants, C. B. et al , 1993).

The baseline characteristics of the 1030 outpatients and the subgroup of 168 patients were broadly similar except that the168 patient group were more likely to be male compared with the 1030 outpatients (41% versus 6%, respectively), more likely to smoke (32% versus 4%, respectively) more likely to have a history of prior MI (20% versus 2%, respectively), and more likely to

have typical angina (29% versus 3%, respectively) or progressive angina (14% versus 2%, respectively). The mean age of the 2 groups was similar; all 1030 outpatients; 55 years (range 45 to 63 years) versus 168 patients referred; 56 years (range 48 to 65 years (Pryor, D. B., Shaw, L., McCants, C. B. et al , 1993).

Of the 168 patients, 109 patients had significant CAD (≥ 75% luminal diameter narrowing of at least one major coronary artery), 45 patients had severe CAD (presence of significant obstruction of all three major arteries or the left main coronary artery), and 12 patients had significant left main coronary artery obstruction. Follow-up information was available in 973 of the 1030 patients (94%). At the end of 3 years, 844 patients were alive (and had not undergone revascularization), 30 had died of cardiovascular causes, 19 had died of non cardiac causes, 18 had undergone angioplasty, and 62 had had coronary artery bypass graft surgery (Pryor, D. B., Shaw, L., McCants, C. B. et al , 1993).

The regression model showed that the following variables were significant predictors for any disease; age, gender, chest pain (type), diabetes, smoking, hyperlipidaemia, prior MI, and significant Q waves and ST-T wave changes. For severe disease, the following variables were significant predictors; age, gender, chest pain (type, frequency, course, nocturnal, length of time present), diabetes, smoking, hyperlipidaemia, hypertension, peripheral or cerebral artery disease, carotid bruit, prior MI, and significant Q waves and ST-T wave changes. For left main disease, the following variables were significant predictors; age, gender, chest pain (type), diabetes, peripheral or cerebral artery disease and carotid bruit. For survival, the following variables were significant predictors; age, gender, chest pain (frequency, course, nocturnal), peripheral or cerebral artery disease, carotid bruit, ventricular gallop, prior MI, significant Q waves and ST-T wave changes, conduction abnormalities, premature ventricular contractions and cardiomegaly on a chest X ray (Pryor, D. B., Shaw, L., McCants, C. B. et al , 1993).

The observed prevalence of significant CAD was nearly identical to the model prediction, indicating that the initial clinical evaluation closely corresponded to

actual findings. Predicted CAD endpoints and survival based on the initial evaluation closely corresponded to actual findings. The ability to separate patients with and without the outcome of interest was assessed using a concordance probability or c-index; the c-index was calculated by pairing each patient who had the outcome with each patient who did not have the outcome and determining the proportion of pairs in which the patient with the outcome had the estimated probability. The c-index ranges from 0 to 1; with 1 corresponding to perfect discrimination, 0.5 to random performance of the predictor, and 0 equating to perfectly incorrect discrimination. The c-index for significant disease was equal to 0.87 (95%CI 0.82 to 0.93) demonstrating that the model correctly rank ordered pairs of patients with respect to their disease state 87% of the time. The c-index for severe disease estimates was 0.78% (95%CI 0.71 to 0.85). The c-index for left main disease estimates was 0.78% (95%CI 0.71 to 0.85). As c-indices for severe and left main disease were lower than for significant disease the model was less able to predict these outcomes. The c-index for survival at 3 years was 0.82% (95%CI 0.64 to 0.99), indicating that 82% of the time a patient who died was given a lower predicted 3 year survival probability compared with a patient who survived (Pryor, D. B., Shaw, L., McCants, C. B. et al , 1993).

Predictions using the initial clinical evaluation were then compared with predictions based on a treadmill exercise test. The initial clinical evaluation was slightly better at distinguishing patients with and without CAD compared with the treadmill exercise test. The initial evaluation and the treadmill exercise test had similar discriminatory performances for patients with and without severe disease and risk of death at 3 years, while for left main disease, the treadmill exercise test was slightly better for identifying patients with left main disease (Pryor, D. B., Shaw, L., McCants, C. B. et al , 1993).

The fifth cohort study examined the clinical characteristics of chest pain and a chest pain score for the prediction of CAD (Wu, E. B., Hodson, F., and Chambers, J. B., 2005). Four hundred and five patients with stable chest pain were recruited. Inclusion criteria were; chest pain for > 1 month without a prior MI, percutaneous coronary intervention, or coronary artery bypass surgery.

Patients were excluded if their ECG showed pathological Q waves or regional wall motion abnormalities on echocardiogram. Patients were evaluated using a chest pain score based on the following; localisation of pain, radiation, quality of pain, duration, length of pain episode, frequency, associated features (breathlessness, digital paraesthesiae, palpitations, light-headedness), precipitation (exercise, rest, any time, neck or back movement, carrying, swallowing, lying flat / stooping, emotional stress, particular situations), exacerbated with inspiration, relieved within 5 minutes with GTN ,and relieved with milk/antacids, belching, local massage or rest). These variables were determined using a questionnaire. A medical history was also taken of hypertension, hypercholesterolemia, diabetes, smoking and number of cigarettes per day, previous MI, alcohol intake per week, medication being used (aspirin, statins, beta blockers, calcium antagonists, nitrates, other). The following were also recorded; weight, height, heart rhythm, blood pressure, heart rate, stigmata of risk (arcus, xanthelasmata, xanthomata, ear lobe crease) on clinical examination, apex position and character, heart murmur and heart sounds from examination of the praecordium and a resting ECG. All patients underwent angiography and CAD was considered significant at > 50% stenosis (Wu, E. B., Hodson, F., and Chambers, J. B., 2005).

The mean age of the 405 outpatients included in the study was 60.6±9.5 years and 66% were male. Sixty percent of patients had significant CAD and 40% had normal coronary anatomy. As detailed in Table 10 multivariate Poisson regression analysis found that only gender ($P < 0.001$), age ($P <$ 001), relief with rest ($P = 0.046$), dizziness ($P = 0.030$), smoking ($P = 0.006$), hypertension ($P = 0.0146$), and the chest pain score ($P = 0.009$) independently differentiated those patients with and without CAD (Wu, E. B., Hodson, F., and Chambers, J. B., 2005).

Table 10

Multivariate Poisson regression analysis of significant univariate variables and demographic data

Variable	RR	Robust SE	Z	95% CI of RR	*p*
Sex (male)	1.69	0.191	4.69	1.36-2.11	<0.0001***
Age	1.02	0.005	5.33	1.02-1.03	<0.0001***
Radiation to back	0.77	0.107	-1.89	0.59-1.01	0.058
Relief with rest	1.20	0.112	2.00	1.00-1.44	0.046*
Relief with nitrate <5minutes	1.25	0.203	1.37	0.91-1.72	0.170
Relief with nitrates	0.94	0.156	-0.37	0.68-1.30	0.715
Tingling with pain	0.94	0.084	-0.66	0.79-1.12	0.512
Palpitations	0.86	0.095	-1.33	0.70-1.07	0.182
Dizziness	0.78	0.090	-2.17	0.62-0.98	0.030*
Smoking	1.23	0.091	2.75	1.06-1.42	0.006**
Family history	0.93	0.065	-1.06	0.81-1.07	0.291
Hypertension	1.19	0.083	2.42	1.03-1.36	0.016*
Hypercholesterolaemia	1.09	0.076	1.24	0.95-1.25	0.214
Diabetes	1.30	0.143	2.41	1.05-1.62	0.016*
Chest pain score = 3	1.20	0.085	2.60	1.05-1.38	0.009**

*p<0.05; **p<0.01; ***p<0.001

Permission requested from source (Wu, E. B., Hodson, F., and Chambers, J. B., 2005).

The sixth cohort study compared the prevalence of CAD in patients with similar chest pain histories from primary and secondary healthcare settings using a logistic chest pain score in order to identify patients with CAD (Sox, H. C., Jr., Hickam, D. H., Marton, K., I et al , 1990). Patients were enrolled only if they had at least 2 episodes of chest pain that led to the index visit. Patients whose index visit led to a diagnosis of acute MI were excluded. The 'training'

set of patients used to develop the score was recruited from patients undergoing elective coronary arteriography (211 patients). Seven clinical characteristics were identified as independent predictors of significant coronary stenosis (> 70% coronary stenosis), namely; age > 60 years, pain brought on by exertion, patient having to stop all activities when pain occurs, history of MI, pain relieved within 3 minutes of taking nitroglycerin, at least 20 pack years of smoking, and male gender. These components were used to develop the chest pain score; a linear combination of the independent predictors, each weighted according to it diagnostic value. The sum of the weights that correspond to a patient's findings is the logistic chest pain score. The following were not independent predictors of disease status; location and radiation of pain, character of pain, history of hypertension, history of hypercholesterolaemia, history of angina pectoris, pain worsened by cough, deep breathing, movement of torso, or movement of arm (Sox, H. C., Jr., Hickam, D. H., Marton, K., I et al , 1990).

The chest pain score was used to test the probability of CAD in patients from two primary care practices (793 patients in total) and one angiography referral practice (170 patients). Each patient was placed in a category based on their chest pain score. Although the patients in the primary and secondary settings had similar chest pain scores derived from the clinical history, the prevalence of CAD in the primary care patients was lower than the angiography patients across the first four scores bands compared with the angiography patients, while the prevalence at the highest score band was similar in both the primary and secondary settings (detailed in **Table 11**). The authors concluded that health care professionals should take in to account the clinical setting when using the patient's history to estimate the probability of disease (Sox, H. C., Jr., Hickam, D. H., Marton, K., I et al , 1990).

Table 11

Distribution of Patients among Chest Pain Score Subgroups

	Training Set			Test Set 1 Secondary care setting			Test Set Primary care setting			Test Set Primary care setting		
Score	CAD+	CAD-	pCAD	CAD+	CAD-	pCAD	CAD+	CAD-	pCAD	CAD+	CAD-	pCAD
0-4	1	9	0.10	1	6	0.14	0	4	0.00	0	98	0.00
5-9	13	20	0.39	4	13	0.24	9	139	0.06	7	118	0.06
10-14	33	16	0.67	31	13	0.70	27	99	0.21	4	35	0.10
15-19	77	8	0.91	49	10	0.83	64	26	0.71	6	14	0.30
20-25	34	0	1.00	37	6	0.86	33	3	0.92	6	1	0.86
Total	158	53	0.76	122	48	0.72	133	271	0.33	23	266	0.08

CAD+ = patients with significant CAD by arteriogram or a clinical diagnosis of CAD; CAD- = patients with insignificant CAD by coronary arteriogram or a clinical diagnosis of non cardiac pain; pCAD = the prevalence of CAD

Permission requested from source (Sox, H. C., Jr., Hickam, D. H., Marton, K., I et al , 1990).

The seventh cohort study examined the symptom of breathlessness as an indicator for angina and CAD (Cook, D. G. and Shaper, A. G., 1989). A total of 7735 men aged between 40 to 59 years were randomly selected from the British Regional Heart Study (Shaper, A. G., Pocock, S. J., Walker, M. et al , 1981) a registry representative of subjects in the primary care setting (Cook, D. G. and Shaper, A. G., 1989).

The men in the study were classified into 3 groups based on the smoking status at selection; never smoked, ex-smoker, or current smoker. A modified version of the Medical Research Council Questionnaire on Respiratory Symptoms (1966 version) was used for the assessment. The participants were asked 3 questions. (1) Do you get short of breath walking with people of your own age on level ground? (2) On walking up hills or stairs do you get

more breathless than people your own age? (3) Do you ever have to stop walking because of breathless? Each affirmative answer was scored 1, giving a score of 0 to 3, where 0 equated to no breathlessness, 1 to mild breathlessness, 2 to moderate breathlessness, and 3 to severe breathlessness. Lung function was recorded. The presence of CAD was determined in one of three ways at the initial evaluation; (1) according the World Health Organization questionnaire on chest pain covering both angina and possible MI which was administered by a nurse (Gillum, R. F., Fortmann, S. P., Prineas, R. J. et al , 1984) (2) recording of a 3-lead ECG where CAD on the ECG includes definite and possible MI and definite myocardial ischaemia, but not possible myocardial ischaemia and (3) recall by the subject of a physician's diagnosis of angina or MI (recall CAD) (Cook, D. G. and Shaper, A. G., 1989).

Increased prevalence of CAD was associated with increasing breathlessness, irrespective of the method of diagnosis, although the strongest association was found for angina diagnosed by questionnaire and patient recall of a physician's diagnosis (Table 12)

Breathlessness was more common in men with angina across all grades compared with no chest pain or non exertional chest pain (**Table 13**).

Table 12

Age-Standardized Prevalence Rates of CAD at Screening by Breathlessness Grade*

Breathlessness	No. of men	Recall (%)	ECG (%)	Possible MI (%)	Angina (%)
None	6394	3.5	6.5	7.0	4.4
Mild	697	8.7	9.1	12.6	15.5
Moderate	358	17.7	14.6	21.6	28.8
Severe	273	27.6	18.5	33.3	40.9
All	7722	5.5	7.6	9.1	7.9

*CAD categories are not mutually exclusive.

CAD = CAD, ECG = electrocardiogram, MI = myocardial infarction

Permission requested from source (Cook, D. G. and Shaper, A. G., 1989).

Table 13

Prevalence of Angina in Relation to Breathlessness

Chest pain	Breathlessness Grade				
	None	Mild	Moderate	Severe	All
None (%)	4550 (89)	370 (7)	142 (3)	70 (1)	5132 (100)
Non-exertional pain (%)	1562 (79)	220 (11)	107 (5)	84 (4)	1973 (100)
Possible angina					
Grade 1 (%)	104 (51)	36 (18)	33 (16)	30 (15)	203 (100)
Grade 2 (%)	11 (31)	3 (9)	6 (17)	15 (43)	35 (100)
Definite angina					
Grade 1 (%)	138 (45)	67 (22)	57 (19)	44 (14)	306 (100)
Grade 2 (%)	18 (30)	1 (2)	12 (20)	29 (48)	60 (100)

Rates are not age-standardized.

Grade 1 angina is brought on by walking uphill, grade 2 angina is brought on by walking on the level.

Permission requested from source (Cook, D. G. and Shaper, A. G., 1989).

During 5 years of follow up of the 7735 subjects there were 166 non fatal MIs, 119 fatal MIs or sudden cardiac deaths, and 155 deaths from non ischaemic causes. At 5 years a postal questionnaire was sent to all subjects, and based on 7275 replies men were classified according to whether they had angina or CAD. **Table 14** details the age-standardised prevalence of angina at 5 years (according to postal questionnaire) to the initial breathlessness finding and the initial diagnosis of angina at presentation. A diagnosis of angina at initial screening was associated with a high prevalence at 5 years, and those

patients with initial moderate or severe breathlessness were more likely to be positive on the angina questionnaire at 5 years. Five percent of patients at presentation that reported no breathlessness (nor were they diagnosed with angina at presentation) were found to have angina at 5 years, suggesting that breathlessness may be an early indicator of angina (Cook, D. G. and Shaper, A. G., 1989).

Table 14

Age-Standardized Prevalence Rate of Angina in Percent (Definite + Possible) Five Years After Initial Screening

Breathlessness at Initial Screening	Angina Present at Initial Screening	
	No	Yes
None	5.8 (317)	47.1 (112)
Mild	13.0 (69)	44.9 (44)
Moderate	24.6 (56)	58.6 (56)
Severe	28.2 (37)	74.4 (73)

The population base comprises the 7.099 men for whom a fifth year chest pain questionnaire is available.

Number of cases of angina given in parenthesis.

Permission requested from source (Cook, D. G. and Shaper, A. G., 1989).

5.1.1.3 Health economic evidence

No health economic evidence was identified from a literature search undertaken for this question.

5.1.1.4 Evidence to recommendations

The GDG found from their appraisal of the evidence that in patients with chest pain, the diagnosis of angina was being made as that due to CAD, although they recognised that symptoms of angina can occur as a consequence of other cardiac pathology. The clinical history in patients with chest pain not only includes a description of the location and nature of the chest pain itself, but other associated features such as its duration, exacerbating and relieving factors and associated symptoms. One high quality systematic review and four well conducted cohort studies have identified single characteristics which when present make the diagnosis of angina more or less likely. However, it is the combination of the characteristics which are usually considered in the clinical history. Two cohort studies have developed chest pain scores, whilst other studies have recognised three distinct categories; typical angina, atypical angina and non-anginal chest pain. Four cohort studies found that the pre-test likelihood that chest pain is due to angina in the presence of CAD can be predicted from the symptom category and that this can be further refined by including age and gender in the assessment. Using these three categories of chest pain together with age and gender, based on the Diamond and Forrester pre-test likelihood of CAD, it is possible to have a high degree of confidence that a given patient with stable chest pain has angina. For example; a man aged 60 to 69 years with typical angina symptoms has a pre-test likelihood of CAD of 94%. In contrast, a woman aged 30 to 39 years with non-anginal chest pain has a pre-test likelihood of CAD of 0.8%. The GDG also found that the pre-test likelihood of patients with chest pain of suspected cardiac origin have angina could be further refined by including the presence or absence of cardiovascular risk factors, such as smoking, diabetes and hyperlipidaemia in the assessment, as well as whether there is any past history of established CAD, for example evidence of a past history of MI. One cohort study found that the prevalence of CAD was lower in patients with

similar symptoms and risk factors presenting to a primary healthcare setting, compared to those presenting to secondary care, with the exception of those with the most typical presentation. However, it was not possible to incorporate where the patient presents into the estimates of pre-test likelihood being recommended in the guideline, other than to recognise that the likelihoods, with the exception of those with the most typical presentation are likely to be an over estimate in primary care healthcare setting.

All patients presenting with chest pain of suspected cardiac origin require a complete and careful clinical history which is used to inform the pre-test likelihood that a patient has angina due to CAD. In some cases this may lead to a diagnosis that either the presenting symptoms are due to angina or non-cardiac chest pain with sufficient certainty that no further diagnostic testing is required. However, in many patients with chest pain of suspected cardiac origin, a diagnosis is not established from the clinical assessment alone, and diagnostic investigations are required. The GDG acknowledged that those diagnosed with angina from a clinical assessment alone may have similar investigations to those undergoing further diagnostic testing, but this is to obtain information about prognosis rather than diagnosis, and is informed by recommendations in angina guidelines. Similarly those with non-cardiac chest pain may have additional investigations to establish a diagnosis. During the course of the clinical assessment, patients may also be found to have cardiovascular risk factors and the management of these is informed by other guidelines, such as the NICE guideline; Lipid modification; Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease CG67, and the NICE guideline; Hypertension: management of hypertension in adults in primary care CG34.

5.1.2 Differences in presentation by gender

5.1.2.1 Evidence statements for presentation by gender

1 One systematic review and meta-analysis on the prevalence of angina in women versus men across 31 countries found that women had a similar or slightly higher prevalence of angina

compared with men. (Hemingway, H., Langenberg, C., Damant, J. et al , 2008)

2 One cohort study in patients with recent onset stable chest pain recruited form 6 rapid access chest pain clinics in the UK (4138 men and 3656 women found that women more often experienced atypical chest pain based on the Diamond-Forrester classification compared with men. (Zaman, M. J., Junghans, C., Sekhri, N. et al , 2008)

3 One small cohort study in patients presenting with stable angina (89 men and 39 women) found that both women and men most frequently describe their symptoms as aching, heavy, tiring-exhausting, and sharp. Women more frequently described their pain as hot burning and tender compared with men. (Kimble, L. P., McGuire, D. B., Dunbar, S. B. et al , 2003)

4 A study that examined the prevalence of CAD in 23 996 unselected subjects at autopsy found that prevalence increased with increasing age and women at all ages had a lower prevalence compared with men. Results of conditional-probability analysis found that the pre-test likelihood of CAD varied widely according to sex, gender and symptoms. For women with typical angina symptoms, the pre-test likelihood was shown to be lower at age ranges less than 59 years compared with men in the comparable age ranges. (Diamond, G. A. and Forrester, J. S., 1979)

Back to recommendations

5.1.2.2 Introduction

Historically, the descriptions of chest pain symptoms associated with ACS have been based on the presentation characteristics of men. Studies from the Framingham cohort have shown that there are important gender differences in the initial presentation of CAD; women tend to present with angina while for men the commonest presentation is MI, and in the Framingham cohort women were found to present with cardiac symptoms approximately 10 years later

than men (Lerner, D. J. and Kannel, W. B., 1986). The Framingham Offspring Study (participants aged 30 to 74 years at the start of the study and a follow up of 16 years) assessed 6 risk factors and the relationship between them (lowest quantile high-density lipoprotein, highest quantile cholesterol, body mass index, systolic blood pressure, triglycerides and plasma glucose). The study showed that about one third of people had a single risk factor, and 17% had 3 of the risk factors. With 16 years of follow up for coronary events defined as MI or sudden death, the event rate among all enrollees was compared with the event rate among those with 3 or more risk factors. The coronary events among women with 3 or more risk factors were 48% compared with 20% in men, indicating that risk factor determination is an important component in the evaluation of women with suspected CAD (Wilson, P. W., Kannel, W. B., Silbershatz, H. et al , 1999).

A systematic review on the sex ratio in angina prevalence (Rose Questionnaire) (search date up to 2006, 74 reports in population-based surveys, 13 331 angina cases in women and 11 511 cases in men, 31 countries) found that angina prevalence varied widely across populations from 0.73% to 14.4% in women (population weighted mean 6.7%) and from 0.76% to 15.1% in men (population weighted mean 5.7%) (Hemingway, H., Langenberg, C., Damant, J. et al , 2008). Angina prevalence was strongly correlated within populations between sexes (r = 0.80, P < 0.001). There was a small female excess in angina prevalence for women with a pooled random-effects sex ratio of 1.20 (95%CI 1.14 to 1.28, P < 0.0001) and this excess was found across countries with widely differing MI mortality rates in women (interquartile range 12.7 to 126.5 per 100 000). The excess was particularly high in the American studies (1.40, 95% CI 1.28 to 1.52) and was higher in non-Caucasian ethnic groups compared with Caucasians. The sex ratio did not significantly differ according to age, year of survey, or the sex ratio for MI mortality (Hemingway, H., Langenberg, C., Damant, J. et al , 2008).

Women with ischaemic heart disease have more adverse outcomes compared with men (Vaccarino, V., Parsons, L., Every, N. R. et al , 1999) despite the repeated documented lower angiographic disease burden and

more often preserved left ventricular function compared with men (Nabel, E. G., Selker, H. P., Califf, R. M. et al , 2004). Hence the recognition that clinical presentation and risk factors differ between men and women is important in the initial assessment of chest pain to determine the need for further evaluation.

5.1.2.3 Clinical evidence

Are the symptoms and description of the symptoms different in women presenting with stable chest pain of suspected cardiac origin compared with men?

Three studies were reviewed, one study was in patients with stable chest pain of suspected cardiac origin (Zaman, M. J., Junghans, C., Sekhri, N. et al , 2008) and two studies were in patients with stable angina (Kimble, L. P., McGuire, D. B., Dunbar, S. B. et al , 2003) (Diamond, G. A. and Forrester, J. S., 1979).

The first cohort study recruited 11 082 consecutive patients with recent onset chest pain suspected to be stable angina from 6 rapid access chest pain clinics in the UK (Zaman, M. J., Junghans, C., Sekhri, N. et al , 2008). These clinics do not accept referrals of patients previously suspected to have CAD, who have received a diagnosis of CAD, or who have received a diagnosis of ACS on the day of the visit. The aim of the study was to examine whether atypical symptoms of angina in women and South Asians impacted on clinical outcomes and clinical management. Information on symptoms in South Asians is reviewed in section 5.1.3 (Zaman, M. J., Junghans, C., Sekhri, N. et al , 2008).

During the history taking of the patient, the cardiologists recorded a descriptor for each of the following 4 components of chest pain: character (aching, constricting, stabbing, nondescript), site (central, left-sided, right-sided, submammary, epigastric, other), duration (seconds, < 5 minutes, 5 to 15 minutes, 15 to 30 minutes, hours or variable) and precipitating factors (none, exercise, exercise and rest, stress, eating, other). Based on the Diamond–Forrester classification (Diamond, G. A. and Forrester, J. S., 1979), typical

pain was considered to be that which the patient described as having a constricting quality, being located centrally or on the left-side of the chest, lasting between a few seconds and 15 minutes, and being provoked by exercise. A “symptom score” was used to classify the patient’s description of pain as typical (3 or more characteristics of typical pain) or atypical (2 or fewer characteristics). The cardiologist made an overall assessment of the patient’s symptoms as typical or atypical (“cardiologist summary”). At the end of the consultation, the cardiologist diagnosed the cause of the patient’s chest pain as either angina or non-cardiac chest pain. Using National Health Service numbers, data from the Office for National Statistics and Hospital Episode Statistics, the outcomes of death from ACS and hospital admission due to ACS (coded according to ICD-10 classification) were determined up to 3 years after the index clinic visit. Successful matching was achieved for 99.5% of the cohort (Zaman, M. J., Junghans, C., Sekhri, N. et al , 2008).

Of 11 082 patients seen at the rapid access chest pain clinics the following patients where excluded; 579 previous CAD, 246 patients diagnosed with ACS on day of visit, 448 prior visit to the unit during study period, 291 no chest pain, 501 due to missing data, 83 pain not diagnosed as angina or non cardiac chest pain, 40 not tracked by the Office for National Statistics, 968 excluded as other ethnic background (not Caucasian or Asian). Thus of the final number of people identified (7794), 2676 were Caucasian women, 2929 were Caucasian men, 980 were South Asian women, and 1209 were South Asian men (Zaman, M. J., Junghans, C., Sekhri, N. et al , 2008).

More women than men reported atypical chest pain symptoms (56.5% versus 54.5%, respectively $P = 0.054$). Cardiologists were more likely to describe the symptoms of women as atypical compared with men (73.3% agreement between cardiologist summary and the symptom score, kappa statistic 0.43). With respect to symptoms and diagnosis, sex did not modify the association between exercise ECG results and receiving a diagnosis of angina, and after excluding patients with a positive exercise test result, cardiologist and typical symptom scores both remained predictive of a diagnosis of angina. With respect to symptoms and prognosis, using cardiologist summaries typical

symptoms in women were more strongly associated with coronary death or ACS (adjusted hazard ratio (adjusted for age, sex, ethnic background, diabetes, hypertension, smoking, and revascularization); 3.74, 95% CI 2.80 to 5.01) than among men (adjusted hazard ratio; 1.51, 95% CI 1.16 to 1.97, $P < 0.001$). This finding was also true for symptom scores (women; adjusted hazard ratio 2.30, 95% CI 1.70 to 3.11, men; adjusted hazard ratio 1.23, 95% CI 0.96 to 1.57, $P < 0.002$). According to the cardiologist summaries and symptom scores, women with typical symptoms were more likely than men to have the coronary outcomes of death due to CAD or ACS and / or hospital admissions with unstable angina after adjustments for age, sex, ethnic background, diabetes, hypertension, smoking, secondary prevention treatment, revascularization and exercise ECG result (cardiologist summaries for women versus men hazard ratio 1.49, 95% CI 1.09 to 2.04, and symptom score for women versus men hazard ratio 1.39, 95% CI 1.06 to 1.84). Women with atypical symptoms were less likely than men with atypical symptoms to experience a coronary outcome (unadjusted log rank test $P = 0.001$) according to symptom score or cardiologist score, although adjusted Cox regression ratios showed that atypical pain had similar prognostic value for coronary outcomes for women and men. The study indicated that compared to those with atypical chest pain, women with typical symptoms had worse clinical outcomes based on both symptom and cardiologist-derived scores (Zaman, M. J., Junghans, C., Sekhri, N. et al , 2008).

The second cohort study randomly recruited patients with a history of CAD, that were currently stable disease and angina documented by cardiologists from 3 cardiology clinics (Kimble, L. P., McGuire, D. B., Dunbar, S. B. et al , 2003). All patients had experienced an episode of chronic stable angina within the previous week. Patients were excluded if they had experienced acute MI, or coronary revascularisation in the previous 6 months. Patients were also excluded if they screened negative on the supplemented Rose questionnaire, or had any active exacerbation of gastrointestinal symptoms. One hundred and thirty patients were recruited and 2 subjects were excluded from the analysis because they had greater than 75% of their data missing on their study questionnaires. Chronic angina pain was measured with the SF-MPQ

(Melzack, R., 1987) based on the original McGill pain questionnaire which measures the sensory and affective pain, and evaluates pain dimensions in patients with a variety of different painful conditions. Pain intensity was measured using a visual analogue scale (VAS) (Melzack, R., 1987) .

Patients ranged in age from 35 to 86 years, and there were 89 men and 39 women, with a mean age of 62.8±11.7 years and 64.1±11.8 years, respectively. Men had been diagnosed with CAD for longer than women with a mean of 12.9±9.6 years versus 8.8±9.8 (*P* = 0.030). There was a greater proportion of African American women compared with African American men (43.6% versus 13.5%, respectively, *P* = 001), more men had a history of acute MI than women (79.8% versus 58.0%, respectively *P* = 0.014) and more men had a history of coronary artery bypass graft surgery compared with women (70.8% versus 28.2%, respectively *P* = 0. 001). There was no difference between men and women in prior history of the following; diabetes, hyperlipidaemia, hypertension, percutaneous transluminal coronary angioplasty, GI problems. There was no difference in family history of CAD and current smoking between men and women (Kimble, L. P., McGuire, D. B., Dunbar, S. B. et al , 2003).

Twelve percent of men and 10% of women reported one chest pain episode in the previous 7 days, and completed the SF-MPQ based on recall of that episode. Those patients experiencing more than 1 episode chose one specific episode to recall, the most commonly reported reason for choice of episode was that it was the most recent (52.9% men, 36.4% women), and the second reason was that it was the most painful (14.7% men, 18.2% women). There was no significant difference in the frequency of angina chest pain within the previous 7 days comparing men with women (mean number of episodes 6.58±7.95 for men and 4.23±3.34 for women). Men reported a mean of 1.7±1.8 days since their last pain episode and women reported a mean of 1.9±1.7 days. For men the most frequent words chosen to describe their angina were aching (74.2%), heavy (70.2%), tiring-exhausting (70.8%) and sharp (56.2%). For women the most frequent words were aching (76.9%), tiring-exhausting (76.9%), heavy (66.7%), hot-burning (61.5%), sharp (53.8%),

and fearful (51.3%). Other descriptors that were chosen less frequently (< 35%) were; throbbing, shooting, stabbing, gnawing, splitting and punishing-cruel. Chi square analysis found that women were more likely to describe their angina as hot-burning (*P* = 0.001) and tender (*P* = 0.007) compared with men. Women reported significantly higher overall pain intensity as measured by VAS (on a range of 0 to 10; women 6.08±2.7 versus men 5.03±2.4, *P* = 0.036). No gender differences were found for total sensory or affective intensity scores, or the number of pain words chosen (Kimble, L. P., McGuire, D. B., Dunbar, S. B. et al , 2003).

The third study assessed the use of analysis of probability as an aid in the clinical diagnosis of CAD according to concepts included in Bayes' theorem of conditional probability (Diamond, G. A. and Forrester, J. S., 1979). The study has been reviewed in section 5.1.1.2. The aim of the study was to demonstrate that using information available from the clinical evaluation in a given patient could determine the probability of CAD prior to testing. The study considered 4952 symptomatic patients referred for coronary angiography, and the results in an unselected population of 23 996 persons at autopsies (Diamond, G. A. and Forrester, J. S., 1979).

As detailed in Table 3, the prevalence of coronary artery stenosis at autopsy from 23 996 unselected persons was associated with both age and gender. For men, the differences ranged from 1.9% for men aged 30 to 39 years, to 12.3% for men aged 60 to 69 years. For women, the differences ranged from 0.3% for women aged 30 to 39 years of age, to 7.5% for women aged 60 to 69 years. Women in all age groups had a lower prevalence of coronary artery stenosis compared with the respective age groups in men (Diamond, G. A. and Forrester, J. S., 1979).

Estimates of pre-test likelihood of CAD varied widely according to age, gender and symptoms as detailed in Table 4. For example the analysis found that a woman in the age range 30 to 39 years with atypical symptoms had a pre-test likelihood of 4% compared with 92% for a man in the age range 50 to 59 years with typical symptoms (Diamond, G. A. and Forrester, J. S., 1979).

5.1.2.4 Health economic evidence

No health economics literature search was conducted, as this question did not readily lend itself to incremental economic evaluation.

5.1.2.5 Evidence to recommendations

CAD is generally less prevalent in women than it is in men of similar age. However, this difference becomes less with increasing age and in those aged 60 to 69 years, the prevalence of CAD in men and women with typical angina symptoms is similar. Men and women may describe their symptoms of chest pain differently, but these differences are small, and cardiovascular risk factors are at least as important in women as in men, if not more so, in determining the likelihood of women having coronary events. The GDG concluded that the likelihood that a patient with chest pain has angina due to CAD is influenced by gender but that the differences in symptomatic presentation between men and women are small and it is the pre-test likelihood of angina and CAD which should influence management, not gender alone.

5.1.3 Differences in presentation by ethnicity

5.1.3.1 Evidence Statements for presentation by ethnicity

1 One cohort study in patients with recent onset chest pain recruited form 6 rapid access chest pain clinics in the UK (2189 South Asian patients and 5605 Caucasian patients) found that South Asians more often experienced atypical chest pain based on the Diamond-Forrester classification compared with Caucasians. (Zaman, M. J., Junghans, C., Sekhri, N. et al , 2008)

2 One cohort study in patients with recent onset chest pain recruited form 6 rapid access chest pain clinics in the UK (2189 South Asian patients and 5605 Caucasian patients) found in those with typical symptoms based on the Diamond-Forrester classification, South Asians were more likely to have a coronary outcome than Caucasians, although using cardiologist summaries the outcomes were similar. (Zaman, M. J., Junghans, C., Sekhri, N. et al , 2008)

3 One cohort study in patients with recent onset chest pain recruited form 6 rapid access chest pain clinics in the UK found that South Asians with typical symptoms had a worse clinical outcome than those with atypical symptoms. (Zaman, M. J., Junghans, C., Sekhri, N. et al , 2008)

Back to recommendations

5.1.3.2 Clinical evidence

Are the symptoms and description of the symptoms different in black and ethnic minorities presenting with suspected stable chest pain compared with Caucasians?

Introduction

The vast majority of studies on the signs, symptoms and risk factors associated with stable angina have been conducted and validated in male Caucasian populations. It is recognized that the prevalence of CAD is higher among people of South Asian descent than among Caucasian people, while the prevalence of CAD in Black people has been reported as lower than in Caucasian populations. It is widely perceived that people of South Asian origin and other ethnic minorities with suspected myocardial ischemia are more likely than Caucasian men to report atypical features of pain. It has also been reported that there is a higher prevalence of risk factors such as of diabetes, hypertension and rates of obesity in ethnic minorities. These risk factors may have differing effects in ethnic groups; with hypertension exerting a particularly deleterious effect among Black people, and diabetes having a particularly deleterious effect among South Asians. The impact of these risk factors is complex; increased cardiovascular mortality has been demonstrated in some ethnic minorities in the presence of less obstructive CAD (Budoff, M. J., Yang, T. P., Shavelle, R. M. et al , 2002) and the disparity in cardiovascular mortality has not been attributed to differences in traditional risk factors (Escobedo, L. G., Giles, W. H., and Anda, R. F., 1997). Given the disparities reported in the literature, it is somewhat surprising that the examination of ethnic differences in the presentation of patients with chest pain of suspected cardiac origin has not been further investigated.

One cohort study was reviewed that recruited 11 082 consecutive patients with recent onset chest pain suspected to be stable angina from 6 rapid access chest pain clinics in the UK (Zaman, M. J., Junghans, C., Sekhri, N. et al , 2008). These clinics do not accept referrals of patients previously suspected to have CAD, who have received a diagnosis of CAD, or who have received a diagnosis of ACS on the day of the visit. The aim of the study was to examine whether atypical symptoms of angina in women and South Asians impacted on clinical outcomes and clinical management. For the purposes of this review information focusing upon symptom presentation data of South Asians versus Caucasians are presented (Zaman, M. J., Junghans, C., Sekhri, N. et al , 2008).

During the history taking of the patient, the cardiologists recorded a descriptor for each of the following 4 components of chest pain; character (aching, constricting, stabbing, nondescript), site (central, left-sided, right-sided, submammary, epigastric, other), duration (seconds, < 5 minutes, 5 to 15 minutes, 15 to 30 minutes, hours or variable) and precipitating factors (none, exercise, exercise and rest, stress, eating, other). Based on the Diamond–Forrester classification, typical pain was considered to be that which the patient described as having a constricting quality, being located centrally or on the left-side of the chest, lasting between a few seconds and 15 minutes, and being provoked by exercise. A “symptom score” was used to classify the patient’s description of pain as typical (3 or more characteristics of typical pain) or atypical (2 or fewer characteristics). The cardiologist made an overall assessment of the patient’s symptoms as typical or atypical (denoted as the “cardiologist summary”). At the end of the consultation, the cardiologist diagnosed the cause of the patient’s chest pain as either angina or non cardiac chest pain. Using National Health Service numbers, data from the Office for National Statistics and Hospital Episode Statistics, the outcomes of death from ACS and hospital admission due to ACS (coded according to ICD-10 classification) were determined up to 3 years after clinic visit. Successful matching was achieved for 99.5% of the cohort (Zaman, M. J., Junghans, C., Sekhri, N. et al , 2008).

Of 11 082 patients seen at the rapid access chest pain clinics the following patients where excluded; 579 previous CAD, 246 patients diagnosed with ACS on day of visit, 448 prior visit to the unit during study period, 291 no chest pain, 501 due to missing data, 83 pain not diagnosed as angina or non cardiac chest pain, 40 not tracked by the Office for National Statistics, 968 excluded as other ethnic background (not Caucasian or Asian). Thus of 7794 people identified, 2676 were Caucasian women, 2929 were Caucasian men, 980 were South Asian women, and 1209 were South Asian men (Zaman, M. J., Junghans, C., Sekhri, N. et al , 2008).

More South Asians compared with Caucasians reported atypical chest pain symptoms (59.9% versus 52.5%, respectively $P < 0.001$), and the cardiologist described more South Asians as having an atypical presentation compared with Caucasians. South Asians were also more likely to report pain that was not associated with exercise. With respect to symptoms and diagnosis, ethnicity did not modify the association between exercise ECG results and receiving a diagnosis of angina, and after excluding patients with a positive exercise test result, cardiologist and typical symptom scores both remained predictive of a diagnosis of angina. According to cardiologist summaries and symptom scores, South Asians with typical symptoms were as likely as Caucasians with typical symptoms to have a coronary outcome for cardiologist summaries (South Asians versus Caucasians hazard ratio (adjusted for age, sex, ethnic background, diabetes, hypertension, smoking, secondary prevention treatment, revascularization and exercise ECG result) 1.27, 95% CI 0.89 to 1.81), and more likely with symptom scores (South Asians versus Caucasians adjusted hazard ratio 1.41, 95% CI 1.04 to 1.91). South Asians with atypical pain were as likely as Caucasians with atypical pain to have a coronary outcome (unadjusted log rank test $P = 0.88$) (finding and statistical result given in a correction from original publication; see http://www.cmaj.ca/cgi/content/full/179/10/1038-a). Adjusted Cox regression ratios showed that atypical pain had similar prognostic value for coronary outcomes across ethnic background according to both cardiologists summary (adjusted hazard ratio 1.38, 95% CI 0.94 to 2.02) and symptom score (adjusted hazard ratio 1.19 95% CI 0.73 to 1.92). The study indicated that

compared to those with atypical chest pain, South Asians with typical symptoms had worse clinical outcomes (Zaman, M. J., Junghans, C., Sekhri, N. et al , 2008).

5.1.3.3 Health economic evidence

No health economics literature search was conducted, as this question did not readily lend itself to incremental economic evaluation.

5.1.3.4 Evidence to recommendations

The GDG asked that the evidence appraised for the guideline was that which was most pertinent to the ethnic minority groups in the UK, and that found examined the presentation of patients of South Asian origin, compared to Caucasians. Symptoms of chest pain were categorised in both patients of South Asian origin and Caucasians as being typical or atypical based on the same criteria. The likelihood of a coronary outcome was at least as high in South Asian patients with typical symptoms as in Caucasians, although atypical pain had similar prognostic value for coronary outcomes across ethnic background. In both groups the likelihood of a coronary outcome was higher in those with typical symptoms compared to those with atypical symptoms.

5.1.4 12-Lead resting ECG

5.1.4.1 Evidence statements for 12-Lead resting ECG

1 One systematic review (search date 2003) found that Q wave on ECG was moderately useful for ruling in a diagnosis of CAD in patients with stable chest pain. Abnormal ST-segment and T wave, ST depression, and any abnormal ECG change were not helpful for the diagnosis of CAD. The absence of ECG changes was not useful for ruling out a diagnosis of CAD (Mant, J., McManus, R. J., Oakes, R.-A. L. et al , 2004).

2 One systematic review (search date 2003) found that for diagnosing CAD in patients with stable chest pain the ECG gave little additional diagnostic information to the history and risk factor findings. (Chun, Andrea Akita and McGee, Steven R., 2004)

3 One study that used a stepwise logistic regression model for predicting the probability of significant CAD in patients with stable chest pain found that ST-T wave changes on ECG was a significant characteristic for predicting significant CAD. (Pryor, D. B., Harrell, F. E., Jr., Lee, K. L. et al , 1983)

4 One study that assessed estimating the likelihood of significant CAD in patients with stable chest pain found that significant Q waves and ST-T wave changes were significant characteristics for predicting severe CAD. Significant Q waves and ST-T wave changes were predictors of any disease. For left main disease ECG results were not significant predictors. For survival at 3 years, significant Q waves and ST-T wave changes were significant predictors. (Pryor, D. B., Shaw, L., McCants, C. B. et al , 1993)

5 No health economic evidence was found on the incremental value of a resting ECG.

Back to recommendations

5.1.4.2 Clinical evidence

What is the utility (incremental value) and cost-effectiveness of a resting ECG in evaluation of individuals with stable chest pain of suspected cardiac origin?

One systematic review (Chun, Andrea Akita and McGee, Steven R., 2004) and two studies utilising logistic regression modelling for the prediction of significant CAD (Pryor, D. B., Harrell, F. E., Jr., Lee, K. L. et al , 1983) (Pryor, D. B., Shaw, L., McCants, C. B. et al , 1993) were reviewed.

The first systematic review identified 12 studies that examined the use of ECG for the diagnosis of CAD (Mant, J., McManus, R. J., Oakes, R.-A. L. et al , 2004). Ten studies were in patients with chronic stable chest pain and 2 studies were in patients with stable angina. Coronary angiography was the reference standard, significant CAD was defined as > 50% coronary stenosis

in 5 studies, ≥ 70% in 1 study, > 70% in 4 studies, > 75% in 1 studies and undisclosed in 1 study. Table 15 details the summary PLR and NLR for the ECG characteristics. Q wave was the most frequently evaluated ECG change and was moderately useful for ruling in a diagnosis of CAD, although the confidence interval was wide (PLR 2.56 95%CI 0.89 to 7.60). One study examined QRS notching which had a high PLR although the confidence interval was very wide (PLR 9.96 95%CI 2.58 to 38.5). ST-segment plus or minus T wave changes were not found to be helpful for a diagnosis of CAD, neither was any abnormality. For ruling out a diagnosis of CAD none of the ECG changes were helpful with NLR ranging from 0.43 to 1.01 (Mant, J., McManus, R. J., Oakes, R.-A. L. et al , 2004).

Table 15

Analysis	Number of studies	PLR	NLR
Abnormal ST-segments and T wave	2	0.99 (95%CI 0.99 to 1.11)	1.01 (95%CI 0.97 to 1.01)
Resting ST depression	1	1.50 (95%CI 1.16 to 1.94)	0.93 (95%CI 0.89 to 0.97)
Q wave	6	2.56 (95%CI 0.89 to 7.30)	0.75 (95%CI 0.68 to 0.79)
Q wave or ST changes	2	2.44 (95%CI 1.55 to 3.84)	0.43 (95%CI 0.33 to 0.56)
QRS notching	1	9.96 (95%CI 2.58 to 38.5)	0.40 (95%CI 0.30 to 0.53)
Any abnormality	3	1.53 (95%CI 1.01 to 2.33)	0.74 (95%CI 0.48 to 1.15)
Permission requested from source (Mant, J., McManus, R. J., Oakes, R.-A. L. et al , 2004).			

The second systematic review (search date 2003) previously described in 5.1.1.2 identified 4 studies that examined the use of ECG for the diagnosis of CAD in patients with intermittent stable chest pain referred for coronary angiography. Both a normal ECG and ST-T wave abnormalities were found to be diagnostically unhelpful. For a normal ECG finding (2 studies, 309 patients in total, sensitivity range 23% to 33%, specificity range 50% to 69%), the PLR was 0.7 (95%CI 0.3 to 1.9) and the NLR was 1.2 (95%CI 0.8 to 1.9) for the diagnosis of CAD. For a ST-T wave abnormalities (3 studies, 2652 patients in total, sensitivity range 14% to 44%, specificity range 73% to 93%), the PLR

was 1.4 (95%CI 0.1 to 1.9) and the NLR was 0.9 (95%CI 0.9 to 1.0) for the diagnosis of CAD (Chun, Andrea Akita and McGee, Steven R., 2004).

The first cohort study aimed to determine which characteristics from the initial clinical assessment of patients with stable chest pain were important for estimating the likelihood of significant CAD (Pryor, D. B., Harrell, F. E., Jr., Lee, K. L. et al , 1983). The study has been reviewed in 5.1.1.2. Stepwise logistic regression analysis was used to develop a model (3627 patients) for predicting the probability of significant CAD. The model used variables taken from the clinical history, risk factors and physical examination, and results of the chest X ray and ECG. The results from the development of the model in the training group (1811 patients) found ST-T wave changes on the ECG was a significant predictor of significant CAD (chi-square = 28) (see Table 8). Other significant predictors were; type of chest pain (typical, atypical or non-anginal), previous MI, sex, age, smoking, hyperlipidaemia, and diabetes. The model based on these positive variables was found to accurately estimate the prevalence of significant CAD in the training population used in the study, and also in an external population (Chaitman, B. R., Bourassa, M. G., Davis, K. et al , 1981).

The second cohort study examined a regression model based on clinical history and risk factors for the diagnosis of CAD in a stable chest pain population with suspected CAD (Pryor, D. B., Shaw, L., McCants, C. B. et al , 1993). The study has been reviewed 5.1.1.2. The study had three diagnostic outcomes of; presence of significant CAD (≥ 75% luminal diameter narrowing of at least one major coronary artery); the presence severe CAD (presence of significant obstruction of all three major arteries or the left main coronary artery), and the presence of significant left main coronary artery obstruction. There was one prognostic outcome of survival at 3 years. The regression model showed that the presence of ST-T wave changes was a significant predictor for significant CAD, severe disease and survival at 3 years, but not for left main disease. The presence of Q waves was also a predictor for significant CAD, severe disease and survival at 3 years, but not for left main disease (Pryor, D. B., Shaw, L., McCants, C. B. et al , 1993).

5.1.4.3 Health economic evidence

No health economic evidence was identified for this question.

5.1.4.4 Evidence to recommendations

An ECG in patients with stable chest pain provides valuable diagnostic information, in addition to that obtained from the history. An abnormal ECG with pathological Q waves consistent with a previous MI, and in some studies also the presence of ST and T wave abnormalities, is associated with an increased likelihood that the patient has CAD. In addition the GDG recognized that other ECG abnormalities, such as left bundle branch block (LBBB), may also be associated with an increased likelihood of CAD, although the studies reviewed did not specifically evaluate this. However, the GDG felt it was important to emphasise that the converse is not true, and a normal ECG does not rule out the diagnosis of CAD.

5.1.5 Chest X ray

5.1.5.1 Evidence statements for chest X ray

1 In a very limited evidence base, two studies in patients with stable chest pain referred for coronary angiography found that cardiomegaly as shown on chest X ray was a poor predictor of significant CAD. (Pryor, D. B., Harrell, F. E., Jr., Lee, K. L. et al , 1983), (Pryor, D. B., Shaw, L., McCants, C. B. et al , 1993)

2 In one study cardiomegaly as shown on chest X ray was a significant predictor of survival at 3 years. (Pryor, D. B., Shaw, L., McCants, C. B. et al , 1993)

3 No health economic evidence was found for this question.

Back to recommendations

5.1.5.2 Clinical evidence

What is the utility (incremental value) and cost-effectiveness of a chest X ray in evaluation of individuals with stable chest pain of suspected cardiac origin?

Two studies utilising logistic regression modelling for the prediction of significant CAD were reviewed (Pryor, D. B., Harrell, F. E., Jr., Lee, K. L. et al , 1983) (Pryor, D. B., Shaw, L., McCants, C. B. et al , 1993).

The first study aimed to determine which characteristics from the initial clinical assessment of patients with stable chest pain were important for estimating the likelihood of significant CAD (Pryor, D. B., Harrell, F. E., Jr., Lee, K. L. et al , 1983). The study has been reviewed in section 5.1.1.2. Stepwise logistic regression analysis was used to develop a model for predicting the probability of significant CAD. The model used variables taken from the clinical history, risk factors and physical examination, and results of the chest X ray and ECG. The model was developed in a test population, and validated for its estimation of the prevalence of significant CAD in both the study training population and an external study population (Chaitman, B. R., Bourassa, M. G., Davis, K. et al , 1981). The results from the development of the model in the training group found that cardiomegaly as shown on chest X ray was a poor predictor of significant CAD (chi-square = 1.41) (see Table 9). Hence the results of a chest X ray was not included in the model that was used to estimate the prevalence of CAD in the test group and the external population (Pryor, D. B., Harrell, F. E., Jr., Lee, K. L. et al , 1983).

The second study examined a regression model based on clinical history and risk factors for the diagnosis of CAD in a stable chest pain population with suspected CAD (Pryor, D. B., Shaw, L., McCants, C. B. et al , 1993). The study has been reviewed in section 5.1.1.2. The regression model found that cardiomegaly as shown on chest X ray was not a significant predictor for the presence of significant CAD (≥ 75% luminal diameter narrowing of at least one major coronary artery), severe CAD (presence of significant obstruction of all three major arteries or the left main coronary artery), or the presence of significant left main coronary artery obstruction. However, cardiomegaly on the chest X ray was found to be a significant predictor of survival at 3 years (Pryor, D. B., Shaw, L., McCants, C. B. et al , 1993).

5.1.5.3 Health economic evidence

Because this question was low priority for economic evaluation, no specific health economics literature search was undertaken for this question. No health economics literature was found in either the scoping search or the update search.

5.1.5.4 Evidence to recommendations

There was very little evidence identified which examined the value of a chest X ray in making a diagnosis of angina in patients with stable chest pain. However, two studies found that cardiomegaly on a chest X ray was not predictive of the presence of significant CAD. Evidence for the value of a chest X ray to diagnose conditions, other than angina, was not searched for. The GDG concluded from the evidence appraised and their clinical experience, that a chest X ray was not helpful in making a diagnosis of angina in patients with stable chest pain, but that it should be performed if other conditions were suspected such as lung cancer or pulmonary oedema.

5.2 Investigations and diagnosis of patients with stable chest pain suspected to be stable angina

5.2.1 Introduction

A universal definition for stable angina has not been agreed internationally, in contrast to that which has been developed for ACS. For the purposes of this guideline, angina is a symptom usually associated with coronary artery narrowing, functional evidence of ischaemia on non-invasive testing or both. It is recognized clinically by its character, its location and its relation to provocative stimuli. The diagnosis of angina may be made on clinical history alone, clinical history in combination with functional tests that demonstrate myocardial ischaemia, clinical history in combination with the finding of significant obstructive CAD on angiography, or all three.

Coronary angiography is used to assess the degree of coronary stenosis (luminal narrowing) that may be the culprit lesion(s) causing angina if the coronary obstruction is sufficiently severe to restrict oxygen delivery to the cardiac myocytes. Generally, invasive angiographic luminal obstruction in an epicardial coronary artery estimated as ≥ 70% diameter stenosis is regarded as “severe” and likely to be a cause of angina, but this will depend on other factors that influence ischaemia independently of lesion severity. There are a number of factors that intensify ischaemia. giving rise to angina with less severe lesions (≥ 50% coronary stenosis), namely, reduced oxygen delivery (anaemia, coronary spasm), increased oxygen demand (tachycardia, left ventricular hypertrophy), large mass of ischaemic myocardium (for example proximally located lesions) and longer lesion length. There are a number of factors that reduce ischaemia, and these may render severe lesions (≥ 70%) asymptomatic, these include a well developed collateral supply, small mass of ischaemic myocardium (for example distally located lesions), and old infarction in the territory of coronary supply. When angina occurs in patients with angiographically “normal” coronary arteries (syndrome X) pathophysiological mechanisms are often unclear although there is sometimes evidence of myocardial hypoperfusion caused by small vessel disease.

5.2.2 Evidence statements for investigations

5.2.2.1 Evidence statements; general

1 The populations identified in systematic reviews were very heterogeneous and the individual studies did not generally provide detailed information on the selected patients, or information on prior diagnostic tests.

2 Most studies reported sensitivity and specificity of single diagnostic tests in patients with chest pain without giving any information on the incremental value of additional testing if the initial test had not established the diagnosis.

5.2.2.2 Evidence Statements for non-invasive stress tests

3 The diagnostic performance of non-invasive tests was evaluated against intra-luminal narrowing as determined by the reference standard of invasive coronary angiography. The majority of the studies selected in systematic reviews for meta-analyses of the diagnostic performance of a non-invasive test considered significant coronary stenosis to be at least > 50% intra-luminal narrowing. In most systematic reviews meta-analyses were performed using studies with different definitions of coronary stenosis, for example ≥ 50%, > 50%, ≥ 70%, > 70% or ≥ 75% luminal narrowing.

4 One systematic review on the diagnostic performance of exercise ECG to detect CAD (search date 1987) found that there was a wide range in sensitivities (weighted mean 68±16%, range 23% to 100%) and specificities (weighted mean 77±17%, range 17% to 100%). The prevalence of CAD was 66%. The reported ranges of sensitivity and specificity could not be completely explained by the variables abstracted from the exercise ECG studies included in the systematic review. The incremental variance identified by the multivariate models accounted for 33% of the variance in sensitivity and 22% of the variance in specificity and there is likely to be incomplete reporting of potentially important data involving both

population and technical factors. Hence incomplete reporting of data, in addition to defects in research methodology and selection bias were likely to account for the wide range in sensitivity and specificity. (Gianrossi, R., Detrano, R., Mulvihill, D. et al , 1989)

5 A Health Technology Assessment (search date 1999) on the diagnostic performance of exercise ECG in patients with chronic chest pain found that the presence of ST depression had PLR of 2.79 (95% CI 2.53 to 3.07) and a NLR of 0.44 (95% CI 0.40 to 0.47) for a 1 mm cutoff, and for a 2 mm cutoff the PLR was 3.85 (95% CI 2.49 to 5.98) the NLR was 0.72 (95% CI 0.65 to 0.81). ST depression at a 1 mm cutoff performed better in men (PLR 2.92, 95% CI 2.17 to 3.93) compared with women (PLR 1.92, 95% CI 1.72 to 2.24). (Mant, J., McManus, R. J., Oakes, R.-A. L. et al , 2004)

6 One systematic review (search date 2002) that compared the diagnostic performance of stress ECG versus myocardial perfusion scintigraphy (MPS) using single photon emission computed tomography (SPECT) to detect CAD selecting studies that compared stress ECG and SPECT head to head, found that for stress ECG the sensitivity range was 42% to 90% (median 65%) and the specificity range of 41% to 88% (median 67%). Meta-analysis was not performed due to considerable variability in the studies with respect to the inclusion and the exclusion criteria (Mowatt, G., Vale, L., Brazzelli, M. et al , 2004)

7 One systematic review (search date 1995) on the diagnostic performance of exercise ECG, exercise thallium myocardial perfusion scintigraphy (both exercise thallium myocardial perfusion scintigraphy and exercise thallium myocardial perfusion scintigraphy with SPECT) and exercise stress echocardiography in women (that did not select studies directly comparing men versus women) found that the tests were moderately sensitive and specific for the identification of CAD. Meta-analyses found that exercise ECG had a

sensitivity of 61% (95%CI 54% to 68%) and a specificity of 70% (95%CI 64% to 77%). There was wide variability in the sensitivity (27% to 91%) and the specificity (46% to 86%), and the prevalence of CAD ranged from 18% to 67%. Exercise thallium myocardial perfusion scintigraphy had a sensitivity of 78% (95%CI 72% to 83%), and a specificity of 64% (95%CI 51% to 77%); the prevalence of CAD ranged from 30% to 75%. Exercise stress echocardiography had a sensitivity of 86% (95%CI 75% to 96%), and specificity of 79% (95%CI 72% to 86%); the prevalence of CAD in the 3 studies ranged form 37% to 51%. (Kwok, Y., Kim, C., Grady, D. et al , 1999)

8. One systematic review (search date 2006) of the diagnostic performance of dobutamine stress echocardiography in women compared with men found that the test was moderately sensitive and specific for the identification of CAD in both men and women. Meta-analyses found that the test had a sensitivity of 77% for both women and men, and a specificity of 81% in women and 77% in men. The weighted mean CAD prevalence was 59% for women and 73% for men. Meta-analysis of the 14 studies which either only recruited women or in which the results in women could be distinguished from men found the sensitivity in women was 72% (range 31% to 95%), and the specificity was 88% (range from 55% to100%). Comparison of dobutamine stress echocardiography (6 studies) with stress nuclear scintigraphy (3 studies dobutamine stress, 2 studies exercise or dipyridamole stress, and 1 study used dobutamine or dipyridamole stress) in women found that that dobutamine echocardiography had a sensitivity was 77% and a specificity of 90%, and stress nuclear scintigraphy had a sensitivity of 73% and a specificity of 70%. (Geleijnse, M. L., Krenning, B. J., Soliman, O. I. et al , 2007)

9. A systematic review (search date 2006) conducted meta-analyses of systematic reviews on stress echocardiography and SPECT for the diagnosis of CAD. For stress echocardiography, the pooled

sensitivities and specificities were as follows; exercise sensitivity 82.7% (95%CI 80.2% to 85.2%) and specificity 84.0% (95%CI 80.4% to 87.6%), adenosine sensitivity 79.2% (95%CI 72.1% to 86.3%) and specificity 91.5% (95%CI 87.3% to 95.7%), dipyridamole sensitivity 71.9% (95%CI 68.6% to 75.2%) and specificity 94.6% (95%CI 92.9% to 96.3%), dobutamine sensitivity 81.0% (95%CI 79.1% to 82.9%), and specificity 84.1% (95%CI 82.0% to 86.1%). The combined pooled results for all the stress echocardiography studies were; sensitivity 79.1% (95%CI 77.6% to 80.5%), and specificity 87.1% (95%CI 85.7% to 88.5%). For SPECT, the pooled sensitivities and specificities were as follows; exercise sensitivity 88.1% (95%CI 85.8% to 90.3%), specificity 68.8% (95%CI 62.8% to 74.8%), adenosine sensitivity 90.5% (95%CI 89.0% to 91.9%) and specificity 81.0% (95%CI 73.5% to 88.6%), dipyridamole sensitivity 90.4% (95%CI 87.3% to 93.5%), specificity 75.4 (95%CI 66.2% to 84.6%), dobutamine sensitivity 83.6% (95%CI 78.4% to 88.8%), specificity 75.1% (95%CI 71.1% to 79.0%). The combined pooled results for all the studies of SPECT were; sensitivity 88.1% (95 %CI 86.6 to 89.6%) and specificity 73.0% (95%CI 69.1% to 76.9%). Within the total groups of stress echocardiography and SPECT, there was no significant difference in diagnostic performance with different stress agents. Within the total group of SPECT studies, the type of isotope used (TI201 versus 99mTc sestamibi) did not significantly affect the diagnostic performance. However, in the dobutamine stress studies, the diagnostic performance in studies using 99mTc sestamibi was lower compared with thallium 201 (Heijenbrok-Kal, M. H., Fleischmann, K. E., and Hunink, M. G., 2007).

10. A systematic review (search date 2006) found that for both stress echocardiography and SPECT, year of publication and the proportion of men were reported as significant predictors of diagnostic performance, diagnostic performance decreased over the years and increased in populations with a higher proportion of

men. In exercise echocardiography studies, diagnostic performance was higher in younger patients. Adenosine SPECT was found to be significantly better when correcting for publication year or patient characteristics compared with exercise SPECT, dobutamine SPECT, and dipyridamole SPECT, and diagnostic performance increased in studies with populations with higher prevalence of significant CAD. For dipyridamole SPECT, the diagnostic performance increased in studies with younger populations. (Heijenbrok-Kal, M. H., Fleischmann, K. E., and Hunink, M. G., 2007)

11. The sensitivities and specificities for the diagnosis of CAD with MPS using SPECT are generally higher compared with exercise ECG. From one systematic review the reported sensitivity with MPS with SPECT is 88.1% (95 %CI 86.6% to 89.6%) and the specificity is 73.0% (95% CI 69.1% to 76.9%). (Heijenbrok-Kal, M. H., Fleischmann, K. E., and Hunink, M. G., 2007).. From a second systematic review the stress MPS with SPECT sensitivity is reported as a range from 63% to 93% (median 81%) and the specificity range is 54% to 90% (median 67%). (Mowatt, G., Vale, L., Brazzelli, M. et al , 2004)

12. Using MR, both myocardial perfusion imaging and stress induced wall motion abnormalities imaging demonstrate similar sensitivities and specificities for the diagnosis of CAD; on a patient level; sensitivity 91% (95% CI 88% to 94%) and specificity 81% (95% CI 77% to 85%) for myocardial perfusion imaging (CAD prevalence 57.4%) and sensitivity 83% (95% CI 79% to 88%) and specificity 86% (95% CI 81% to 91%) for stress induced wall motion abnormalities imaging (CAD 70.5%). From a coronary territory summary analysis, the sensitivities and specificities per-coronary territory were 84% (95% CI 80% to 87%) and 85% (95% CI 81% to 88%), respectively for myocardial perfusion imaging and 79% (95% CI 71% to 86%) and 93% (95% CI 81% to 100%), respectively for

stress induced wall motion abnormalities imaging. (Nandalur, K. R., Dwamena, B. A., Choudhri, A. F. et al , 2007)

13. A randomised controlled trial in patients with stable chest pain that recruited patients if they had been referred for coronary angiography with established or suspected chronic stable angina and had an exercise ECG warranting referral for angiography, examined the use of functional tests and found that for the primary outcome of exercise time (modified Bruce) at 18 months follow up, exercise time was similar in patients who underwent stress echocardiography and SPECT compared with the control coronary angiography group. Patients that underwent MR perfusion imaging had a lower mean exercise time compared with the control angiography group (mean 35 seconds ($P < 0.05$) with an upper limit of the CI 1.14 minutes less in the MR perfusion imaging group than in the coronary angiography group) (Sharples, L., Hughes, V., Crean, A. et al , 2007)

14. A distillation of the evidence did not yield a significant difference in the sensitivities and specificities of the following three functional tests; stress echocardiography, stress MPS using SPECT and first pass contrast enhanced MR perfusion imaging.

15 In an economic evaluation conducted alongside a randomised controlled trial, for patients referred for invasive coronary angiography following exercise ECG testing, there was no evidence of a cost or clinical benefit (measured in QALYs) for additional non-invasive tests (stress echocardiography, stress MR perfusion imaging or MPS with SPECT) prior to invasive coronary angiography. (Sharples, L., Hughes, V., Crean, A. et al , 2007)

16. In published studies of non-invasive tests (exercise ECG, echocardiography and MPS using SPECT) the sensitivity and specificity have tended to decline with later year of publication.

5.2.2.3 Evidence statements for calcium scoring

17. Three calcium score cohort studies of over 5730 symptomatic patients demonstrated that a Agatston calcium score > 0 had a high sensitivity of 96% to 100% to predict obstructive coronary angiographic disease, while the specificity was poor (range 23% to 40%). One study (1763 patients) found that calcium score > 0 had a negative predictive value of 97% in men and 100% women to predict obstructive coronary angiographic disease. (Knez, A., Becker, A., Leber, A. et al , 2004) (Budoff, M. J., Diamond, G. A., Raggi, P. et al , 2002) (Haberl, R., Becker, A., Leber, A. et al , 2001)

18 A small cohort study of 38 patients who were symptomatic but had atypical chest pain and an intermediate probability of CAD found a highly significant correlation between the Agatston calcium score and degree of CAD on coronary angiography (stenosis >75%). On the basis of the calcium score, ROC curve analysis found no conclusive cut-off point for predicting the presence of haemodynamically relevant coronary stenoses. Using calcium score cut off of > 400, sensitivity and specificity, positive predictive and negative predictive values were; 66.7%, 80.0%, 75.0%, and 72.7%, respectively. (Herzog, C., Britten, M., Balzer, J. O. et al , 2004)

19. A cohort study of 108 patients with CAD or suspected CAD, 78 of whom had had previous percutaneous angioplasty or coronary artery bypass surgery, found that for an Agatston calcium score ≥ 1 (the sensitivity and negative predictive value in patients with a moderate stenosis (≥ 50%) on coronary angiography were lower compared with patients with a severe stenosis (≥ 70%), while, specificity and positive predictive value were higher in patients with moderate stenosis compared with severe stenosis patients. (Kitamura, A., Kobayashi, T., Ueda, K. et al , 2005)

20. A small cohort study of 70 patients with suspected CAD referred for coronary angiography found that with extreme coronary calcification (Agatston calcium score > 400) the diagnostic accuracy of 64 slice

CT coronary angiography to detect significant coronary stenoses was lower than when the calcium score was ≤ 400. The specificity and negative predictive values were reduced with a calcium score > 400 compared with calcium scores ≤ 400. (Raff, G. L., Gallagher, M. J., O'Neill, W. W. et al , 2005)

21. A cohort study in 340 symptomatic patients referred for coronary angiography found that 92 patients (27%) had Agatston calcium scores estimated from mutislice CT coronary angiography of 0 (44 women and 48 men). No stenosis was detected in the 44 women. In 6 men (6.5%) with calcium scores of 0, coronary angiography found stenoses ≥ 50%; single vessel disease in 3 men, 2 vessel disease in 2 men, and 3 vessel disease in 1 man. (Konieczynska, M., Tracz, W., Pasowicz, M. et al , 2006)

22 A cohort study in 1088 symptomatic patients with typical and atypical chest pain referred for coronary angiography found that the sensitivity and specificity of an Agatston score > 0 was 99% and 31%, respectively, and the sensitivity and specificity a Volume score > 0 was 99% and 32%, respectively for the prediction of CAD defined as ≥ 50%; coronary stenosis. (Becker, A., Leber, A., White, C. W. et al , 2007)

23. A small cohort study of 60 patients in patients referred for coronary angiography found that there was little difference in the diagnostic accuracy of 16-slice and 64-slice CT coronary angiography between four Agatston calcium score groups (0 to 100, 101 to 400, > 400 and > 100. (Pundziute, G., Schuijf, J. D., Jukema, J. W. et al , 2007)

24. A small cohort study of 50 patients with suspected CAD referred for outpatient coronary angiography found that the sensitivity of a multislice CT Agatston calcium score ≥ 1 to detect significant CAD (stenosis ≥ 50%) was 97%, and that the sensitivity for the combination of CT angiography and Agatston calcium score was 100%. The ability of the calcium score to discriminate between the

presence and absence of coronary stenosis was greater for patients than for individual vessels and segments as demonstrated by ROC curve analysis (area under ROC curve 0.88, 0.84 and 0.74, respectively). (Lau, G. T., Ridley, L. J., Schieb, M. C. et al , 2005)

25. With increasing thresholds of Agatston calcium score ranges, (from > 0 to 100, and > 100 in 3 studies, and from > 0 to 100, >100 to 400, and > 400 in 3 studies) the sensitivity decreased and the specificity increased for the detection of significant CAD. (Knez, A., Becker, A., Leber, A. et al , 2004) (Becker, A., Leber, A., White, C. W. et al , 2007) (Raff, G. L., Gallagher, M. J., O'Neill, W. W. et al , 2005) (Budoff, M. J., Diamond, G. A., Raggi, P. et al , 2002) (Kitamura, A., Kobayashi, T., Ueda, K. et al , 2005) (Haberl, R., Becker, A., Leber, A. et al , 2001).

26. No evidence was found for the diagnostic accuracy of coronary calcium scores to diagnose significant CAD in ethnic minority groups in the UK.

27. From economic modelling undertaken for this guideline, there is evidence that for patients with a low pre-test-probability of CAD (<25%), 64-slice CT coronary angiography preceded by testing using calcium scoring is cost-effective compared to functional testing and invasive coronary angiography.

5.2.2.4 Evidence statements for anatomical coronary artery imaging (non-invasive and invasive)

28. For the diagnosis of CAD five systematic reviews (search date 2007 for 2 reviews, and 2006 for 3 reviews) of 64-slice CT coronary angiography reported from meta-analyses higher sensitivities of 97%, 96%, 98%, 99% and 99% and specificities of 88%, 91%, 92%, 93% and 97% respectively compared with the non-invasive tests of stress echocardiography ((sensitivity 79.1% (95% CI 77.6% to 80.5%) and specificity 87.1% (95%CI 85.7% to 88.5%)), stress MPS using SPECT ((sensitivity 88.1% (95%CI 86.6 to 89.6%)) and

specificity 73.0% (95%CI 69.1% to 76.9%)), stress MR perfusion imaging ((sensitivity 91% (95%CI 88% to 94%) and specificity 81% (95%CI 77% to 85%)) and stress MR wall motion abnormalities ((sensitivity 83% (95%CI 79% to 88%)) and specificity 86% (95% CI 81% to 91%)). (Abdulla, J., Abildstrom, S. Z., Gotzsche, O. et al , 2007) (Sun, Z., Lin, C., Davidson, R. et al , 2008) (d'Othee Janne, B., Siebert, U., Cury, R. et al , 2008) (Vanhoenacker, Piet K., Heijenbrok-Kal, Majanka H., Van, Heste Ruben et al , 2007) (Mowatt, G., Cummins, E., Waugh, N. et al , 2008)

29. MR coronary angiography overall demonstrates lower sensitivity compared with all other non-invasive anatomical tests. A systematic review (search date 2004) found that the sensitivities for patient-level, coronary artery -level and coronary artery segment-level and were 86%, 75% and 73%, respectively. The specificity of 56% at the patient level was low. The specificities for the coronary artery -level and coronary artery segment-level were 85% and 86%, respectively. (Danias, P. G., Roussakis, A., and Ioannidis, J. P., 2004)

30. A systematic review (search date 2005) that compared MR coronary angiography with multislice CT coronary angiography (up to 16 slice) using selected studies that were not head to head comparisons found that multislice CT coronary angiography had greater sensitivity of 85% (95%CI 86% to 88%) and specificity of 95% (95%CI 95%) compared with a sensitivity 72% (95%CI 69% to 75%), and specificity of 87% (95%CI 86% to 88%) for MR coronary angiography. Multislice CT coronary angiography had a higher odds ratio (16.9-fold) for the presence of significant stenosis (≥ 50%) compared with MR coronary angiography (6.4 - fold). (Schuijf, J. D., Bax, J. J., Shaw, L. J. et al , 2006)

31. A study that estimated lifetime attributable risk of cancer incidence from a single 64-slice CT coronary angiography scan using simulations models found that cancer risk varied markedly with age

and gender. Younger subjects and women had a considerably greater risk compared with men and older subjects. A woman aged 20 years had estimated lifetime attributable risk of 1 in 143 (0.70%) while a man aged 20 years had estimated lifetime attributable risk of 1 in 686 (0.15%) and this was equivalent to the risk of a woman aged 70 years. A man aged 20 years had a 5 fold relative risk of cancer incidence compared with an 80 year old man. A 20 year old woman had a 23 fold relative risk of cancer compared with an 80 year old man. (Einstein, A. J., Henzlova, M. J., and Rajagopalan, S., 2007).

32. Evidence from the published economic literature and from modelling undertaken for this guideline has indicated that when the prevalence of CAD is high (60% or greater), the most cost-effective strategy for investigation is directly to invasive coronary angiography(Mowatt, G., Vale, L., Brazzelli, M. et al , 2004),(Hernandez, R. and Vale, L., 2007),(Dewey, M. and Hamm, B., 2007),(Rumberger, J. A., Behrenbeck, T., Breen, J. F. et al , 1999), (Mowatt, G., Cummins, E., Waugh, N. et al , 2008).

33. Economic models indicate that 64-slice CT coronary angiography is more cost-effective than MPS with SPECT over a range of pre-test probability of CAD (10% to 70%). This result holds even when the most conservative current estimates of 64-slice CT coronary angiography sensitivity (89%) and specificity (80%) are used. (Mowatt, G., Cummins, E., Waugh, N. et al , 2008)

34. There is evidence from short term diagnostic economic models that for patients with a low to moderate pre-test likelihood of CAD, 64-slice CT coronary angiography (with or without prior exercise ECG) as the initial investigation is cost-effective compared to invasive coronary angiography alone. (Mowatt, G., Cummins, E., Waugh, N. et al , 2008), *(Dewey, M. and Hamm, B., 2007)*]

35. Due to the high sensitivity [define] and negative predictive value of 64-slice CT coronary angiography, short term diagnostic economic models indicate that replacing invasive coronary angiography with 64-slice CT coronary angiography will save resources (1/3 – ¼ savings) with minimal impact on diagnostic performance (small number of additional false positives) and may confer a small survival advantage. The modelled cost-savings diminish in populations with a high prevalence of CAD. (Mowatt, G., Cummins, E., Waugh, N. et al , 2008)

36. There is evidence from economic models comparing the cost-effectiveness of exercise ECG, MPS with SPECT, stress echocardiography [but not 64-slice CT coronary angiography] and coronary angiography, that in populations with moderate to high pre-test likelihood of CAD (CAD greater than 30%), invasive coronary angiography as the initial investigation is likely to be the most cost-effective strategy using a threshold cost-effectiveness of £20,000/QALY. *(Mowatt, G., Vale, L., Brazzelli, M. et al , 2004)* , *(Hernandez, R. and Vale, L., 2007)*

37. From economic models comparing the cost-effectiveness of exercise ECG, MPS with SPECT, stress echocardiography [but not 64-slice CT coronary angiography] with invasive coronary angiography that in populations with low to moderate pre-test likelihoods of CAD, (10%-30%) initial use of non-invasive test strategies (MPS with SPECT or stress echocardiography) followed by confirmatory invasive coronary angiography are likely to be the most cost-effective strategies using a willingness to pay threshold of £20,000/QALY. *(Mowatt, G., Vale, L., Brazzelli, M. et al , 2004)* , *(Hernandez, R. and Vale, L., 2007)*

38 In women with a low CAD population prevalence (5.5%), economic modelling has indicated that initial use of MPS with SPECT followed by confirmatory invasive coronary angiography for SPECT positive women, is likely to confer both cost and outcome advantages

compared to exercise ECG and invasive coronary angiography only based strategies due to higher sensitivity and specificity of MPS with SPECT compared with exercise ECG in women. *(Mowatt, G., Vale, L., Brazzelli, M. et al , 2004)* , *(Hernandez, R. and Vale, L., 2007)*

Back to recommendations

5.2.3 Clinical evidence

5.2.3.1 Background to reviewing diagnostic studies

Diagnostic accuracy studies measure the level of agreement between the results of a test under evaluation and that of the reference 'gold' standard. The majority of studies on diagnostic performance report estimates of sensitivity and specificity, where sensitivity is defined as the number of true positive tests divided by the total number of subjects with the disease, and specificity is defined as the number of true negative test results divided the total number of subjects without the disease.

Diagnostic accuracy of a given test can be evaluated using likelihood ratios. A positive likelihood ratio (PLR) measures how much more likely is a positive (abnormal) test to be found in a subject with the disease than in a person without the condition, while a negative likelihood ratio (NLR) measures how much more likely is a negative (normal) test to be found in a subject without the disease than in a subject with the condition. PLR values are usually > 1, and NLR values are usually in the range of 0 to 1. If the LR is 1 the probability of a positive result in the diseased and non diseased subjects are equal, hence the test is useless in ruling in or ruling out a disease. The further that the LR deviates from 1, the better the test is at ruling in (PLR) or ruling out (NLR) the target disease. As a measure of test performance the LR has advantages over sensitivity and specificity in that it changes with disease prevalence and can be used to calculate post test probability.

The positive predictive value (PPV) is the proportion of subjects with positive test results who have the target disease (post test probability of a positive test). The negative predictive value (NPV) is the proportion of subjects with

negative test results who do not have the target disease (post test probability of a negative test). For example a PPV of 80% means that 80% of subjects with a positive test result have the disease.

As with other interventions, the diagnostic accuracy of a test can be determined by computing weighted averages of the sensitivities, specificities or likelihood ratio using random or fixed effects methods (inverse variance approach; weighting each study according to its study size). This relies on the absence of variability in the diagnostic threshold. Receiver Operating Characteristic (ROC) curves can assess threshold effects. ROC curves show the pattern of sensitivities and specificities observed when the test is evaluated at several diagnostic thresholds. A ROC curve is a plot of sensitivity versus 1 – specificity. The overall diagnostic accuracy of a test can be determined by the area under the curve; a value of 0.5 indicates that the test is useless, while a test with excellent diagnostic accuracy will have an area under the curve close to 1. If sensitivities and specificities vary with the thresholds used (cut off points for determining test positives), it is important to analyse sensitivities and specificities as pairs and examine the effect of thresholds on the study results. To account for the problem of interdependence the summary Receiver Operating Characteristic (sROC) method can be used for the meta-analysis of studies reporting pairs of sensitivities and specificities. The sROC method converts each pair of sensitivity and specificity to a single measure of accuracy, namely the diagnostic odds ratio (OR). The diagnostic odds ratio is an unconditional measure of test accuracy which expresses the odds of positive test results in subjects with disease compared with subjects without the disease. Odds ratios from the individual studies are combined using a standard random-effects meta-analysis and the sROC curve is constructed from the pooled odds ratios (with 95% confidence intervals) by calculating the values of specificity for every possible value of sensitivity and a. weighted ‘pooled’ value for diagnostic ratio (with 95% confidence intervals).

Heterogeneity of sensitivity and specificity can be estimated separately using the I^2 index that ascertains the percentage of the total variability in a set of

effect sizes that is due to between-studies variability. For example, a meta-analysis with $I^2 = 0$ means that all variability in effect size estimates is due to sampling error within studies. On the other hand, a meta-analysis with $I^2 = 50$ means that half of the total variability among effect sizes is not caused by sampling error, but by true heterogeneity between studies. The I^2 index has been developed from the Q test that was defined by Cochrane in 1954. The Q test only provides information regarding the presence versus the absence of heterogeneity, and it does not report on the extent of such heterogeneity while the I^2 index quantifies the magnitude of such heterogeneity.

There are a variety of diagnostic tests available for the determination of myocardial ischaemia or obstructive CAD such as exercise stress ECG, stress echocardiography, MRI, myocardial perfusion scintigraphy using SPECT, MSCT coronary angiography and invasive coronary angiography. As part of the reviewing of the evidence for the diagnostic investigations, the GDG was interested in details of any prior diagnostic tests that had been performed on the populations in the diagnostic studies being appraised. A patient may undergo a number of tests, and an estimation of pre-test (which will be informed by the results of any prior diagnostic investigations) and post-test probability for each test gives an estimate of the incremental diagnostic value of the test. This assists in determining the added diagnostic value if potentially more resource-intensive diagnostic testing in a given diagnostic care pathway is used. In the systematic reviews identified on the diagnostic performance of both non invasive and invasive tests, information on prior investigations was either very poorly described or not recorded. Furthermore, investigation of the individual original diagnostic studies that were used in meta-analyses showed that these original diagnostic reports did not provide any further details about types or numbers of diagnostic tests conducted before the patient underwent the test under evaluation.

Primarily very little data were available for patient characteristics in systematic reviews, and the focus of these studies was on describing how the test was performed and the accuracy of the test. Prevalence was reported in most systematic reviews; however, these were often reported as ranges rather than

weighted pool values. Studies included in the systematic reviews were frequently heterogeneous in terms of their participants. For example some studies included patients with suspected CAD; some studies included patients with CAD only, while other studies had a mixture of both these populations.

The threshold for diagnostic performance defined using coronary artery stenosis also varied considerably in the studies and these included ≥ 50%, > 50%, ≥ 70%, > 70% or ≥ 75% luminal narrowing shown on invasive coronary angiography. The majority of the systematic reviews using meta-analysis to determine the diagnostic accuracy of a given test did not take into account the varying definitions of CAD in the studies that they included in their determination of the summary diagnostic performance statistics.

5.2.3.2 Overview Of functional stress testing

A number of different functional stress tests can be used to detect myocardial ischaemia. The exercise ECG uses the development of ECG abnormalities, whilst others use different imaging modalities including nuclear imaging, echocardiography, and magnetic resonance imaging.

Exercise ECG

Exercise ECG is widely used for the non invasive detection of myocardial ischaemia (usually due to obstructive CAD). Exercise is used to induce stress with either treadmill and cycle ergometer devices, and ECG, blood pressure, heart rate and the development of chest pain and or other symptoms are monitored. If there are no adverse events, exercise is continued until symptoms develop or a heart rate > 85% of the maximum age predicted heart rate is achieved and maintained. Exercise testing is a low-risk investigation even in patients with known CAD, but serious complications occur in 2 to 4 per 1000 tests and death may occur at a rate of 1 to 5 per 10 000 tests (Mowatt, G., Vale, L., Brazzelli, M. et al , 2004). The absolute contraindications to exercise testing include; acute MI within 2 days, unstable angina, uncontrolled cardiac arrhythmias, symptomatic severe aortic stenosis, uncontrolled symptomatic heart failure, acute endocarditis, myocarditis or pericarditis and acute aortic dissection. The advantages of exercise testing

are that it takes less than 1 hour to perform, it determines exercise capacity, it has a long history of use and trained personnel are readily available and myocardial ischaemia is assessed. Disadvantages are that exercise testing does not localise the coronary territory of ischaemia, it has lower sensitivity and specificities compared with other diagnostic tests, and it may be inappropriate in some patients, for example, in patients with pulmonary or peripheral artery disease and those patients that are unable to walk or pedal a cycle ergometer.

Exercise ECG testing should be performed by a healthcare professional who is appropriately trained and suitable emergency support should be available. The interpretation of the exercise ECG includes exercise capacity, hemodynamic response, ECG changes and the occurrence of ischaemic chest pain / discomfort consistent with angina. The most important ECG findings are ST-segment depression and ST-segment elevation, and the most commonly used definition for a positive test is ≥ 1 mm of horizontal or downsloping ST-segment depression or elevation for ≥ 60 to 80 ms after the end of the QRS complex either during or after exercise. Throughout the test the ECG, heart rate, and blood pressure should be carefully monitored for abnormalities such as transient rhythm disturbances, and ST changes.

Myocardial perfusion scintigraphy (MPS) using single photon emission computed tomography (SPECT)

Myocardial perfusion scintigraphy (MPS) uses a radiopharmaceutical tracer to assess regional myocardial blood flow while the myocardium is under stress and at rest, in order to detect ischaemia or infarction. The distribution of the tracer in the myocardium, reflecting regional blood flow at the time of the injection of the tracer, is determined by tomographic imaging using a gamma camera. ECG gating of image acquisition allows assessment of left ventricular function.

Myocardial stress is induced either by exercise, or more commonly by pharmacological agents (adenosine, dipyridamole or dobutamine). Adenosine and dipyridamole are coronary vasodilators that increase myocardial blood

flow in normal coronary arteries but not in arteries distal to a stenosis. Side effects due stress agents occur in 50% to 80% of patients but they are usually transient and relatively well tolerated. These include shortness of breath, headache, dizziness, nausea, flushing, and arrhythmias. Severe side effects are rare but in patients with airways obstruction, acute bronchospasm may occur. Dobutamine is a positive inotrope that increases myocardial blood flow that may provoke ischaemia. As with adenosine or dipyridamole, minor side effects are common including nausea, anxiety, headache, tremors, arrhythmias, and angina or atypical chest pain. However, severe adverse events are rare.

Two gamma emitting tracers are available: thallium (Tl-201) or technetium (Tc-99m). Thallium-201 is administered as the chloride and there are two technetium-99m tracers licensed in the UK, Tc-99m sestamibi (MIBI) or Tc-99m tetrofosmin. Technetium containing radiopharmaceuticals have become the preferred agent, as the radiation emitted produces improved imaging.

Areas of reduced tracer uptake on the images obtained correlate with areas of reduced blood flow. In summary, reduced regional uptake at both stress and rest represents infarction, reduced regional uptake at stress with greater uptake at rest represents ischaemia. Defect size, position and depth are important features that correlate with extent, distribution and intensity of ischaemia and infarction.

Advantages of MPS with SPECT include the fact that scanning equipment is relatively open and claustrophobia is extremely uncommon. There is no absolute patient weight limit for patient to have MPS with SPECT, although the image quality in patients over 140kg deteriorates with increasing body weight. The disadvantages of nuclear perfusion imaging compared with the other functional imaging techniques are that it involves a significant radiation dose (6 to 8mSv) and in general requires attendance on two separate days for a rest and stress examination, whereas both MR perfusion imaging and stress echocardiography can be performed on one day within an hour. Artefacts due to breast attenuation in women and attenuation due to abdominal obesity need to be born in mind during interpretation of MPS with SPECT.

Stress echocardiography

Stress echocardiography utilises the reflection of ultrasound waves by tissue of differing properties. The imaging examines left ventricular wall motion and thickening during stress compared with baseline. Exercise or pharmacological agents can be used to induce stress. The positive inotrope dobutamine is the preferred pharmacological stress agent compared with the vasodilators adenosine or dipyridamole. Echocardiography examines the dobutamine-enhanced myocardial contractile performance and wall motion, affording the identification of any wall motion abnormalities. Continuous or staged echocardiographic monitoring is used throughout to look for changes in regional function. Echocardiographic findings suggestive of myocardial ischemia include; a decrease in wall motion in at least one left ventricular segment with stress, a decrease in wall thickening in at least one left ventricular segment with stress, and compensatory hyperkinesis in complementary non ischaemic wall segments.

Stress echocardiography has advantages for patients with suspected ischaemia in whom there is also suspected valve disease or a murmur of unknown aetiology, as this can all be evaluated during a single investigation. The lack of radiation exposure and wide availability of the necessary equipment are major advantages. However, the disadvantages are that stress echocardiography is technically demanding for the operator and accuracy is highly observer dependant. It is difficult or impossible to use when the acoustic window is poor, for example in some obese patients and or those with chronic obstructive airways disease or chest deformity, and it is best reserved for those patients whose body habitus suggests they will be good candidates for transthoracic echocardiography. Patients with LBBB exhibit abnormal septal motion that may limit the interpretation of stress echocardiograms. Patients with atrial fibrillation may have unpredictable heart rate responses during dobutamine infusion, and alteration of inotropic status between long and short cycles may interfere with proper interpretation of wall motion during stress.

Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) is a relatively new technique for the examination of the heart compared with other non invasive techniques. MR imaging allows cardiac visualisation with high spatial and temporal resolution and can be performed using two very different techniques. The first is dynamic first-pass perfusion imaging that assesses inducible perfusion defects indicating impaired perfusion reserve, and the second is stress-induced wall motion abnormalities that evaluates impairment of regional endocardial excursion and myocardial thickening, also indicating underlying myocardial ischaemia. MR imaging uses the pharmacological stress agents adenosine, dipyridamole, or dobutamine. Combining stress perfusion with delayed enhancement also allows clear distinction between infarcted and viable myocardium. MR perfusion imaging therefore may have advantages in patients with suspected ischaemia and impaired left ventricular function. MR perfusion imaging can be used to assess valve disease but is less well proven in this respect compared with echocardiography. In patients with impaired left ventricular function and valve disease stress echocardiography is preferred.

Absolute contra indications for MR imaging are the same as those for all MR techniques (ferromagnetic magnet intracranial surgical clips, metallic intraocular foreign bodies, pace makers etc). Cardiac magnets have an internal bore of 55 or 60 cm which effectively precludes patients much over 100 kg in women and 120 kg in men. It can also be claustrophobic (approximately 5% refusal, although some of these patients subsequently have the investigation with sedation).

5.2.3.3 Stress tests

Exercise ECG

A systematic review (search date 1987) on the diagnostic accuracy of exercise ECG to detect CAD identified 147 studies (24 074 patients) which used coronary angiography as the reference standard (Gianrossi, R., Detrano, R., Mulvihill, D. et al , 1989). There were 150 study groups included in the 147 reports. From the 147 studies, 15 893 (66%) patients had angiographic CAD as defined as > 50% diameter stenosis of at least one major vessel, and 8181

patients did not. Owing to missing data only 144 study groups were used in sensitivity analysis and 132 study groups in specificity analysis. There was wide variability in sensitivity and specificity between the studies identified by the review, the weighted mean difference for sensitivity was 68±16% (range 23% to100%) and for specificity was 77±17% (range 17% to 100) (Gianrossi, R., Detrano, R., Mulvihill, D. et al , 1989).

A number of study variables were examined for an association with sensitivity and specificity. Bivariate analysis was applied to dichotomous variables using the non paired t test, and Pearson correlation coefficients were calculated for continuous variables. The following characteristics were found to be independently and significantly related to sensitivity by bivariate analysis; treatment of equivocal results which decreased sensitivity (*P* = 0.0001), comparison with a 'better' test such as thallium scintigraphy which decreased sensitivity (*P* = 0.0001), exclusion of patients on digitalis which increased sensitivity (*P* = 0.0002), and exclusion of patients with LBBB which increased sensitivity (*P* = 0.02). Characteristics that were not related to sensitivity by bivariate analysis included; gender, mean age, publication year, exercise protocol, angiographic definition of CAD (50% coronary stenosis versus 70% coronary stenosis), treatment of upsloping ST depression being considered abnormal, and exclusion of patients with the following; prior MI, left ventricular hypertrophy, RBBB and long acting nitrate therapy. The characteristics independently and significantly related to specificity were; treatment of upsloping ST depression being considered abnormal which decreased specificity (*P* = 0.01), and exclusion of patients with prior MI (*P* = 0.005) which decreased specificity. Characteristics that were not related to specificity by bivariate analysis included; gender, mean age, publication year, exercise protocol, treatment of equivocal results, comparison with a 'better' test such as thallium scintigraphy, angiographic definition of CAD (50% coronary stenosis versus 70% coronary stenosis), and exclusion of patients with the following; left ventricular hypertrophy, RBBB, patients on long acting nitrate therapy and patients on digitalis therapy (Gianrossi, R., Detrano, R., Mulvihill, D. et al , 1989).

The following variables were entered in a multivariate linear regression analysis, with sensitivity and specificity as dependent variables; age, gender, exclusion due to prior MI, LBBB, RBBB, left ventricular hypertrophy, mitral valve prolapse, exclusion due to beta blockers therapy, long acting nitrate therapy, or digitalis therapy, publication year, hyperventilation used before exercise, exercise protocol, continent of study, smallest amount of ST depression deemed normal, upsloping ST-segment considered abnormal, point in time measurements were made, ST depressions adjusted for heart rate, number of leads, use of computer algorithm, angiographic definition of CAD (> 50% versus > 70% diameter stenosis), comparison with a 'better' test, avoidance of work up bias, and treatment of equivocal results. The following characteristics were found to independently and significantly associate with a decrease in sensitivity by stepwise linear regression; equivocal results included and considered normal (P = 0.0001), comparison with a 'better' test such as thallium scintigraphy (P = 0.0003), exclusion of patients on digitalis (P = 0.008), and publication year (P = 0.047). The following characteristics were found to independently and significantly associate with specificity by stepwise linear regression; treatment of upsloping ST depression being considered abnormal (P = 0.05), exclusion of patients with prior MI (P = 0.005), exclusion of patients with LBBB (P = 0.002), and use of hyperventilation before exercise (P = 0.04). The incremental variance identified by the multivariate models accounted for 33% of the variance in sensitivity and 22% of the variance in specificity. Therefore the results of the meta-analysis and the reported ranges of sensitivity and specificity cannot be completely explained by the variables abstracted from the exercise ECG studies included in the systematic review. There is likely to be incomplete reporting of potentially important data involving both population and technical factors. Hence incomplete reporting of data, in addition to defects in research methodology and selection bias are likely to account for the wide range in sensitivity and specificity (Gianrossi, R., Detrano, R., Mulvihill, D. et al , 1989).

A Health Technology Assessment (search date 1999) identified a total of 111 studies on the diagnostic utility of exercise ECG in the evaluation of patients with chronic chest pain (Mant, J., McManus, R. J., Oakes, R.-A. L. et al ,

2004). Many of the studies excluded patients with significant resting ECG abnormalities. Seventy one studies included data for ST depression of 1 mm, 12 studies included data for ST depression of 2 mm, 13 studies included data for ST slope, and 6 studies examined combinations of features such as treadmill score. LRs were calculated from the numbers of true positives, false positives, true negatives and false negatives in the included in the studies, and a weighted average of the pooled results using the standard Mantel-Haenszel method for risk ratios with 95%CIs. Chi squared analysis indicated that there was heterogeneity in the studies (Mant, J., McManus, R. J., Oakes, R.-A. L. et al , 2004).

As detailed in Table 16, the presence of ST depression had PLR of 2.79 (95% CI 2.53 to 3.07) for a 1 mm cutoff and a PLR of 3.85 (95% CI 2.49 to 5.98) for a 2 mm cutoff. The corresponding NLRs were 0.44 (95% CI 0.40 to 0.47) for 1 mm and 0.72 (95% CI 0.65 to 0.81) for 2 mm. The ST slope showed similar performance with PLR 2.01 (95% CI 1.74 to 2.31) for cutoffs below 2 μV/beats/minute increasing to 3.91 (95% CI 2.51 to 6.09) when slopes steeper than 2 μV/beats/minute were used (Mant, J., McManus, R. J., Oakes, R.-A. L. et al , 2004).

Table 16
Exercise ECG for chronic chest pain – different definitions of positive

Analysis	No. of studies	PLR	NLR
ST depression 1mm – all studies	71	2.79 (95% CI 2.53 to 3.07)	0.44 (95% CI 0.40 to 0.47)
ST depression 2mm – all studies	12	3.85 (95% CI 2.49 to 5.98)	0.72 (95% CI 0.65 to 0.81)
ST slope – all data points	13	2.41 (95% CI 1.81 to 3.2)	0.37 (95% CI 0.72 to 0.50)
ST slope – cutoff point <2μV/beats/minute	7	2.01 (95% CI 1.74 to 2.31)	0.59 (95% CI 0.53 to 0.66)
ST slope – cutoff point >2μV/beats/minute	6	3.91 (95% CI 2.51 to 6.09)	0.32 (95% CI 0.20 to 0.50)
Combinations	6	1.83 (95% CI 1.72 to 1.95)	0.36 (95% CI 0.33 to 0.40)

Permissions requested from original source (Mant, J., McManus, R. J., Oakes, R.-A. L. et al , 2004).

Table 17 shows the sensitivity analysis performed, detailing the number of studies used in each of the analyses. No prior history of CAD was found to

significantly decrease the PLR of ST depression as a diagnostic test. The most common form of exercise test was the Bruce protocol and sensitivity analysis found that the type of exercise test protocol (Bruce protocol, other treadmill protocol, bicycle protocol) did not significantly alter diagnostic performance. The sensitivity analysis also examined 9 studies where patients were not taking drugs which might have influenced the exercise ECG. These studies had a greater PLR of 5.24 (95% CI 3.35 to 8.20) and a lower NLR of 0.38 (95% CI 3.35 to 8.20) compared with the 71 studies that examined data for ST depression of 1 mm (PLR of 2.79 (95% CI 2.53 to 3.07) and NLR 0.44 (95% CI 0.40 to 0.47)). Note that the NLR 95%CI for the 9 studies where patients were not taking drugs quoted in the study appear to be incorrect as they do not tally with the meta-analysis estimate (Mant, J., McManus, R. J., Oakes, R.-A. L. et al , 2004).

Table 17
Exercise ECG studies for chronic chest pain

Analysis	No. of studies	PLR	NLR
Overall	71	2.79 (95% CI 2.53 to 3.07)	0.44 (95% CI 0.40 to 0.47)
Other disease and treatment			
<20% previous MI	43	2.39 (95% CI 2.17 to 2.62) *P*= 0.001 [a]	0.44 (95% CI 0.40 to 0.49) *P*=0.51[a]
Known to have no previous cardiac history	8	2.41 (95% CI 1.95 to 2.98) *P* =0.002 [a]	0.41 (95% CI 0.32 to 0.53) *P* =0.71[a]
Known to have no other drugs	9	5.24 (95% CI 3.34 to 8.20) *P* =0.14 [a]	0.38 (95% CI 3.35 to 8.20) *P* =0.09[a]
No history or drugs	1	7.05 (95% CI 3.08 to 16.12)	0.16 (95% CI 0.09 to 0.30)
Type of test			
Bruce	41	2.75 (95% CI 2.46 to 3.08)	0.46 (95% CI 0.42 to 0.50)
Bicycle	17	3.20 (95% CI 2.38 to 4.29) *P* =0.54 [b]	0.39 (95% CI 0.33 to 0.45) *P* =0.13 [b]
Other features			
Studies with 12-lead ECG	39	2.50 (95% CI 2.25 to 2.77) *P* =0.04 [a]	0.45 (95% CI 0.44 to 0.47) *P* =0.34 [a]
Studies not using 12-lead ECG	32	3.36 (95% CI 2.73 to 4.14) *P* =0.04 [a]	0.42 (95% CI 0.38 to 0.46) *P* =0.34 [a]
ST-upsloping segments considered abnormal	24	2.96 (95% CI 2.51 to 3.50) *P* =0.55 [a]	0.46 (95% CI 0.41 to 0.52) *P* =0.37 [a]
Studies stating method for dealing with equivocal results	22	2.84 (95% CI 2.39 to 3.38) *P* =0.95 [a]	0.41 (95% CI 0.35 to 0.47) *P* =0.35 [a]

[a] Compared with all studies not fitting this criterion
[b] Compared with all studies using the Bruce method
Permissions requested from original source (Mant, J., McManus, R. J., Oakes, R.-A. L. et al , 2004).

The Health Technology Assessment examined the use of ST depression as a diagnostic tool in men versus women. Nineteen studies were identified that recruited men only, and a further 19 studies that recruited women only. In the studies in men, the PLR was 2.92 (95% CI 2.17 to 3.93) for 1 mm of ST depression and for the studies in women the PLR was lower at 1.92 (95% CI 1.72 to 2.24), for 1 mm of ST depression. While the PLR was lower in women compared with men, the difference was not statistically significant.

Exercise ECG, exercise echocardiography and exercise thallium myocardial perfusion scintigraphy (MPS) in women

A systematic review (search date 1995) on the diagnostic performance of exercise tests identified 19 studies for exercise ECG, 5 studies for exercise thallium myocardial perfusion scintigraphy (MPS) (3 studies thallium MPS; 1 study thallium MPS using SPECT) and 3 studies for exercise stress echocardiography for the detection of CAD in women (Kwok, Y., Kim, C., Grady, D. et al , 1999). All studies used coronary angiography as the reference standard. In the exercise ECG studies, 8 studies used ≥ 50% diameter coronary artery stenosis as the threshold for significant disease and 11 studies used ≥ 70%. In the exercise thallium MPS studies, 3 studies used ≥ 50% diameter coronary artery stenosis as the threshold for significant disease and 2 studies used ≥ 70%. All three exercise stress echocardiography studies used ≥ 50% diameter coronary artery stenosis as the threshold for significant disease. Meta-analysis of the exercise ECG studies (3721 women, mean age 56 years) gave a sensitivity of 61% (95%CI 54% to 68%), a specificity of 70% (95%CI 64% to 77%), positive likelihood ratio (PLR) of 2.25 (95%CI 1.84 to 2.66), and negative likelihood ratio (NLR) of 0.55 (95%CI 0.44 to 0.62). There was wide variability in the sensitivities for exercise ECG (27% to 91%) and also in the specificities (46% to 86%). The variability was found not to be associated with the exclusion of patients with baseline ECG changes. The weighted mean of prevalence of CAD in the 19 stress ECG studies was not reported, but the prevalence ranged from 18% to 67% (Kwok, Y., Kim, C., Grady, D. et al , 1999).

Meta-analysis of the exercise thallium MPS studies (842 women, mean age 57 years) gave a sensitivity of 78% (95%CI 72% to 83%), a specificity of 64% (95%CI 51% to 77%), PLR of 2.87 (95%CI 1.0 to 4.96), and NLR of 0.55 (95%CI 0.27 to 0.44). The prevalence of CAD in the 5 studies ranged from 30% to 75% (Kwok, Y., Kim, C., Grady, D. et al , 1999).

The sensitivity for exercise thallium MPS was higher compared with exercise ECG (78% versus 61%, respectively); while the specificity was lower (64% versus 70%, respectively) (Kwok, Y., Kim, C., Grady, D. et al , 1999).

Meta-analysis of the 3 studies of exercise stress echocardiography (296 women, mean age 58 years) found that the test had a sensitivity of 86% (95%CI 75% to 96%), and specificity of 79% (95%CI 72% to 86%), PLR of 4.29 (95%CI 2.93 to 5.65), and NLR of 0.18 (95%CI 0.05 to 0.31). The prevalence of CAD in the 3 studies ranged form 37% to 51% (Kwok, Y., Kim, C., Grady, D. et al , 1999).

The systematic review compared the findings from their meta-analysis with a previous study that included studies in predominately male populations. (Gianrossi, R., Detrano, R., Mulvihill, D. et al , 1989). Using the stated comparison, exercise ECG in women had a lower diagnostic accuracy compared with men, with sensitivity of 61% versus 68%, respectively, and a specificity of 70% versus 77%, respectively. The authors speculated reasons for the lower accuracies were; the prevalence of CAD could be lower in women compared with men although values were not reported although sensitivity and specificity values are not associated with prevalence of CAD, the digoxin-like effect of oestrogen, inappropriate catecholamine response to exercise in women, a higher incidence of mitral valve prolapse, and different wall anatomy. Also the thresholds for defining abnormal ECG changes were established almost exclusively in men. Sensitivity and specificity in the studies of women were found to be highly correlated suggesting that different studies may have had different thresholds for interpreting a test as positive (Kwok, Y., Kim, C., Grady, D. et al , 1999).

The systematic review compared the findings from their meta-analyses with a previous study which was considered to have a population that was predominately male ((Detrano, R., Janosi, A., Lyons, K. P. et al , 1988). Using the stated comparison, exercise thallium MPS in women had a lower diagnostic accuracy compared with men, with a sensitivity of 78% versus 85%, respectively, and a specificity of 64% versus 85%, respectively. The speculated reason for the lower accuracies was greater image blurring due to smaller left ventricular chamber size and / or breast tissue (Kwok, Y., Kim, C., Grady, D. et al , 1999).

Stress ECG versus myocardial perfusion scintigraphy (MPS) using single photon emission computed tomography (SPECT)

A Health Technology Assessment (search date 2002) compared the diagnostic accuracy of MPS with SPECT with stress ECG for the detection of CAD (Mowatt, G., Vale, L., Brazzelli, M. et al , 2004). Sixteen studies were identified in patients with a suspicion or a history of CAD (search date 2002). Only studies that used coronary angiography as the reference standard and that directly compared MPS with SPECT with stress ECG were included; in 12 studies the angiographic definition of CAD was ≥ 50% diameter stenosis, in 1 study ≥ 60% diameter stenosis, in 2 studies ≥ 70% diameter stenosis and in 1 study ≥ 75% diameter stenosis. Two studies enrolled only women, 1 study only men, and 3 studies provided results for men and women separately. Eleven studies used Tl-201 as the tracer, and 5 studies used MIBI. Eleven studies used exercise stress, 2 studies either exercise or pharmacological stress, 1 study used pharmacological stress, and 2 studies gave no information as to the type of stress used (Mowatt, G., Vale, L., Brazzelli, M. et al , 2004).

There was considerable variability in the studies with respect to the inclusion and the exclusion criteria, hence, the results of the studies were not analysed by meta-analyses, but rather the studies were summarised as medians and ranges (chi-squared test for sensitivity and specificity $P < 0.001$ in each case). The methodological quality of the studies in the defined subsets varied considerably. Studies differed with respect to the following; definition of

coronary artery stenosis, patients characteristics (mean age, gender, prior MI), severity of the disease (single vessel disease versus multi-vessel disease), use of beta-blocking medications, time between SPECT, stress ECG and coronary angiography, technical factors such as interpretation of test findings (visual versus quantitative reading analysis of SPECT, diagnostic versus non-diagnostic results of stress ECG), angiographic referral (the results of the SPECT and / or stress ECG determined who did or did not undergo CA) and blinding of test results (Mowatt, G., Vale, L., Brazzelli, M. et al , 2004).

The sensitivity values of SPECT tended to be higher than those of stress ECG; SPECT sensitivities ranged from 63% to 93% (median 81%) compared with stress ECG sensitivities ranging from 42% to 92% (median 65%). Specificity values for SPECT and stress ECG were similar; for SPECT the specificities ranged from 54% to 90% (median 65%), and for stress ECG the specificities ranged from 41% to 88% (median 67%) (Mowatt, G., Vale, L., Brazzelli, M. et al , 2004).

The median of sensitivity for SPECT in the subset of studies excluding patients with MI, was higher (median 92%, range 76% to 93%) than that of the subset of studies enrolling patients with MI (median 76%, range 63% to 93%). Stress ECG median of sensitivities were similar for patients with (median 63%, range 44% to 92%) and without previous MI (median 66%, range 42% to 85%). Specificity values for SPECT and stress ECG in both subsets of studies were also similar. However, overall these findings are based on a small number of studies which have varying inclusion / exclusion criteria and patient characteristics. In addition, the 10 studies including patients with prior MI did not consist solely of patients with prior MI. It was reported in the HTA that no firm conclusions about the overall accuracy of SPECT and stress ECG and their comparison could be made due to significant heterogeneity and there was insufficient evidence to evaluate the incremental value of SPECT over stress ECG in the diagnosis of CAD (Mowatt, G., Vale, L., Brazzelli, M. et al , 2004).

Twelve of the 16 studies had sufficient information for the calculation of LRs. The range of PLR was 0.95 to 8.99 (median 2.33) for SPECT and 1.14 to 5.60 (median 2.06) for stress ECG. The pooled weighted PLR using a random effects model for SPECT was 2.29 (95% CI 1.68 to 3.12) and for stress ECG was 1.83, (95% CI 1.48 to 2.2.6). There was significant heterogeneity (*P* < 0.001) found for both tests, furthermore the overall estimate of 2.29 for SPECT was outside the 95% CIs of five of the 12 included studies, and the overall estimate of 1.83 for stress ECG was outside the 95% CIs of six of the 12 included (Mowatt, G., Vale, L., Brazzelli, M. et al , 2004).

The NLR for SPECT ranged from 0.09 to 1.12 (median 0.29) for stress ECG ranged from 0.18 to 0.91 (median 0.57). The summary estimate of the NLR for SPECT was 0.25 (95% CI 0.17 to 0.37) and for stress ECG was 0.51 (95% CI 0.39 to 0.67), however there was heterogeneity in the included studies for both tests (P < 0.001) (Mowatt, G., Vale, L., Brazzelli, M. et al , 2004).

Dobutamine stress echocardiography comparing diagnostic accuracy in women compared with men

A systematic review (search date 2006) assessed the diagnostic accuracy of dobutamine stress echocardiography for the detection of CAD in women (Geleijnse, M. L., Krenning, B. J., Soliman, O. I. et al , 2007). Fourteen studies were identified; 7 studies that reported data on women alone, 4 studies that compared women versus men, and 3 studies that allowed subgroup calculations of women versus men. Coronary angiography was the reference standard. In the 7 studies that afforded comparisons of women (482 patients) versus men (966 patients), CAD was less prevalent in women compared with men in all studies except for one with an overall weighted mean of 59% versus 73%, respectively (*P* < 0.001). Coronary artery stenosis was defined as significant when there was ≥ 50% diameter stenosis in all 7 studies. It was reported that CAD was more often reported as single vessel disease in women compared with men although further information was not given. Using meta-analysis the sensitivity was the same in women and in men, both 77%. Specificities were 81% in women and 77% in men. Confidence intervals were not quoted. Meta-analysis of the 14 studies which either only recruited women

or in which the results in women could be distinguished from men (903 patients, mean age 65 years) found the sensitivity in women was 72% (range 31% to 95%), and the specificity was 88% (range from 55% to 100%). Ten studies defined CAD as ≥ 50% diameter stenosis and 2 studies used a cut off ≥ 70% (Geleijnse, M. L., Krenning, B. J., Soliman, O. I. et al , 2007).

In 6 studies the diagnostic performance of dobutamine stress echocardiography was compared with stress nuclear scintigraphy (3 studies used dobutamine stress, 2 studies used exercise or dipyridamole stress, and 1 study used dobutamine or dipyridamole stress). Coronary angiography was the reference standard; 5 studies defined CAD as ≥ 50% diameter stenosis, and 1 study used a cut off ≥ 70%. Meta analysis found that dobutamine stress echocardiography had a sensitivity of 77% and a specificity of 90%. The sensitivity for stress nuclear scintigraphy was 73% and the specificity was 70%. The specificity of dobutamine stress echocardiography was significantly greater than that of stress nuclear scintigraphy ($P < 0.0001$) (Geleijnse, M. L., Krenning, B. J., Soliman, O. I. et al , 2007).

Stress echocardiography versus myocardial perfusion scintigraphy (MPS) using SPECT

A systematic review (search date from 1990 to 2006) conducted meta-analyses of systematic reviews of stress echocardiography and SPECT for the diagnosis of CAD (Heijenbrok-Kal, M. H., Fleischmann, K. E., and Hunink, M. G., 2007). Coronary angiography was the reference standard. Nine non-invasive imaging tests were evaluated in 11 systematic reviews which had a combined number of 565 patient series. Of these, 214 identical series were excluded, giving a final data set of 351 patient series that included 35 268 patients in total. The echocardiography tests examined were; exercise stress echocardiography (55 datasets), adenosine stress echocardiography (11 datasets), dipyridamole stress echocardiography (58 datasets), and dobutamine stress echocardiography (102 datasets), giving 226 diagnostic datasets for all stress echocardiography combined. The stress agents examined with SPECT were; exercise (48 datasets), adenosine (14 datasets), dipyridamole (23 datasets), and dobutamine (16 datasets), giving 103

diagnostic datasets for all SPECT studies combined (Heijenbrok-Kal, M. H., Fleischmann, K. E., and Hunink, M. G., 2007).

The overall weighted mean prevalence of CAD in each of the datasets was not reported. However, the following ranges were given from the results of the identified systematic reviews; exercise stress echocardiography 66% to 74%; adenosine stress echocardiography; 73% to 77%, dipyridamole stress echocardiography; 71% and dobutamine stress echocardiography; 69% to 73%, exercise SPECT 66% to 74%; adenosine SPECT 80% (80% reported in 2 systematic reviews), dipyridamole SPECT 71% (1 systematic review only), and dobutamine SPECT 80% (1 systematic review only) (Heijenbrok-Kal, M. H., Fleischmann, K. E., and Hunink, M. G., 2007).

For stress echocardiography, the pooled sensitivities and specificities were as follows; exercise sensitivity 82.7% (95%CI 80.2% to 85.2%) and specificity 84.0% (95%CI 80.4% to 87.6%), adenosine sensitivity 79.2% (95%CI 72.1% to 86.3%) and specificity 91.5% (95%CI 87.3% to 95.7%), dipyridamole sensitivity 71.9% (95%CI 68.6% to 75.2%) and specificity 94.6% (95%CI 92.9% to 96.3%), dobutamine sensitivity 81.0% (95%CI 79.1% to 82.9%), and specificity 84.1% (95%CI 82.0% to 86.1%).

The combined pooled results for all the studies of stress echocardiography were; sensitivity 79.1% (95%CI 77.6% to 80.5%), and specificity 87.1% (95%CI 85.7% to 88.5%) (Heijenbrok-Kal, M. H., Fleischmann, K. E., and Hunink, M. G., 2007).

For SPECT, the pooled sensitivities and specificities were as follows; exercise sensitivity 88.1% (95%CI 85.8% to 90.3%), specificity 68.8% (95%CI 62.8% to 74.8%), adenosine sensitivity 90.5% (95%CI 89.0% to 91.9%) and specificity 81.0% (95%CI 73.5% to 88.6%), dipyridamole sensitivity 90.4% (95%CI 87.3% to 93.5%), specificity 75.4 (95%CI 66.2% to 84.6%), dobutamine sensitivity 83.6% (95%CI 78.4% to 88.8%), specificity 75.1% (95%CI 71.1% to 79.0%).

The combined pooled results for all the studies of SPECT were; sensitivity 88.1% (95 %CI 86.6% to 89.6%) and specificity 73.0% (95%CI 69.1% to 76.9%) (Heijenbrok-Kal, M. H., Fleischmann, K. E., and Hunink, M. G., 2007).

Multiple regression analysis was conducted to determine significant predictors of diagnostic performance. For stress echocardiography studies, significant predictors of diagnostic performance were stated as the year of publication (odds ratio (OR) 0.96, 95%CI 0.91 to 1.00), and the proportion of men (OR 1.01, 95%CI 1.00 to 1.01). Diagnostic performance decreased over the years and increased in populations with a higher proportion of men. However ORs were close to 1 suggesting that the significance is marginal. Regression analysis found that diagnostic performance was not dependant on the type of stress agent (exercise, adenosine, dobutamine or dipyridamole). Within the total group of SPECT studies, the type of isotope used (TI201 versus 99mTc sestamibi) did not significantly effect the diagnostic performance. However, in the dobutamine stress studies, the diagnostic performance in studies using 99mTc sestamibi was lower compared with thallium 201 (OR 0.34 95%CI 016 to 0.73). In exercise echocardiography studies, diagnostic performance was higher in younger patients (OR 0.89 95%CI 0.82 to 0.96). As found for stress echocardiography studies, year of publication (OR 0.94, 95%CI 0.89 to 0.96), and the proportion of men (OR 1.01, 95%CI 1.00 to 1.02) were reported as significant predictors of SPECT diagnostic performance, hence, diagnostic performance decreased significantly over time and increased in populations with a higher population of men. The diagnostic performance of adenosine SPECT (OR 1.96 95%CI 1.09 to 3.51) was better than that of dipyridamole SPECT (OR 1.09 95%CI 0.65 to 1.82), dobutamine stress (OR 0.79 95%CI 0.46 to 1.38) and exercise (OR 1.0), and also increased in studies with populations with higher prevalence of significant CAD (OR 18 95%CI 1.90 to 172). For dipyridamole SPECT, the diagnostic performance increase in studies with younger populations (OR 0.75 95%CI 0.65 to 0.88) (Heijenbrok-Kal, M. H., Fleischmann, K. E., and Hunink, M. G., 2007).

The results indicated that there were no significant differences in the diagnostic performance between SPECT and stress echocardiography

imaging modalities, and the results did not alter after correcting for type of stress, publication year, or patient characteristics. However, adenosine SPECT was found to be significantly better when correcting for publication year or patient characteristics compared with exercise SPECT and dobutamine SPECT (Heijenbrok-Kal, M. H., Fleischmann, K. E., and Hunink, M. G., 2007).

Stress magnetic resonance imaging (MRI)

A systematic review (search date 2007) of the diagnostic performance of stress MRI to detect CAD identified 37 studies with a total of 1918 patients in the final analyses (Nandalur, K. R., Dwamena, B. A., Choudhri, A. F. et al , 2007). Coronary angiography was the reference standard. There were 14 datasets for summary performance estimates of stress perfusion imaging at the patient level (1183 patients) and 11 datasets for estimates of stress induced wall motion abnormalities (735 patients). Perfusion imaging had a sensitivity of 91% (95%CI 88% to 94%) and a specificity 81% (95%CI 77% to 85%), PLR of 5.10 (95%CI 3.92 to 6.28) and a NLR, 0.11 (95%CI 0.07 to 0.15). The prevalence of CAD was 57% (679 of 1183) (Nandalur, K. R., Dwamena, B. A., Choudhri, A. F. et al , 2007).

Meta-analyses of stress induced wall motion abnormalities imaging gave a sensitivity 83% (95%CI 79% to 88%) and a specificity 86% (95%CI 81% to 91%). The PLR was 5.24 (95%CI 3.28 to 7.21), and the NLR was 0.19 (95%CI 0.15 to 0.24). The prevalence of CAD was 71% (518 of 735). Further meta-analysis to determine coronary territory-level summary performance estimated for per-coronary territory (pooled datasets 16 with 1911 coronary territories) demonstrated a sensitivity of 84% (95%CI 80% to 87%) and specificity of 85% (95%CI 81% to 88%). Per-coronary territory meta-analysis of stress-induced wall motion abnormalities imaging (pooled 4 datasets with 289 coronary territories) gave a sensitivity of 79% (95%CI 71% to 86%) and specificity of 93% (95%CI 81% to 100%). It was noted that there was moderate heterogeneity in the sensitivities between perfusion imaging studies (I^2 = 0.44, P < 0.04), and the specificities between stress induced wall motion abnormality studies (I^2 = 0.73, P < 0.001). For coronary territory levels meta-

analyses, there was heterogeneity for between-studies in the specificities of both perfusion (I^2 = 0.62, P < 0.001) and stress-induced wall abnormality studies (I^2 = 0.85, P < 0.001) (Nandalur, K. R., Dwamena, B. A., Choudhri, A. F. et al , 2007).

Stress MR perfusion imaging versus myocardial perfusion scintigraphy (MPS) using single photon emission computed tomography (SPECT) and stress echocardiography

A randomised controlled trial in patients stable chest pain with known or suspected CAD who were referred for non urgent coronary angiography assessed the use of functional cardiac tests (CECat) (Sharples, L., Hughes, V., Crean, A. et al , 2007). Patients were included if they had established or suspected chronic stable angina and were referred for coronary angiography following an exercise ECG result which in the opinion of the referring clinician warranted referral for angiography (due to symptoms or ECG changes or inadequate exercise). Eight hundred and ninety eight patients were randomised to coronary angiography (n = 222), SPECT (n = 224), MR perfusion imaging (n = 226) or stress echocardiography (n = 226). The primary clinical outcome measure was exercise time (Modified Bruce protocol) at 18 months. The aim of the study was to demonstrate equivalence in exercise time between those randomised to functional tests compared with coronary angiography (Sharples, L., Hughes, V., Crean, A. et al , 2007).

After initial testing, there were unequivocal results for 98% of coronary angiography, 94% of SPECT (P = 0.05), 78% of MR perfusion imaging (P < 0.001) and 90% of stress echocardiography patients (P < 0.001). Twenty two percent of SPECT patients, 20% of MR perfusion imaging patients and 25% of stress echocardiography patients were not subsequently referred for an angiogram. Positive functional tests were confirmed by positive coronary angiography in 83% of SPECT patients, 89% of MR perfusion imaging patients and 84% of stress echocardiography patients. Negative functional tests were followed by positive coronary angiograms in 31% of SPECT patients, 52% of MR perfusion imaging patients and 48% of stress echocardiography patients tested. Coronary artery bypass graft surgery was

performed in 10% of the coronary angiography group, 11% in the MR perfusion imaging group and 13% in both the SPECT and stress echocardiography group. Percutaneous coronary artery intervention was performed in 25% of the coronary angiography group, 18% in the SPECT group and 23% in both the MR perfusion imaging and stress echocardiography group (Sharples, L., Hughes, V., Crean, A. et al , 2007).

At 18 months, there was no clinical difference in total exercise time comparing SPECT and stress echocardiography with coronary angiography. Clinical significance was defined a priori as the confidence interval for mean difference from angiography lying within ± 1 minute. The MR perfusion imaging group had a significantly shorter mean total exercise time compared with the coronary angiography group (mean 35 seconds, $P < 0.05$) with an upper limit of the CI 1.14 minutes less than in the coronary angiography group). At 6 months post-treatment, the SPECT and coronary angiography groups had equivalent mean exercise times. Compared with coronary angiography, the MR perfusion imaging and stress echocardiography groups had significantly shorter mean total exercise times of 37 and 38 seconds, respectively. It was stated that patients in these groups had a range of treatments indicating that these treatments should be investigated for each investigation. During the 18 months there were 24 deaths (13 from cardiac causes, 3 other cardiovascular causes, 8 from other causes), and these were evenly distributed in the four groups. There were 148 non fatal events in 103 patients and these were predominantly hospital admissions for chest pain. There were significantly more non-fatal adverse events (mostly admissions for chest pain) in the stress echocardiography group (rate relative to angiography: 1.95, 95%CI 1.23 to 3.08, $P = 0.012$). However, there were no differences in the number of patients reporting non fatal adverse events for all tests (relative rate compared with the angiography group = 1.59, 95%CI 0.90 to 2.79) (Sharples, L., Hughes, V., Crean, A. et al , 2007).

The authors stated that as 20% to 25% of patients who underwent a functional test did not go on to have an angiogram, functional testing can act as a gateway to coronary angiography without substantial effects on outcomes.

SPECT was as useful as coronary angiography in identifying patients who should undergo coronary revascularisation. MR perfusion imaging had the highest number of test failures, while stress echocardiography had a 10% failure rate, a shorter total exercise time and time to angina at 6 months, and a greater number of adverse events, mostly composed of admission to hospital with chest pain (Sharples, L., Hughes, V., Crean, A. et al , 2007).

5.2.3.4 Calcium scoring, non-invasive and invasive coronary angiography

Calcium scoring

What is the utility and cost effectiveness of coronary artery calcium scoring in evaluation of patients with stable chest pain?

Introduction

Calcification of coronary arteries is characteristic of atherosclerotic disease and can be quantified using electron beam computed tomography (EBCT) and multislice CT coronary angiography. The majority of studies which quantify calcification use the Agatston score (Agatston, A. S., Janowitz, W. R., Hildner, F. J. et al , 1990) although some studies use the Volume score (Callister, T. Q., Cooil, B., Raya, S. P. et al , 1998).The ability of calcium scoring to predict future coronary events in symptomatic subjects has been demonstrated in multiple studies. A multicenter study of 491 patients undergoing coronary angiography and EBCT scanning found that higher calcium scores were associated with an increased risk of coronary events over the next 30 months compared with patients in the lowest quartile of score (odds ratio 10.8, 95% confidence interval 1.4 to 85.6). A second study in 288 symptomatic persons who underwent coronary angiography and calcium scanning and were followed up for a mean of 6.9 years found that age and calcium score were the only independent predictors of future coronary events (relative risk ratio 3.20, 95% CI 1.17 to 8.71). From stepwise multivariate analysis, neither angiographic stenosis nor conventional coronary risk factors (except age) were found to predict cardiac events (Keelan, P. C., Bielak, L. F., Ashai, K. et al , 2001).

The main advantages of calcium scoring are that calcium scanning takes approximately 5 minutes to perform and interpret, there is minimal radiation exposure (1.5 to 3 mSv) compared with multislice coronary angiography, no contrast material is required, the quantification of plaque (calcium score) enables non invasive temporal tracking of atherosclerosis burden and, although not of direct relevance to the investigation of CAD, it detects significant extra-cardiac findings in 2% to 3% as a coincidental finding. The disadvantages include the following; does not assess whether significant coronary stenoses are present, does not make a functional assessment of myocardial ischaemia, and left ventricular function is not assessed. Although coronary artery calcium is well correlated with total plaque volume or atherosclerotic burden it is not a direct marker of the vulnerable plaque at risk of rupture. However, the greater the calcium score the greater the potential for increased numbers of potentially lipid-rich plaques.

No systematic reviews were identified. Study selection in the guideline focused on identifying those studies that examined populations with low to intermediate risk of CAD. Papers were selected if they used multislice CT coronary angiography- or electron beam CT (EBCT)-determined calcium score using either the Agatston score alone, or if they compared the Agatston score with the Volume score. Ten studies were reviewed in total (Callister, T. Q., Cooil, B., Raya, S. P. et al , 1998).

The first cohort study evaluated the EBCT determined ability of the Agatston (Agatston, A. S., Janowitz, W. R., Hildner, F. J. et al , 1990) and Volume score (Callister, T. Q., Cooil, B., Raya, S. P. et al , 1998) to predict coronary stenosis (Knez, A., Becker, A., Leber, A. et al , 2004). Coronary angiography was the reference standard. Two thousand one hundred and fifteen consecutive patients were recruited. All patients were referred by primary care physicians for suspected myocardial ischaemia, and the patients had no prior established CAD. The most common indication for referral to coronary angiography was chest pain (typical or atypical) in 1697 patients (80%), 253 patients (12%) had unexplained exertional dyspnoea, and 160 patients (8%)

were referred for suspected congestive heart failure. Patient characteristics are shown in Table 18 (Knez, A., Becker, A., Leber, A. et al , 2004).

Table 18
Patient characteristics

	Men	Women	Total
Number	1404	711	2115
Age (years; mean±SD)	63±18	59±15	62±19
Hypertension	901 (64%)	521 (73%)	1422 (66%)
Hypercholesterolemia	632 (45%)	391 (55%)	1023 (48%)
Diabetes mellitus	291 (21%)	179 (25%)	470 (22%)
Current smokers	243 (17%)	120 (17%)	486 (23%)
Permissions requested from original source (Knez, A., Becker, A., Leber, A. et al , 2004).			

All scans were examined by one observer who was unaware of the results of the coronary angiogram. Coronary angiography was performed within 4±3 days after the EBCT scan. The decision to perform coronary angiography was not influenced by the results of the EBCT scan. The maximum percent diameter stenosis in any coronary segment was visually assessed by one observer who was unaware of the EBCT results. Narrowing of the lumen diameter by ≥ 50% was defined as significant CAD (Knez, A., Becker, A., Leber, A. et al , 2004).

EBCT and coronary angiography was performed on all patients without complication. Of all 2115 study patients, 1789 (84%) had a positive calcium score (i.e. total calcium score > 0). The mean calcium scores for the Agatston and Volume scores were 323±842 (range 0 to 7224, median 115) and 310±714 (range 0 to 5490, median 114), respectively. The Pearson's correlation coefficient was 0.99 between the two methods. Coronary angiography showed significant CAD in 62% of men (872 out of 1404) and 54% of women (383 of 711). Total calcium scores for patients with and without CAD were significantly different with both methods; 492±1124 versus 76±217 for Agatston score, respectively ($P < 0.01$), and 486±940 versus 53±175 for the Volume score, respectively ($P < 0.01$) (Knez, A., Becker, A., Leber, A. et al , 2004).

No CAD was found in 326 patients (208 men) without coronary calcium. This population was symptomatic but represented a very low risk of significant CAD cohort. However no calcium was found in 7 of 872 men (0.7%) and in 1 of 383 women (0.02%) who had significant luminal stenosis on coronary angiography. Seven of these patients were < 45 years. Overall sensitivity and specificity was 99% and 28%, respectively, for the presence of any coronary calcium being predictive of obstructive angiographic disease (Knez, A., Becker, A., Leber, A. et al , 2004).

Table 19 details age and gender based calcium score percentiles for the Volume and Agatston scores in the entire study population. Independent of their angiographic status, men had a significant difference in prevalence and extent of calcification in comparison with women for the two methods (Knez, A., Becker, A., Leber, A. et al , 2004).

Table 19
Volume / Agatston calcium score nomogram for 2115 symptomatic patients

	Age (years)				
	<40	40-50	50-60	60-70	>70
Men (n=1404)	(n=102)	(n=201)	(n=432)	(n=464)	(n=205)
25th percentile	0/0	2/4	23/27	75/92	108/127
50th percentile	11/13	41/59	79/83	153/176	203/243
75th percentile	54/63	79/83	155/158	283/370	402/498
90th percentile	231/269	408/456	539/624	610/712	794/887
Women (n=711)	(n=34)	(n=94)	(n=168)	(n=212)	(n=203)
25th percentile	0/0	0/0	3/15	32/58	57/58
50th percentile	0/0	11/15	31/58	100/146	208/364
75th percentile	18/25	57/73	184/223	228/279	301/529
90th percentile	27/41	153/178	467/525	548/728	768/923

Permissions requested from original source (Knez, A., Becker, A., Leber, A. et al , 2004).

The diagnostic accuracy of the Volume score at different calcium score cut-off points is detailed in Table 20. For prediction of coronary stenosis a Volume score in the ≥ 75th percentile represented the best compromise of a sensitivity of 85% and specificity of 80%; the Agatston score values were similar with a sensitivity of 86% and a specificity of 75% (Knez, A., Becker, A., Leber, A. et al , 2004).

Table 20
Diagnostic accuracy of Volume calcium scoring for prediction of obstructive CAD using different calcium score cut-off points*

Volume calcium score	>0	>10	>100	>25th	>50th	>75th
Sensitivity	99%	94%	87%	95%	91%	85%
Specificity	28%	70%	79%	45%	55%	80%
Predictive accuracy	70%	84%	83%	75%	77%	82%
*Agatston calcium score produced comparable results						
Permissions requested from original source (Knez, A., Becker, A., Leber, A. et al , 2004).						

ROC curves were created to determine the relationship between total coronary calcium score and the presence of CAD. Curves ≥ 0.7 were defined as an acceptable diagnostic performance. The ROC curves for all age and gender groups with and without significant CAD are listed in Table 21, and indicate that the Agatston and Volume score have sufficient power for the determination of CAD in all age and gender groups (Knez, A., Becker, A., Leber, A. et al , 2004).

Table 21
Receiver operating characteristic curve areas for patients by age, gender, and presence/absence of CAD for Volume calcium score (VCS) versus Agatston calcium score (ACS)

	VCS / ACS Without Significant CAD		VCS / ACS With Significant CAD	
Age (yrs)	Men	Women	Men	Women
<40	0.86 / 0.84	0.87 / 0.88	0.87 / 0.82	0.87 / 0.90
40-50	0.76 / 0.75	0.78 / 0.79	0.78 / 0.86	0.78 / 0.84
50-60	0.83 / 0.87	0.84 / 0.80	0.79 / 0.86	0.79 / 0.81
60-70	0.84 / 0.79	0.80 / 0.88	0.84 / 0.77	0.84 / 0.83
>70	0.75 / 0.79	0.73 / 0.81	0.83 / 0.81	0.81 / 0.81
Permissions requested from original source (Knez, A., Becker, A., Leber, A. et al , 2004).				

The results indicate that the presence of any calcium was highly sensitive (99%) for the diagnosis of obstructive CAD, but any calcium was limited by its low specificity (28%) (Knez, A., Becker, A., Leber, A. et al , 2004).

The second cohort study evaluated EBCT derived calcium scores to predict significant CAD, with coronary angiography as the reference standard (Budoff, M. J., Diamond, G. A., Raggi, P. et al , 2002). One thousand, eight hundred and fifty one patients (1169 men and 682 women, mean age 58±11 years with range of 21 to 86 years) were recruited from a population of patients referred for coronary angiography. EBCT and coronary angiography were performed within 2 weeks of each other in 92% of patients. Exclusion criteria included; patients who had EBCT scans performed > 3 months from the angiogram, and patients who had undergone previous coronary interventional procedures (Budoff, M. J., Diamond, G. A., Raggi, P. et al , 2002).

The Agatston scoring method was used (Agatston, A. S., Janowitz, W. R., Hildner, F. J. et al , 1990), and the observer who scored the scans was blinded to the clinical, ECG, and angiographic information. Narrowing of the lumen diameter by ≥ 50% was defined as significant CAD (Budoff, M. J., Diamond, G. A., Raggi, P. et al , 2002).

A multivariate logistic prediction model was developed in the dataset of 1851 patients, dividing the two samples by random number generation. The training sample of 932 patients was used to generate four different logistic models; (1) a pre-test model based on age, age squared and sex, (2) a test model based on the square root of coronary artery vessel-specific calcium score, (3) a combined model based on age, and 4 vessel specific calcium scores, plus 2 age dependent calcium scores, and (4) a model that corrected for bias in the combined model. The resultant prediction model was used to estimate the pre- or post-test probability of angiographically significant CAD in each of these 932 patients from which the model was derived (training sample), and as well as in the independent 919 patients (validation model) (Budoff, M. J., Diamond, G. A., Raggi, P. et al , 2002).

Of the 1851 patients, 1466 (79%) had a total calcium score of > 0 (range from 1 to 6649). The overall sensitivity was 96% and the specificity was 40% for calcium scoring to predict obstructive CAD. With calcium scores > 20, > 80 and > 100, the sensitivity to predict coronary stenosis decreased from 90% to 79% to 76%, respectively, and the specificity increased from 58% to 72% to

75%, respectively. Of 1851 patients, 938 (53%) had luminal stenosis ≥ 50% in 1 or more vessels, and their mean total calcium score was 608 (range 0 to 6646). Calcium scores were significantly lower for patients without obstructive disease (838 patients, mean calcium score 123 with range 0 to 3761, *P* > 0.001) compared with patients with obstructive disease (Budoff, M. J., Diamond, G. A., Raggi, P. et al , 2002).

The calibration and discrimination in the validation cohort of the 4 models derived form the training dataset are shown in Table 22. Test 2 based on the square root of coronary artery vessel-specific calcium score and test 3 based on age, and 4 vessel specific calcium scores, plus 2 age dependent calcium scores showed excellent discrimination (Budoff, M. J., Diamond, G. A., Raggi, P. et al , 2002).

Table 22
Calibration and discrimination in the validation sample for each model

Model	Calibration (Goodness of fit)	Discrimination (ROC area ± SEM)
Pre-test (1)	1.8 (P = 0.94)	0.672 ± 0.019
Test (2)	15.4 (P = 0.03)	0.842 ± 0.020
Combined (3)	9.0 (P = 0.44)	0.842 ± 0.023
Adjusted (4)	12.4 (P = 0.19)	0.830 ± 0.024

Permissions requested from original source (Budoff, M. J., Diamond, G. A., Raggi, P. et al , 2002).

ROC curve analyses of the EBCT derived calcium scores compared with age and sex alone showed that calcium scoring adds independent and incremental information to predict obstructive disease (0.84 and 0.67, respectively, *P* < 0.001). Table 23 demonstrates that calcium scoring considerably alters the post test probability across a wide range of patients. Those patients that exhibited the greatest change from pre- to post-test probability were those patients with pre-test probabilities ranging from 20% to 70% (Budoff, M. J., Diamond, G. A., Raggi, P. et al , 2002).

Table 23
Post-test probabilities (%) for obstructive CAD for a variety of pre-test and post-test EBCT Scores in men and women

Pre-Test Probability %	Age 40			Age 50			Age 60		
	Score 0	Score 100	Score 400*	Score 0	Score 100	Score 400*	Score 0	Score 100	Score 400*
Men									
10	1.7	25.9	**68.1**	1.2	23.0	**61.0**	0.9	20.4	**53.3**
20	3.7	**44.1**	82.8	2.8	**40.2**	**77.9**	2.0	36.5	**72.0**
30	**6.2**	**57.4**	**89.2**	**4.6**	**53.6**	**85.8**	**3.5**	**49.7**	**81.5**
40	**9.3**	**67.7**	**92.8**	**7.0**	**64.2**	**90.4**	**5.3**	**60.5**	**87.3**
50	**13.3**	**72.9**	**93.4**	**10.2**	**72.9**	**93.4**	**7.7**	**69.7**	**91.1**
60	**18.7**	**82.5**	**96.7**	**14.5**	**80.2**	**95.5**	**11.1**	77.5	**93.3**
70	**26.4**	88.0	97.8	**20.9**	86.3	97.0	**16.3**	84.3	96.0
80	**38.0**	92.6	98.7	**31.2**	91.5	98.3	**25.1**	90.2	97.6
90	**58.0**	96.6	99.4	**50.5**	96.0	99.2	**42.9**	95.4	98.9
Women									
10	**0.9**	15.9	**53.7**	0.7	13.9	**45.8**	0.5	12.2	**38.2**
20	**2.0**	29.9	**72.3**	1.5	26.7	**65.6**	1.1	23.8	**58.2**
30	**3.4**	42.2	**81.7**	**2.6**	38.5	**76.5**	**1.9**	34.8	**70.4**
40	**5.2**	53.2	**87.4**	**3.9**	49.3	**83.5**	**2.9**	45.4	**78.8**
50	**7.7**	63.0	**91.2**	**5.8**	59.3	**88.4**	**4.3**	55.5	**84.8**
60	**11.1**	71.9	**94.0**	**8.4**	68.6	**91.9**	**6.4**	65.1	**89.3**
70	**16.2**	79.9	**96.1**	**12.5**	77.3	**94.7**	**9.6**	74.4	**92.8**
80	**24.9**	87.2	97.7	**19.7**	85.4	96.8	**15.3**	83.3	95.7
90	**42.8**	93.9	98.9	**35.6**	92.9	98.6	**29.0**	91.8	98.0

*Total score based on equal distribution of calcification in each major epicardial artery
*Bold values represent 20% shift between pre-test and post-test probability on the basis of EBCT score

Permissions requested from original source (Budoff, M. J., Diamond, G. A., Raggi, P. et al , 2002).

The third cohort study correlated EBCT calcium scores with the results of coronary angiography in symptomatic patients in order to assess calcium score values to predict or exclude significant CAD (Haberl, R., Becker, A., Leber, A. et al , 2001). The study comprised a total of 1764 consecutive patients (1225 men and 539 women between 20 and 80 years) who were referred for coronary angiography because of suspected CAD. Inclusion criteria were; typical or atypical chest pain and / or signs of myocardial ischemia on non-invasive tests (bicycle stress test, in most cases) and a clinical indication for cardiac catheterization. Exclusion criteria were; previous documented CAD by previous cardiac catheterisation or specific referral for coronary interventions (Haberl, R., Becker, A., Leber, A. et al , 2001).

The Agatston scoring method was used (Agatston, A. S., Janowitz, W. R., Hildner, F. J. et al , 1990). Analysis of the coronary angiograms was done by an independent, experienced observer who was unaware of the calcium score. The decision to perform angiography was not influenced by the calcium score. Angiography was performed within 4 days after the scan in 78% of patients and within 10 days in 98% of patients. Significant stenosis was defined as ≥ 50% luminal narrowing of any epicardial coronary artery (Haberl, R., Becker, A., Leber, A. et al , 2001).

Chest pain typical of angina was reported by 65% of the patients. A stress test was available in 920 patients, which was abnormal (including borderline results) in 52% of patients. Significant coronary stenosis of ≥ 50% stenosis was found in 56% of men and 47% of women and stenosis ≥ 75% was found in 37% of men and 30% of women. Normal coronary angiograms were found in 302 men (25%) and 220 women (41%). Table 24 details the mean calcium scores for men and women. Men had higher calcium scores compared with women, increasing age was associated with higher scores, and calcium scores in patients with CAD were higher than those patients without CAD (Haberl, R., Becker, A., Leber, A. et al , 2001).

Table 24
Calcium score in symptomatic men and women

	Men		Women	
Age (years)	n	Score	n	Score
Without significant CAD				
Age				
<40	78	4 ± 8	86	5 ± 11
40-50	93	36 ± 88	25	4 ± 15
50-60	164	115 ± 345	45	45 ± 126
60-70	149	191± 328	80	53 ± 89
>70	56	275 ± 308	48	151 ± 211
Σ	540	123 ± 289*	284	49 ± 121*
With significant CAD				
Age				
<40	91	122 ± 184	39	108 ± 162
40-50	96	358 ± 590	56	116 ± 265
50-60	156	620 ± 910	46	222 ± 374
60-70	202	862 ± 1,066	67	396 ± 522
>70	140	1196 ± 1,407	47	942 ± 1,146
Σ	685	706 ± 1,047*	255	360 ± 655*

*P < 0.001, also true for all age groups. Score values are presented as mean ± SD.
Permissions requested from (Haberl, R., Becker, A., Leber, A. et al , 2001).

No calcium was detected in 128 (23.7%) of 540 men and in 116 (40.8%) of 284 women without significant CAD, as compared with 5 (0.7%) of 685 men and 0 of 255 women with coronary stenoses ≥ 50% (Table 25). Thus, exclusion of coronary calcification was associated with an extremely low probability of coronary stenoses ≥ 50% in men and women.

Table 25
Exclusion of calcium score (score = 0)

Age (yrs)	Men n	Score	Women n	Score
Significant CAD (Stenosis ≥ 50%)				
	No	Yes	No	Yes
Age (years				
<40	43/78 (55%)	0/91 (0%)	47/86 (55%)	0/39
40-50	30/93 (32%)	1/96 (1%)	21/25 (84%)	0/56
50-60	35/164 (21%)	2/156 (1%)	18/45 (40%)	0/46
60-70	18/149 (12%)	1/202 (0%)	26/80 (32%)	0/67
>70	2/56 (4%)	1/140 (1%)	4/48 (8%)	0/47
Total	128/540 (24%)	5/685 (0.7%)	116/284 (41%)	0/255

Data are presented as the number of patents with score = 0 / total number of patients in that age group, with percentages in parenthesis.

Permissions requested from (Haberl, R., Becker, A., Leber, A. et al , 2001).

Table 26 (a-d) details the sensitivities and specificities of coronary calcium scores at various score ranges. The sensitivities for calcium scores were higher than their respective specificities and this was especially marked for a score > 0 (any calcium detected) (sensitivities; 99% in men and 100% in women, specificities; 23% in men and 40% in women) (Haberl, R., Becker, A., Leber, A. et al , 2001).

Table 26 Sensitivities and specificities of coronary calcium scores at various score ranges				
a. Sensitivity and specificity of coronary calcifications in different score levels				
	Score > 0 (any calcium detected)			
	Stenosis			
	≥ 50%	≥ 50%	≥ 75%	≥ 75%
	Male	Female	Male	Female
Sensitivity	99%	100%	99%	99%
Specificity	23%	40%	39%	49%
Positive predictive value	62%	66%	57%	53%
Negative predictive value	97%	100%	99%	99%
Data are presented as the number of patents with score = 0 / total number of patients in that age group, with percentages in parenthesis.				
b. Sensitivity and specificity of coronary calcifications in different score levels				
	Score ≥ 20			
	Stenosis			
	≥ 50%	≥ 50%	≥ 75%	≥ 75%
	Male	Female	Male	Female
Sensitivity	97%	98%	98%	98%
Specificity	62%	69%	51%	64%
Positive predictive value	62%	70%	48%	59%
Negative predictive value	95%	91%	96%	94%
Data are presented as the number of patents with score = 0 / total number of patients in that age group, with percentages in parenthesis.				
c. Sensitivity and specificity of coronary calcifications in different score levels				
	Score ≥ 100			
	Stenosis			
	≥ 50%	≥ 50%	≥ 75%	≥ 75%
	Male	Female	Male	Female
Sensitivity	93%	82%	95%	89%
Specificity	75%	76%	79%	79%
Positive predictive value	76%	78%	71%	73%
Negative predictive value	79%	72%	85%	81%
Data are presented as the number of patents with score = 0 / total number of patients in that age group, with percentages in parenthesis.				
d. Sensitivity and specificity of coronary calcifications in different score levels				
	Score ≥ 75% percentile of age group			
	Stenosis			
	≥ 50%	≥ 50%	≥ 75%	≥ 75%
	Male	Female	Male	Female
Sensitivity	81%	76%	78%	75%
Specificity	72%	77%	83%	85%
Positive predictive value	65%	71%	67%	72%
Negative predictive value	70%	69%	77%	75%
Data are presented as the number of patents with score = 0 / total number of patients in that age group, with percentages in parenthesis. Permissions requested from (Haberl, R., Becker, A., Leber, A. et al , 2001).				

The fourth cohort study examined the accuracy of 4-slice CT coronary angiography calcium scoring in the assessment of CAD using coronary angiography as the reference standard (Herzog, C., Britten, M., Balzer, J. O.

et al , 2004). Thirty eight patients (30 men and 8 women) with symptomatic but atypical chest pain were consecutively recruited. The mean age for the study cohort was 61.9 years (range 29 to 65 years). Inclusion criteria were an intermediate pre-test likelihood for CAD, but at the same time symptomatic chest pain. Intermediate pre-test likelihood for CAD was defined by Diamond and Forrester criteria (Herzog, C., Britten, M., Balzer, J. O. et al , 2004).

Agatston scoring method was used (Agatston, A. S., Janowitz, W. R., Hildner, F. J. et al , 1990) and the investigator interpreting the coronary angiogram was blinded to the 4-slice CT coronary angiography results. A relevant coronary stenosis was defined as a stenosis > 75% on the coronary angiogram (Herzog, C., Britten, M., Balzer, J. O. et al , 2004).

The sensitivities and specificities for haemodynamically relevant (> 70%) coronary stenoses detected by multislice CT coronary angiography, and calcium score (> 0 and > 400) are detailed in Table 27

Table 27

Sensitivity and specificity of calcium scoring (Ca-Sc) and multislice CT coronary angiography coronary angiography (MSCT) for the detection of hemodynamically relevant stenoses (>75%). Results for each technique alone and in combination. *PPV* positive predictive value. *NPV* negative predictive value.

	Sensitivity	Specificity	PPV	NPV
Ca-Sc (> 0)	17 of 18 (94.4)	4 of 16 (25.0)	17 of 33 (51.5)	4 of 5 (80.0)
Ca-Sc (> 400)	12 of 18 (66.7)	4 of 16 (25.0)	12 of 16 (75.0)	16 of 22 (72.7)
MSCT	13 of 18 (72.2)	20 of 20 (100)	13 of 13 (100)	20 of 25 (80.0)
MSCT + Ca-Sc	3 of 15 (20.0)	20 of 20 (100)	15 of 15 (100)	20 of 23 (87.0)

Permissions requested from (Herzog, C., Britten, M., Balzer, J. O. et al , 2004).

Results are presentment as number of patients with diagnostic test statistic in parenthesis

There was a highly significant correlation between calcium score and the degree of CAD by the Kruskal-Wallis test (see Table 28). Patients with no signs of atherosclerosis from coronary angiography (20 patients) had mean total scores of 104 (range 0 to 1459), patients with > 75% stenosis and only single vessel involvement had a median score of 482 (range 23 to 2450, 12

patients), and patients with > 75% stenosis and three-vessel disease had median score of 3740 (range 2635 to 4716, 3 patients). A correlation was also found between the calcium score and the location of CAD (see Table 28) (Herzog, C., Britten, M., Balzer, J. O. et al , 2004).

Table 28

Correlation between degree of coronary heart disease (CHD) and calcium score. Kruskal-Wallis test results. RCA right coronary artery, LCA left coronary artery, LCX left circumflex branch.

	Degree of CHD	Calcium score (range)	*P* value
RCA	<75% stenosis >75% stenosis	30.4 (0-1306.7) 412.6 (24.9-2287)	<0.01
LCA	<75% stenosis >75% stenosis	76.6 (0-1630.1) 531.7 (0-1674)	0.01
LCX	<75% stenosis >75% stenosis	0 (0-441) 133 (0-1357)	0.04
Total	No vessel > 75% stenosis 1 vessel > 75% stenosis 2 vessel > 75% stenosis 3 vessel > 75% stenosis	104 (0-1459) 408 (0-1873.7) 482 (0-2450.6) 3740 (2635-4716)	<0.01

Permissions requested from original source (Herzog, C., Britten, M., Balzer, J. O. et al , 2004).

On the basis of the calcium score, ROC curve analysis found no conclusive cut-off point for predicting the presence of a haemodynamically relevant stenosis (area under the curve of only 0.23). For calcium score of < 400, sensitivity and specificity, positive predictive and negative predictive values were; 66.7% (95%CI 58.6% to 94.6%), 80.0% (95%CI 56.3% to 94.3%), 75.0% (95%CI 47.6% to 92.7%), and 72.7% (95%CI 49.8% to 89.3%), respectively (Herzog, C., Britten, M., Balzer, J. O. et al , 2004).

A combination of calcium scoring and multislice CT coronary angiography led to a sensitivity and specificity of 83.3% (95%CI 58.6% to 96.4%) and 100% (95%CI 86.1% to 100%), respectively, for the detection of haemodynamically relevant stenosis (Table 27). The positive predictive value was 100% (95%CI 81.9% to 100%) and the negative predictive value was 87.0% (95%CI 66.4% to 97.2%). Combination of both methods thus increased the negative

predictive value by 7% and the specificity by 75%, however, neither compared with calcium scoring (*P* = 0.73) nor multislice CT coronary angiography calcium scoring (*P* = 0.25) reached statistical significance (Herzog, C., Britten, M., Balzer, J. O. et al , 2004).

The fifth cohort study evaluated the efficacy of coronary calcium scoring by 4-slice CT coronary angiography for the detection of coronary atherosclerosis with coronary angiography as the reference standard (Kitamura, A., Kobayashi, T., Ueda, K. et al , 2005). One hundred and eight patients (94 men, 14 women age, mean age 65.7 years range 48 to 78 years) with or with suspected CAD underwent unenhanced 4-slice CT coronary angiography. Seventy eight of the 108 patients had previously undergone percutaneous coronary interventions or coronary artery bypass surgery (Kitamura, A., Kobayashi, T., Ueda, K. et al , 2005).

The 4-slice CT coronary angiography scans were assessed by one observer for all lesions in the coronary arteries and the score was computed by the Agatston method (Agatston, A. S., Janowitz, W. R., Hildner, F. J. et al , 1990). Of 432 vessels, 118 vessels were excluded that had been treated with percutaneous coronary interventions or coronary artery bypass surgery, as well as 55 vessels that were difficult to evaluate due to motion artefacts. A panel of observers who were blinded to the 4-slice CT coronary angiography results interpreted the coronary angiograms, a moderate luminal stenosis was defined as a reduction in luminal diameter $\geq$ 50% and a severe stenosis was defined as a reduction of $\geq$ 70% (Kitamura, A., Kobayashi, T., Ueda, K. et al , 2005).

The sensitivities, specificities, positive and negative predictive values for coronary calcification (calcium score $\geq$ 1) in severe and moderate stenosis are shown in Table 29. The sensitivity and negative predictive value in patients with moderate stenosis were lower compared with patients with severe stenosis, while, specificity and positive predictive value were higher in patients with moderate stenosis compared with severe stenosis patients.

Table 29

Sensitivity, specificity, and predictive values of coronary calcification for the detection of severe and moderate stenosis

	Severe stenosis	Moderate stenosis
Sensitivity (%)	89 (32/36)	84 (59/70)
Specificity (%)	43 (96/223)	47 (89/189)
Positive predictive value (%)	20 (32/159)	37 (59/159)
Negative predictive value (%)	96 (96/100)	89 (89/100)

Permissions requested from original source (Kitamura, A., Kobayashi, T., Ueda, K. et al , 2005).

The results of calcium scoring to detect severe stenosis in individual coronary arteries are shown in Table 30. The sensitivity and specificity values for calcium scoring in the left main and left anterior descending artery were the highest, while the respective values for the right coronary artery were lowest.

Table 30

Sensitivity, specificity, and predictive values of calcification for the detection of severe stenosis of individual coronary arteries

	Total	LM+LAD	LCX	RCA
Sensitivity (%)	89 (32/36)	100 (15/15)	91 (10/11)	70 (7/10)
Specificity (%)	43 (95/223)	47 (62/131)	37 (22/59)	36 (12/33)
Positive predictive value (%)	20 (32/160)	18 (15/84)	21 (10/47)	25 (7/28)
Negative predictive value (%)	96 (95/99)	100 (62/62)	96 (22/23)	80 (12/15)

LM: Left main coronary artery, LAD: Left anterior descending coronary artery, LCX: Left circumflex coronary artery, RCA: right coronary artery

Permissions requested from original source (Kitamura, A., Kobayashi, T., Ueda, K. et al , 2005).

The sensitivities, specificities, positive and negative predictive values for severe stenosis according to the calcium score are shown in Table 31. ROC curve analysis for the prediction of severe and moderate stenosis using calcium scoring were 0.80±0.04 ($P < 0.001$) and 0.75±0.04 ($P < 0.001$).

Table 31

Sensitivity, specificity, and predictive value for the detection of severe stenosis by calcium score level

Calcium Score	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
0.1	89 (32/36)	43 (96/223)	20 (32/159)	96 (96/100)
10	83 (30/36)	56 (124/223)	23 (30/129)	95 (124/130)
50	81 (29/36)	71 (159/223)	31 (29/93)	96 (159/166)
100	72 (26/36)	81 (181/223)	38 (26/68)	95 (181/191)
200	53 (19/36)	86 (192/223)	38 (19/50)	92(192/209)
300	33 (12/36)	91 (202/223)	36 (12/33)	89 (202/226)
400	28 (10/36)	94 (210/223)	43 (10/23)	89 (210/236)
500	22 (8/36)	95 (211/223)	40 (8/20)	89 (211/239)
800	14 (5/36)	99 (220/223)	63 (5/8)	88 (220/251)
900	14 (5/36)	99 (222/223)	83 (5/6)	88 (222/253)
1000	11 (4/36)	100 (223/223)	100 (4/4)	87 (223/255)

Permissions requested from original source (Kitamura, A., Kobayashi, T., Ueda, K. et al , 2005).

The sixth cohort study examined the relative accuracy of 4-slice CT coronary angiography calcium scoring and both methods combined in demonstrating coronary artery stenoses using coronary angiography as the reference standard (Lau, G. T., Ridley, L. J., Schieb, M. C. et al , 2005). Fifty consecutive outpatient patients were recruited who were in sinus rhythm, and who were undergoing coronary angiography; 40 men, mean age 62 years (range 37 to 78 years), 10 women, mean age 61 years (range 36 to 75 years). The overall mean study age of patients was 62±11 years. Patients were excluded if they had previously undergone coronary artery stent placement or bypass grafting, if their creatinine was higher than the normal range, or they were allergic to iodine or contrast material (Lau, G. T., Ridley, L. J., Schieb, M. C. et al , 2005).

Two observers that were blinded to each others results assessed the 4-slice CT coronary angiography image evaluation of the number of segments, the segmental atherosclerotic plaque load, and degree of stenosis. The results were averaged unless the variation was greater than 10%, then the differences were resolved by consensus. Significant coronary luminal stenosis was defined as a reduction in luminal diameter ≥ 50%. Calcification was determined using the Agatston method (Agatston, A. S., Janowitz, W. R., Hildner, F. J. et al , 1990) and assessed independently by 2 observers, and then the results were averaged. The calcium score in each segment, vessel and patient were termed the calcium segment, calcium vessel, and the calcium patient score, respectively. Two observers who were blinded to the 4-slice CT coronary angiography results interpreted the coronary angiograms, significant coronary luminal stenosis was defined as a reduction in luminal diameter ≥ 50%. 4-slice CT coronary angiography and coronary angiography were performed with 3 days of one another (Lau, G. T., Ridley, L. J., Schieb, M. C. et al , 2005).

Coronary stenosis ≥ 50% on 4-slice CT coronary angiography was present in 56 (12%) of 479 segments, 51 (26%) of 199 vessels and 30 (60%) of 50 patients. Fourteen patients had single vessel disease, and sixteen patients had multivessel disease. The sensitivities and specificities for segments, vessels and patients and the respective calcium scores are shown in Table 32. Three calcium thresholds were evaluated; ≥ 1, ≥ 50 and ≥ 400. The sensitivity and specificity varied according to the threshold used. When the calcium score sensitivity was very similar to the sensitivity of the 4-slice CT coronary angiography, the specificity for the calcium score was always lower (Lau, G. T., Ridley, L. J., Schieb, M. C. et al , 2005).

Table 32

Sensitivity (sens) and specificity (spec) of CT angiography alone, calcium score at varying thresholds, and CT angiography combined with high-specificity calcium score thresholds, according to segment, vessel or patient

	CT angiography alone		Calcium score threshold ≥ 1		Calcium score threshold ≥ 50		Calcium score threshold ≥ 400		CT angiography with calcium score	
	Sens (%)	Spec (%)	Sens (%)	Spec (%)	Sens (%)	Spec (%)	Sens (%)	Spec (%)	Sens (%)	Spec (%)
Segment (*n* = 479)	79	95	84	53	57	79	5	100	80	93
Vessel (*n* = 199)	80	96	98	39	82	72	23	98	82	93
Patient (*n* = 50)	93	85	97	25	90	55	69	100	100	85

Permissions requested from original source (Lau, G. T., Ridley, L. J., Schieb, M. C. et al , 2005).

Mean calcium scores were higher in patients with coronary stenosis compared with patients without stenosis; 114±139 versus 32±63 for segments, 272±254 versus 62±107 for vessels and 700±541 versus 99±140 for patients, respectively ($P < 0.001$ for all comparisons). The ability of the calcium score to discriminate between the presence or absence of stenosis was greater for patients than for individual vessels and segments as demonstrated by ROC curve analysis (area under ROC curve 0.88, 0.84 and 0.74, respectively) (Lau, G. T., Ridley, L. J., Schieb, M. C. et al , 2005).

The seventh cohort study examined the diagnostic accuracy of 64-slice CT coronary angiography to detect significant coronary stenosis in a given patient according to calcium score (Raff, G. L., Gallagher, M. J., O'Neill, W. W. et al , 2005). Seventy consecutive patients were selected that were scheduled to undergo coronary angiography (reference standard) for suspected CAD. The mean age was 59±11 years (range 22 to 81 years), and 75% were men. 64-

slice CT coronary angiography was performed within 30 days of the angiogram. Exclusion criteria included the following; irregular heart rate, patients at risk for iodinated contrast medium (congestive heart failure, allergy or elevated serum creatinine), contra-indications to beta blocking drugs (Raff, G. L., Gallagher, M. J., O'Neill, W. W. et al , 2005).

64-slice CT coronary angiography diagnostic accuracy was compared to coronary angiography according to the following: (1) per segment analysis, comparing each segment in every vessel, (2) per artery, examining the presence of significant lesions in each of the major coronary arteries (right coronary artery, left circumflex, left anterior descending, and left main, (3) per patient analysis evaluating the presence of any significant lesion in a given patient. 64-slice CT coronary angiography scans were analysed by the consensus of two observers unaware of the clinical data and blinded to the results of coronary angiography. The coronary angiograms were evaluated by a single observer blind to the 64-slice CT coronary angiography results. Significant CAD was defined as stenosis > 50% in any artery (Raff, G. L., Gallagher, M. J., O'Neill, W. W. et al , 2005).

The Agatston calcium score was used (Agatston, A. S., Janowitz, W. R., Hildner, F. J. et al , 1990); patients were ranked by total calcium score, and segment and artery calcium was rated where; 0 = non calcified, 1 = calcium present no image impairment, 2 = calcium covering < 50% of lumen, 3 = calcium covering > 50% of lumen in all planes including the cross section (Raff, G. L., Gallagher, M. J., O'Neill, W. W. et al , 2005).

For 64-slice CT coronary angiography, the sensitivity, specificity, and positive and negative predictive values for the presence of significant stenosis were; by segment (n = 935), 86%, 95%, 66% and 98%, respectively; by artery (n = 279), 91%, 92%, 80% and 97%, respectively; by patient (n = 70) 95%, 90%, 93% and 93%, respectively. The mean Agatston score in patients was 326±472, 35 out of 70 had scores from 0 to 100, 17 out of 70 had scores of 101 to 400, and 18 out of 70 had scores of 401 to 1804. The accuracy of 64-slice CT coronary angiography to detect a significant stenosis in a given

patient according to calcium score is detailed in Table 33 (Raff, G. L., Gallagher, M. J., O'Neill, W. W. et al , 2005).

Table 33
The effect of coronary calcification on diagnostic accuracy of coronary CT compared with coronary angiography. PPV positive predictive value, NPV negative predictive value.

	Sensitivity %	Specificity %	PPV %	NPV %
Patients calcium score				
0-100 (n = 35)	15/16 (94%)	18/19 (95%)	15/16 (94%)	18/19 (95%)
101-400 (n = 17)	9/9 (100%)	7/8 (88%)	9/10 (90%)	7/7 (100%)
401-1804 (n = 18)	14/15 (93%)	2/3 (67%)	14/15 (93%)	2/3 (67%)
Calcium rating: arteries				
None	22/25 (88%)	144/147 (98%)	144/147 (98%)	144/147 (98%)
Mild	10/11 (91%)	21/25 (84%)	10/14 (71%)	21/22 (95%)
Moderate	10/11 (91%)	16/19 (84%)	10/13 (77%)	16/17 (94%)
Severe	21/22 (95%)	12/18 (67%)	21/27 (78%)	12/13 (92%)
Calcium rating: segments				
None	27/35 (77%)	660/674 (98%)	27/41 (66%)	660/668 (99%)
Mild	13/15 (87%)	69/74 (93%)	13/18 (72%)	69/71 (97%)
Moderate	11/12 (92%)	30/36 (83%)	11/17 (65%)	30/31 (97%)
Severe	28/30 (93%)	42/58 (72%)	28/44 (64%)	42/44 (95%)

Calcium scores are in Agatston units, values re in percentages

Permissions requested from original source (Raff, G. L., Gallagher, M. J., O'Neill, W. W. et al , 2005).

When a calcium score was low (0 to 100), sensitivity, specificity and positive and negative predictive values for the presence of significant stenosis were 94%, 95%, 94% and 95%. 64-slice CT coronary angiography diagnostic accuracy was also excellent when the score was between 101 to 400, however, with extreme calcification the specificity and negative predictive values were reduced (both 67%), although the it was noted that the small patient numbers made the result inconclusive (Table 33) (Raff, G. L., Gallagher, M. J., O'Neill, W. W. et al , 2005).

The eighth cohort study evaluated the usefulness of the calcium score estimated with 3-slice CT coronary angiography in the identification of the risk

of coronary artery stenosis (Konieczynska, M., Tracz, W., Pasowicz, M. et al , 2006). Coronary angiography was used as the reference standard. Three hundred and forty patients (222 men and 118 women) admitted to hospital with symptoms of CAD were consecutively recruited. The mean age was 59.7±9.38 years (range 34 to 81 years). The exclusion criteria were; previous percutaneous angioiplasty or surgical revascularisation, valve replacement, pacemaker implantation, cardiac arrhythmia. The 340 patients constituted 95% of all patients referred for testing. In 19 patients, artefacts hampered a reliable evaluable of scans. Of the 340 patients recruited, 144 (42.4%) had MI and the mean coronary artery calcium score was obtained using the Agatston method (Agatston, A. S., Janowitz, W. R., Hildner, F. J. et al , 1990). A coronary stenosis ≥ 50% on coronary angiography was considered significant. Coronary angiography and MULTISLICE CT CORONARY ANGIOGRAPHY were performed within 3 days of one another (Konieczynska, M., Tracz, W., Pasowicz, M. et al , 2006).

The mean calcium score in the 340 patients was 271±606 (range 0 to 7002). In 92 patients the score was 0 and in 248 patients the calcium score was above 0. No significant angiographic lesions were found in 162 of 340 patients (48%), 107 of 162 patients (66%) in this group did not have any atherosclerotic lesions in any arteries, 17 patients (11%) had lesions reducing luminal area by less than 30%, and 38 (24%) of patients presented with stenotic lesions of 30% to 40% (Konieczynska, M., Tracz, W., Pasowicz, M. et al , 2006).

In 178 patients with significant stenosis, 67 patients (37%) had 1 vessel disease, 48 patients (27%) had 2 vessel disease, and 63 patients (35%) had 3 vessel disease. Mean calcium scores increased with CAD severity. The calcium score mean differences were significant comparing patients without coronary stenosis with patients with 1, 2 and 3 vessel disease.

Table 34

Total calcium score value distribution depending on CAD severity in angiography. The difference between mean values of calcium score in groups without significant stenosis and 1-, 2- or 3- vessel disease are significant (*P* < 0.001)

Number of vessels with significant stenosis	Number of patients	Calcium score mean ± SD	min to max
0	162	29.4±63.6	0-444.8
1	67	163.4± 207.0	0-1025.1
2	48	388.4±309.9	0-1584.0
3	63	917.6±130.3	0-7001.5
Whole Group	340	271±605.9	0-7001.5

Permissions requested from original source (Konieczynska, M., Tracz, W., Pasowicz, M. et al , 2006).

ROC curves were computed to evaluate calcium scoring in the assessment of the presence of coronary stenosis. As shown in Table 35 the individual optimal cut-off points were established for the total calcium score and the individual arteries detailed, and their respective sensitivities, specificities, positive and negative predictive values were calculated. For a total calcium score ≥ 56 the sensitivity and specificity was 85.7% and 85.3%, respectively, and the positive predictive and negative predictive values were 0.863 and 0.848, respectively. The cut-off points established for individual arteries were characterised by low positive predictive values, indicating that these calcium scores had limited use for the prediction of stenosis in the individual arteries (Konieczynska, M., Tracz, W., Pasowicz, M. et al , 2006).

Table 35

The analysis of ROC curves for total calcium score, CS LAD, CS LM, CS RCA and CS CX in order to establish cut-off point for the significant stenosis in particular arteries

Localisation	Cut-off optimal point	Area under ROC curve	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Total calcium score	56.0	0.907	0.857	0.853	0.863	0.848
LAD	24.8	0.832	0.819	0.697	0.602	0.873
LM	6.99	0.706	0.583	0.838	0.116	0.892
RCA	3.22	0.799	0.807	0.738	0.623	0.876
CX	4.47	0.733	0.615	0.799	0.546	0.841

Permissions requested from original source (Konieczynska, M., Tracz, W., Pasowicz, M. et al , 2006).

Table 36 details the results of logistic regression analysis of factors associated with significant stenosis. A total calcium score ≥ 56 had the highest odds ratio (13.345), hence, the greatest influence on the presence of a significant stenosis in the study group (Konieczynska, M., Tracz, W., Pasowicz, M. et al , 2006).

Table 36
Results of the logistic regression analysis of the effects of analysed factors on the presence of significant coronary stenosis

Factor	Regression coefficient β	Odds ratio
Total calcium score ≥ 56	2.598	13.435
Obesity	2.161	8.683
Cigarette smoking	0.803	2.232
Positive family history	0.629	1.875
Diabetes mellitus	0.519	1.681
Lipid disorders	0.505	1.658
Age	0.011	1.011

Permissions requested from original source (Konieczynska, M., Tracz, W., Pasowicz, M. et al , 2006).

Further analysis was conducted in patients with no observed calcification. There were 92 patients (27%) with calcium scores of 0; 44 women and 48 men. Coronary angiography did not find any coronary stenosis in the 44 women. In 6 men (6.5%) with calcium scores of 0, coronary angiography found stenoses; single vessel disease in 3 men, 2 vessel disease in 2 men, and 3 vessel disease in 1 man. The likelihood of absence of significant stenosis in the whole study population was 93.5% in men and in women was 100% (Konieczynska, M., Tracz, W., Pasowicz, M. et al , 2006).

The ninth cohort study examined the diagnostic accuracy of the Agatston calcium score (Agatston, A. S., Janowitz, W. R., Hildner, F. J. et al , 1990) and the Volume score (Callister, T. Q., Cooil, B., Raya, S. P. et al , 1998) using 4-slice CT coronary angiography for the prediction of obstructive CAD and using different calcium score thresholds (Becker, A., Leber, A., White, C. W. et al , 2007). The inclusion criterion was referral with suspected CAD. Patients were excluded for the following reasons; severe arrhythmias, unstable clinical conditions, documented CAD or bypass surgery, referral for coronary

intervention. One thousand three hundred and forty seven patients were enrolled, 803 were men, and the mean age was 62±20 years (range 27 to 82 years). The majority of the study population (84%) underwent coronary angiography as the reference standard for assessment of atypical and typical chest pain, while 175 (13%) patients with exertional dyspnea and 40 patients (3%) with unexplained heart failure were excluded. The angiograms were reviewed by investigators blinded to the 3-slice CT coronary angiography results. 3-slice CT coronary angiography was performed 1 to 2 days before the angiogram. Each coronary vessel was examined visually and significant CAD was defined as ≥ 50% luminal diameter stenosis of any epicardial coronary artery (Becker, A., Leber, A., White, C. W. et al , 2007).

Coronary angiography and 3-slice CT coronary angiography were performed on 1088 patients (627 male), and of these, 81% had a positive calcium score. A score of 0 was found in 259 patients (176 men). The mean Agatston score and Volume score were 401±382 (range 0 to 6941) and 348±299 (range 0 to 5827), respectively. Total calcium scores were higher for men compared with women regardless of angiographic status (*P* = 0.001), and patients with significant disease had higher mean scores than individuals without CAD independent of age and sex; Agatston score 497±987 versus 97±112 (*P* = 0.01), respectively, Volume score 483±527 versus 89±201 (*P* = 0.01), respectively. 3-slice CT coronary angiography results were negative with both scoring methods in 254 patients (41%) and positive in 373 patients (59%) with negative coronary angiographic findings, as compared with 4 out of 419 men (0.9%) and 1 out of 301 women (0.3%) with significant coronary stenosis (negative predicative value 98%) (Becker, A., Leber, A., White, C. W. et al , 2007).

The diagnostic accuracy of both calcium scores are shown in Table 37. When a calcium score ≥ 1 was used as a cut-off the overall sensitivity and specificity for both scores to predict stenosis was 99% and 37%, respectively. There was a close correlation in diagnostic accuracy of the Agatston score compared with the Volume score (r = 0.99). Exclusion of coronary calcium was highly

accurate for the ruling out of CAD in patients older than 50 years (predictive accuracy = 98%) (Becker, A., Leber, A., White, C. W. et al , 2007).

Table 37
Diagnostic accuracy of Volume score and Agatston score for prediction of obstructive disease using different calcium score thresholds and different percentile score values

	>0	> 10	> 100	≥ 25th	≥ 50th	≥ 75th
Volumetric calcium score						
Sensitivity (%)	99	94	87	96	93	86
Specificity (%)	32	68	81	46	55	80
Predictive accuracy (%)	65	81	84	70	74	83
Agatston calcium score						
Sensitivity (%)	99	97	89	97	95	89
Specificity (%)	31	65	80	44	54	78
Predictive accuracy (%)	64	82	84	70	75	84

Permissions requested from original source (Becker, A., Leber, A., White, C. W. et al , 2007).

The tenth cohort study evaluated the impact of a coronary artery calcium score on the diagnostic accuracy of 16-slice CT coronary angiography (41 patients, 30 men, mean age 58±13 years) and 64-slice CT coronary angiography (60 patients, 47 men, mean age 60±11 years) (Pundziute, G., Schuijf, J. D., Jukema, J. W. et al , 2007). Coronary angiography was the reference standard, and the median interval between coronary angiography and multislice CT coronary angiography was 4 weeks (range 0 to 27 weeks). A coronary calcium score was obtained using the Agatston method (Agatston, A. S., Janowitz, W. R., Hildner, F. J. et al , 1990). Multislice CT angiograms obtained with 16- and 64-slice scanners were retrospectively evaluated by the same two experienced observers (within a limited period of time), who were blinded to the results of the conventional angiogram. The following protocol was used; the 3 dimensional volume-rendered images were evaluated first to obtain a general impression of the left and right coronary arteries. The coronary arteries were divided into 17 segments and regarded as interpretable or un-interpretable by visual inspection. The interpretable segments were evaluated for the presence of obstructive stenoses (≥ 50%

reduction of luminal diameter) by both scrolling through the axial images and inspecting curved multi-planar reconstructions. Coronary angiograms were evaluated by the consensus of 2 experienced observers blinded to the multislice CT coronary angiography data (Pundziute, G., Schuijf, J. D., Jukema, J. W. et al , 2007).

For analysis, the coronary segments and patients were divided into 3 groups according to overall Agatston score (0 to 100, 101 to 400, and > 400). The overall mean Agatston score in the 16-slice CT coronary angiography population was 340±530 (range 0 to 2546). In the 0 to 100 group, the mean score was 18 ±21 (range 0 to 81), in the 101 to 400 group the mean score was 281±100 (range 102 to 397), and in the > 400 group the mean was 1077±731 (range 428 to 2546). The overall mean Agatston score in the 64-slice CT coronary angiography population was 446±877 (range 0 to 6264). In the 0 to 100 group, the mean score was 14 ±21 (range 0 to 70), in the 101 to 400 group the mean score was 213±74 (range 111 to 336), and in the > 400 group the mean was 1088±1306 (range 410 to 6264) (Pundziute, G., Schuijf, J. D., Jukema, J. W. et al , 2007).

Of the total 101 patients enrolled in the study, 57 patients (57%) had known CAD, 53 patients (53%) had prior MI, and 56 patients (56%) had a previous percutaneous intervention. Known CAD was present 23 patients (56%) examined with 16-slice CT coronary angiography, and 34 patients (57%) examined with 64-slice CT coronary angiography. Prevalence of coronary risk factors was as follows; 21 patients (21%) diabetes, 57 patients (57%) hypercholesterolaemia, 51 patients (51%) hypertension, 38 patients (38%) family history of CAD, and 49 patients (49%) current or history of previous smoking. There was no difference in the prevalence of risk factors between patients in the 16-slice and 64-slice groups. The mean overall Agaston scores in the 16-slice group and 64-slice group were 340±530 (range 0 to 2546) and 446±877 (range 0 to 6264), respectively.

In the 41 patients who underwent 16-slice CT coronary angiography, 570 coronary segments were examined, and 30 stented segments and 47 coronary segments were could not be interpreted resulting in the analysis of

493 segments. Reasons for that segments could not be interpreted included small vessel size, motion artefacts, insufficient contrast enhancement and missing slice or trigger artefact. Of all segments, 11% were excluded in the Agatston score of 0 to 100 group, 9% were in the scores of 101 to 400, and 3% in the group with scores of greater than 400 (Pundziute, G., Schuijf, J. D., Jukema, J. W. et al , 2007).

In the 60 patients who underwent 64-slice CT coronary angiography, 800 segments were examined, and 43 stented segments and 13 coronary segments could not be interpreted. Of all segments, no segments were excluded in the Agatston score of 0 to 100 group, 8% were excluded in the score of 101 to 400 group, and 2% in the group with scores of greater than 400. The percentages of false positive and false negatives segments and the overall Agatston score groups are shown in Table 38. The only difference in the percentage of false negatives segments in the groups with Agatston scores of 0 to 100, 101 to 400 and > 400 was found in 16-slice CT (0%, 5.3% and 2.9%, *P* = 0.0005) (Pundziute, G., Schuijf, J. D., Jukema, J. W. et al , 2007).

Table 38
Percentage of interpretable, false positive and false negative segments in groups with different calcium scores

	Agatston score			*P* value
	0 to 100	101 to 400	> 400	
16-slice CT				
Interpretable [No. (%)]	219/247 (89)	169/185 (91)	105/108 (97)	0.03
False positive [No. (%)]	1/219 (0.5)	2/169 (1.2)	3/105 (2.9)	0.1*
False negative [No. (%)]	0/219 (0)	9/169 (5.3)	3/105 (2.9)	<0.0005*
64-slice CT				
Interpretable [No. (%)]	253/253 (100)	266/274 (97)	281/286 (98)	0.03
False positive [No. (%)]	1/253 (0.4)	7/266 (2.6)	5/281 (1.8)	0.07*
False negative [No. (%)]	4/253 (1.6)	5/266 (1.9)	7/281 (2.5)	0.55*

*Lowest P values of comparisons between groups. Permissions requested from original source (Pundziute, G., Schuijf, J. D., Jukema, J. W. et al , 2007).

The results of the per-vessel analysis are shown in Table 39. In the patient group examined with 16-slice CT coronary angiography, coronary angiography detected 33 (21%) coronary vessels with obstructive coronary lesions. The overall 16-slice CT coronary angiography sensitivity and

specificity for all vessels were 76% and 97%, respectively. In the patient group examined with 64-slice CT coronary angiography, coronary angiography detected 57 (24%) coronary vessels with obstructive coronary lesions and the sensitivity and specificity for all vessels were 79% and 96%, respectively. There was no difference in the diagnostic accuracy of 16- and 64-slice CT coronary angiography between the two Agatston groups (0 to 100, and 101 to 400) (Pundziute, G., Schuijf, J. D., Jukema, J. W. et al , 2007).

Table 39
Diagnostic accuracy of MSCT in patient vessels with different calcium scores

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
16-slice MSCT				
All vessels (n = 159)	76 (61-91)	97 (94-100)	86 (73-98)	94 (90-98)
Agatston score of 0-100 (n = 120)	67 (43-91)	99 (97-100)	91 (74-100)	95 (91-99)
Agatston score of > 100 (n = 39)	83 (66-100)	86 (71-100)	83 (66-100)	86 (71-100)
64-slice MSCT				
All vessels (n = 159)	79 (68-89)	96 (93-99)	87 (78-96)	94 (91-97)
Agatston score of 0-100 (n = 120)	77 (71-93)	97 (94-100)	83 (68-98)	96 (93-99)
Agatston score of > 100 (n = 39)	81 (67-95)	92 (85-98)	89 (77-100)	84 (72-96)

Permissions requested from original source (Pundziute, G., Schuijf, J. D., Jukema, J. W. et al , 2007).

The results of the diagnostic performance of multislice CT coronary angiography in the detection of obstructive lesions in the 3 Agatston score groups on a per patient bases are shown in Table 40. In the patient group examined with 16-slice CT coronary angiography, coronary angiography detected obstructive coronary lesions in 18 (44%) patients, and the overall sensitivity and specificity was 89% and 87%, respectively. In the patient group examined with 64-slice CT coronary angiography, coronary angiography detected obstructive coronary lesions in 32 (53%) patients, and the overall sensitivity and specificity was 91% and 96%, respectively. There was little difference in the diagnostic accuracy of 16- and 64-slice CT coronary angiography between the 4 Agatston groups (0 to 100,101 to 400, > 400 and > 100) (Pundziute, G., Schuijf, J. D., Jukema, J. W. et al , 2007).

Table 40
Diagnostic accuracy of MSCT in patient groups with different calcium scores

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
16-slice CT coronary angiography				
All patients (n = 41)	89 (75-100)	87 (73-100)	84 (68-100)	91 (79-100)
Agatston score of 0-100 (n = 18)	100	93 (80-100)	80 (45-100)	100
Agatston score of 101-400 (n = 14)	75 (45-100)	83 (53-100)	86 (60-100)	71 (37-100)
Agatston score of >400 (n = 9)	100	67 (29-100)	86 (60-100)	100
Agatston score of >100 (n = 23)	86 (68-100)	78 (51-100)	86 (68-100)	78 (51-100)
64-slice CT coronary angiography				
All patients (n = 60)	91 (81-100)	96 (89-100)	97 (91-100)	90 (79-100)
Agatston score of 0-100 (n = 19)	83 (53-100)	100	100	93 (80-100)
Agatston score of 101-400 (n = 20)	83 (62-100)	88 (65-100)	91 (74-100)	78 (51-100)
Agatston score of >400 (n = 21)	100	100	100	100
Agatston score of >100 (n = 41)	92 (82-100)	93 (80-100)	96 (88-100)	88 (72-100)

Permissions requested from original source (Pundziute, G., Schuijf, J. D., Jukema, J. W. et al , 2007).

64-slice CT coronary angiography

Introduction

Multislice CT coronary angiography combines the use of X rays to visualise blood flow in the coronary arteries and the use of computerised analysis of the images to create a three-dimensional picture of the anatomy of the heart. Multislice CT coronary angiography technology has been rapidly advancing in recent years; 4-slice CT scanners first appeared in 1998, 16-slice CT scanners in 2001, and 64-slice CT scanners at the end of 2004. Imaging of the heart can be difficult due to continuous motion during the cardiac cycle. The introduction of the 64-slice CT scanner has the benefit of increased number of acquired images and high temporal resolution (time required to obtain one image) resulting in a reduction of overall scan time which is now approximately 8 seconds. As image quality is dependent upon the patient's ability to suspend respiration in a single breath hold, respiratory motion and image quality has improved with 64-slice CT scanners compared with lower slice CT scanners. Additionally, the improvement in software technology with

64-slice CT scanners has also increased spatial resolution (the number of pixels of information that make up a software image) and this has overcome quality problems associated with earlier scanners. Owing to the advances in technology with 64-slice CT scanners, the GDG group considered that only evidence on 64-slice CT coronary angiography should be examined, and evidence on lower slice CT scanners was not appraised.

64-slice CT coronary angiography provides a non-invasive image of the coronary artery lumen and wall, and its advantages compared with coronary angiography are that it is less invasive, it can capture thousands of images of a beating heart in seconds, and it may also be relatively less expensive. Coronary angiography requires the invasive insertion of an arterial catheter and guide wire and the most serious complications of coronary angiography are death (0.1 to 0.2%), non fatal MI (0.1%), and cerebrovascular events (0.1%) (Mowatt, G., Vale, L., Brazzelli, M. et al , 2004).

Although coronary angiography is considered to be the ‘gold’ reference standard because of high temporal and spatial resolution, it is possible technological advances with multislice scanners may provide a diagnostic and cost-effective alternative to coronary angiography. However 64-slice CT coronary angiography requires an injection of radioactive iodine-containing contrast and it is regarded as a moderate to high radiation diagnostic technique (12 to 15 mSv). Technical advances have improved radiation efficiency.

A recent study has estimated the life attributable risk (LAR) of cancer incidence associated with radiation exposure from 64-slice CT coronary angiography (Einstein, A. J., Henzlova, M. J., and Rajagopalan, S., 2007). The relation of radiation exposure and the variables of age, sex and scan protocol was investigated. Using standard spiral CT protocols and Monte Carlo simulations methods the organ radiation doses from 64-slice CT coronary angiography for standardised phantom male and female patients were estimated. Age- and sex-specific LARs of individual cancers were estimated for those malignancies specified in the Biological Effects of Ionizing Radiation (BEIR) VII report. Whole body LAR was estimated by summing site

specific LARs for these organs and adding a composite equivalent dose for the BEIR VII categories (Einstein, A. J., Henzlova, M. J., and Rajagopalan, S., 2007).

The computed values derived from the simulation model indicated that the LAR of cancer incidence associated with radiation from a single scan varied markedly with gender and age as follows; woman aged 20 years; LAR 1 in 143 (0.70%), woman aged 40 years; LAR 1 in 284 (0.35%), woman aged 60 years; LAR 1 in 446 (0.22%), woman aged 80 years; LAR 1 in 1388 (0.075%). The estimated LAR for men was considerably lower, man aged 20 years; LAR 1 in 686 (0.15%), man aged 40 years; LAR 1 in 1007 (0.099%), man aged 60 years; LAR 1 in 1241 (0.081%), man aged 80 years; LAR 1 in 3261 (0.044%).

The relative risks of attributable cancer incidences associated with a single 64-slice CT coronary angiography scan for men and women at differing ages relative to an 80 year old man are detailed in Table 41 (Einstein, A. J., Henzlova, M. J., and Rajagopalan, S., 2007).

Table 41
Estimated relative risks of attributable cancer incidence associated with a single computed tomography coronary angiography scan [a]

		Heart scanned		Heart and aorta scanned	
Age (y)	Sex	Standard	Tube current modulation	Standard	Tube current modulation
80	Male	1.0	0.7	1.4	0.9
60	Male	2.6	1.7	3.8	2.4
40	Male	3.2	2.1	4.7	3.0
20	Male	4.8	3.1	6.9	4.5
80	Female	2.4	1.6	3.1	2.0
60	Female	7.0	4.6	8.9	5.8
40	Female	11.5	7.5	14.2	9.3
20	Female	22.9	14.9	28.6	18.6

[a] Comparison to an 80-year-old man receiving a standard cardiac scan. Standard indicates tube current modulation not used.
Permissions requested from original source (Einstein, A. J., Henzlova, M. J., and Rajagopalan, S., 2007).

A 20 year old man has a 5 fold relative risk of attributable cancer incidence compared with an 80 year old man. A 20 year old woman has 23 times the risk, and an 80 year old woman has 2.4 times the risk compared with an 80 year old man. The estimates indicate that the use of 64 slice CT coronary

angiography is associated with non-negligible LAR of cancer. The effective dose of radiation from single scan was reported as a range from 9 to 29 mSv (Einstein, A. J., Henzlova, M. J., and Rajagopalan, S., 2007).

Further disadvantages of 64-slice CT coronary angiography include; poor correlation with coronary angiography in calcified vessels as extensive calcification obscures imaging of coronary arteries, poor correlation with coronary angiography for quantifying stenosis severity when > 50% and in vessels < 2 mm, no functional assessment of myocardial ischaemia, the potential for motion artefacts due to beating of the heart, and the fact that scanners may not be readily available. The image quality in 64-slice CT coronary angiography significantly improves when a patient's heart rate is lowered to below 65 bpm and to achieve optimal image quality heart the rate should be lowered to below 60 bpm. This limitation can be overcome with oral or intravenous beta blockers that lower heart rate. Image quality is also susceptible to cardiac arrhythmias. Further advances in the technology beyond 64-slice CT coronary angiography are currently ongoing, with the development of a 128-slice CT coronary angiography, and the prospect of a 256-slice scanner in the not to distant future. It has been speculated that these developments may facilitate coverage of the entire heart in one single rotation, with spatial and temporal resolution remaining unchanged. This would make the technology less susceptible to limitations with cardiac arrhythmias, and potentially less scanning time may be required reducing the radiation dose.

While the very recent publications on the diagnostic accuracy of 64-slice CT have reported excellent sensitivity, specificity, PPV and NPV compared with other non-invasive test it should be noted that there is a possibility of publication bias. The evaluation of new technologies is often performed in highly selected populations that have been referred for coronary angiography. The evaluation of 64-slice CT coronary angiography has been performed on patients that have high pre-test likelihoods of CAD (high median prevalence of CAD). However in everyday clinical practice, 64-slice CT coronary angiography is likely to be performed in patients where there is a low to

intermediate probability, and the diagnostic performance of the test requires evaluation in unselected populations.

The first systematic review (search date 2007) examined the diagnostic value of 64-slice CT coronary angiography for the detection of CAD using invasive coronary angiography as the reference standard (Abdulla, J., Abildstrom, S. Z., Gotzsche, O. et al , 2007). Twenty-seven studies were identified of which 13 studies analysed data at the patient level and 19 studies at the coronary artery segment level. Of the segment-based studies, all 19 studies examined native coronary arteries, 4 included coronary bypass grafts and 5 studies included an analysis for in-stent restenosis following PCI. Of the patient-based studies, all were confined to native coronary arteries. The prevalence of native coronary stenosis in per patient- and per segment-populations were 58% and 19% respectively. There were differences in the sensitivity and specificities in the per-patient analysis versus the per-segment analysis due to the calculated higher prevalence of CAD in the per-patient data (Abdulla, J., Abildstrom, S. Z., Gotzsche, O. et al , 2007).

Meta-analysis for the comparison of the diagnostic performance of 64-slice CT coronary angiography with invasive coronary angiography for per segment analysis of coronary arteries found that the sensitivity, specificity, PPV and NPV for native coronary arteries were 97.5% (95%CI 96% to 99%), 91% (95%CI 87.5% to 94%), 93%, and 96.5% respectively by per-patient analysis (Abdulla, J., Abildstrom, S. Z., Gotzsche, O. et al , 2007).

Meta-analysis for the comparison of the diagnostic performance of 64-slice CT coronary angiography with invasive coronary angiography for per patient analysis of native coronary arteries found that the sensitivity, specificity, PPV and NPV for native coronary arteries were; 86% (95%CI 85% to 87%), 96% (95%CI 95.5% to 96.5%), 83%, and 96.5% respectively by per-segment analysis (Abdulla, J., Abildstrom, S. Z., Gotzsche, O. et al , 2007).

For studies of patients with prior CABG surgery (4 studies), meta-analysis for the comparison of the diagnostic performance of 64-slice CT coronary angiography with invasive coronary angiography found that sensitivity,

specificity, PPV and NPV for native coronary arteries were 98.5% (95%CI 96% to 99.5%), 96% (95%CI 93% to 97.5%), 92% and 99% respectively. All coronary bypass graft segments could be assessed in the studies (n = 810) (Abdulla, J., Abildstrom, S. Z., Gotzsche, O. et al , 2007).

For studies of in-stent restenosis in patients with prior PCI (5 studies), meta-analysis for the comparison of the diagnostic performance of 64-slice CT coronary angiography with invasive coronary angiography found that sensitivity, specificity, PPV and NPV were 80% (95%CI 70% to 88.5%), 95% (95%CI 92% to 97%), 80%, and 95% respectively to detect in-stent restenosis. In 2 studies all segments could be assessed, and the percent of stents which could not be assessed in the other 3 studies was 2%, 12% and 42% of segments respectively (Abdulla, J., Abildstrom, S. Z., Gotzsche, O. et al , 2007).

For overall segment analysis (native, CABG and in-stents restenosis after PCI, 27 studies, 1740 patents, number of segments 18 920, the percent of segments which could not be assessed 4%, prevalence of coronary stenosis 19%) the sensitivity, specificity, PPV and NPV were 87% (95%CI 86.5% to 88%), 96% (95%CI 95.5% to 96.5%), 83.5%, and 97% respectively (Abdulla, J., Abildstrom, S. Z., Gotzsche, O. et al , 2007).

The authors stated that the per-segment analyses showed significant heterogeneity for all accuracy analyses (all $P < 0.001$). The heterogeneity was significant ($P < 0.001$) even after excluding small studies with populations of less than 50 patients. Meta-regression analyses of 27 studies were performed by including four important covariates, which the authors' hypothesised were the most likely source of heterogeneity (age, prevalence of CAD, heart rate during scanning, and percent of inaccessible segments. This analysis found that age, prevalence of CAD, and heart rate had no significant influence on heterogeneity ($P = 0.69$, $P = 0.64$, $P = 0.83$, respectively). However, the percent of inaccessible segments had a significant influence ($P = 0.03$) and after including all the other covariates in the model this influence was still of border-line significance ($P = 0.053$). Per-patient analyses only showed

significant heterogeneity for specificity ($P < 0.001$) and positive likelihood ratio ($P < 0.001$) (Abdulla, J., Abildstrom, S. Z., Gotzsche, O. et al , 2007).

The authors concluded that 64-slice CT coronary angiography is a potential alternative to invasive coronary angiography for ruling in and ruling out CAD in carefully selected populations suspected of having CAD. They also noted that clinicians should be aware of the high radiation dose, and the risk of the need for re-evaluation with invasive coronary angiography in the case of indeterminate results of 64-slice CT coronary angiography (Abdulla, J., Abildstrom, S. Z., Gotzsche, O. et al , 2007).

The second systematic review (search date 2007) examined the diagnostic performance of 64-slice CT coronary angiography compared with invasive coronary angiography as the reference standard in the detection of CAD (Sun, Z., Lin, C., Davidson, R. et al , 2008). Fifteen studies were identified, from which assessment was made at the patient level (12 studies), vessel-based level (6 studies) and segment-based level (12 studies). The prevalence of CAD was 74% (95%CI 64% to 84%) (Sun, Z., Lin, C., Davidson, R. et al , 2008).

For the patient based evaluation in 12 studies; sensitivity and specificity was 97% (95%CI 94% to 99%) and 88% (95%CI 79% to 97%), respectively. The PPV and NPV were 94% (95%CI 91% to 97%), and 95% (95%CI 90% to 99%), respectively (Sun, Z., Lin, C., Davidson, R. et al , 2008).

For the vessel-based analysis in 6 studies; sensitivity and specificity was 92% (95%CI 85% to 99%) and 92% (95%CI 88% to 99%), respectively. PPV and NPV were 78% (95%CI 66% to 91%), and 98% (95%CI 95% to 99%), respectively (Sun, Z., Lin, C., Davidson, R. et al , 2008).

For the segment-based analysis in 12 studies, sensitivity and specificity was 90% (95%CI 85% to 94%), and 96% (95%CI 95% to 97%), respectively. PPV and NPV were 75% (95%CI 68% to 82%), and 98% (95%CI 98 % to 99%), respectively (Sun, Z., Lin, C., Davidson, R. et al , 2008).

The review further examined the diagnostic value of 64-slice CT coronary angiography in the four main coronary arteries in 6 studies including: LMS, LAD, RCA and LCX. For the LMS, the pooled estimates and 95%CI of sensitivity, specificity, PPV and NPV were 100%, 99% (97% and 100%), 90% (69% and 100%) and 100%, respectively (Sun, Z., Lin, C., Davidson, R. et al , 2008).

For the LAD, the pooled estimates and 95%CI of sensitivity, specificity, PPV and NPV were 93% (84% and 99%), 93% (89% and 97%), 80% (65% and 94%) and 98% (96% and 99%), respectively (Sun, Z., Lin, C., Davidson, R. et al , 2008).

For the RCA, the pooled estimates and 95%CI of sensitivity, specificity, PPV and NPV were 93% (89% and 98%), 92% (82% and 99%), 82% (75% and 89%) and 97% (95% and 99%), respectively (Sun, Z., Lin, C., Davidson, R. et al , 2008).

For the LCX, the pooled estimates and 95%CI of sensitivity, specificity, PPV and NPV were 83% (82% and 99%), 91% (81% and 99%), 79% (71% and 86%) and 97% (95% and 100%), respectively. A significant difference was only found in the sensitivity of 64-slice CT coronary angiography when comparing LMS with RCA and LMS with LCX (both $P < 0.05$), and no significant different was found among other comparisons ($P > 0.05$) (Sun, Z., Lin, C., Davidson, R. et al , 2008).

In 5 studies an evaluation of 64-slice CT coronary angiography was possible for the detection of CAD in proximal, middle and distal segments of individual arteries. In comparing distal artery segments to proximal segments there was a trend towards decreased accuracy, although this was not statistically significant overall. However, for the proximal versus distal RCA segment there was a significant difference in sensitivity ($P > 0.05$) (Sun, Z., Lin, C., Davidson, R. et al , 2008).

The authors stated that presence of calcification and its relationship to calcium score could not be examined due to variable criteria applied in the 3 studies that performed this analysis. The relationship between body mass index and

diagnostic accuracy of 64-slice CT coronary angiography was examined in 1 study which found that sensitivity, specificity, PPV, and NPV were highest in patents with a normal BMI (less than 25 kg/m^2), and although it was still accurate in overweight patients (more than 25 kg/m^2), the diagnostic accuracy was reduced in obese patients (Sun, Z., Lin, C., Davidson, R. et al , 2008).

Heterogeneity in the identified studies was not discussed (Sun, Z., Lin, C., Davidson, R. et al , 2008).

The third systematic review (search date 2006) assessed the diagnostic accuracy of 4-, 8- and 16- and 64-slice CT coronary angiography methods to detect CAD (d'Othee Janne, B., Siebert, U., Cury, R. et al , 2008).

Five studies assessed 64-slice CT coronary angiography and study sizes ranged from 35 to 84 (308 patients in total). Meta-analysis of the 64-slice CT coronary angiography studies found that pooled summary estimates for sensitivity of all coronary segments, for only coronary segments which could be assessed and for patients were 98%, 97% and 98%, respectively. The pooled summary estimates for specificity of all coronary segments, for only coronary segments which could be assessed and for patients were 91%, 96% and 92%, respectively (d'Othee Janne, B., Siebert, U., Cury, R. et al , 2008).

For 4- and 8-slice CT coronary angiography (11 studies, 588 patients), the sensitivity for all coronary segments, for only coronary segments which could be assessed and for patients were 89%, 85% and 97%, respectively. The specificity for all coronary segments, for only coronary segments which could be assessed and for patients were 84%, 96% and 81%, respectively (d'Othee Janne, B., Siebert, U., Cury, R. et al , 2008).

For 16-slice CT coronary angiography (12 studies, 772 patents), the sensitivity for all coronary segments, for only coronary segments which could be assessed and for patients were 86%, 98% and 99%, respectively. The specificity for all coronary segments, for only coronary segments which could be assessed and for patients were 95%, 96% and 83%, respectively (d'Othee Janne, B., Siebert, U., Cury, R. et al , 2008).

Very little information was given on study populations except that patients were all scheduled to undergo invasive coronary angiography. The authors stated that there was considerable heterogeneity between the studies (I^2 > 99%), but further identification of possible confounders was not done (d'Othee Janne, B., Siebert, U., Cury, R. et al , 2008).

The fourth systematic review (search date 2006) compared the diagnostic accuracy of 4-slice (22 studies), 16-slice (26 studies), and 64-slice (6 studies) CT coronary angiography with invasive coronary angiography as the reference standard level (Vanhoenacker, Piet K., Heijenbrok-Kal, Majanka H., Van, Heste Ruben et al , 2007). The overall mean prevalence of CAD was 67%. Unit of analysis was based at the patient level, vessel level and segment level. A total of 30 775 segments, 2692 vessels, and 1474 patients were analysed (Vanhoenacker, Piet K., Heijenbrok-Kal, Majanka H., Van, Heste Ruben et al , 2007).

The sensitivity and specificity from a patient-based analysis for 64-slice CT coronary angiography were 99% (95%CI 97% to 100%) and 93% (95%CI 89% to 98%), respectively. Sensitivity and specificity from a patient-based analysis for 16-slice CT coronary angiography were 97% (95%CI 94 to 99%) and 81% (95%CI 72% to 90%), respectively. For 4-slice CT coronary angiography sensitivity and specificity were 91% (95%CI 87% to 95%) and 83% (95%CI 68 to 99%), respectively (Vanhoenacker, Piet K., Heijenbrok-Kal, Majanka H., Van, Heste Ruben et al , 2007).

The sensitivity and specificity from a vessel-based analysis for 64-slice CT coronary angiography were 95% (95%CI 91% to 99%) and 93% (95%CI 90 to 95%), respectively. Sensitivity and specificity for 16-slice CT coronary angiography from a vessel based analysis were 93% (95%CI 89% to 97%) and 92% (95%CI 89% to 96%), respectively, and for 4-slice CT coronary angiography sensitivity and specificity were 87% (95%CI 78% to 96%) and 87% (95%CI 73% to 100%), respectively (Vanhoenacker, Piet K., Heijenbrok-Kal, Majanka H., Van, Heste Ruben et al , 2007).

The pooled sensitivity and specificity for detecting a greater than 50% coronary stenosis per segment were; 93% (95%CI 88% to 97%) and 96% (95%CI 96% to 97%) for 64-slice CT coronary angiography, 83% (95%CI 76% to 90%) and 96% (95%CI 95% to 97%) for 16-slice CT coronary angiography, and 84% (95%CI 81% to 88%) and 93% (95%CI 91% to 95%) for 4-slice CT coronary angiography, respectively (Vanhoenacker, Piet K., Heijenbrok-Kal, Majanka H., Van, Heste Ruben et al , 2007).

Meta-regression sROC analysis found that the relative diagnostic odds ratio of 64-slice CT coronary angiography was significantly greater compared with that of 4-slice CT coronary angiography (odds ratio, 3.95, 95%CI 1.20 to 12.94). Multiple regression analysis found that the proportion of coronary segments which could not be assessed was significantly lower in studies in which 16- or 64- slice CT scanners were used instead of a 4-slice CT scanner. The mean heart rate, prevalence of significant disease, and mean age were also significant predictors of performance (Vanhoenacker, Piet K., Heijenbrok-Kal, Majanka H., Van, Heste Ruben et al , 2007).

The authors stated that heterogeneity was present among the studies on all levels. Results of the per-patient analysis showed the least heterogeneity (I^2 = 65.95%), whereas results of the other two analyses showed considerably greater heterogeneity (per-vessel I^2 = 82.09%, per-segment I^2 = 94.04%). Publication bias was considerable in the per-segment analysis (intercept, 5.19; $P < 0.05$) and lower in the I^2 =per patient analysis (intercept, 2.82; $P < 0.05$). No publication bias could be detected in the per-vessel analysis (intercept, 3.27; $P > 0.5$), however there were only a limited number of studies which presented analysis on a per-vessel basis (Vanhoenacker, Piet K., Heijenbrok-Kal, Majanka H., Van, Heste Ruben et al , 2007)}.

The authors concluded that the diagnostic performance of newer generations of MSCT scanners was significantly improved, and the proportion of segments which could not be assessed was decreased (Vanhoenacker, Piet K., Heijenbrok-Kal, Majanka H., Van, Heste Ruben et al , 2007).

The fifth systematic review was a Health Technology Assessment (search date 2006) examined the diagnostic accuracy of 64-slice CT coronary angiography to diagnose CAD compared with invasive coronary angiography as the reference standard (Mowatt, G., Cummins, E., Waugh, N. et al , 2008). Twenty-one diagnostic studies (1286 patients) were identified. Meta-analysis was performed at the following levels; patient (18 datasets), segment (17 datasets), LMS artery (5 datasets), LAD overall (7 datasets), LAD proximal (5 datasets), LCX (7 datasets), RCA overall (7 datasets), stents (6 datasets), and in patients who had previously undergone CABGs (4 datasets) (Mowatt, G., Cummins, E., Waugh, N. et al , 2008).

The median prevalence of CAD for the patient level studies was 58% (range 23% to 96%) defined as coronary stenosis ≥ 50%. For the diagnosis of CAD, the sensitivities ranged from 94% to 100% with a pooled sensitivity of 99% (95%CI 97% to 99%). Specificity ranged from 50% to 100% with a pooled specificity of 89% (95%CI 83% to 94%). Across studies the median PPV was 93% (range 64% to 100%), while the median NPV was 100% (range 86% to 100%). There was no evidence of substantial heterogeneity with respect to sensitivity or specificity (Mowatt, G., Cummins, E., Waugh, N. et al , 2008).

For coronary segment-based analysis sensitivity ranged from 72% to 100% with a pooled sensitivity of 90% (95%CI 85% to 94%). Specificity ranged from 76% to 99% with a pooled specificity of 97% (95%CI 95% to 98%). Across studies the median PPV was 76% (range 44% to 93%), while the median NPV was 99% (range 95% to 100%). There was evidence of substantial statistical heterogeneity across the studies in terms of both sensitivity (I^2 = 80.1%) and specificity (I^2 = 95.1%). The studies were heterogeneous in terms of their participants. In some studies the participants all had suspected CAD, in others they were all known to have CAD or a mixture of both, or had had previous CABG or LBBB (Mowatt, G., Cummins, E., Waugh, N. et al , 2008).

Sensitivity for the LMS artery ranged from 90% to 100%, with a pooled sensitivity of 95% (95%CI 84% to 99%). All five studies reported a specificity of 100%, with a pooled specificity of 100% (95%CI 99% to 100%). Across studies the median PPV was 100% (range 90% to 100%), while all five

studies reported a NPV of 100%. There was no evidence of statistical heterogeneity for sensitivity or specificity (Mowatt, G., Cummins, E., Waugh, N. et al , 2008).

Sensitivity for the LAD artery ranged from 78% to 100%. The pooled sensitivity was 92% (95%CI 83% to 97%). Specificity ranged from 90% to 100%. The pooled specificity was 96% (95%CI 91% to 98%). Across studies the median PPV was 86% (range 63% to 100%), while the median NPV was 98% (range 95% to 100%). There was evidence of substantial statistical heterogeneity for both sensitivity (I^2 = 55.8%) and specificity (I^2 = 83.0%) (Mowatt, G., Cummins, E., Waugh, N. et al , 2008).

Sensitivity for the proximal LAD ranged from 91% to 100%, with a pooled sensitivity of 97% (95%CI 87% to 99%). Specificity ranged from 91% to 100% with a pooled specificity of 97% (95%CI 90% to 99%). Across studies the median PPV was 95% (range 85% to 100%), while the median NPV was 98% (range 90% to 100%). There was evidence of substantial statistical heterogeneity in terms of specificity (I^2 = 65.7%), although not for sensitivity (Mowatt, G., Cummins, E., Waugh, N. et al , 2008).

Sensitivity for the LCX artery ranged from 59% to100% with a pooled sensitivity of 85% (95%CI 69% to 94%). Specificity ranged from 92% to 100% with a pooled specificity of 96% (95%CI 92% to 99%). Across studies the median PPV was 81% (range 56% to 100%), while the median NPV was 98% (range 93% to 100%). There was evidence of substantial statistical heterogeneity in terms of both sensitivity (I^2 = 67.5) and specificity (I^2 = 71.4) (Mowatt, G., Cummins, E., Waugh, N. et al , 2008).

Sensitivity for the RCA ranged from 52% to 100% with a pooled sensitivity of 87% (95%CI 77% to 95%). Specificity ranged from 95% to 99% with a pooled specificity of 97% (95%CI 92% to 98%). Across studies the median PPV was 82% (range 74% to 91%), while the median NPV was 98% (range 94% to 100%). There was evidence of substantial statistical heterogeneity in terms of sensitivity (I^2 = 78.7%), but not specificity (Mowatt, G., Cummins, E., Waugh, N. et al , 2008).

In the 4 studies that examined the accuracy of 64-slice CT coronary angiography to detect ≥ 50% stenosis in patients who had previously undergone CABG surgery, the sensitivity ranged from 97% to 100% with a pooled sensitivity of 99% (95%CI 95% to 100%), and the specificity ranged from 89% to 98%, with a pooled specificity of 96% (95% CI 86% to 99%). The median PPV was 93% (range 90% to 95%) and the median NPV was 99% (range 98% to 100%) (Mowatt, G., Cummins, E., Waugh, N. et al , 2008).

Most of the studies were conducted in mixed populations of known and suspected CAD. However, the authors noted that better sensitivity, PPV and NPV, but worse specificity, were reported in studies in patients with known CAD alone, compared with studies in patients with suspected CAD alone. For segment level analysis, better sensitivity was reported with those patients with suspected CAD and better PPV for those with known CAD. Specificity and NPV were similar in both populations (Mowatt, G., Cummins, E., Waugh, N. et al , 2008).

The authors concluded that 64-slice CT coronary angiography is highly sensitive for detecting significant CAD, and the high NPV indicates that if 64-slice MSCT coronary angiography is negative, patients may not require further evaluation with invasive coronary angiography (Mowatt, G., Cummins, E., Waugh, N. et al , 2008).

MR coronary angiography

The advent of ultrafast MR imaging has lead to the development of MR coronary angiography. Images are generated by technique known as "flow-related enhancement" 2 dimensional (2D) and 3 dimensional (3D) time-of-flight sequences), where most of the signal on an image is due to blood which has recently moved into that plane. Initial studies using 2D time-of-flight sequences had relatively poor resolution. The introduction of 3D imaging improved resolution. In addition, 3D imaging has thinner slices, superior signal to noise ratio and superior coverage of the coronary arteries compared with 2D imaging. However there are still major challenges with the spatial resolution, coverage, compensation of cardiac and respiratory motion, and signal to noise ratios. Studies on the diagnostic performance of MR coronary

angiography have been conflicting, with wide variations in reported sensitivities and specificities.

A systematic review (search date 2004) which examined the diagnostic accuracy of magnetic resonance coronary angiography for the diagnosis of CAD identified 39 studies which used coronary angiography as the reference standard (Danias, P. G., Roussakis, A., and Ioannidis, J. P., 2004). The main analysis was performed at the level of coronary artery segments, as the retrieved studies focused on this level of information. Separate segment level analysis was performed for each coronary vessel, in addition to combined segment analysis. Secondary analyses compared available data at the vessel level and at the patient level. The review did not report the weighted mean prevalence of CAD in the studies identified. In the 39 studies identified the prevalence of CAD ranged from 17% to 100%, and the percentage of men ranged from 50 to 95% (Danias, P. G., Roussakis, A., and Ioannidis, J. P., 2004).

Diagnostic data was available at the segment level from 25 studies (27 comparisons, 4620 segments of 993 subjects). Diagnostic data was available at the vessel level from 16 studies (2041 vessels of 624 subjects). Diagnostic data was available at the subject level from 13 studies (607 subjects). Significant CAD on coronary angiography was defined using the > 50% diameter stenosis cutoff in the majority of studies; two studies however used ≥ 70% as the cutoff, and another study used > 30% stenosis (Danias, P. G., Roussakis, A., and Ioannidis, J. P., 2004).

For the combined segment level studies (27 studies, 4620 patients) the weighted pooled sensitivity for detection of coronary artery stenoses > 50% was 73% (95%CI 69% to 77%) and the specificity was 86% (95%CI 80% to 90%). It was noted that there seemed to be clusters of studies; one with low sensitivity (< 70%) and high specificity (> 85%), another with high sensitivity (> 80%) and also high specificity (> 85%), and a third study with variable sensitivity (60% to 92%) and low specificity (50% to 75%). There was significant between-study heterogeneity in the sensitivity and specificity (Danias, P. G., Roussakis, A., and Ioannidis, J. P., 2004).

At the segment level, the diagnostic accuracy was relatively similar for the left main stem (LMS) artery, left anterior descending (LAD) artery, and right coronary artery (RCA). For the LMS artery, there were 19 studies (802 patients) and the sensitivity was 69% (95%CI 56% to 79%) and the specificity was 91% (95%CI 84% to 95%). For the LAD artery (21 studies, 1058 patients) the sensitivity was 79% (95%CI 73% to 84%) and the specificity was 81% (95%CI 71% to 88%). For RCA (21 studies, 990 patients) the sensitivity was 71% (95%CI 64% to 78%) and the sensitivity was 84% (95%CI 77% to 88%). The sensitivity was considerably lower for the left circumflex (LCX) coronary artery (21 studies, 674 patients) compared with the diagnostic accuracy for LMS artery, LAD artery and RCA; only slightly higher than half the lesions were detected (sensitivity 61% (95%CI 52% to 69%). The specificity was similar for LCX artery compared with the other arteries (85%, 95%CI 78% to 90%). There was significant between-study heterogeneity in the specificity for the segment analyses in all arteries, while for sensitivity, heterogeneity was detected in the LMS artery and RCA results (Danias, P. G., Roussakis, A., and Ioannidis, J. P., 2004).

At the subject level (13 studies, 607 patients) the sensitivity was 88% (95%CI 82% to 92%) and the specificity was 56% (95%CI 43% to 68%). At the vessel level (11 studies 1271 patients) the sensitivity was 75% (95%CI 68% to 80%) and the specificity was 85% (95%CI 78% to 90%). There was significant heterogeneity between-studies for the sensitivity and the specificity at the vessel level, and at the subject level there was heterogeneity in the specificity (Danias, P. G., Roussakis, A., and Ioannidis, J. P., 2004).

Further analysis in the systematic review found that for subjects with an estimated pre-test probability of CAD of 5%, 20%, 50%, and 80%, positive magnetic resonance coronary angiography would slightly increase the probability of CAD to 10%, 33%, 66%, and 89%, respectively. Given the same pre-test probabilities, a negative test would decrease the probability of CAD to 1.1%, 5%, 18%, and 46%, respectively. In summary, the results indicated that magnetic resonance coronary angiography had a moderately high sensitivity for detecting significant proximal stenoses, and may therefore be useful in the

exclusion of significant multivessel CAD in selected patients being considered for diagnostic cardiac catheterisation (Danias, P. G., Roussakis, A., and Ioannidis, J. P., 2004).

MR coronary angiography versus multislice computed tomography (CT) coronary angiography (CT)

A systematic review (search date 2005) examined the accuracy of MR coronary angiography and multislice CT coronary angiography in the detection of significant coronary artery lesions compared to conventional angiography as reference standard in 51 studies (Schuijf, J. D., Bax, J. J., Shaw, L. J. et al , 2006).

The diagnostic performance of MR coronary angiography was determined in 28 studies with a total of 903 patients, the reported prevalence of CAD in the studies ranged from 59% to 100% and the reported percentage of men in the studies ranged from 60% to 90%. The systematic review quoted the definition of significant CAD in 27 out of the 28 studies to be > 50% diameter stenosis, with 1 study defining CAD as > 30% diameter stenosis (Schuijf, J. D., Bax, J. J., Shaw, L. J. et al , 2006).

The diagnostic performance of multislice CT coronary angiography (up to 16-slice) was determined in 24 studies with a total of 1300 patients, the reported prevalence of CAD in the studies ranged from 53% to 100% and the reported percentage of men in the studies ranged from 56% to 96%. The systematic review quoted the definition of significant CAD in 23 out of the 24 studies to be > 50% diameter stenosis, with 1 study defining CAD as > 70% diameter stenosis (Schuijf, J. D., Bax, J. J., Shaw, L. J. et al , 2006).

Meta-analyses found that multislice CT coronary angiography had greater sensitivity (85%, 95%CI 86% to 88%) and specificity (95% 95%CI 95%) compared with MR coronary angiography (sensitivity 72%, 95%CI 69% to 75%, and specificity 87%, 95%CI 86% to 88%). Multislice CT coronary angiography had a significantly higher odds ratio (16.9-fold) for the presence of significant stenosis (≥ 50%) compared with MR coronary angiography (6.4 - fold) ($P < 0.0001$) (Schuijf, J. D., Bax, J. J., Shaw, L. J. et al , 2006).

Meta-regression analysis was used to determine the relationship between diagnostic specificity and disease prevalence. Multislice CT coronary angiography specificity was found to have an inverse relationship with CAD prevalence (*P* = 0.056), and this was consistent when controlling for average age and the proportion of men enrolled in the studies. No relationship was observed between specificity and CAD prevalence for MR coronary angiography. In summary the results of the meta-analyses indicate that multislice CT coronary angiography has a significantly better diagnostic accuracy for the detection of CAD compared with MR coronary angiography (Schuijf, J. D., Bax, J. J., Shaw, L. J. et al , 2006).

Coronary angiography

Coronary angiography is considered to be the 'gold standard' in the diagnosis of CAD and the determination of severity of CAD. An X ray contrast agent is injected into a major coronary artery by a catheter that has been advanced through the arterial system from an artery in the wrist, groin or forearm. Coronary angiography provides anatomical information. The functional significance of coronary stenoses might be uncertain, and nor does it indicate which plaques are most liable to lead to an acute coronary event. The most serious complications of coronary angiography are death (0.1 to 0.2%), non fatal MI (0.1%), and cerebrovascular events (0.1%) (Mowatt, G., Vale, L., Brazzelli, M. et al , 2004).

5.2.4 Cost-effectiveness evidence- economics of imaging investigations

5.2.4.1 Summary of evidence

From the health economic literature search, six full economic evaluations were included as part of the health economic evidence review (Mowatt, G., Vale, L., Brazzelli, M. et al , 2004), (Hernandez, R. and Vale, L., 2007), (Sharples, L., Hughes, V., Crean, A. et al , 2007), (Rumberger, J. A., Behrenbeck, T., Breen, J. F. et al , 1999), (Dewey, M. and Hamm, B., 2007), (Mowatt, G., Cummins, E., Waugh, N. et al , 2008).

Mowatt 2004 HTA (Mowatt, G., Vale, L., Brazzelli, M. et al , 2004)

Aims and methods

Mowatt and colleagues (Mowatt, G., Vale, L., Brazzelli, M. et al , 2004) conducted a systematic review to assess the clinical and cost-effectiveness of MPS with SPECT for the management of angina and MI. A systematic review of relevant economic evaluations indicated that strategies involving MPS with SPECT were likely to be cost-effective, but there was less agreement about which strategy was optimal. Therefore, an economic model was developed to assess the cost-effectiveness of MPS with SPECT relative to exercise ECG and invasive coronary angiography (CA) for the diagnosis and management of significant CAD. A short-term decision tree model (DTM) was used for the diagnosis decision and a Markov model was created to model longer term costs and consequences, specifically for the management of patients with suspected CAD. The population modelled was a hypothetical cohort of 60 year old male patients with varying levels of CAD prevalence (10.5% to 85%). A subgroup analysis was conducted for a hypothetical cohort of women aged 60 years.

The short term diagnostic model was "static," but in reality the decision may have taken weeks or even months. Only the costs of the three diagnostic tests (exercise ECG, MPS with SPECT and invasive coronary angiography) were included in the short term model and outputs were measured as the percent receiving an accurate diagnosis. The longer term Markov model used a time horizon of 25 years and estimated costs over the cohort's lifetime (medical management, MI, and revascularization). Quality-adjusted life years (QALYs) were used as the measure of effectiveness in the longer term model. The authors presented an incremental cost-effectiveness analysis of both the short and the longer term models, with the final outcome of interest being the cost per QALY gained of one strategy relative to the next best strategy.

The perspective of the analysis was that of the NHS, currency was UK pounds and costs were from 2001/2002. No discounting was used for the short term diagnostic decision model, but costs and effects were discounted at 6% and 1.5% per annum respectively in the longer term Markov model. The diagnostic

tests were combined to produce four strategies which were thought representative of current practice:

1 Exercise ECG – SPECT – CA

2 Exercise ECG – CA

3 SPECT – CA

4 CA only

Patients would move to the next test in the strategy if the first or subsequent test was positive or indeterminate. Patients would undergo no further testing if they received a negative test result at any stage in the diagnostic strategy. In the base case, prevalence of CAD was estimated to be 10.5%, although cost-effectiveness estimates were calculated for additional prevalence values of 30%, 50% and 85%.

Sensitivity values for exercise ECG and MPS with SPECT were 66% and 83% respectively, whilst corresponding specificity values were 60% and 59%. Indeterminacy for exercise ECG and MPS with SPECT were modelled as 18% and 9%, respectively. Invasive coronary angiography was assumed to be the gold standard and therefore had 100% sensitivity and specificity and 0% indeterminacy. Each strategy carried a small risk of immediate death, 0.005% for exercise ECG and MPS with SPECT and 0.15% for Invasive coronary angiography. Costs of exercise ECG, MPS with SPECT and invasive coronary angiography were £107, £220 and £1,100, respectively.

Results

Results indicate that as prevalence increases, cost increases, and the proportion of correct diagnoses and QALYs decrease. At all levels of prevalence, the rank order of strategies is the same. Incremental cost-effectiveness ratios (ICERs) were presented for the base case (10.5% CAD prevalence) per true positive diagnosed, per accurate diagnoses and per QALY. Table **Error! Reference source not found.** summarises these results as well as those from the other prevalence rates modelled.

Table 42
Stepwise incremental cost-effectiveness

CAD Prevalence (%)	Strategy	Incremental cost per accurate diagnosis (£)	Incremental cost per QALY (£)
Base case, 10.5	ECG-SPECT-CA		
	ECG-CA	17267	23648
	SPECT-CA	9295	8723
	CA	24998	42225
30	ECG-SPECT-CA		
	ECG-CA	5230	5098
	SPECT-CA	5339	4711
	CA	7225	7331
50	ECG-SPECT-CA		
	ECG-CA	2535	2345
	SPECT-CA	4283	3807
	CA	3380	3178
85	ECG-SPECT-CA		
	ECG-CA	882	792
	SPECT-CA	3630	3242
	CA	1030	927

Adapted from Mowatt et al. 2004(Mowatt, G., Vale, L., Brazzelli, M. et al , 2004)

At the baseline CAD prevalence of 10.5%, SPECT-CA was cost-effective whereas invasive CA alone, although generating more QALYs, did so at a relatively high incremental cost per QALY (£42,225). At this level of prevalence, exercise ECG-CA was ruled out through extended dominance, and when removed from the incremental analysis, the ICER for SPECT-CA compared to exercise ECG-SPECT-CA became £14,123. At 30% CAD prevalence, SPECT-CA was still cost-effective, but the invasive CA strategy produced more QALYs at a relatively low incremental cost-effectiveness ratio (£7,331). At higher prevalence rates (50% and 85%), the SPECT-CA strategy was extendedly dominated by the exercise ECG-CA and invasive CA strategies. In other words, over a defined range, if some patients received exercise ECG-CA with the rest receiving CA, the costs would be lower and the QALYs higher than if SPECT-CA alone was used.

Uncertainty

To allow for uncertainty in some of the parameters in the economic evaluation a number of deterministic sensitivity analyses were performed. The first

analysis assessed the effect of changing sensitivity and specificity values for exercise ECG and MPS with SPECT. As expected, when the sensitivity or specificity of a given test is higher, strategies involving that test tend to perform better. For example, at a high sensitivity for exercise ECG the exercise ECG-CA strategy dominates SPECT-CA, whereas for low specificity of exercise ECG the exercise ECG-SPECT-CA strategy dominates exercise ECG-CA. Similarly, for low levels of MPS with SPECT sensitivity, exercise ECG-CA dominates the SPECT-CA strategy, but for high levels SPECT-CA dominates invasive CA alone. High levels of specificity for MPS with SPECT also result in the exercise ECG-CA strategy being dominated by SPECT-CA.

The second sensitivity analysis assessed the effect of allowing MPS with SPECT to independently identify patients with significant CAD, who would not need to progress to invasive coronary angiography. This effect was illustrated by varying the proportion of patients testing positive, whose condition might satisfactorily be managed medically. In the base case, the proportion of these patients was zero. When this proportion was increased to 50%, the cost-effectiveness of MPS with SPECT strategies improved compared to the base case.

The third analysis assessed the effect of changing the rates of indeterminate results. With a higher rate of indeterminacy for exercise ECG (30% vs. 18% in the base case) and lower rate of indeterminacy for MPS with SPECT (2% vs. 9% in the base case), the result is improved cost-effectiveness for MPS with SPECT strategies.

In another sensitivity analysis the cost of exercise ECG was varied from £25 to £225 (base case £107), and of coronary angiography from £895 to £1724 (base case £1100). The results showed no change in rank order of strategies with regard to cost-effectiveness. The cost of MPS with SPECT was varied between £128 to £340 (base case £220) and even at the high cost of MPS with SPECT the incremental cost per QALY of SPECT-CA versus exercise ECG-CA was <£16,000.

Another sensitivity analysis showed that as the time horizon of the analysis reduces, the incremental cost per QALY increases because the costs of initial diagnosis and treatment are not offset by survival and quality of life gains.

Another sensitivity analysis assessed the effect of changing the time it takes a false negative to be correctly diagnosed. In the base case, all survivors are correctly diagnosed by year 10. Sensitivity analysis changed this to 2 years, 5 years, and never. Allowing false negatives to be re-diagnosed sooner improves the cost-effectiveness of non-invasive strategies compared with invasive coronary angiography alone. Conversely, increasing the time to re-diagnosis increases the penalty associated with misdiagnosis and reduces the cost-effectiveness of non-invasive strategies compared with invasive coronary angiography.

Other sensitivity analysis results indicated that if invasive coronary angiography (CA) (assumed to provide perfect information in the base case) did not provide perfect information, then the relative cost-effectiveness of a non-invasive strategy would improve. If the risks of MI for all risk states were allowed to increase, there would be no difference in the cost-effectiveness rank order of the strategies compared to the base case. When discounting rates for costs and benefits was set at 0% for both, and 6% for both, there was one change in the order of the strategies compared to base case. For low cost values for MPS with SPECT and zero discount rates, SPECT-CA dominates the exercise ECG-CA strategy. When QALY values were allowed to vary due to mortality risk reduction after revascularisation, no changes were observed in the order of strategies compared to base case.

A subgroup analysis was conducted for a hypothetical cohort of women aged 60. This analysis used improved diagnostic sensitivities and specificities for both exercise ECG and MPS with SPECT and a lower prevalence of CAD. It also used different MI and mortality rates for women aged 60 years at diagnosis. When these parameters were varied, exercise ECG-SPECT-CA was less costly than in the base case and exercise ECG-CA and CA alone were dominated by the SPECT-CA strategy.

Summary

The economic model presented in the Mowatt 2004 HTA suggested that, for low prevalence patient groups, the incremental cost per unit of output (true positives diagnosed, accurate diagnosis, QALY) for the move from exercise ECG-SPECT-CA and from exercise ECG-CA to SPECT-CA might be considered worthwhile. At 30% CAD prevalence, although SPECT-CA is cost-effective, the CA only strategy produces more QALYs at a relative low additional cost. At higher prevalence rates (50% and 85%), the SPECT-CA strategy is extendedly dominated by the exercise ECG-CA and CA strategies.

A series of sensitivity analyses appraised the sensitivity of the model outputs, to changes in the model's key assumptions and parameters. Results of the modelling were shown to be sensitive to a variety of variables, including the diagnostic accuracy and indeterminacy of the tests, the time horizon chosen, time to re-diagnosis and the ability of MPS with SPECT to diagnose and guide management independently of confirmatory invasive coronary angiography.

Hernandez et al. 2007: Probabilistic Sensitivity Analysis (Hernandez, R. and Vale, L., 2007)

The second economic analysis identified from the literature is a revised and expanded analysis of the 2004 HTA by Mowatt and colleagues (Mowatt, G., Vale, L., Brazzelli, M. et al , 2004) presented above. Two of the HTA authors developed their deterministic model (presented above) into a probabilistic model (Hernandez, R. and Vale, L., 2007), in which the key input point estimates were replaced by probability distributions. Probabilistic models facilitate the assessment of the statistical variability of modelled outputs, through the use of random sampling from the assumed input parameter distributions. The structure of the Hernandez probabilistic model is identical to that of the deterministic model presented in the Mowatt 2004 HTA, and comprises both the short term diagnostic model and the longer term Markov model. The same assumptions were used to define how and when patients move from one test to the next in any given diagnostic pathway. The base

case analysis evaluates the same four testing strategies as those included in the HTA, but in a sensitivity analysis the model is expanded to assess the cost-effectiveness of two strategies using stress echocardiography (stress echo-CA and stress echo-SPECT-CA). The model was run separately over a range of CAD prevalence values: 10.5% in the base case, 30%, 50% and 85%. Lower levels of CAD prevalence (0.1%, 0.5%, 1% and 5%) were explored in further sensitivity analyses.

As in the 2004 HTA(Mowatt, G., Vale, L., Brazzelli, M. et al , 2004), the perspective of the analysis was that of the NHS, currency was UK pounds and costs were from 2001/2002. Effectiveness was measured in QALYs generated over the 25-year follow up simulated in the longer term Markov model. No discounting was used for the short term diagnostic decision model, but costs and QALYs were discounted 6% and 1.5% per annum respectively in the longer term Markov model. Model results were presented in the form of incremental cost-effectiveness ratios, and cost-effectiveness acceptability curves.

Conventional methods were used to specify prior probability distributions. As only mean costs and ranges were available, triangular distributions were used for the cost variables. Beta distributions were used for variables taking a value between 0 and 1 (e.g. sensitivity and specificity of diagnostic tests). Gamma distributions were used where probability distributions were skewed towards a value of zero (e.g. immediate risk of death during exercise ECG), and log-normal distributions were used for relative risks (i.e. relative risk of death for high-risk patients).

Results of one thousand Monte Carlo simulation iterations were generated and used to calculate credible intervals for the model's deterministic results and to construct cost-effectiveness acceptability curves (CEACs). CEACs illustrate the probability that an intervention is optimal for any maximum value of willingness to pay for an extra QALY.

Some of the sensitivity analyses that were performed in the original HTA were repeated using the probabilistic model. Three additional sensitivity analyses

were run to look at each of the following: the impact of reducing the assumed perfect accuracy of invasive coronary angiography, the potential cost-effectiveness of stress echocardiography and the impact of even lower levels of CAD prevalence.

Results

Deterministic results were very similar to those presented in the HTA. It is unclear why there are small differences between the studies, but the conclusions are the same. At low levels of CAD prevalence (10.5% and 30%) exercise ECG-SPECT-CA is the least costly and least effective strategy, and the move to SPECT-CA is likely to be considered cost-effective with an ICER of £15,241 per QALY. Exercise ECG-CA is ruled out through extended dominance by the combination of exercise ECG-SPECT-CA and SPECT-CA. At 10.5%, a CA only strategy, although generating more QALYs than SPECT-CA, did so at a relatively high incremental cost per QALY (£48,576). However, at 30% CAD prevalence, the CA only strategy had a more acceptable ICER (£7,893) over SPECT-CA.

For assumed CAD prevalences of 50% and 85%, the rank order of the strategies remains the same, but now the SPECT-CA strategy is extendedly dominated by exercise ECG-CA and CA only. At both these levels of prevalence, model indicates that the QALY gain associated with the move to CA only from exercise ECG-CA, is likely to come at an acceptable incremental cost.

Results of the probabilistic sensitivity analysis were presented as CEACs for each level of CAD prevalence modelled. At CAD prevalence of 10.5%, if decision makers are only willing to pay £8,000 per QALY, then exercise ECG-SPECT-CA is most likely to be the optimal strategy. At a ceiling ratio of £20,000 per QALY SPECT-CA has a 90% chance of being the most cost-effective strategy. At this level of CAD prevalence, the willingness to pay threshold would need to be greater than £75,000/QALY for CA alone to be the most cost-effective option.

For CAD prevalence of 30%, exercise ECG-SPECT-CA is the optimal strategy for a willingness to pay of up to £5,000 per QALY. SPECT-CA is likely to be optimal between £5,000 and £20,000, and above £20,000, CA is the optimal decision. When CAD prevalence is greater than 50%, CA is the optimal decision for a willingness to pay threshold of any value over £10,000 per QALY gained.

Further Sensitivity Analyses

The probabilistic model produced very similar results to those presented in the HTA. The authors reported that the model outputs are sensitive to the prevalence of CAD and to test accuracies. When other sources of test sensitivity and specificity were used for exercise ECG and MPS with SPECT, the results changed in a predictable way. When the sensitivity or specificity of a given test was increased, strategies involving that test tended to perform better. When MPS with SPECT performance was poor, SPECT-CA never appears on the frontier of optimal strategies, but at 10.5% CAD prevalence, exercise ECG-SPECT-CA is optimal at a ceiling ratio of up to £5,000 per QALY. When better performance data is used for MPS with SPECT, results are similar to the base case, and CA is still optimal for CAD prevalence greater than 60% and a willingness to pay threshold of more than £16,000 per QALY. Results were also sensitive to the time horizon of the analysis, time to re-diagnosis and test indeterminacy. The subgroup analysis for women returned the same results as in the HTA, namely that MPS with SPECT-based strategies appeared to perform more favourably than in the base case.

The authors wanted to explore the assumption made with regard to invasive coronary angiography being the gold standard. To do this, they assigned beta distributions with a mean of 99% and standard deviation of 0.5% to the sensitivity and specificity of invasive coronary angiography. Model outputs were relatively insensitive to this variation.

The authors also wanted to explore the potential cost-effectiveness of stress echocardiography based strategies as part of a sensitivity analysis. When the two stress echocardiography based strategies were added to the model, results indicated evidence of cost-effectiveness. At a CAD prevalence of

10.5%, stress ECHO-SPECT-CA dominated both exercise ECG-SPECT-CA and exercise ECG-CA strategies, whereas stress ECHO-CA dominated both exercise ECG-CA and SPECT-CA strategies.

In a final sensitivity analysis, the authors looked at the impact of running the model with very low levels of CAD prevalence (0.1%, 0.5%, 1% and 5%). Results indicate that at low levels of CAD prevalence (up to 1%), the exercise ECG-SPECT-CA strategy dominates all others. When prevalence is between 1% and 4%, SPECT-based strategies dominated non-SPECT strategies. At 5% CAD prevalence, only the SPECT-CA strategy dominated the CA alone strategy.

Summary

When the prevalence of CAD is below 30%, the analysis indicates that the move from exercise ECG-SPECT-CA to SPECT-CA is likely to be considered cost-effective. Probabilistic sensitivity analysis suggests that the exercise ECG-CA strategy is highly unlikely ever to be the optimal strategy, and that SPECT-CA is more likely to be optimal when CAD prevalence is less than 30%. Above 30%, the invasive coronary angiography option is more likely to be considered optimal.

The analysis also points to a possible role for stress echocardiography, although this should be interpreted with some caution. The data used to inform the diagnostic performance of stress echocardiography was based on an ad hoc review of the literature and indirect test comparisons. Also, sensitivity and specificity data from the HTA systematic review indicate that the stress echocardiography input parameters may be optimistic. This would have the effect of magnifying the favourable results obtained for echo.

CECaT Trial (Sharples, L., Hughes, V., Crean, A. et al , 2007)

Another HTA (Sharples, L., Hughes, V., Crean, A. et al , 2007) which aimed to assess the cost-effectiveness of functional cardiac testing as a gateway to invasive coronary angiography in the diagnosis and management of patients with known or suspected CAD was reviewed for this guideline. This HTA

involved an economic evaluation alongside a randomised clinical trial, the methods and results of which have been presented in the clinical effectiveness review of this guideline.

The study randomised 898 patients to Group 1: invasive coronary angiography (n=222); Group 2: MPS with SPECT (n=224); Group 3: stress MR perfusion imaging (n=226) or Group 4: stress echocardiography (n=226). Outcome measures included exercise time (modified Bruce protocol), QALYs and costs at 18 months post randomisation. The number of QALYs over 18 months was estimated using EQ-5D questionnaire data which was collected as part of the trial. A large British sample valued EQ-5D health states on a "utility" scale on which being dead scores zero and perfect health scores one. The costing perspective was that of the UK health service and personal social services. For all four diagnostic groups, patient-specific resource use data were collected for 18 months post randomisation. All cost reported were based on 2005/2006 prices. An annual discount rate of 3.5% was applied to all costs and QALYs incurred between 12 and 18 months post-randomisation. Health-care resources were measured and valued for: diagnostic tests, subsequent treatment including revascularisation procedures and hospital admissions, adverse events, outpatient and GP visits and medications. Cost estimates were taken from a variety of sources including unit costs specific to the NHS hospital trust (diagnostic tests), NHS reference costs (revascularisation) and national published estimates (GP consultations).

Sensitivity of results to the following inputs was assessed: use of the SF-5D utility measure instead of EQ-5D; inclusion of uncertainty around the point estimates of unit test costs; potential for cost saving if all negative functional tests were not followed by confirmatory invasive coronary angiography; removing patients with very high and very low costs to assess the influence of outliers; and subgroup analysis by type of referring clinician, classed as interventionist or non-interventionist.

Results

The mean total costs (standard deviation) per patient at 18 months post randomisation for the four diagnostic groups were: invasive coronary

angiography £3,360 (£3,405); MPS with SPECT £4,045 (£4,136); stress MR perfusion imaging £4,056 (£3,825); and stress echocardiography £4,452 (£5,383). Mean (SD) QALYs per patient at 18 months post randomisation were: invasive coronary angiography 1.13 (0.34); SPECT 1.17 (0.27); MR perfusion imaging 1.14 (0.31); and stress echocardiography 1.17 (0.29). The mean (SD) costs per QALY gained, relative to invasive coronary angiography, were: MPS with SPECT £11,463 (£162,299); MR perfusion imaging £44,573 (£1,245,321); and stress echocardiography £22,157 (£484,426).

There were no statistically significant differences in costs between the MPS with SPECT and MR perfusion imaging groups and the invasive coronary angiography group. There was a significant difference in costs between stress echocardiography and invasive coronary angiography. This was mainly due to more hospital admissions as a result of non-fatal adverse events; in particular one patient had seven admissions for chest pain in addition to both PCI and CABG surgery. QALY estimates did not show any statistically significant differences between the four diagnostic groups.

Uncertainty

Sensitivity analysis showed that by using QALYs based on SF-6D utilities, the QALY estimates at 18 months post-randomisation were lower compared with estimates based on the EQ-5D, but no significant differences were detected between the three non-invasive test groups and invasive coronary angiography.

Alternative cost estimates for the initial imaging tests were used (latest NHS reference costs vs. hospital unit costs) in a second sensitivity analysis. The total costs for all four test groups increased, with the MPS with SPECT group having the largest increase (£900). The overall impact on the cost comparison with the invasive coronary angiography group indicated that the MPS with SPECT group had higher mean costs over 18 months, and as a result the MPS with SPECT strategy cost significantly more than invasive coronary angiography alone. Another analysis removed the costs of confirmatory

invasive coronary angiography. In the trial 20% of patients in each of the three imaging test groups had confirmatory invasive coronary angiography following a negative test result. In this scenario the costs of confirmatory invasive coronary angiography were removed for all patients having a negative functional test result. The mean total costs for the three test groups fell compared to base case. Compared to the invasive coronary angiography group cost differences decreased by £100-£200 for all three groups and these differences were not significantly greater than zero. In a further sensitivity analysis cost "outliers" were removed by removing the bottom and top 2.5% of the cost distributions. As a result the mean cost comparisons for the MPS with SPECT and MR perfusion imaging groups with the invasive coronary angiography group were relatively unchanged whereas the cost differences with the stress echocardiography group fell by approximately £300. This confirms the large impact of the cost "outliers" in the stress echocardiography group on the overall results of the base case analysis.

Finally, in a post hoc subgroup analysis, clinicians were divided into interventional cardiologists and non-interventional cardiologists, according to their clinical practice outside of the trial. The interventionists were much more likely to refer patients with negative functional tests for invasive coronary angiography and were more likely to intervene in the event of a positive test. Thus, all four groups had higher mean costs compared with the non-interventionists had lower mean costs. There were no significant QALY differences between interventionist and non-interventionist patient sub-groups.

Summary of results and sensitivity analysis

The base case results indicate that the strategy of going straight to invasive coronary angiography is cheaper but (marginally) less effective than undergoing a 'gateway' functional test such as MPS with SPECT, MR perfusion imaging or stress echocardiography. Although the non-invasive tests are slightly more effective, the benefit is so close to zero in all three cases that the ICERs are unstable. Although the cost-effectiveness acceptability curves suggest that MPS with SPECT and stress echocardiography are more likely to be cost-effective at a QALY threshold of

£30,000, a simple cost-minimisation approach may be more appropriate and would clearly favour the invasive coronary angiography strategy.

The various sensitivity analyses demonstrate that the rank ordering of costs and QALYs, and the magnitude of the differences between options, are sensitive to reasonable alternative methods of estimation. However, in no case do the 18-month costs of the three non-invasive alternatives fall below those of invasive coronary angiography, and the alternative estimation of QALYs makes all three alternatives less effective than invasive coronary angiography.

The authors note that, although the results indicate that non-invasive strategies are slightly more expensive than invasive coronary angiography alone, and with no accompanying QALY gain, the overall results suggest that functional testing may have a valuable place in the diagnostic pathway for the assessment of chest pain in an outpatient population, because of 'process' advantages to the patients, clinicians, or hospital. All three tests can avoid invasive diagnostic procedures in a significant proportion of patients.

Rumberger et al. 1999 (Rumberger, J. A., Behrenbeck, T., Breen, J. F. et al , 1999)

The fourth study identified was an economic analysis undertaken by Rumberger and colleagues (Rumberger, J. A., Behrenbeck, T., Breen, J. F. et al , 1999). The authors used a decision analytic model to assess the average cost-effectiveness of different technologies for the diagnosis of obstructive CAD. The analysis compared the use of exercise ECG, stress echocardiography, stress thallium myocardial scintigraphy and EBCT as initial diagnostic tests, where only those patients with a positive or indeterminate test result would subsequently undergo an invasive coronary angiography. For strategies using EBCT as the initial test, 4 different Agatston calcium scores thresholds (>0; >37; >80; >168) were used to define a positive result. An additional strategy which sent patients directly for an invasive coronary angiography was also included. Average cost-effectiveness of the 8 diagnostic strategies was assessed for hypothetical cohorts of 100 patients with 10%, 20%, 50%, 70% and 100% disease prevalence.

Model assumptions, including test sensitivities and specificities, are summarised in Table 43

Table 43
Rumberger et al. model parameters

Test	Sensitivity	Specificity	Indeterminacy	Cost
Exercise ECG	68%	77%	15%	$301
Stress Thallium	90%	77%	5%	$1,244
Stress Echo	84%	87%	5%	$943
EBCT (>0)	95%	46%	2%	$377
EBCT (=37)	90%	77%	2%	$377
EBCT (=80)	84%	84%	2%	$377
EBCT (=168)	71%	90%	2%	$377
CA	100%	100%	0%	$2,940
Adapted from Rumberger et al.1999(Rumberger, J. A., Behrenbeck, T., Breen, J. F. et al , 1999)				

It was unclear what costing perspective the authors took, but only direct costs of diagnosis and associated complications were included in the analysis. No future costs arising from a false negative diagnosis were included. Costs were measured in US dollars, but no year was reported. Model outputs were reported as the average cost per correct diagnosis with obstructive CAD.

Although the authors presented their results in terms of average cost-effectiveness, they did so in such a way that an incremental cost-effectiveness analysis could be undertaken. Therefore, an incremental analysis of the study's published finding is presented below, with results summarised in Table 44

Table 44

Incremental Cost-Effectiveness of Rumberger et al. (Hypothetical cohort of 100 patients)

Prevalence	Initial Strategy	Total Cost ($)	Incremental Cost ($)	Total Effect (correct CAD diagnosis)	Incremental Effect	ICER ($/correct CAD diagnosis)	False Negatives
10%	EBCT (>168)	105112		7			3
	EBCT (>80)	126400	21288	8	1	21288	2
	EBCT (>37)	151236	24836	9	1	24836	1
	Exercise ECG	166019	14783	7	-2	dominated	3
	ECHO	191295	40059	9	0	dominated	1
	THALLIUM	241083	49788	9	0	dominated	1
	EBCT (>0)	247030	95794	10	1	95794	0

	CA	354000	106970	10	0	dominated	0
20%	EBCT (>168)	126392		14		ext dom.	6
	EBCT (>80)	151232	24840	17	3	8280	3
	EBCT (>37)	171864	20632	18	1	20632	2
	Exercise ECG	180210	8346	15	-3	dominated	5
	ECHO	216121	35911	17	2	dominated	3
	EBCT (>0)	261212	89348	19	1	89348	1
	THALLIUM	265914	4702	18	-1	dominated	2
	CA	354000	92788	20	1	92788	0
50%	EBCT (>168)	186696		36			14
	EBCT (>80)	222180	35484	42	6	5914	8
	Exercise ECG	222804	624	36	-6	dominated	14
	EBCT (>37)	243450	21270	45	3	7090	5
	ECHO	283542	40092	43	-2	dominated	7
	EBCT (>0)	303792	60342	48	3	20114	2
	THALLIUM	333315	29523	45	-3	dominated	5
	CA	354000	50208	50	2	25104	0
70%	EBCT (>168)	229350		50		ext dom	20
	Exercise ECG	247605	18255	51	1	ext dom	19
	EBCT (>80)	268273	20668	59	8	2584	11
	EBCT (>37)	289548	21275	63	4	5319	7
	ECHO	329640	40092	60	-3	dominated	10
	EBCT (>0)	332119	42571	67	4	ext dom	3
	CA	353990	21871	70	3	7290	0
	THALLIUM	377748	23758	63	-7	dominated	7
100%	Exercise ECG	290175		73		ext dom	27
	EBCT (>168)	293112	2937	72	-1	dominated	28
	EBCT (>80)	335664	45489	84	11	ext dom	16
	CA	354000	18336	100	16	1146	0
	EBCT (>37)	356940	2940	90	-10	dominated	10
	EBCT (>0)	374680	17740	95	5	dominated	5
	ECHO	397035	22355	85	-10	dominated	15
	THALLIUM	446810	49775	91	6	dominated	9

Adapted from Rumberger et al. (Rumberger, J. A., Behrenbeck, T., Breen, J. F. et al , 1999)

Results of the incremental analysis show that strategies using stress echocardiography and stress thallium testing as initial tests are dominated at every level of disease prevalence modelled. Results also show that exercise ECG as an initial diagnostic strategy is dominated at 10%, 20% and 50% disease prevalence and is extendedly dominated at 70% and 100%.

At 10% disease prevalence, the least costly strategy is EBCT with a calcium score threshold of >168, followed by EBCT with thresholds >80 and >37. EBCT with a threshold of >0 is the most costly and most effective strategy with an ICER of $95,800 per additional correct diagnosis compared to EBCT >37. EBCT >0 dominated the direct to invasive coronary angiography strategy at this level of prevalence.

At 20% prevalence, EBCT >168 is ruled out through extended dominance. EBCT >80 is the least costly strategy, with EBCT >37 more costly and more effective with an ICER of $20,600 per additional correct diagnosis. EBCT >0 is more expensive and more effective with an ICER of $89,350 compared with EBCT >37. The most expensive and effective strategy is direct to invasive coronary angiography with an ICER of $92,800 per additional correct diagnosis.

At 50% prevalence, EBCT >168 is the least costly strategy, and EBCT >80 is more costly and more effective with an ICER of $6,000. EBCT >37 is slightly more effective than EBCT >80 with an ICER of $7,000 per correct diagnosis. It should be noted that these three strategies result in 14, 8 and 5 false negative diagnoses respectively. EBCT >0 is more costly and more effective than EBCT >37 with an ICER of $20,100. The most expensive and effective strategy remains direct to invasive coronary angiography with an ICER of $25,100 per additional correct diagnosis.

At 70% prevalence, EBCT >168 and >0 are ruled out through extended dominance. EBCT >80 is the least costly strategy and EBCT >37 is more effective, but with an ICER of $5,300. These two strategies produce 11 and 7 false negatives respectively. The most costly and most effective strategy is direct to invasive coronary angiography with an ICER of $7,300 per additional correct diagnosis.

At 100% disease prevalence the only strategy not dominated or extendedly dominated is direct to invasive coronary angiography.

No sensitivity analysis was undertaken by the authors.

Alternative Analysis

If calcium score thresholds greater than 0 are removed from the analysis, and it is assumed that EBCT >0 is the only calcium scoring technology of interest, the ranking and cost-effectiveness of strategies changes slightly. See Table 45 for summary of incremental analysis of strategies excluding EBCT >37, >80 and >168.

Table 45
Incremental Analysis with EBCT >0 only (Hypothetical cohort of 100 patients)

Prevalence	Initial Strategy	Total Cost ($)	Incremental Cost ($)	Total Effect (correct CAD diagnosis)	Incremental Effect	ICER ($/correct CAD diagnosis)	False Negatives
10%	Exercise ECG	166019	-	7	-	ext dom	3
	ECHO	191295	25276	9	2	12638	1
	THALLIUM	241083	49788	9	0	dominated	1
	EBCT (>0)	247030	55735	10	1	55735	0
	CA	354000	106970	10	0	dominated	0
20%	Exercise ECG	180210	-	15	-	12014	5
	ECHO	216121	35911	17	2	17956	3
	EBCT (>0)	261212	45091	19	2	22546	1
	THALLIUM	265914	4702	18	-1	Dominated	2
	CA	354000	92788	20	1	92788	0
50%	Exercise ECG	222804	-	36	-	ext dom	14
	ECHO	283542	60738	43	7	ext dom	7
	EBCT (>0)	303792	20250	48	5	4050	2
	THALLIUM	333315	29523	45	-3	Dominated	5
	CA	354000	50208	50	2	25104	0
70%	Exercise ECG	247605	-	51	-	ext dom	19
	ECHO	329640	82035	60	9	ext dom	10
	EBCT (>0)	332119	2479	67	7	354	3
	CA	353990	21871	70	3	7290	0
	THALLIUM	377748	23758	63	-7	Dominated	7
100%	Exercise ECG	290175	-	73	-	ext dom	27
	CA	354000	63825	100	27	2364	0
	EBCT (>0)	374680	20680	95	-5	Dominated	5
	ECHO	397035	22355	85	-10	Dominated	15
	THALLIUM	446810	49775	91	6	Dominated	9

Summary results of this limited incremental analysis show that stress thallium testing is still dominated at each of the modelled disease prevalences. Stress echocardiography is only dominated or extendedly dominated at 50% or greater prevalence. Direct to invasive coronary angiography is still likely to be the most cost-effective strategy at 70% and 100% disease prevalence.

The rank order of strategies at 10% and 20% disease prevalence changes when EBCT with higher calcium thresholds are removed. Stress echocardiography becomes the least costly strategy at 10% prevalence, followed by EBCT >0 with an ICER of $55,700 per additional correct diagnosis. At this level of prevalence, exercise ECG is ruled out through extended dominance.

At 20% disease prevalence, exercise ECG becomes the least cost strategy, and stress echocardiography is slightly more effective with an ICER of $18,000. EBCT >0 is a more effective strategy than stress echocardiography with an ICER of $22,500 per additional correct diagnosis. Invasive coronary angiography is the most costly and most effective strategy, with an ICER of $92,800 compared to EBCT >0.

At 50% and 70% prevalence, EBCT >0 and invasive coronary angiography dominate or extendedly dominate all other strategies. At 100% prevalence, invasive coronary angiography dominates or extendedly dominates all other strategies.

Summary

The incremental analysis which includes all 8 strategies shows that EBCT using any calcium score threshold (>0; >37; >80; >168) is cost saving compared with stress echocardiography and stress thallium testing. At low to moderate disease prevalence (10% to 20%), EBCT using thresholds of >37, >80 or >168 are cost saving compared with exercise ECG.

It is difficult to determine which strategy is most cost-effective at 50% disease prevalence because there is no explicit willingness-to-pay (WTP) threshold for additional cost per additional correct diagnosis. If for instance, the WTP for each additional correct diagnosis was $10,000, then the most cost-effective strategy would be EBCT (>37) and EBCT (>0) and invasive coronary angiography would not likely be considered cost-effective. If, on the other hand, the WTP for each additional correct diagnosis was $30,000, then direct to invasive coronary angiography would be an acceptably cost-effective strategy at 50% prevalence. Unfortunately, no WTP threshold exists to benchmark cost-effectiveness acceptability in this study. But, it is clear that EBCT strategies with higher calcium score thresholds are less expensive than an EBCT strategy with a low calcium score thresholds (>0). However, the lower sensitivity of higher calcium score thresholds means that many true positives are misdiagnosed as negatives. At high prevalence (70% to 100%), direct to invasive coronary angiography appears to be the most cost-effective strategy.

In the alternative analysis where EBCT strategies with higher calcium score thresholds are removed, stress echocardiography is the least cost strategy at 10% prevalence and EBCT >0 is the next most cost effective strategy. At 20% prevalence, the lack of an explicit willingness to pay threshold makes it difficult to determine the most cost-effective strategy. At 50% prevalence, EBCT >0 is least costly and direct to invasive coronary angiography has an ICER of $25,000 per additional correct diagnosis. At high prevalence, a strategy of direct to invasive coronary angiography appears to be the most cost-effective strategy.

Dewey and Hamm 2007 (Dewey, M. and Hamm, B., 2007)

The fifth study identified was a cost-effectiveness analysis by Dewey and Hamm (Dewey, M. and Hamm, B., 2007). The authors used a decision analytic model to assess the average cost-effectiveness of different technologies for the diagnosis of CAD. The analysis compared the use of exercise ECG, dobutamine stress echocardiography, dobutamine stress MRI, EBCT with calcium scoring and multislice CT coronary angiography as initial diagnostic tests, where only those patients with a positive or indeterminate test result would subsequently undergo invasive coronary angiography. No Agatston score threshold for EBCT was specified for a positive diagnosis. An additional strategy which sent patients directly for invasive coronary angiography was also included. Average cost-effectiveness of the 6 diagnostic strategies was assessed for hypothetical cohorts of 100 patients with disease prevalence of 10% to 100% at 10% intervals. For all tests except multislice CT coronary angiography, test accuracies used in the model were drawn from published meta-analyses of diagnostic performance. For multislice CT coronary angiography parameters, the authors used the results of their own interim analysis of a meta-analysis which included studies with at least 12-slice CT coronary angiography. Model parameters are summarized in Table 46.

Table 46
Dewey and Hamm Model Parameters

Strategy	Sensitivity	Specificity	Indeterminacy	Cost	Rate of Complications
Exercise ECG	67%	84%	18%	€32.98	0.05%
Stress MRI	86%	86%	11%	€164.18	0.038%
Stress Echo	85%	77%	15%	€131.22	0.038%
EBCT	92.3%	51.2%	2%	€94.28	0%
MSCT	95.6%	78.8%	1.15%	€175.28	0.004%
CA	100%	100%	0%	€630.99	1.5%

Adapted from Dewey and Hamm (Dewey, M. and Hamm, B., 2007)

The authors took a partial societal perspective, including direct costs of diagnosis and both direct and indirect costs associated with complications arising from diagnostic investigations. Future costs arising from false negatives were discounted at 5% per annum for a total of 10 years. Costs were measured in 2000 Euros and were based on the German outpatient reimbursement system. Model outputs were reported as the average cost per correct diagnosis of CAD.

The authors only presented their results in terms of average cost-effectiveness and did so only in graphical form. In order find the incremental cost-effectiveness of the different strategies, the results were estimated and used to conduct a rough incremental analysis.

Results of the incremental analysis indicate that strategies using stress echocardiography, stress MRI and calcium scoring with EBCT as initial diagnostic tests are dominated at every level of disease prevalence modelled. Results also show that exercise ECG as an initial strategy is extendedly dominated up to 50% CAD prevalence and dominated up to 100% thereafter. The only two non-dominated strategies in this analysis are multislice CT coronary angiography and invasive coronary angiography. At 10% to 40% prevalence, multislice CT coronary angiography is the least cost non-extendedly dominated strategy. At 50%, multislice CT coronary angiography is the least cost strategy. And finally, from 60% to 70%, invasive coronary

angiography is the least cost non-dominated or extendedly dominated strategy, and from 80% to 100% it is the least cost strategy.

Sensitivity Analysis

The authors conducted a series of one way sensitivity analyses and reported their effect on the average cost-effectiveness results. These were not applied to the incremental analysis, but certain conclusions can still be made.

At a maximally increased and decreased accuracy within the 95%CI, multislice CT coronary angiography remained the most effective and least costly strategy up to 60% and 50% CAD prevalence, respectively. If diagnostic accuracy of multislice CT coronary angiography was reduced maximally (within the 95%CI) and increased maximally for EBCT, multislice CT coronary angiography remained more effective than EBCT.

Neither increasing nor decreasing the complication rates of coronary angiography changed the ranking of diagnostic tests: invasive coronary angiography had the lowest average cost per correctly identified CAD patient for CAD prevalence of greater than 50%. At higher and lower complication-related costs (€15,000 and €5,000), multislice CT coronary angiography remained most effective and least costly up to 60% and 70% CAD prevalence.

An increase (€750) and decrease (€500) of the reimbursement for invasive coronary angiography meant that invasive coronary angiography was more effective and less expensive than multislice CT coronary angiography from 80% and 50% CAD prevalence and higher, respectively.

Up to a reimbursement rate of €260, multislice CT coronary angiography was the non-invasive diagnostic test with the lowest average cost per correctly identified CAD patient at all modelled levels of CAD prevalence.

Summary

Based on this analysis, multislice CT coronary angiography clearly dominates exercise ECG, stress echocardiography, stress MRI and calcium scoring with EBCT as initial diagnostic strategies for CAD at all levels of disease

prevalence modelled. Up to 40% CAD prevalence, multislice CT coronary angiography is the least cost non-extendedly dominated strategy. At 50%, multislice CT coronary angiography is the least cost strategy. And finally, from 60% to 70%, invasive coronary angiography is the least cost non-dominated or extendedly dominated strategy, and from 80% to 100% it is the least cost strategy.

Mowatt 2008 HTA (Mowatt, G., Cummins, E., Waugh, N. et al , 2008)

Aims and methods

Mowatt and colleagues (Mowatt, G., Cummins, E., Waugh, N. et al , 2008) conducted a systematic review of the literature to assess the cost-effectiveness of 64-slice CT coronary angiography compared with exercise ECG, MPS with SPECT and invasive coronary angiography in the investigation of CAD. A systematic review of the economic literature identified analyses relating to other strategies, but none had evaluated multislice CT coronary angiography. Therefore, cost-effectiveness was estimated, using a short-term diagnostic decision model, for a hypothetical cohort of 50 year old male patients with chest pain. In addition, a longer-term Markov model was constructed to explore the 25-year costs and consequences of diagnosis and misdiagnosis of suspected CAD.

The diagnostic tests were combined to produce eight strategies for patient assessment:

1. exercise ECG – SPECT
2. exercise ECG – CT – CA
3. exercise ECG – CA
4. SPECT – CA
5. CT – CA
6. CA alone
7. exercise ECG – CT

8. CT alone

Patients would move to the next test in the strategy if the first or subsequent test was positive or indeterminate. For strategies ending with 64-slice CT coronary angiography (strategies 7 and 8), it was assumed that any patients with indeterminate test results still go on to invasive coronary angiography. Patients would undergo no further testing if they received a negative test results at any stage in the diagnostic pathway. CAD prevalence was assumed to be 10% in the base case, but cost-effectiveness estimates were calculated for additional prevalence values of 30%, 50% and 70%. Whilst all eight strategies were evaluated in the short term decision model, only strategies 2, 3 and 7 were evaluated as part of the longer term model.

The short term diagnostic model included costs of diagnostic tests, with the longer term model including costs of initial tests, and the costs of treating CAD, including MI. The perspective was that of the NHS, currency was UK pounds, and prices were current (circa 2007/2008). Presented outputs of the short term model included costs, the number of true and false positives diagnosed and CAD-negative deaths. Outputs of the longer term model included total costs and total QALYs for strategies 2, 3 and 7. For the longer-term model only, a discount rate of 3.5% was applied to both costs and benefits.

Test sensitivity values for exercise ECG and MPS with SPECT were 67% and 86% respectively, whilst corresponding specificity values were 69% and 64%. Indeterminacy for exercise ECG and SPECT were modelled as 24% and 6%, respectively. 64-slice CT coronary angiography was assumed to be 99% sensitive, 89% specific and 2% indeterminate, based on the findings of their systematic review. Invasive coronary angiography was assumed to be the gold standard, and so 100% sensitivity and specificity were assumed. Each test carried a small risk of immediate death, 0.005% for exercise ECG and MPS with SPECT, 0% for 64-slice CT coronary angiography and 0.15% for invasive coronary angiography. Base case costs of exercise ECG, SPECT, 64-slice CT angiography and invasive coronary angiography were £66, £293, £206 and £320, respectively.

Results

Results for short-term diagnostic model

The authors present the results of their short-term diagnostic modelling as the total costs and consequences of each diagnostic strategy. These results are presented in Table 47 No incremental cost-effectiveness results were reported. In the base case, strategies involving 64-slice CT coronary angiography in place of MPS with SPECT are superior in all dimensions. However, as modelled CAD prevalence increases, the cost-savings of 64-slice CT coronary angiography compared to MPS with SPECT gradually reduce.

Table 47
Total costs and consequences of different diagnostic strategies

	Strategy 1 ECG-SPECT-CA	**Strategy 2** ECG-CT-CA	**Strategy 3** ECG-CA	**Strategy 4** SPECT-CA	**Strategy 5** CT-CA	**Strategy 6** CA	**Strategy 7** ECG-CT	**Strategy 8** CT
10% CAD Prevalence								
TPs	6.50	7.41	7.48	8.67	9.89	9.99	7.42	9.90
FPs	0.00	0.00	0.00	0.00	0.00	0.00	4.61	9.70
CAD-negative deaths	0.03	0.01	0.06	0.05	0.02	0.14	0.00	0.00
Cost	£28,876	£21,085	£22,695	£43,553	£27,449	£32,000	£17,283	£21,240
30% CAD Prevalence								
TPs	19.49	22.22	22.44	26.01	29.66	29.96	22.26	29.71
FPs	0.00	0.00	0.00	0.00	0.00	0.00	3.59	7.55
CAD-negative deaths	0.02	0.01	0.05	0.04	0.01	0.11	0.00	0.00
Cost	£33,430	£26,572	£24,446	£46,561	£32,969	£32,000	£18,445	£21,240
50% CAD Prevalence								
TPs	32.48	37.04	37.40	43.35	49.44	49.93	37.09	49.51
FPs	0.00	0.00	0.00	0.00	0.00	0.00	2.56	5.39
CAD-negative deaths	0.01	0.00	0.04	0.03	0.01	0.08	0.00	0.00
Cost	£37,985	£32,058	£26,197	£49,569	£38,488	£32,000	£19,607	£21,240
70% CAD Prevalence								
TPs	45.47	51.85	52.37	60.70	69.21	69.90	51.93	69.31
FPs	0.00	0.00	0.00	0.00	0.00	0.00	1.54	3.23
CAD-negative deaths	0.01	0.00	0.02	0.02	0.01	0.05	0.00	0.00
Cost	£42,539	£37,544	£27,948	£52,577	£44,007	£32,000	£20,770	£21,240

Adapted from Mowatt et al. 2008 (Mowatt, G., Cummins, E., Waugh, N. et al , 2008)

When CAD prevalence is low, the high specificity of 64-slice CT coronary angiography makes it a good test for ruling out disease in a high proportion of patients. However, as prevalence of CAD rises, the need to rule out patients decreases because a greater number of patients are referred on to invasive coronary angiography.

In terms of diagnostic accuracy, a strategy of sending all patients for immediate invasive coronary angiography performs better than any other strategy at all levels of CAD prevalence modelled. It is considerably better than strategies involving MPS with SPECT, but only marginally better than those involving 64-slice CT coronary angiography. 64-slice CT coronary angiography produces very few false negatives and as a result the number of additional true positives detected by the immediate invasive coronary angiography strategy is only marginally greater than those sent first for a 64-slice CT coronary angiography. The authors assert that given the assumed death rate of 0.15% for invasive coronary angiography, it may be that the avoidance of CAD-negative deaths from invasive coronary angiography may sufficiently outweigh the marginally fewer true positives detected by strategies involving 64-slice CT coronary angiography first.

Results of sensitivity analyses to assess uncertainty in the diagnostic model

The cost of invasive coronary angiography is uncertain and in the base case it was estimated to be £320 although another analysis used a cost of £1,556. A mid point estimate of £900 was used in sensitivity analysis. This has an effect most profoundly on the cost-effectiveness of strategies where 64-slice CT coronary angiography replaces invasive coronary angiography, but not much of an effect on those where 64-slice CT coronary angiography precedes invasive coronary angiography in the diagnostic pathway. To render strategies ending with 64-slice CT coronary angiography more expensive than those ending with invasive coronary angiography at 10% CAD prevalence, the additional cost of a false positive would have to be around £7,000. For CAD prevalence of 70% cost range of a false positive would have to be £20,000 to £30,000.

Uncertainty regarding effectiveness of 64-slice CT coronary angiography was dealt with in sensitivity analysis by using the lower confidence limit values for sensitivity (97% vs. 99% in the base case) and specificity (83% vs. 89% in the base case) for 64-slice CT coronary angiography. This change caused strategies which included 64-slice CT coronary angiography to perform slightly worse when set against those strategies where patients go straight to invasive coronary angiography, or to invasive coronary angiography after exercise ECG.

Results for longer-term model

The authors chose to explore the possible longer-term effects of diagnosis and misdiagnosis for CAD for the diagnostic strategies they felt had the greatest uncertainty around their relative cost-effectiveness: strategy 2 (exercise ECG-CT-CA), strategy 3 (exercise ECG-CA) and strategy 7 (exercise ECG-CT). Table 48 presents the outputs from the longer-term model, including total costs and total QALYs. The authors did not report any incremental cost-effectiveness results.

Table 48
Total costs and QALYs of diagnostic strategies included in longer-term modelling

	Strategy 2 ECG-CT-CA	**Strategy 3** ECG-CA	**Strategy 7** ECG-CT
10% CAD Prevalence			
Cost	£616,732	£618,196	£618,629
QALYs	1060.5	1060.0	1056.9
30% CAD Prevalence			
Cost	£642,800	£640,966	£639,186
QALYs	1005.2	1005.0	1002.6
50% CAD Prevalence			
Cost	£668,868	£663,736	£659,743
QALYs	949.9	949.9	948.3
70% CAD Prevalence			
Cost	£694,935	£686,506	£680,300
QALYs	894.6	894.9	894.0

Adapted from Mowatt et al. 2008 (Mowatt, G., Cummins, E., Waugh, N. et al , 2008)

Results of sensitivity analyses to assess uncertainty in the longer-term model

In the longer-term model higher costs for invasive coronary angiography increases the anticipated savings from using strategy 7 to around £300 per patient at 10% CAD prevalence and to around £450 per patient at 70% CAD prevalence. In the longer term model, lower values for sensitivity and specificity of 64-slice CT coronary angiography lead to a lower aggregate QALY for strategy 7. But given the tightness of the confidence intervals for sensitivity and specificity bounds, the impact of this is limited.

Summary and Discussion

64-slice CT coronary angiography appears to be superior to MPS with SPECT for the diagnosis of CAD in all clinical dimensions and also in terms of cost. The report concludes that the high sensitivity and negative predictive value of 64-slice CT coronary angiography suggest scope for avoiding unnecessary invasive coronary angiography in those referred for investigation but who do not have CAD. Given the small risk of death associated with invasive coronary angiography, 64-slice CT coronary angiography might also confer a small immediate survival advantage. Avoidance of unnecessary invasive coronary angiography may result in cost savings, even if positive results require confirmation by invasive coronary angiography. However, at higher CAD prevalence, these cost savings are likely to disappear.

The authors note from the results presented for their longer term cost-utility (QALY) model that the QALY differences are very small for the three strategies presented. Similarly small QALY differences have been demonstrated in other relevant modelling studies published during the development of this guideline. (Ladapo, J. A., Hoffmann, U., Bamberg, F. et al , 2009)(Khare, R. K., Courtney, D. M., Powell, E. S. et al , 2008).

The authors stop short of presenting incremental cost-utility analysis. Doing so would indicate that for the CAD prevalences modelled, strategies 2 (exercise ECG-CT-CA) and 3 (exercise ECG-CA) appear more cost-effective than strategy 7 (exercise ECG-CT). However, the results from the short term model

indicate these three strategies may be subject to dominance by other strategies that were not included in the longer-term analysis.

Also, the economic evaluation presented in the HTA did not present all of the outcomes of the two by two false/true, negative/positive matrix, notably the false negative rate, which could carry significant health implications for the patient.

5.2.4.2 Economic analysis of calcium scoring

The cost-effectiveness evidence identified in the health economic literature search covered most technologies used in the diagnosis of significant CAD. However, the GDG identified several areas where more evidence was needed. First, the GDG felt that the parameters used in the Mowatt 2008 HTA (Mowatt, G., Cummins, E., Waugh, N. et al , 2008) were overly optimistic for 64-slice CT coronary angiography and that the cost of invasive coronary angiography was unrealistically low. Second, the GDG was interested in looking at the role calcium scoring might play as a discrete step in a diagnostic pathway. In particular, they wished to examine the cost-effectiveness of two additional strategies beginning with calcium scoring, followed by 64-slice CT coronary angiography with and without a confirmatory invasive coronary angiography.

Consequently, with the cooperation of the developers of the original HTA model, a replica of the Mowatt 2008 short term diagnostic model was built, and an alternative set of incremental economic analysis based on the incremental cost per correct diagnosis is presented. The model was subsequently enhanced to include two more diagnostic strategy arms which incorporated the use of calcium scoring using 64-slice CT as a precursor to full 64-slice CT coronary angiography. The latter was investigated as a way of minimising the risk of radiation from 64-slice CT coronary angiography, a risk which was not explicitly incorporated into the existing model. The results of this analysis are summarised below; further details are reported in Appendix F.

Model inputs (summarised in Table 49) were gathered from a variety of sources including the economic literature previously presented, the clinical review, and expert opinion. The costing perspective was that of the NHS and currency was UK pounds. Model outputs were total diagnostic costs of each strategy and the proportion of patients correctly diagnosed. An incremental analysis was performed and results were presented as the additional cost per additional correct diagnosis of a strategy compared to the next most effective strategy. Results were estimated for varying levels of CAD prevalence: 5%, 20%, 40%, 60% and 80%.

Table 49

Test characteristics	Exercise ECG	MPS with SPECT	64-slice CT	Calcium Scoring	CA
Death Rate	0.005%	0.005%	0.001%	0.000%	0.020%
Indeterminacy	24%	6%	2%	2%	0%
Sensitivity	67%	86%	80%	89%	100%
Specificity	69%	64%	89%	43%	100%
Cost	£66	£293	£206*	£103	£850

*** The cost of calcium scoring is estimated to be 50% of the total cost of 64-slice CT coronary angiography. The cost of doing 64-slice CT coronary angiography following calcium scoring is the remaining 50% of the total cost of 64-slice CT coronary angiography. If 64-slice CT coronary angiography is done without calcium scoring as a discrete step in the diagnostic pathway, then 64-slice CT coronary angiography costs the full £206.**

A series of one way sensitivity analyses were also performed, each testing the robustness of the results to alternative assumptions about the sensitivity of 64-slice CT coronary angiography and threshold score used in calcium scoring.

Results of the base case analysis indicate that for lower risk groups (5% and 20%), the use of calcium scoring as a first line testing strategy is likely to be cost-effective and should be followed by either 64-slice CT coronary angiography alone or with additional invasive coronary angiography as a confirmatory 3rd test. In higher risk populations, (CAD prevalence greater than 40%), a strategy of sending all patients directly to invasive coronary angiography is likely to be cost-effective.

The model indicates that MPS with SPECT is excluded through dominance or extended dominance at every level of CAD prevalence. It also indicates that exercise ECG is only cost-effective as a first line investigation strategy at 5%

CAD prevalence, but that even in this instance replacing exercise ECG with calcium scoring is likely to improve effectiveness at a reasonable level of additional cost.

The sensitivity analysis shows that the overall results of the base case are relatively robust to the parameters varied. The only noteworthy change is that when a calcium score threshold of >100 is used (lower sensitivity and higher specificity than the base case), strategy 5 (CT-CA) becomes the likely cost-effective strategy at 20% CAD prevalence. This differs from the base case where the same strategy was unlikely to be cost-effective at this level of CAD prevalence (strategy 10 was likely to be most cost-effective at 20% CAD prevalence in base case).

All of the above analyses are based on assumptions about the diagnostic accuracy and costs of the five technologies included in the model. The validity of the outputs is clearly highly dependent on the appropriateness of the input assumptions.

5.2.4.3 Economic analysis of first line functional testing for angina

An economic model (presented above and detailed in Appendix F), built for this Guideline, and based on the model presented by Mowatt and colleagues (2008), *(Mowatt, G., Cummins, E., Waugh, N. et al , 2008)* has given support to use of anatomical imaging (64-slice CT coronary angiography preceded by calcium scoring in low risk CAD patients, and invasive coronary angiography in high risk patients) for patients presenting with stable chest pain.

This model was however predicated on diagnosis of CAD based on a threshold degree of stenosis (typically 50% or 70%) of the coronary arteries. The GDG indicated that the existing model may not be appropriate because for some patients, the degree of stenosis may not be unequivocal in respect of a clear rule-in or rule out for a diagnosis of angina. Furthermore, it is anticipated that this group of patients could constitute a relatively large group of patients in the context of the stable chest pain care pathway. The GDG believed that there was likely to be a role for first line functional testing for this group of patients, and requested that alternative economic model be built.

The details of the model and the economic analysis are presented in appendix F but are summarised here. The model evaluates the cost-effectiveness of first line functional testing using MPS with SPECT, compared to first line anatomical testing, in patients presenting with stable chest pain. Because the GDG was happy to make recommendations, based on the published evidence and the results of the existing model for the lowest and highest pre-test likelihood patient groups, this model only considers patient populations with pre-test likelihood of angina ranging from 20% to 60%.

Model Structure, Input, and Outputs

The model structure, which was developed with input from the GDG, is illustrated in a decision tree presented in Appendix F. There are two alternative treatment arms/pathways in the model: first line function testing using MPS with SPECT; and first line anatomical testing using invasive coronary angiography. The first branch of the decision tree allows for the possibility of an equivocal (uncertain) functional test result. Patients with an equivocal first line functional test result, go on to have a second line coronary angiogram, which is assumed to be 100% sensitive and specific with no equivocal outcomes. In the working base case it has been assumed that the sensitivity and specificity results for SPECT used in the Mowatt 2008 model (Mowatt, G., Cummins, E., Waugh, N. et al, 2008) are appropriate). The structure of the first line anatomical arm is effectively a replica of the first line functional arm, except that patients in this arm of the model have invasive coronary angiography as first line test (in a sensitivity analysis, invasive coronary angiography is replaced with 64-slice CT coronary angiography). The model allows for the possibility of a small proportion of patients having invasive coronary angiography to die from the procedure. Patients with an equivocal invasive coronary angiography result, go on to have a second line functional test (MPS with SPECT). The base case assumes all second line test results are unequivocal. The cost of MPS with SPECT (£293) in the base case is taken from the Mowatt 2008 HTA(Mowatt, G., Cummins, E., Waugh, N. et al , 2008). Base case cost of invasive coronary angiography is assumed to be £850 which approximates to an average cost quoted for invasive coronary angiography in recent publications. (*(Mowatt, G., Vale, L., Brazzelli,*

M. et al , 2004) (Sharples, L., Hughes, V., Crean, A. et al , 2007)(Sculpher, M., Smith, D., Clayton, T. et al , 2002), (Department of Health, 2008)). All base case input parameter values are presented in Table **Error! Reference source not found.**.

Table 50		
Test characteristics	MPS	CA
Death Rate	0.000%	0.020%
Indeterminacy	6.00%	Pt%
Sensitivity	86%	100%
Specificity	64%	100%
Cost	£293	£850

For a given prevalence (pre-test likelihood) of CAD in the modelled population, the model then calculates the expected number of true positive (TP), true negative (TN), false positive (FP), and false negative (FN) results based on the assumed test sensitivities and specificities for both arms of the model.

Methods of Analysis

Our literature search did not identify the proportion of stable chest pain patients likely to have an equivocal invasive coronary angiography result for diagnosis of angina. As such, the model has been used to identify the threshold proportion (Pt) of equivocal 64-slice CT coronary angiography results. That is, the threshold at which decision makers are likely to be indifferent between first line functional and first line anatomical testing. Our analysis assumes a threshold willingness to pay of £20,000 per proportion of cases correctly diagnosed as previous analysis has indicated that this may be a reasonable proxy for the cost per QALY ICER (see appendix for details). Having identified the threshold proportion of equivocal invasive coronary angiography results (Pt), if decision makers believe that the likely proportion of equivocal invasive coronary angiography results (p) is higher than the identified threshold value (Pt) estimated by the model, then the model

indicates that first line functional testing is likely to be cost-effective compared to first line anatomical testing and vice versa.

Results

Base Case

In a base case scenario in which the pre-test likelihood of CAD is assumed to be 50%, the model indicates that first line MPS with SPECT is the least cost of the two modelled options, costing £344,000 per 1,000 patients. 76.5% of patients would get a correct diagnosis. Assuming that invasive coronary angiography is 100% accurate and unequivocal, then the modelled cost of the first line coronary angiography treatment arm is £850,000. The incremental cost per proportion of patients correctly diagnosed is £21,549. Given that this is an optimistic scenario for invasive coronary angiography, the model indicates that use of first line invasive coronary angiography does not look cost-effective compared with first line functional testing.

Sensitivity on Pre-test likelihood

The following table presents the resulting modelled threshold value of indifference, for the proportion of equivocal invasive coronary angiography stenoses (Pt), for a range of assume prevalence assumptions. As the pre-test likelihood rises from 20% to 40%, the model indicates that the proportion of equivocal invasive coronary angiography results would have to be less than 9.5% (20% pre-test likelihood) and less than 0.6% (40% pre-test likelihood) for first line anatomical testing using invasive coronary angiography to have an ICER below £20,000. This analysis assumes that invasive coronary angiography is 100% accurate for the test results deemed to be unequivocal.

Pre-test Likelihood	20%	30%	40%	50%
Pt	9.5%	5.3%	0.6%	N/A

Sensitivity replacing invasive coronary angiography with 64-slice CT coronary angiography

Previous modelling presented in this guideline has indicated that first line 64-slice CT coronary angiography is a cost-effective diagnostic testing strategy for low pre-test likelihood populations. A sensitivity analysis using the current model was created, assuming a pre-test likelihood of 20%, and substituting invasive coronary angiography with 64-slice CT coronary angiography. Test characteristic assumptions used for 64-slice CT coronary angiography, were those used in the previous model (Table **Error! Reference source not found.**).

Table 51	
Test characteristics	64CT
Death Rate	0.00125%
Indeterminacy	2%
Sensitivity	0.8
Specificity	0.89
Cost	£206

In this scenario, first line anatomical testing using 64-slice CT coronary angiography dominates first line functional testing using MPS with SPECT, that is, 64-slice CT coronary angiography costs less, (£212,800 per thousand patients compared with £305,360 respectively), and produces a greater proportion of accurately diagnosed patients (86.9% versus 69.5%). For first line testing using 64-slice CT coronary angiography not to be considered cost-effective compared to first line functional testing in this scenario, (using a £20,000 per proportion correctly diagnosed decision threshold), the model estimates that more than 74% of the 64-slice CT coronary angiography results would have to give an equivocal result.

Summary and Discussion

A model comparing first line functional testing, (using MPS with SPECT), with first line anatomical testing using invasive coronary angiography, for patient groups with an intermediate pre-test likelihood (20%-50%) was built for this Guideline. For pre-test likelihoods of 30% to 50%, the model indicated that first line functional testing is the least costly testing strategy. In a base case scenario using a pre-test likelihood of 50%, the estimated ICER for invasive coronary angiography is above £21,500 per proportion of cases correctly diagnosed compared to first line functional testing. Above 30% pre-test likelihood, invasive coronary angiography would have to provide 100% sensitivity and specificity, and an uncertainty proportion better than 5.3% for it likely to be considered cost-effective compared to first line functional testing. The model also lent further to support to the use of 64-slice CT coronary angiography in low risk stable chest pain populations. For a pre-test likelihood of 20%, the model indicated that first line testing using 64-slice CT coronary angiography dominated first line functional testing (that is, more accurate and less costly).

The model results appear robust to sensitivity analysis. We used best case estimates for the sensitivity and specificity of invasive coronary angiography, and relatively conservative estimates of the test accuracy of 64-slice CT coronary angiography. The former cannot be improved upon, and the latter would have to deteriorate substantially in order to change the conclusions of the economic analysis. The evidence appears to indicate that our base case estimate of £850 may be at the lower end of the likely cost estimate distribution. This lends further support to our conclusions regarding the relative cost-effectiveness of first line functional testing compared to first line invasive coronary angiography. Given that the Sharples HTA(Sharples, L., Hughes, V., Crean, A. et al , 2007) indicated that MPS with SPECT, stress echocardiography, and stress MR perfusion imaging were not significantly different from each other in terms of costs and QALY outcomes, we would probably have reached similar conclusions had we modelled stress echocardiography or stress MR perfusion imaging to represent functional testing.

Partly because of the diagnostic boundary to the scope of the Guideline, the economic analysis undertaken for the Guideline has been confined to the modelling of the shorter term cost and diagnostic outcomes. There is some evidence that longer term cost per QALY modelling, as well as adding a not inconsiderable amount of complexity and uncertainty, may not have added much value in term of information for decision makers. This is discussed at greater length in Appendix F. Future research in this area may wish to address the longer term economic and health implications of these and emerging technologies in the diagnosis and treatment of patients presenting with chest pain.

5.2.5 Evidence to recommendations

Patients may be diagnosed with angina following clinical assessment without the need for further diagnostic investigations and in which case they should be managed as recommended in angina guidelines. Similarly those with non cardiac chest pain may be diagnosed following clinical assessment, and alternative explanations other than angina should be explored. However, in many patients with chest pain of suspected cardiac origin there will still be uncertainty about the cause of the chest pain following the clinical assessment and these patients require further diagnostic investigation.

The GDG recognised that the diagnostic tests were either anatomical tests which identified if there were luminal narrowings in the coronary arteries leading to reduced coronary blood flow, or functional tests which identify myocardial ischaemia. The diagnostic performance of such tests has often been evaluated in patient groups selected by healthcare setting or predetermined management plan such as referral for coronary angiography, rather than pre-test likelihood of CAD and no studies were found which examined diagnostic performance by the pre-test likelihood of disease. The GDG acknowledged that the evidence which has informed the recommendations has been translated into these more defined populations, with the assumption that the performance of the test is comparable to that in the published study populations, and between populations with different levels of pre-test likelihood of having CAD. In addition most studies have reported

sensitivity and specificity of single diagnostic tests in patients with chest pain without giving information on the incremental value of additional testing if an initial test has not established the diagnosis.

Systematic reviews were identified to determine the diagnostic performance of the tests under examination. The systematic reviews identified were mostly conducted in the last 3 years, facilitating detailed examination of the most up to date meta-analyses which identified the prior individual diagnostic studies. Across all reviews over 600 diagnostic studies were considered in meta-analyses. Within these systematic reviews, heterogeneity in the meta-analyses was almost universally reported and attributed to a number of factors such as; patient inclusion and exclusion criteria populations, small number of patients in diagnostic study cohorts differences in the prevalence of CAD in the studies meta-analyzed, and the inclusion and meta-analysis of studies with varying definitions of CAD (which ranged from > 50% to > 75% coronary artery stenosis). While acknowledging these caveats, the quality of the methodology of the identified systematic reviews themselves was predominantly excellent, with comprehensive identification of relevant diagnostic studies and diagnostic performance to inform the GDG in developing recommendations.

The clinical assessment of patients with chest pain estimates the pre-test likelihood of CAD, rather than angina. However, the GDG agreed that in the majority of patients angina is due to CAD, with the caveat that other causes should be considered in patients with typical angina if flow limiting disease in the epicardial coronary arteries has been excluded. A review of the evidence for this was not undertaken, but possible causes include for example small vessel disease, cardiomyopathy, and aortic stenosis (aortic stenosis in particular though will usually be a suspected clinical diagnosis during the initial clinical assessment). The GDG examined the evidence for the most appropriate diagnostic testing strategy depending on a patient's pre-test likelihood from the initial clinical assessment and resting 12 lead ECG. However, it was accepted that the pre-test likelihood was based on evidence from older publications, and there was a lack of precision of the point

estimates for the prevalence of CAD. The recommended thresholds are to help guide clinical decision making, not dictate clinical decision making. It was also acknowledged that some patients might have absolute or relative contra-indications to particular investigations that must be taken into account.

In those with the highest pre-test likelihood, evidence was found that invasive coronary angiography without any other prior non-invasive diagnostic testing was most the cost-effective strategy in this group, and based on this health economic evidence and clinical consensus, the GDG considered that patients with a high pre-test likelihood of CAD (> 60%) should be offered invasive coronary angiography rather than non-invasive functional imaging or multislice CT coronary angiography, providing invasive testing was clinically appropriate, acceptable to the patient, and coronary revascularisation would be considered. Not all patients will wish to have invasive coronary angiography though, and in some it may not be appropriate, and the GDG debated which investigation is preferred in these patients. The health economic evidence had found that 64 slice CT coronary angiography was more cost-effective than MPS with SPECT in diagnosing CAD over a range of pre-test probability of CAD (10-70%). This analysis was done using a high sensitivity and specificity for diagnosing CAD with 64 slice CT coronary angiography and all patients with a positive or indeterminate result had invasive coronary angiography. However, these patients that the GDG were discussing are most likely to have CAD, and 64 slice CT coronary angiography is less accurate in assessing the severity of CAD, as opposed to diagnosing the presence of CAD, and thus the functional significance of disease may be uncertain. The GDG concluded that 64 slice CT coronary angiography would demonstrate whether patients had CAD, but may be less accurate in demonstrating the severity of this, and therefore a functional imaging test could also be considered. Invasive coronary angiography would still be needed if revascularisation were later being considered, irrespective of which investigation was used. The GDG acknowledged that there have been significant improvements in the resolution of CT imaging at the artery level with improvements in technology, from 4 to 16 slice to 64 slice and above, and emphasised that multislice CT coronary angiography should be with 64 slice

or above. It is also expected that there will be further improvements in CT image resolution in the future which may lead to improvements in the accuracy of assessment of the severity of coronary stenoses.

Evidence was found from published economic analysis that in patients with a moderate pre-test likelihood of CAD, 64 slice CT coronary angiography was cost-effective compared with MPS with SPECT. However, the GDG felt from their clinical experience that a first line functional test was more efficient and that the economic model did not reflect this at it was predicated on being able to diagnose CAD (not angina specifically) based on the degree of stenosis seen on anatomical testing. Anatomical testing might find intermediate coronary lesions of uncertain functional significance, making it difficult to interpret if this was the cause of the chest pain. Hence the assumption that invasive coronary angiography is 100% sensitive and specific was not valid. The use of functional imaging in patients with a lower pre-test likelihood of CAD is also consistent with the MPS TAG which states that MPS with SPECT is recommended as part of an investigational strategy for the diagnosis of suspected CAD in people with a lower likelihood of CAD.

Further health economic modelling was requested by the GDG in this group, and found that for the range of pre-test likelihood of 30% to 50%, the model indicated that first line functional testing is the least cost testing strategy. The GDG accepted this analysis, and were of the opinion that the pre-test likelihood above which invasive coronary angiography should be recommended as first line was greater than 60%. When the pre-test likelihood was 20%, 64 slice CT coronary angiography dominates first line functional testing and the GDG agreed that the threshold of CAD prevalence at which 64 slice coronary CT angiography was the preferred first line testing strategy was less than 30%. The GDG also appraised the evidence for MR coronary angiography, but found that its lower sensitivity favoured the use of 64 slice (or above) CT coronary angiography.

Exercise ECG may be considered as a functional test and the GDG acknowledged that this is often used as the first line diagnostic test in current clinical practice. However, the overall diagnostic performance of exercise

ECG in the diagnosis of CAD was not of sufficient accuracy for the GDG to recommend this in patients with no prior history of CAD, particularly when taking into account the better performance of the available functional imaging tests which the GDG recommended in preference. Evidence from the health economic studies was consistent with this.

Various functional imaging modalities are available and MPS with SPECT, stress echocardiography, first pass contrast enhanced MR perfusion or MR imaging for stress induced wall motion abnormalities were all considered. However, the diagnostic performance for diagnosing CAD did not support the use of one functional imaging test in preference to another and the GDG concluded that the tests were generally comparable and any could be used. The GDG noted that the diagnostic performance of non-invasive testing decreased with increasing year of publication, possibly due to the initial reporting of diagnostic performance being in highly selected patients, and with stringent analysis of results. Further studies and everyday clinical practice may be in more diverse populations, and the thresholds for the interpretation of tests may be lower. The treatment of indeterminate results of tests may also be analysed differently and or inadequately. It is known that imaging modalities may have limitations in some patients and for example, in patients with poor acoustic windows for echocardiography, MPS with SPECT or MR based imaging will be preferred, whereas in those with claustrophobia MR based imaging will be avoided. The choice of imaging modality will not only be determined by patients' characteristics, but also by whether a particular functional imaging test is available locally, with the appropriate expertise for interpretation.

In patients with a low pre-test likelihood of CAD diagnostic testing is only required if there is remaining concern following clinical assessment that the pain may be cardiac in origin, and then it will generally be to rule out CAD. Health economic analysis found that 64 slice (or above) CT coronary angiography was cost-effective compared with MPS with SPECT. However, the GDG had some concerns about the radiation exposure associated with CT coronary angiography, particularly as patients in this group are more likely to

be younger and women with the risk of breast irradiation. A coronary calcium score can help discriminate between those with and without CAD. It can be obtained in all patients having 64 slice (or above) CT coronary angiography, and can also be done without proceeding to angiography, with reduced imaging time required and with far less radiation exposure. The GDG felt that an initial coronary calcium score could be used prior to 64 slice (or above) CT coronary angiography and discriminate those who may still have CAD from those who do not, with anatomical testing only being needed in those who might. Additional health economic analysis was requested to look at this further. This analysis concluded that for lower risk groups, the use of coronary calcium scoring as a first line testing strategy is likely to be cost-effective, followed by either 64 slice (or above) CT coronary angiography alone or with additional invasive coronary angiography.

A coronary calcium score of zero is highly sensitive for ruling out CAD and it was acknowledged that low scores, which are not zero, are also highly sensitive. The GDG debated the inclusion of a higher coronary calcium score to rule out CAD to minimise the number of patients requiring 64 slice (or above) CT coronary angiography with the attendant costs and risks, including being exposed to a higher radiation dose. They accepted that those with a coronary calcium score in single figures had a high sensitivity for excluding CAD, but were concerned that there was no good evidence to inform what the upper threshold should be, and that once the score was > 0, the variability of the test results was more. All test results are interpreted in the context of the clinical assessment of the patient, but the GDG also accepted that the logistics of testing, meant that a recommendation to review the coronary calcium score in the context of the history was not practical as CT coronary angiography immediately follows coronary calcium scoring rather than being a separate test done at a different time. The GDG erred on the side of caution, and maintained the recommendation to use a coronary calcium score of > 0 for the threshold to proceed to angiography, and included a research recommendation that this was an area for further evaluation for both clinical and cost-effectiveness. It was recognised there is little evidence for coronary calcium scoring in South Asian populations, but any differences may be due to

differences in baseline likelihood of CAD rather than a differential performance of the test by ethnicity, and pre-test likelihood, not ethnicity should be used to determine test strategy.

The GDG further debated the testing strategy when the coronary calcium score is above zero. The diagnostic performance of multislice CT coronary angiography in being able to identify if coronary stenoses are significant decreases as the coronary calcium score increases, and this is particularly so with extreme coronary calcification (coronary calcium score above 400). Thus in patients with a calcium score > 0, the GDG agreed to recommend invasive coronary angiography if the calcium score was greater than 400, and 64 slice (or above) CT coronary angiography if the coronary calcium score was 1 to ≤ 400.

Many patients with chest pain of suspected cardiac origin in each of the pre-test likelihood groups will be diagnosed with either angina or non cardiac chest pain following the initial diagnostic strategy. However, in some patients, uncertainty about the cause of the chest pain may still remain and in which case additional testing will be required. The GDG agreed that if the functional significance of coronary artery stenoses found during invasive coronary angiography or 64 slice (or above) CT coronary angiography was uncertain functional testing for myocardial ischaemia was required. Similar testing will also be required in patients with known CAD with chest pain of suspected cardiac origin, but in whom the diagnosis of angina is not secure. Any of the non-invasive functional imaging tests could be used, and the GDG reconsidered whether exercise ECG might be used in this group. The GDG had excluded exercise ECG as a primary diagnostic test in favour of functional imaging due to the relatively poor diagnostic performance of the exercise ECG to diagnose CAD. However, in patients with established CAD, and in whom further testing was to assess functional capacity and the presence of myocardial ischaemia, exercise ECG might be considered, providing patients were able to exercise adequately and there were no baseline ECG abnormalities which would make interpretation inaccurate. However, the GDG felt that functional imaging was likely to be preferred particularly in selected

patient groups in whom exercise ECG poses particular problems of poor sensitivity (such as in women), in those after MI or coronary reperfusion (reference to the MPS TAG) and when evaluation of the coronary territory of myocardial ischaemia, not only presence of ischaemia, is required.

Patients with chest pain of suspected cardiac origin may have indeterminate results from functional imaging undertaken as the first line diagnostic test and such patients will also require further testing. Clinical consensus was for an anatomical test, not a different functional imaging test, and that was with invasive coronary angiography.

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