Chest pain of recent onset:

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

Full Guideline

Final Draft - January 2010

National Clinical Guideline Centre for Acute and Chronic Conditions

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Key Priorities for Implementation

Presentation with acute chest pain

- Take a resting 12-lead electrocardiogram (ECG) as soon as possible. When people are referred, send the results to hospital before they arrive if possible. Recording and sending the ECG should not delay transfer to hospital. **[1.2.2.1]**
- Do not exclude an acute coronary syndrome (ACS) when people have a normal resting 12-lead ECG. **[1.2.2.5]**
- Do not routinely administer oxygen, but monitor oxygen saturation using pulse oximetry as soon as possible, ideally before hospital admission. Only offer supplemental oxygen to:
    - people with oxygen saturation (SpO_2) of less than 94% who are not at risk of hypercapnic respiratory failure, aiming for SpO_2 of 94–98%
    - people with chronic obstructive pulmonary disease who are at risk of hypercapnic respiratory failure, to achieve a target SpO_2 of 88–92% until blood gas analysis is available. **[1.2.3.3]**
- Do not assess symptoms of an ACS differently in ethnic groups. There are no major differences in symptoms of an ACS among different ethnic groups. **[1.2.1.6]**

Presentation with stable chest pain

- Diagnose stable angina based on one of the following:
    - clinical assessment alone **or**
    - clinical assessment plus diagnostic testing (that is, anatomical testing for obstructive coronary artery disease (CAD) and/or functional testing for myocardial ischaemia). **[1.3.1.1]**
- If people have features of typical angina based on clinical assessment and their estimated likelihood of CAD is greater than 90% (see table 1), further diagnostic investigation is unnecessary. Manage as angina. **[1.3.3.5]**
- Unless clinical suspicion is raised based on other aspects of the history and risk factors, exclude a diagnosis of stable angina if the pain is non-anginal

(see recommendation 1.3.3.1). Other features which make a diagnosis of stable angina unlikely are when the chest pain is:

- continuous or very prolonged **and/or**
- unrelated to activity **and/or**
- brought on by breathing in **and/or**
- associated with symptoms such as dizziness, palpitations, tingling or difficulty swallowing.

Consider causes of chest pain other than angina (such as gastrointestinal or musculoskeletal pain). **[1.3.3.6]**

- In people without confirmed CAD, in whom stable angina cannot be diagnosed or excluded based on clinical assessment alone, estimate the likelihood of CAD (see table 1). Take the clinical assessment and the resting 12-lead ECG into account when making the estimate. Arrange further diagnostic testing as follows:
    - If the estimated likelihood of CAD is 61–90%, offer invasive coronary angiography as the first-line diagnostic investigation if appropriate (see recommendations 1.3.4.4 and 1.3.4.5).
    - If the estimated likelihood of CAD is 30–60%, offer functional imaging as the first-line diagnostic investigation (see recommendation 1.3.4.6).
    - If the estimated likelihood of CAD is 10–29%, offer CT calcium scoring as the first-line diagnostic investigation (see recommendation 1.3.4.7). **[1.3.3.16]**
- Do not use exercise ECG to diagnose or exclude stable angina for people without known CAD. **[1.3.6.5]**

All Recommendations

(Numbers correspond to NICE guideline)

1.1 Providing information for people with chest pain

Hyperlink to Information Chapter

1.1.1.1 Discuss any concerns people (and where appropriate their family or carer/advocate) may have, including anxiety when the cause of the chest pain is unknown. Correct any misinformation.

1.1.1.2 Offer people a clear explanation of the possible causes of their symptoms and the uncertainties.

1.1.1.3 Clearly explain the options to people at every stage of investigation. Make joint decisions with them and take account of their preferences:

- Encourage people to ask questions.
- Provide repeated opportunities for discussion.
- Explain test results and the need for any further investigations.

1.1.1.4 Provide information about any proposed investigations using everyday, jargon-free language. Include:

- their purpose, benefits and any limitations of their diagnostic accuracy
- duration
- level of discomfort and invasiveness
- risk of adverse events.

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

1.1.1.6 Address any physical or learning difficulties, sight or hearing problems and difficulties with speaking or reading English, which may affect people's understanding of the information offered.

1.1.1.7 Offer information after diagnosis as recommended in the relevant disease management guidelines[1].

1.1.1.8 Explain if the chest pain is non-cardiac and refer people for further investigation if appropriate.

1.1.1.9 Provide individual advice to people about seeking medical help if they have further chest pain.

1.2 People presenting with acute chest pain

This section of the guideline covers the assessment and diagnosis of people with recent acute chest pain or discomfort, suspected to be caused by an acute coronary syndrome (ACS). The term ACS covers a range of conditions including unstable angina, ST-segment-elevation myocardial infarction (STEMI) and non-ST-segment-elevation myocardial infarction (NSTEMI).

The guideline addresses assessment and diagnosis irrespective of setting, because people present in different ways. Please note that 'Unstable angina and NSTEMI' (NICE clinical guideline XX) covers the early management of these conditions once a firm diagnosis has been made and before discharge from hospital.

1.2.1 Initial assessment and referral to hospital

Hyperlink to evidence statements on initial assessment

1.2.1.1 Check immediately whether people currently have chest pain. If they are pain free, check when their last episode of pain was, particularly if they have had pain in the last 12 hours.

1.2.1.2 Determine whether the chest pain may be cardiac and therefore whether this guideline is relevant, by considering:

[1] For example, 'Unstable angina and NSTEMI' (NICE clinical guideline X), 'Anxiety' (NICE clinical guideline 22) and 'Dyspepsia' (NICE clinical guideline 17).

- the history of the chest pain
- the presence of cardiovascular risk factors
- history of ischaemic heart disease and any previous treatment
- previous investigations for chest pain.

1.2.1.3 Initially assess people for any of the following symptoms, which may indicate an ACS:

- pain in the chest and/or other areas (for example, the arms, back or jaw) lasting longer than 15 minutes
- chest pain associated with nausea and vomiting, marked sweating, breathlessness, or particularly a combination of these
- chest pain associated with haemodynamic instability
- new onset chest pain, or abrupt deterioration in previously stable angina, with recurrent chest pain occurring frequently and with little or no exertion, and with episodes often lasting longer than 15 minutes.

1.2.1.4 Do not use people's response to glyceryl trinitrate (GTN) to make a diagnosis.

Hyperlink to evidence statements on gender differences

1.2.1.5 Do not assess symptoms of an ACS differently in men and women. Not all people with an ACS present with central chest pain as the predominant feature.

1.2.1.6 Do not assess symptoms of an ACS differently in ethnic groups. There are no major differences in symptoms of an ACS among different ethnic groups.

1.2.1.7 Refer people to hospital as an emergency if an ACS is suspected (see recommendation 1.2.1.3) and:

- they currently have chest pain **or**
- they are currently pain free, but had chest pain in the last 12 hours, and a resting 12-lead ECG is abnormal or not available.

1.2.1.8 If an ACS is suspected (see recommendation 1.2.1.3) and there are no reasons for emergency referral, refer people for urgent same-day assessment if:

- they had chest pain in the last 12 hours, but are now pain free with a normal resting 12-lead ECG **or**
- the last episode of pain was 12–72 hours ago.

1.2.1.9 Refer people for assessment in hospital if an ACS is suspected (see recommendation 1.2.1.3) and:

- the pain has resolved **and**
- there are signs of complications such as pulmonary oedema.

Use clinical judgement to decide whether referral should be as an emergency or urgent same-day assessment.

1.2.1.10 If a recent ACS is suspected in people whose last episode of chest pain was more than 72 hours ago and who have no complications such as pulmonary oedema:

- carry out a detailed clinical assessment (see recommendations 1.2.4.2 and 1.2.4.3)
- confirm the diagnosis by resting 12-lead ECG and blood troponin level
- take into account the length of time since the suspected ACS when interpreting the troponin level.

Use clinical judgement to decide whether referral is necessary and how urgent this should be.

1.2.1.11 Refer people to hospital as an emergency if they have a recent (confirmed or suspected) ACS and develop further chest pain.

1.2.1.12 When an ACS is suspected, start management immediately in the order appropriate to the circumstances (see section 1.2.3) and take

a resting 12-lead ECG (see section 1.2.2). Take the ECG as soon as possible, but do not delay transfer to hospital.

1.2.1.13 If an ACS is not suspected, consider other causes of the chest pain, some of which may be life-threatening (see recommendations 1.2.6.5, 1.2.6.6 and 1.2.6.7).

1.2.2 Resting 12-lead ECG

Hyperlink to evidence statements on ECG

1.2.2.1 Take a resting 12-lead ECG as soon as possible. When people are referred, send the results to hospital before they arrive if possible. Recording and sending the ECG should not delay transfer to hospital.

1.2.2.2 Follow local protocols for people with a resting 12-lead ECG showing regional ST-segment elevation or presumed new left bundle branch block (LBBB) consistent with an acute STEMI until a firm diagnosis is made. Continue to monitor (see recommendation 1.2.3.4).

1.2.2.3 Follow 'Unstable angina and NSTEMI' (NICE clinical guideline XX) for people with a resting 12-lead ECG showing regional ST-segment depression or deep T wave inversion suggestive of a NSTEMI or unstable angina until a firm diagnosis is made. Continue to monitor (see recommendation 1.2.3.4).

1.2.2.4 Even in the absence of ST-segment changes, have an increased suspicion of an ACS if there are other changes in the resting 12-lead ECG, specifically Q waves and T wave changes. Consider following 'Unstable angina and NSTEMI' (NICE clinical guideline XX) if these conditions are likely. Continue to monitor (see recommendation 1.2.3.4).

1.2.2.5 Do not exclude an ACS when people have a normal resting 12-lead ECG.

1.2.2.6 If a diagnosis of ACS is in doubt, consider:

- taking serial resting 12-lead ECGs
- reviewing previous resting 12-lead ECGs
- recording additional ECG leads.

Use clinical judgement to decide how often this should be done. Note that the results may not be conclusive.

1.2.2.7 Obtain a review of resting 12-lead ECGs by a healthcare professional qualified to interpret them as well as taking into account automated interpretation.

1.2.2.8 If clinical assessment (as described in recommendation 1.2.1.10) and a resting 12-lead ECG make a diagnosis of ACS less likely, consider other acute conditions. First consider those that are life-threatening such as pulmonary embolism, aortic dissection or pneumonia. Continue to monitor (see recommendation 1.2.3.4).

1.2.3 Immediate management of a suspected acute coronary syndrome

Management of ACS should start as soon as it is suspected, but should not delay transfer to hospital. The recommendations in this section should be carried out in the order appropriate to the circumstances.

Hyperlink to evidence statements on pain management

1.2.3.1 Offer pain relief as soon as possible. This may be achieved with GTN (sublingual or buccal), but offer intravenous opioids such as morphine, particularly if an acute myocardial infarction (MI) is suspected.

Hyperlink to evidence statements on antiplatelet therapy

1.2.3.2 Offer people a single loading dose of 300 mg aspirin as soon as possible unless there is clear evidence that they are allergic to it.

If aspirin is given before arrival at hospital, send a written record that it has been given with the person.

Only offer other antiplatelet agents in hospital. Follow appropriate guidance ('Unstable angina and NSTEMI' [NICE clinical guideline XX] or local protocols for STEMI).

Hyperlink to evidence statements on oxygen therapy

1.2.3.3 Do not routinely administer oxygen, but monitor oxygen saturation using pulse oximetry as soon as possible, ideally before hospital admission. Only offer supplemental oxygen to:

- people with oxygen saturation (SpO_2) of less than 94% who are not at risk of hypercapnic respiratory failure, aiming for SpO_2 of 94–98%
- people with chronic obstructive pulmonary disease who are at risk of hypercapnic respiratory failure, to achieve a target SpO_2 of 88–92% until blood gas analysis is available.

1.2.3.4 Monitor people with acute chest pain, using clinical judgement to decide how often this should be done, until a firm diagnosis is made. This should include:

- exacerbations of pain and/or other symptoms
- pulse and blood pressure
- heart rhythm
- oxygen saturation by pulse oximetry
- repeated resting 12-lead ECGs **and**
- checking pain relief is effective.

1.2.3.5 Manage other therapeutic interventions using appropriate guidance ('Unstable angina and NSTEMI' [NICE clinical guideline XX] or local protocols for STEMI).

1.2.4 Assessment in hospital for people with a suspected acute coronary syndrome

Hyperlink to evidence statements on assessment

1.2.4.1 Take a resting 12-lead ECG and a blood sample for troponin I or T measurement (see section 1.2.5) on arrival in hospital.

1.2.4.2 Carry out a physical examination to determine:

- haemodynamic status
- signs of complications, for example pulmonary oedema, cardiogenic shock **and**
- signs of non-coronary causes of acute chest pain, such as aortic dissection.

1.2.4.3 Take a detailed clinical history unless a STEMI is confirmed from the resting 12-lead ECG (that is, regional ST-segment elevation or presumed new LBBB). Record:

- the characteristics of the pain
- other associated symptoms
- any history of cardiovascular disease
- any cardiovascular risk factors **and**
- details of previous investigations or treatments for similar symptoms of chest pain.

1.2.5 Use of biochemical markers for diagnosis of an acute coronary syndrome

Hyperlink to evidence statements on biomarkers

1.2.5.1 Take a blood sample for troponin I or T measurement on initial assessment in hospital. These are the preferred biochemical markers to diagnose acute MI.

1.2.5.2 Take a second blood sample for troponin I or T measurement 10–12 hours after the onset of symptoms.

1.2.5.3 Do not use biochemical markers such as naturetic peptides and high sensitivity C-reactive protein to diagnose an ACS.

1.2.5.4 Do not use biochemical markers of myocardial ischaemia (such as ischaemia-modified albumin) as opposed to markers of necrosis when assessing people with acute chest pain.

1.2.5.5 Take into account the clinical presentation, the time from onset of symptoms and the resting 12-lead ECG findings when interpreting troponin measurements.

1.2.6 Making a diagnosis

1.2.6.1 When diagnosing MI, use the universal definition of myocardial infarction[2]. This is the detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit, together with evidence of myocardial ischaemia with at least one of the following:

- symptoms of ischaemia
- ECG changes indicative of new ischaemia (new ST-T changes or new LBBB)
- development of pathological Q wave in the ECG
- imaging evidence of new loss of viable myocardium or new regional wall motion abnormality[3].

The clinical classification of MI includes:

- Type 1: spontaneous MI related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring or dissection.

[2] Thygesen K, Alpert JS, White HD et al. on behalf of the joint ESC/ACCF/AHA/WHF Task Force for the redefinition of myocardial infarction (2007). Universal definition of myocardial infarction. Journal of the American College of Cardiology 50:2173–2195.

[3] The Guideline Development Group did not review the evidence for the use of imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in the diagnosis of MI, but recognised that it was included as a criterion in the universal definition of MI. The Guideline Development Group recognised that it could be used, but would not be done routinely when there were symptoms of ischaemia and ECG changes.

- Type 2: MI secondary to ischaemia due to either increased oxygen demand or decreased supply, such as coronary spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension.

1.2.6.2 When a raised troponin level is detected in people with a suspected ACS, reassess to exclude other causes for raised troponin (for example, myocarditis, aortic dissection or pulmonary embolism) before confirming the diagnosis of ACS.

1.2.6.3 When a raised troponin level is detected in people with a suspected ACS, follow the appropriate guidance ('Unstable angina and NSTEMI' [NICE clinical guideline XX] or local protocols for STEMI) until a firm diagnosis is made. Continue to monitor (see recommendation 1.2.3.4).

1.2.6.4 When a diagnosis of ACS is confirmed, follow the appropriate guidance ('Unstable angina and NSTEMI' [NICE clinical guideline XX] or local protocols for STEMI).

1.2.6.5 Reassess people with chest pain without raised troponin levels (determined from appropriately timed samples) and no acute resting 12-lead ECG changes to determine whether their chest pain is likely to be cardiac.

If myocardial ischaemia is suspected, follow the recommendations on stable chest pain in this guideline (see section 1.3). Use clinical judgement to decide on the timing of any further diagnostic investigations.

1.2.6.6 Consider a chest X-ray to help exclude complications of ACS such as pulmonary oedema, or other diagnoses such as pneumothorax or pneumonia.

1.2.6.7 Only consider early chest computed tomography (CT) to rule out other diagnoses such as pulmonary embolism or aortic dissection, not to diagnose ACS.

1.2.6.8 If an ACS has been excluded at any point in the care pathway, 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).

1.3 People presenting with stable chest pain

This section of the guideline addresses the assessment and diagnosis of intermittent stable chest pain in people with suspected stable angina.

Angina is usually caused by coronary artery disease (CAD). Making a diagnosis of stable angina caused by CAD in people with chest pain is not always straightforward, and the recommendations aim to guide and support clinical judgement. Clinical assessment alone may be sufficient to confirm or exclude a diagnosis of stable angina, but when there is uncertainty, additional diagnostic testing (functional or anatomical testing) guided by the estimates of likelihood of coronary artery disease in table 1, is required.

1.3.1.1 Diagnose stable angina based on one of the following:

- clinical assessment alone **or**
- clinical assessment plus diagnostic testing (that is, anatomical testing for obstructive CAD and/or functional testing for myocardial ischaemia).

1.3.2 Clinical assessment

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

1.3.2.1 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, such as breathlessness
- any history of angina, MI, coronary revascularisation, or other cardiovascular disease **and**
- any cardiovascular risk factors.

1.3.2.2 Carry out a physical examination to:

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

1.3.3 Making a diagnosis based on clinical assessment

1.3.3.1 Anginal pain is:

- constricting discomfort in the front of the chest, or in the neck, shoulders, jaw, or arms
- precipitated by physical exertion
- relieved by rest or GTN within about 5 minutes.

Use clinical assessment and the typicality of anginal pain features listed below to estimate the likelihood of CAD (see table 1):

- Three of the features above are defined as typical angina.
- Two of the three features above are defined as atypical angina.
- One or none of the features above are defined as non-anginal chest pain.

Table 1 Percentage of people estimated to have coronary artery disease according to typicality of symptoms, age, sex and risk factors

	Non-anginal chest	Atypical angina	Typical angina

	pain											
	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 coronary artery disease (CAD)[4].
Hi = High risk = diabetes, smoking and hyperlipidaemia (total cholesterol > 6.47 mmol/litre).
Lo = Low risk = none of these three.
Note:
These results are likely to overestimate CAD in primary care populations.
If there are resting ECG ST-T changes or Q waves, the likelihood of CAD is higher in each cell of the table.

Hyperlink to evidence statements for gender differences

1.3.3.2 Do not define typical and atypical features of anginal chest pain and non-anginal chest pain differently in men and women.

Hyperlink to evidence statements for ethnic differences

1.3.3.3 Do not define typical and atypical features of anginal chest pain and non-anginal chest pain differently in ethnic groups.

1.3.3.4 Take the following factors, which make a diagnosis of stable angina more likely, into account when estimating people's likelihood of angina:

- increasing age
- whether the person is male
- cardiovascular risk factors including:
  - a history of smoking
  - diabetes
  - hypertension
  - dyslipidaemia

[4] Pryor DB, Shaw L, McCants CB et al. (1993) Value of the history and physical in identifying patients at increased risk for coronary artery disease. Annals of Internal Medicine 118(2):81–90.

  - family history of premature CAD
  - other cardiovascular disease
- history of established CAD, for example previous MI, coronary revascularisation.

1.3.3.5 If people have features of typical angina based on clinical assessment and their estimated likelihood of CAD is greater than 90% (see table 1), further diagnostic investigation is unnecessary. Manage as angina.

1.3.3.6 Unless clinical suspicion is raised based on other aspects of the history and risk factors, exclude a diagnosis of stable angina if the pain is non-anginal (see recommendation 1.3.3.1). Other features which make a diagnosis of stable angina unlikely are when the chest pain is:

- continuous or very prolonged **and/or**
- unrelated to activity **and/or**
- brought on by breathing in **and/or**
- associated with symptoms such as dizziness, palpitations, tingling or difficulty swallowing.

Consider causes of chest pain other than angina (such as gastrointestinal or musculoskeletal pain).

1.3.3.7 If the estimated likelihood of CAD is less than 10% (see table 1), first consider causes of chest pain other than angina caused by CAD.

1.3.3.8 Consider investigating other causes of angina, such as hypertrophic cardiomyopathy, in people with typical angina-like chest pain and a low likelihood of CAD (estimated at less than 10%).

1.3.3.9 Arrange blood tests to identify conditions which exacerbate angina, such as anaemia, for all people being investigated for stable angina.

1.3.3.10 Only consider chest X-ray if other diagnoses, such as a lung tumour, are suspected.

1.3.3.11 If a diagnosis of stable angina has been excluded at any point in the care pathway, 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).

Hyperlink to evidence statements for ECG

1.3.3.12 For people in whom stable angina cannot be diagnosed or excluded on the basis of the clinical assessment alone, take a resting 12-lead ECG as soon as possible after presentation.

1.3.3.13 Do not rule out a diagnosis of stable angina on the basis of a normal resting 12-lead ECG.

1.3.3.14 A number of changes on a resting 12-lead ECG are consistent with CAD and may indicate ischaemia or previous infarction. These include:

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

Note that the results may not be conclusive.

Consider any resting 12-lead ECG changes together with people's clinical history and risk factors.

1.3.3.15 For people with confirmed CAD (for example, previous MI, revascularisation, previous angiography) in whom stable angina

cannot be diagnosed or excluded based on clinical assessment alone, see recommendation 1.3.4.8 about functional testing.

1.3.3.16 In people without confirmed CAD, in whom stable angina cannot be diagnosed or excluded based on clinical assessment alone, estimate the likelihood of CAD (see table 1). Take the clinical assessment and the resting 12-lead ECG into account when making the estimate. Arrange further diagnostic testing as follows:

- If the estimated likelihood of CAD is 61–90%, offer invasive coronary angiography as the first-line diagnostic investigation if appropriate (see recommendations 1.3.4.4 and 1.3.4.5).
- If the estimated likelihood of CAD is 30–60%, offer functional imaging as the first-line diagnostic investigation (see recommendation 1.3.4.6).
- If the estimated likelihood of CAD is 10–29%, offer CT calcium scoring as the first-line diagnostic investigation (see recommendation 1.3.4.7).

1.3.3.17 Consider aspirin only if the person's chest pain is likely to be stable angina, until a diagnosis is made. Do not offer additional aspirin if there is clear evidence that people are already taking aspirin regularly or are allergic to it.

1.3.3.18 Follow local protocols for stable angina[5] while waiting for the results of investigations if symptoms are typical of stable angina.

1.3.4 Diagnostic testing for people in whom stable angina cannot be diagnosed or excluded by clinical assessment alone

This guideline addresses only the diagnostic value of tests for stable angina. The prognostic value of these tests was not considered and is addressed in other guidelines (for example, guidelines for stable angina).

[5] NICE is developing the clinical guideline 'The management of stable angina' (publication expected July 2011).

The Guideline Development Group carefully considered the risk of radiation exposure from diagnostic tests. It discussed that the risk needs to be considered in the context of radiation exposure from everyday life, the substantial intrinsic risk that a person will develop cancer during their lifetime and the potential risk of failing to make an important diagnosis if a particular test is not performed. The commonly accepted estimate of the additional lifetime risk of dying from cancer with 10 millisieverts of radiation is 1 in 2000[6]. The Guideline Development Group emphasised that the recommendations in this guideline are to make a diagnosis of chest pain, not to screen for CAD. Most people diagnosed with non-anginal chest pain after clinical assessment need no further diagnostic testing. However in a very small number of people, there are remaining concerns that the pain could be ischaemic, in which case the risk of undiagnosed angina outweighs the risk of any potential radiation exposure.

Hyperlink to evidence statements for anatomical tests

1.3.4.1 Include the typicality of anginal pain features and the estimate of CAD likelihood (see recommendation 1.3.3.16) in all requests for diagnostic investigations and in the person's notes.

1.3.4.2 Use clinical judgement and take into account people's preferences and comorbidities when considering diagnostic testing.

1.3.4.3 Take into account people's risk from radiation exposure when considering which diagnostic test to use.

1.3.4.4 For people with chest pain in whom stable angina cannot be diagnosed or excluded by clinical assessment alone and who have an estimated likelihood of CAD of 61–90% (see recommendation 1.3.3.16), offer invasive coronary angiography after clinical assessment and a resting 12-lead ECG if:

[6] Gerber TC et al.(2009) Ionizing radiation in cardiac imaging: a science advisory from the American Heart Association Committee on Cardiac Imaging of the Council on Clinical Cardiology and Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention. Circulation 119(7):1056–1065.

- coronary revascularisation is being considered **and**
- invasive coronary angiography is clinically appropriate and acceptable to the person.

1.3.4.5 For people with chest pain in whom stable angina cannot be diagnosed or excluded by clinical assessment alone and who have an estimated likelihood of CAD of 61–90% (see recommendation 1.3.3.16), offer 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.

1.3.4.6 For people with chest pain in whom stable angina cannot be diagnosed or excluded by clinical assessment alone and who have an estimated likelihood of CAD of 30–60% (see recommendation 1.3.3.16), offer non-invasive functional imaging for myocardial ischaemia. See section 1.3.6 for further guidance on non-invasive functional testing.

1.3.4.7 For people with chest pain in whom stable angina cannot be diagnosed or excluded by clinical assessment alone and who have an estimated likelihood of CAD of 10–29% (see recommendation 1.3.3.16) offer CT calcium scoring. If the calcium score is:

- zero, consider 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 section 1.3.6 for further guidance on non-invasive functional testing.

1.3.4.8 For people with confirmed CAD (for example, previous MI, revascularisation, previous angiography), offer non-invasive

functional testing when there is uncertainty about whether chest pain is caused by myocardial ischaemia. See section 1.3.6 for further guidance on non-invasive functional testing. An exercise ECG may be used instead of functional imaging.

1.3.5 Additional diagnostic investigations

1.3.5.1 Offer non-invasive functional imaging (see section 1.3.6) for myocardial ischaemia if invasive coronary angiography or 64-slice (or above) CT coronary angiography has shown CAD of uncertain functional significance.

1.3.5.2 Offer invasive coronary angiography as a second-line investigation when the results of non-invasive functional imaging are inconclusive.

1.3.6 Use of non-invasive functional testing for myocardial ischaemia

Hyperlink to evidence statements for non-invasive stress tests

1.3.6.1 When offering non-invasive functional imaging for myocardial ischaemia use:

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

Take account of locally available technology and expertise, the person and their preferences, and any contraindications when deciding on the imaging method. [This recommendation updates and replaces ‘Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction’ (NICE technology appraisal guidance 73)].

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

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

1.3.6.4 Do not use MR coronary angiography for diagnosing stable angina.

1.3.6.5 Do not use exercise ECG to diagnose or exclude stable angina for people without known CAD.

1.3.7 Making a diagnosis following investigations

1.3.7.1 Confirm a diagnosis of stable angina and follow local guidelines for angina[7] when:

- significant CAD (see box 1) is found during invasive or 64-slice (or above) CT coronary angiography **and/or**
- reversible myocardial ischaemia is found during non-invasive functional imaging.

Box 1 Definition of significant coronary artery disease

Significant coronary artery disease (CAD) found during invasive coronary angiography is ≥ 70% diameter stenosis of at least one major epicardial artery segment or ≥ 50% diameter stenosis in the left main coronary artery:

- Factors intensifying ischaemia. Such factors allow less severe lesions (for example ≥ 50%) to produce angina:
  - Reduced oxygen delivery: anaemia, coronary spasm.
  - Increased oxygen demand: tachycardia, left ventricular hypertrophy.
  - Large mass of ischaemic myocardium: proximally located lesions.
  - Longer lesion length.
- Factors reducing ischaemia. Such factors may render severe lesions (≥ 70%) asymptomatic:
  - Well developed collateral supply.
  - Small mass of ischaemic myocardium: distally located lesions, old infarction in the territory of coronary supply.

[7] NICE is developing the clinical guideline 'The management of stable angina' (publication expected July 2011).

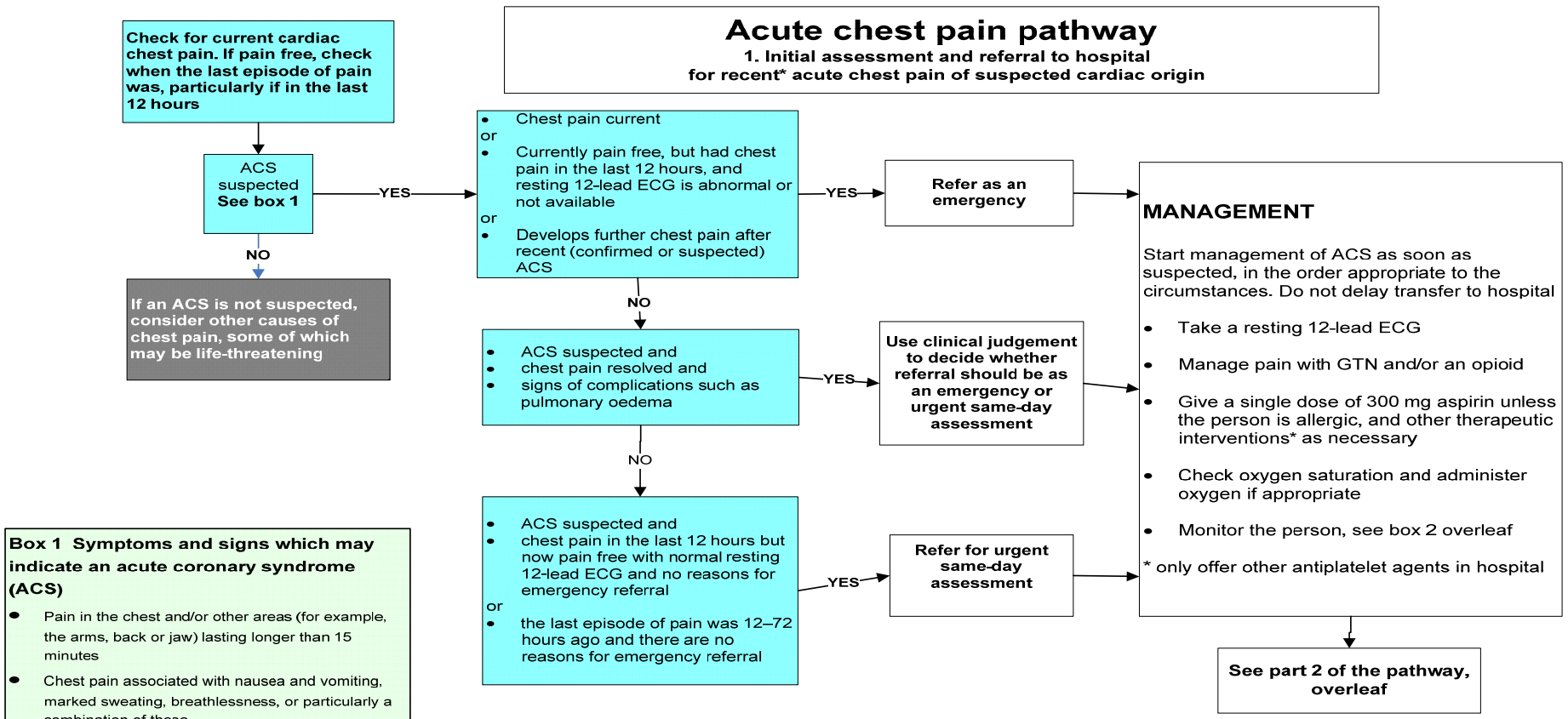
1.3.7.2 Investigate other causes of chest pain when:

- significant CAD (see box 1) is not found during invasive coronary angiography or 64-slice (or above) CT coronary angiography **and/or**
- reversible myocardial ischaemia is not found during non-invasive functional imaging **or**
- the calcium score is zero.

1.3.7.3 Consider investigating other causes of angina, such as hypertrophic cardiomyopathy or syndrome X, in people with typical angina-like chest pain if investigation excludes flow-limiting disease in the epicardial coronary arteries.

Acute Chest Pain Care Pathway

The pathway (1 & 2) should be read with the recommendations in this document.



Acute chest pain pathway

2. Investigation and diagnosis in hospital

Assessment in hospital

- Resting 12-lead ECG
- Blood sample for troponin I or T on arrival
- Physical examination
- Clinical history (unless a STEMI is confirmed from the resting 12-lead ECG)

Box 2 Monitoring people with acute chest pain

Use clinical judgement to decide how often this should be done, until a firm diagnosis is made. Include:

- exacerbations of pain and/or other symptoms
- pulse and blood pressure
- heart rhythm
- oxygen saturation by pulse oximetry
- repeated resting 12-lead ECGs and
- checking pain relief is effective

Box 3 Diagnostic criteria for MI

Rise and /or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischaemia with at least one of the following:

- symptoms of ischaemia
- ECG changes indicative of new ischaemia [new ST-T changes or new left branch bundle block (LBBB)]
- development of pathological Q wave changes in the ECG
- imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Resting 12-lead ECG consistent with an acute STEMI

YES → **Follow local protocols for acute STEMI until firm diagnosis made (see box 3). Continue to monitor (see box 2)**

NO

Resting 12-lead ECG suggestive of NSTEMI or unstable angina

YES → Follow 'Unstable angina and NSTEMI'* until firm diagnosis made (see box 3). Continue to monitor (see box 2)

If troponin raised, reassess to exclude other reasons for this

→ **Follow 'Unstable angina and NSTEMI'* or local protocols for acute STEMI until firm diagnosis made (see box 3). Continue to monitor (see box 2)**

Take a second blood sample for troponin I or T measurement 10–12 hours after onset of symptoms.

Diagnostic criteria met? See box 3

YES → **Follow 'Unstable angina and NSTEMI'* or local protocols for acute STEMI**

Uncertain

- Continue to monitor
- Consider chest CT or chest X-ray to exclude other diagnoses/ complications

NO

- **Consider chest CT or chest X-ray to exclude other diagnoses**
- **After reassessment, if myocardial ischaemia is suspected, follow the recommendations on stable chest pain**
- **If an ACS is excluded 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)**

NO

- Increase suspicion of an ACS if there are other changes in the resting 12-lead ECG (specifically Q waves, T wave changes)
- Do not exclude an ACS if resting 12-lead ECG is normal
- Consider following 'Unstable angina and NSTEMI'*, if these are very likely. Continue to monitor (see box 2)

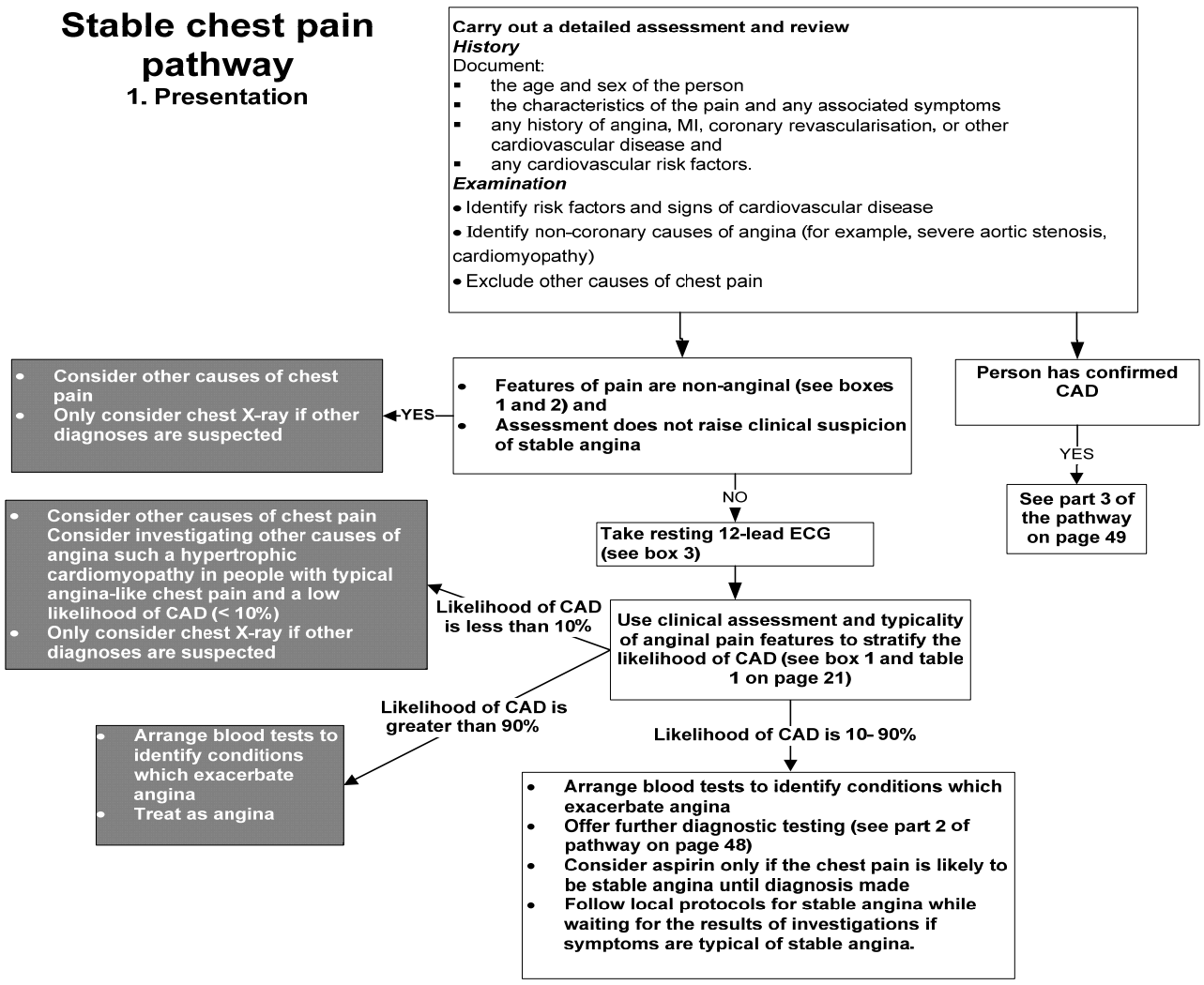
If diagnosis of ACS is in doubt:

- Continue monitoring
- Consider taking serial resting 12-lead ECGs, reviewing previous resting 12-lead ECGs and recording additional ECG leads. Use clinical judgement to decide how often this should be done. Note results may not be conclusive
- Repeat troponin measurement 10–12 hours after onset of symptoms
- Consider other acute conditions, firstly life-threatening conditions
- If diagnostic criteria met, follow 'Unstable angina and NSTEMI'* or local protocols for acute STEMI.

* NICE clinical guideline XX

Stable Chest Pain Care Pathway

The pathway (1, 2 & 3) should be read with the recommendations in this document.



Box 1 Typical stable angina symptoms

- Constricting discomfort in the front of the chest, in the neck, shoulders, jaw, or arms
- Precipitated by physical exertion
- Relieved by rest or GTN within about 5 minutes

Typical angina: all of the above
Atypical angina: two of the above
Non-anginal chest pain: one or none of the above

See recommendation 1.3.3.4 for risk factors which make angina more likely.

Box 2
Stable angina is unlikely if chest pain is:

- continuous or very prolonged and/or
- unrelated to activity and/or
- brought on by breathing in and/or
- associated with symptoms such as dizziness, palpitations, tingling or difficulty swallowing

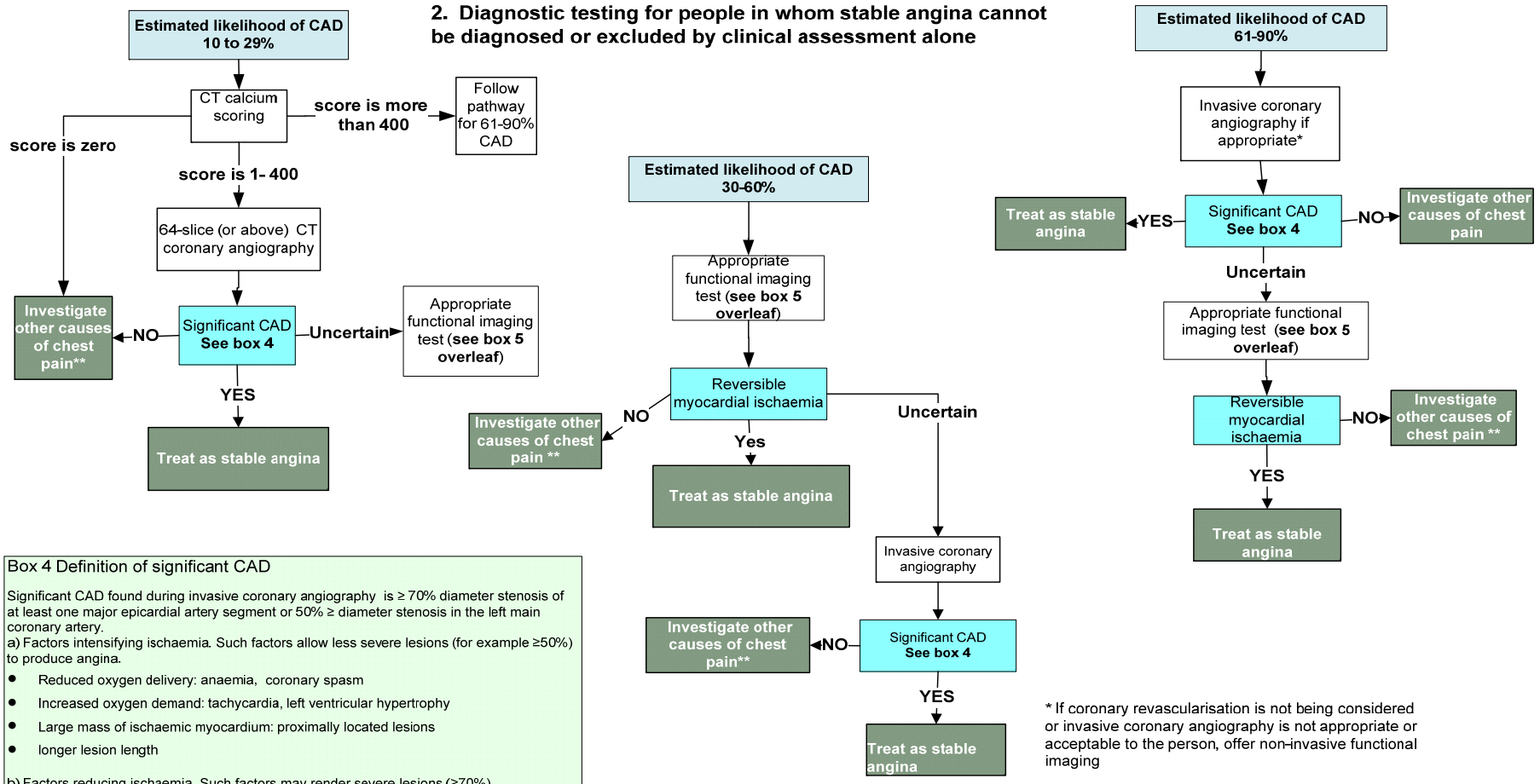
Box 3 Changes on a resting 12-lead ECG consistent with CAD and may indicate ischaemia or previous infarction

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

Results may not be conclusive. Consider resting 12-lead ECG changes together with people's clinical history and risk factors. Note that a normal resting 12-lead ECG does not rule out stable angina.

Stable chest pain pathway

2. Diagnostic testing for people in whom stable angina cannot be diagnosed or excluded by clinical assessment alone



Box 4 Definition of significant CAD

Significant CAD found during invasive coronary angiography is ≥ 70% diameter stenosis of at least one major epicardial artery segment or 50% ≥ diameter stenosis in the left main coronary artery.
a) Factors intensifying ischaemia. Such factors allow less severe lesions (for example ≥50%) to produce angina.

- Reduced oxygen delivery: anaemia, coronary spasm
- Increased oxygen demand: tachycardia, left ventricular hypertrophy
- Large mass of ischaemic myocardium: proximally located lesions
- longer lesion length

b) Factors reducing ischaemia. Such factors may render severe lesions (≥70%) asymptomatic.

- Well developed collateral supply
- Small mass of ischaemic myocardium: distally located lesions, old infarction in the territory of coronary supply.

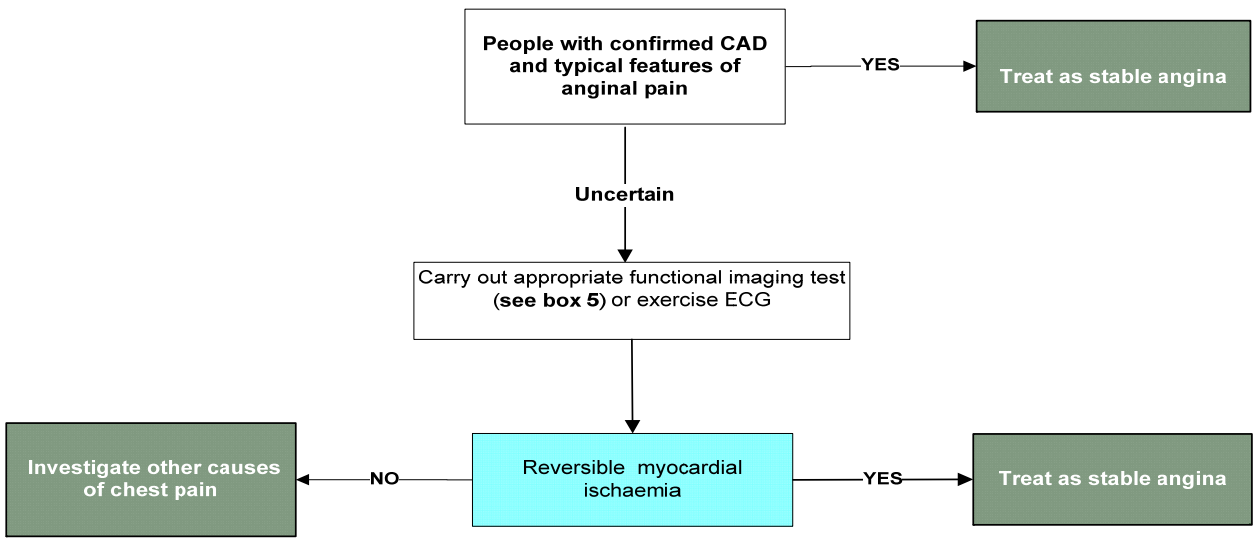
* If coronary revascularisation is not being considered or invasive coronary angiography is not appropriate or acceptable to the person, offer non-invasive functional imaging

**Consider investigating other causes of angina, such as hypertrophic cardiomyopathy or syndrome X in people with typical angina-like chest pain if investigation excludes flow-limiting disease in the epicardial coronary arteries.

1

Stable chest pain pathway

3. Established prior diagnosis of coronary artery disease



Box 5
When offering non-invasive functional imaging for myocardial ischaemia use:

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

Take account of locally available technology and expertise, the person and their preferences, and any contraindications, when deciding on the imaging method.

1 Introduction Chapter

1.1 Epidemiology

Coronary heart disease (CHD) is the most common cause of death in the UK, around one in five men and one in seven women die from the disease. From 2006 to 2007 there were over 94 000 deaths attributed to CHD. CHD is also the most common cause of premature death in the UK; 19% of premature deaths in men and 10% of premature deaths in women were from CHD. From 2006 to 2007 there were over 31 000 premature deaths attributed to CHD. Although the death rate from CHD has been decreasing since the early 1970's, the death rate in the UK is still higher than many countries in Western Europe. Over 2 million people are living with CHD in the UK. (http://www.heartstats.org/temp/2008.Chaptersp1.pdf). It is estimated that more than 275 000 people have a myocardial infarction annually (http://www.heartstats.org/datapage.asp?id=1122.)

The 2006 Health Survey for England found that approximately 8% of men and 3% of women aged 55 to 64, and about 14% of men and 8% of women aged 65 to 74 have or have had angina. Using the combined age specific prevalence rates, it has been estimated that there are about 726 000 men aged between 35 and 75 living in the UK who have had angina and about 393 000 women giving a total of over 1.1 million (http://www.heartstats.org/datapage.asp?id=1122).

From these prevalence rates it has been estimated that there are about 619 000 men aged between 55 and 75 living in the UK who have or have had angina and about 336 000 women giving a total of just over 955 000. From the combined age-specific prevalence rates it has been estimated that there are about 726 000 men aged between 35 and 75 living in the UK who have had angina and about 393 000 women giving a total of over 1.1 million. For all people older than 35 there are about 1132 000 men living in the UK who have had angina and about 849 000 women giving a total of more than 1.98 million (http://www.heartstats.org/datapage.asp?id=1122).

A recent systematic review of observational data (6 studies) found that the total mortality rate in angina patients was 2.8% to 6.6% per annum, compared with 1.4% to 6.5% per annum mortality rate for cardiovascular disease, and 0.3% to 5.5% per annum for non fatal MI (Jones, M., Rait, G., Falconer, J. et al, 2006). The incidence of angina and ACS has been shown to vary according to risk factors such as age, gender and ethnicity.

Chest pain is a very common symptom from 20% to 40% of the general population will experience chest pain in their lives (Ruigomez, A., Rodriguez, L. A., Wallander, M. A. et al, 2006). In the UK, up to 1% of visits to a general practitioner are due to chest pain (Nilsson, S., Scheike, M., Engblom, D. et al, 2003). Approximately 5% of visits to the emergency department are due to a complaint of chest pain, and up to 40% of emergency hospital admissions are due to chest pain (Murphy, N. F., MacIntyre, K., Capewell, S. et al, 2004) (Goodacre, S., Cross, E., Arnold, J. et al, 2005) (Blatchford, O., Capewell, S., Murray, S. et al, 1999).

1.2 Aim of the guideline

Chest pain or discomfort caused by acute coronary syndromes (ACS) or angina has a potentially poor prognosis, emphasising the importance of prompt and accurate diagnosis. Treatments are available to improve symptoms and prolong life, hence the need for this guideline.

This guideline covers the assessment and diagnosis of people with recent onset chest pain or discomfort of suspected cardiac origin. In deciding whether chest pain may be cardiac and therefore whether this guideline is relevant, a number of factors should be taken into account. These include the person’s history of chest pain, their cardiovascular risk factors, history of ischaemic heart disease and any previous treatment, and previous investigations for chest pain.

For pain that is suspected to be cardiac, there are two separate diagnostic pathways presented in the guideline. The first is for people with acute chest pain in whom ACS is suspected, and the second is for people with intermittent stable chest pain in whom stable angina is suspected. The guideline includes

how to determine whether myocardial ischaemia is the cause of the chest pain and how to manage the chest pain while people are being assessed and investigated.

The diagnosis and management of chest pain that is clearly unrelated to the heart (e.g. traumatic chest wall injury, herpes zoster infection) is not considered once myocardial ischaemia has been excluded. The guideline makes no assumptions about who the patient consults, where that consultation takes place (primary care, secondary care, emergency department) or what diagnostic facilities might be available. It recognizes that while atherosclerotic CAD is the usual cause of angina and ACS, it is not a necessary requirement for either diagnosis. Similarly, it recognises that in patients with a prior diagnosis of CAD, chest pain or discomfort is not necessarily cardiac in origin.

1.3 Approach

This guideline addresses the assessment and diagnosis of patients with *recent* onset chest pain or discomfort of *suspected* cardiac origin. In deciding whether the chest pain may be of cardiac origin, and therefore this guideline is relevant, consider the:

- history of the chest pain
- presence of cardiovascular risk factors
- history of ischaemic heart disease and any previous treatment
- previous investigations for chest pain

There are two separate diagnostic pathways presented in this guideline. The first is for patients with acute chest pain (see glossary definition) in whom an ACS is suspected. The second is for patients with intermittent stable chest pain (see glossary definition) in whom stable angina is suspected.

The adverse prognostic correlates of chest pain or discomfort caused by an acute coronary syndrome or angina emphasise the importance of prompt and accurate diagnosis because treatments are available to ameliorate symptoms

and prolong life. Assessing the clinical value of a diagnostic test, however, poses special difficulties that do not arise when making treatment recommendations based on the results of clinical trials. For diagnostic tests, the conventional measures of efficacy are sensitivity and specificity set against a “gold-standard” which, for tests of stable angina, is angiographic CAD. This angiographic gold standard poses immediate problems:

- CAD is variably defined across different studies, not all using the conventional ≥50% luminal obstruction.
- Coronary artery disease, while being the usual cause of angina, is neither necessary nor sufficient for diagnostic purposes (see above).
- The requirement for invasive coronary angiography to define a test’s efficacy ensures a level of work-up bias that may over-estimate its diagnostic value for real-world patients presenting for the first time with undifferentiated chest pain or discomfort.

Add to this the paucity of data on the incremental value of diagnostic tests, over and above the information available from simple clinical assessment, and the virtual absence of adequately powered outcome studies and the difficulties inherent in developing guideline recommendations for diagnostic testing become clear.

Acute coronary syndromes include myocardial infarction and unstable angina which are defined in the glossary (below). They usually present acutely with chest pain or discomfort that is unprovoked and unremitting. The mortality risk is highest early after presentation, particularly in patients with myocardial infarction, in whom emergency treatment saves lives. This guideline, therefore, recommends a low diagnostic threshold for acute coronary syndromes. It also recommends a low threshold for starting treatment in suspected myocardial infarction, based on the initial clinical assessment and electrocardiogram, pending the results of biomarker tests of myocardial necrosis (troponins). If the tests are positive, in the patient presenting with chest pain, myocardial infarction is confirmed but if the tests are negative a diagnosis of unstable angina can often be made based on

unstable symptoms and or ECG changes. In either event the patient receives no further consideration within this guideline, and their further management is informed by other treatment guidelines. However, there remains a group of troponin negative patients in whom the cause of chest pain remains unclear and who remain within the diagnostic pathway requiring additional tests described in this guideline.

Diagnostic probability in suspected angina notwithstanding the difficulties in defining the clinical value of a diagnostic test, this guideline makes recommendations for diagnosis that are cost-effective in identifying a high proportion of the at-risk population with chest pain / discomfort. It considers not only a test's diagnostic accuracy, as influenced by disease prevalence, but also its potential incremental value, recognising that in many cases a test will add little or nothing once a critical level of diagnostic probability has been achieved. For example, if a 65 year old hypertensive diabetic woman gives a history of constricting chest discomfort provoked by exertion, she has angina and further diagnostic tests whether positive or negative will not affect that diagnosis. Similar considerations apply to the 20 year old with localised, unprovoked stabbing chest pains in whom a non-cardiac diagnosis will be uninfluenced by further testing. These examples lie at the extremes of diagnostic probability and pose no problem to the clinician, but difficulties arise when the clinical assessment (or the result of a diagnostic test) is less clear-cut. At what level of diagnostic probability are we permitted to make a diagnosis and proceed with treatment? The answer to this question is driven in part by the prognostic consequences of an incorrect diagnosis. These are particularly high for myocardial infarction for which this guideline recommends a very low diagnostic threshold (see above). For patients with suspected angina the threshold for initiating treatment must be higher and we have chosen an > 90% probability of CAD for diagnostic rule-in and a < 10% probability of CAD for diagnostic rule-out. In setting these arbitrary thresholds, we accept that occasional false positive and false negative diagnoses are an inevitable consequence of our recommendations and also that patients with cardiac chest pain or discomfort unrelated to epicardial CAD may fall through the diagnostic net and require special consideration.

To measure the “pre-test” probability of CAD in the patient with stable chest pain undergoing initial clinical assessment, this guideline has used the Diamond and Forrester algorithm based on age, gender and the typicality of symptoms assessed by the response to 3 questions: 1). Is there constricting discomfort in the front of the chest, or in the neck, shoulders, jaw, or arms? 2). Is pain precipitated by physical exertion? 3). Is pain relieved by rest or GTN within about 5 minutes?

Patients who answer yes to all 3 questions are determined to have typical chest pain. Patients who answer yes to 2 of the questions have atypical chest pain, and patients who answer yes to only 1 or none of the questions have non-anginal chest pain. Application of the Diamond and Forrester algorithm provides a probability estimate of CAD based on the disease prevalence (%) in western populations. These probability estimates may be modified by other determinants of risk apart from age and gender and this is reflected in Table 1 which provides a range for each estimate from “Low” to “High” risk depending on the presence of the additional factors of diabetes, smoking, and hyperlipidaemia (Table 1). These additional factors should be taken into account when ascribing probability estimates of CAD in individual cases.

Table 1

Percentage of people estimated to have CAD according to typicality of symptoms, age, sex and risk factors

	Non-anginal 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.

Adapted from (Pryor, D. B., Shaw, L., McCants, C. B. et al, 1993).

Hi = High risk = diabetes, smoking and hyperlipidaemia (total cholesterol > 6.4 mmol/L)

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.

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

1.4 Diagnostic pathway

Central to this guideline are the diagnostic pathways for patients presenting with acute and stable chest pain or discomfort. In both cases the pathways start with the clinical assessment that is preceded by (acute and unstable symptoms) or followed by (stable symptoms) a 12 lead electrocardiogram. Thereafter there are recommendations, as indicated, for circulating biomarker assay for people presenting with acute chest pain.

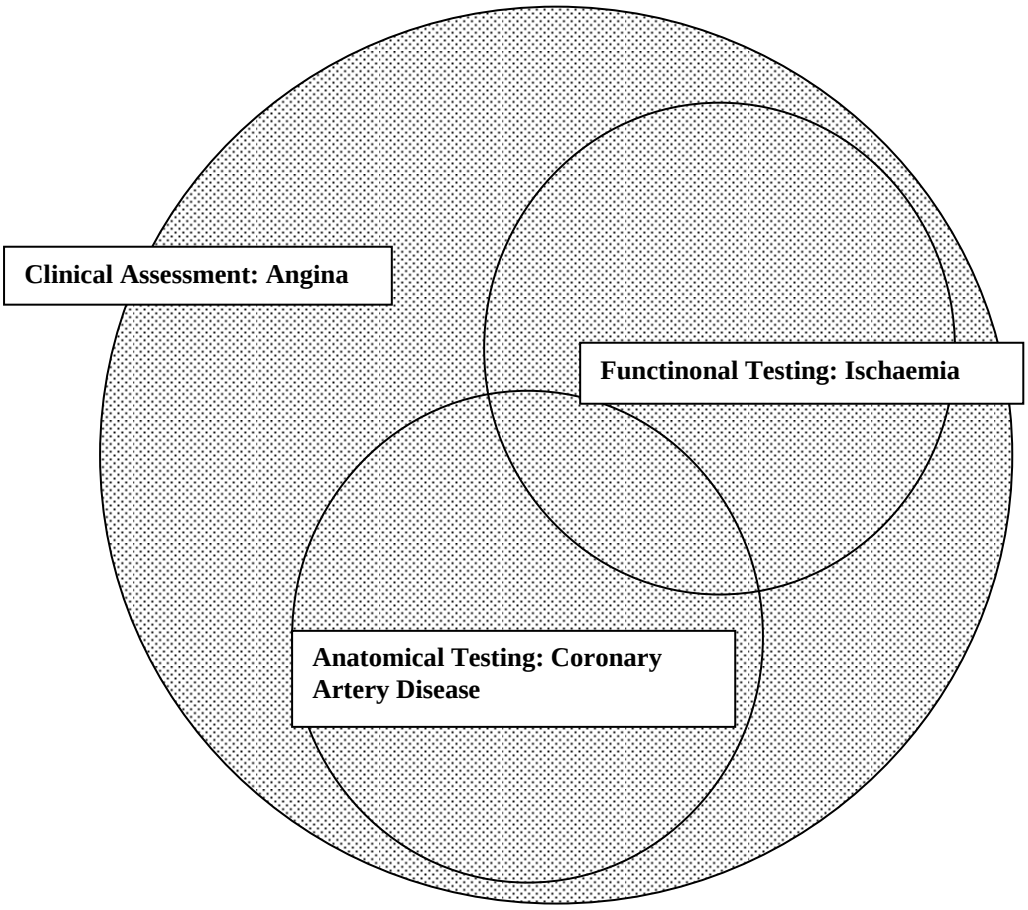
When people present with stable chest pain of suspected cardiac origin, it is possible to arrive at a diagnosis by one (or all) of 3 methods, the precise nature of the diagnosis depending on the method(s) that is chosen.

1. Clinical assessment. Application of the Diamond Forrester algorithm, as modified by consideration of additional risk factors, may permit a diagnosis of ANGINA if the probability estimate is sufficiently high (say > 90%).

2. Non-invasive functional testing. A variety of such tests (exercise electrocardiogram, myocardial perfusion scintigraphy with SPECT (MPS), stress echocardiography, stress magnetic resonance imaging (stress MRI)) may permit a diagnosis of MYOCARDIAL ISCHAEMIA. However, it is important to emphasise that demonstrable myocardial ischaemia is neither necessary nor sufficient for a diagnosis of angina.

3. Anatomical testing, using 64-slice CT coronary angiography or invasive coronary angiography may permit a diagnosis of obstructive CAD. However, it is important to emphasise that obstructive CAD is neither necessary nor sufficient for a diagnosis of angina.

Note that only the clinical assessment is necessary - and often sufficient - for diagnosing (or excluding) angina, but when there is uncertainty (diagnostic probability 10-90%), additional functional or anatomical testing will help confirm or exclude the diagnosis. It is possible, therefore, to consider the diagnostic process in terms of a Venn diagram as follows:



Because diagnostic thresholds for stable angina may often be met by simple clinical assessment, many patients exit the pathway without need for either functional or anatomical testing. Others, in whom the probability of CAD is intermediate between 10 and 90% require one or sometimes two further diagnostic tests. Similarly many patients exit the acute chest pain pathway with a diagnosis of myocardial infarction after a brief history, an electrocardiogram, and measurement of circulating biomarkers. This is not to say that patients in both pathways might not benefit from additional tests for risk assessment or work-up for revascularisation, but these are not a part of the diagnostic process and are not therefore a part of this guideline.

1.5 How the guideline is set out

This guideline is actually two separate guidelines, one for patients presenting with acute chest pain or discomfort suspected of being an ACS (which will be referred to as acute chest pain) and a second for patients presenting with stable chest pain suspected of being angina (which will be referred to as stable chest pain). They are different in their presentation, investigative

pathways and diagnostic criteria. Therefore, there are two entirely separate, and largely unrelated, sections in the clinical chapters. One is the 'Presentation with Acute Chest Pain' the other is the 'Presentation with Stable Chest Pain'. This guideline finishes, in both cases, once the likely diagnosis is determined, where the reader is referred to other relevant guidance.

The first two chapters describe the context and methods for both sections of the guideline. Chapter 3 gives guidance on information for patients with acute or stable chest pain. The evidence in this chapter was largely derived from unselected populations all presenting with acute chest pain. Recommendations are for the identification of patients with chest pain of cardiac origin. The view of the Guideline Development Group (GDG) was, however, that the recommendations on information are relevant to all patients presenting with chest pain which may or may not be of cardiac origin.

The approach to writing a guideline is first to pose the clinical questions that will be asked in the guideline, then to search, review and distil this evidence, from which the recommendations are derived. This is detailed in the Methods chapter. The GDG addresses each question in turn. Thus, the 'Full Guideline' is structured by the topics and questions, so that the reader may follow the trail from the recommendations back to the evidence that underpins them as well as the discussion of the GDG.

In the consultation version, the recommendations were in the same order as the chapters. This means, however, that the recommendations are not necessarily in the order in which they should be carried out when a patient presents with chest pain. For example, all of the recommendations and evidence on the choice, timing and interpretation of biomarkers are together as that was how the evidence was reviewed. Following stakeholder comments where there was a great deal of confusion, we have re-ordered the recommendations making clearer the pathway of care. But, as there are many permutations at each decision point, this has necessitated frequent cross-referencing to avoid repeating recommendations several times. The reader is directed to the care pathways, contained in Chapter 2 of this guideline and

repeated in the NICE guideline, to view the recommendations as a patient pathway.

Patients may present in a number of ways including via primary care, the ambulance service, NHS Direct, or directly to A&E. As they all require similar assessment and management, regardless of where they present, the guideline has not been specific about what should take place where particularly as protocols may vary in different health communities. However, both because of their potentially unstable condition and the benefit of rapid access to treatments such as intensive medical treatment and early coronary revascularisation, the guideline makes clear that in people with a suspected ACS, pre-hospital assessment and management should not delay transfer.

Note: Permission was sought to re-produce the tables in this guideline from the original research papers. Most cases this was either freely given or there was only a nominal charge and we have re-produced them. Where there was a significant fee, we have been unable to do so. We have referenced the table so that the reader may refer to it.

1.6 Scope

The guideline was developed in accordance with a scope given by the National Institute for Health and Clinical Excellence (NICE, 'the institute') the scope set the remit of the guideline and specified those aspects of the management of chest pain / discomfort of recent onset to be included and excluded. The scope was published in March 2008 and is reproduced in Appendix A.

The guideline covers adults who have recent onset chest pain or discomfort of suspected cardiac origin, with or without a prior history and / or diagnosis of cardiovascular disease. It includes those presenting with either acute or stable chest pain.

The guideline addresses assessment and investigation irrespective of setting including:

a) Assessment at initial presentation.

b) Early, initial pharmacological interventions such as oxygen, anti-platelet therapy and pain relief before a cause is known.

c) Choice and timing of investigations

d) Education and information provision in particular involving patients in decisions.

e) Where relevant and where associated with chest pain / discomfort, the special needs of people from different groups are considered.

The guideline does not cover the management, including prognostic investigations, and symptom control once the cause of chest pain / discomfort is known. It does not address non-ischaemic chest pain (for example, traumatic chest injury) or pain which is known to be related to another condition, or when there are no cardiac symptoms.

1.7 Responsibility and support for guideline development

1.7.1 The National Collaborating Centre for Primary Care (NCC-PC)

The NCC-PC was a partnership of primary care professional associations and was formed as a collaborating centre convened in 2001 to develop guidelines under contract to NICE. Unlike many of the other centres which focus on a particular clinical area, the NCC-PC had a broad range of topics relevant to primary care. However, it does not develop guidelines exclusively for primary care each guideline may, depending on the scope, provide guidance to other health sectors in addition to primary care.

Until April 2009, Royal College of General Practitioners (RCGP) acted as the host organisation. The Royal Pharmaceutical Society and the Community Practitioners and Health Visitors' Association were partner members with representation from other professional and lay bodies on the Board. In April 2009, at the time of the submission of the consultation draft the NCC-PC merged with three other collaborating centres. From this point, this guideline was developed in the National Clinical Guideline Centre for Acute and Chronic

Conditions (NCGCACC) based at the Royal College of Physicians. This guideline will therefore be published by the NCGCACC.

1.7.2 The Development Team

The development team had the responsibility for this guideline throughout its development. They were responsible for preparing information for the Guideline Development Group (GDG), for drafting the guideline and for responding to consultation comments. The development team working on this guideline consisted of the:

- **Guideline lead**
  who is a senior member of the Centre who has overall responsibility for the guideline
- **Information scientist**
  who searched the bibliographic databases for evidence to answer the questions posed by the GDG
- **Reviewer (Senior Health Services Research Fellow**)
  who appraised the literature and abstracted and distilled the relevant evidence for the GDG
- **Health economists**
  who reviewed the economic evidence, constructed economic models in selected areas and assisted the GDG in considering cost-effectiveness
- **Project manager**
  who was responsible for organising and planning the development, for meetings and minutes and for liaising with the Institute and external bodies
- **Clinical advisor**
  a clinician with an academic understanding of the research in the area and its practical implications to the service, who advised the development team on searches and the interpretation of the literature

- **Chairman**
  who was responsible for chairing and facilitating the working of the GDG meetings

The members of the development team attended the GDG meetings and participated in them. The development team also met regularly with the Chair of the GDG and the Clinical Advisor during the development of the guideline to review progress and plan work.

1.7.3 The Guideline Development Group (GDG)

A Chair was chosen for the group and his primary role was to facilitate and chair the GDG meetings.

Guideline Development Groups (GDGs) are working groups consisting of a range of members with the experience and expertise needed to address the scope of the guideline. Nominations for GDG members were invited from the public and relevant stakeholder organisations which were sent the draft scope of the guideline with some guidance on the expertise needed. Two patient representatives and nine healthcare professionals were invited to join the GDG.

Nominees who were not selected for the GDG were invited to act as Expert Peer Reviewers and were sent drafts of the guideline by the Institute during the consultation periods and invited to submit comments using the same process as stakeholders.

Each member of the GDG served as an individual expert in their own right and not as a representative of their organisation.

In accordance with guidance from NICE, all GDG members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, fellowships, and support from the healthcare industry. Details of these can be seen in Appendix B.

The names of GDG members appear listed below.

Full GDG members

- Professor Adam Timmis (Chair)
  Professor of Clinical Cardiology, Barts and the London Queen Mary's School of Medicine and Dentistry, London
- Dr Jane Skinner (Clinical Advisor)
  Consultant Community Cardiologist, Royal Victoria Infirmary, Newcastle Upon Tyne
- Dr Philip Adams
  Cardiologist Consultant, Royal Victoria Infirmary, Newcastle Upon Tyne
- Dr John Ashcroft
  General Practitioner, Old Station Surgery, Ilkeston, Derbyshire
- Ms Liz Clark
  Patient representative
- Dr Richard Coulden
  Consultant Cardiothoracic Radiologist, Glenfield Hospital, Leicester
- Professor Harry Hemingway
  Public Health Physician Epidemiologist, UCL Medical School, London
- Mrs Cathryn James
  Clinical Pathways Advisor / Emergency Care Practitioner, Yorkshire Ambulance ServiceAS HQ, Wakefield
- Ms Heather Jarman
  Consultant Nurse in Emergency Care, St Georges Healthcare NHS Trust, London
- Dr Jason Kendall
  Consultant in Emergency Medicine, Frenchay Hospital, Bristol
- Mr Peter Lewis
  Chief Clinical Physiologist, Prince Charles Hospital, Merthyr, Tedfyl, Wales

- Dr Kiran Patel
  Consultant Cardiologist, Lyndon, West Bromwick, West Midlands
- Professor Liam Smeeth
  Professor of Clinical Epidemiology, London School of Hygiene and Tropical Medicine, London
- Mr John Taylor
  Patient representative

Members of the GDG from the Centre were:

- Nancy Turnbull
  Guideline Lead
- Dr Angela Cooper
  Senior Health Services Research Fellow
- Katrina Sparrow
  Health Services Research Fellow
- Dr Neill Calvert
  Head of Health Economics
- Laura Sawyer
  Health Economist
- David Hill
  Project Manager
- Marian Cotterell
  Information Scientist , (until January 2009)

Co-opted GDG Members

- Dr Paul Collinson
  Consultant in Chemical Pathology and Head of Vascular Risk Management, St George's Hospital, London
- Dr Dorothy Frizelle
  Clinical Health Psychologist, Department of Clinical Psychology, University of Hull, Hull
- Professor Steve Goodacre

Professor of Emergency Medicine, Medical Care Research Unit, Sheffield

- Dr Marcus Hardbord
  Consultant Physician & Gastroenterologist, Chelsea & Westminster Hospital, London
- Ms Helen Williams
  Consultant Pharmacist for Cardiovascular Disease, Southwark Health and Social Care

Observers

- Ms Sarah Willett
  Commissioning Manager, National Institute for Health and Clinical Excellence

1.7.4 Guideline Development Group meetings

The GDG met at 5 to 6 weekly intervals from December 2007 until April 2009 to review the evidence identified by the development team, to comment on its quality and relevance, and to develop recommendations for clinical practice based on the available evidence. The recommendations were agreed by the full GDG.

2 Methods Chapter

2.1 Introduction

This chapter sets out in detail the methods used to generate the recommendations for clinical practice that are presented in the subsequent chapters of this guideline. The methods are in accordance with those set out by the Institute in 'The guidelines manual'. April 2007. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk/guidelinesmanual. *The Guideline Development Process – an overview for stakeholders, the public and the NHS* describes how organisations can become involved in the development of a guideline.

2.2 Developing key clinical questions (KCQs)

The first step in the development of the guideline was to refine the guideline scope into a series of key clinical questions (KCQs). These KCQs formed the starting point for the subsequent review and as a guide to facilitate the development of recommendations by the Guideline Development Group (GDG).

The KCQs were developed by the GDG and with assistance from the methodology team. The KCQs were refined into specific evidence-based questions (EBQs) specifying interventions to search and outcomes to be searched for by the methodology team and these EBQs formed the basis of the literature searching, appraisal and synthesis.

The total list of KCQs identified is listed in Appendix C1. The development team, in liaison with the GDG, identified those KCQs where a full literature search and critical appraisal were essential.

2.3 Literature search strategy

Systematic literature searches are undertaken to identify published evidence to answer the clinical questions identified by the methodology team and the GDG. The information scientist developed search strategies for each question, with guidance from the GDG, using relevant MeSH (medical subject

headings) or indexing terms, and free text terms. Searches were conducted between May 2007 and November 2008. Update searches for all questions were carried out in April 2009 identify any recently published evidence. Full details of the sources and databases searched and the strategies are available in Appendix C2.

An initial scoping search for published guidelines, systematic reviews, economic evaluations and ongoing research was carried out on the following databases or websites: National Library for Health (NLH) Guidelines Finder, National Guidelines Clearinghouse, National Institute for Health and Clinical Excellence (NICE) Guidelines, Scottish Intercollegiate Guidelines Network (SIGN), Canadian Medical Association (CMA) Infobase (Canadian guidelines), National Health and Medical Research Council (NHMRC) Clinical Practice Guidelines (Australian Guidelines), New Zealand Guidelines Group, Guidelines International Network (GIN), OMNI, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Heath Technology Assessment Database (HTA), NHS Economic Evaluations Database (NHSEED), TRIP, Health Evidence Bulletin Wales, BMJ Clinical Evidence, DH Data, and King's Fund.

For each clinical question the following bibliographic databases were searched from their inception to the latest date available: Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Database (HTA), MEDLINE, EMBASE, CINAHL, and CENTRAL (Cochrane Controlled Trials Register). When appropriate to the question PsycINFO and AMED were also searched.

The search strategies were developed in MEDLINE and then adapted for searching in other bibliographic databases. Methodological search filters designed to limit searches to systematic reviews or randomised controlled trials were used. These were developed by the Centre for Reviews and Dissemination (CRD) and The Cochrane Collaboration. For all other questions, no restriction was placed on study design.

The economic literature was identified by conducting searches in NHS Economic Evaluations Database (NHSEED) and in MEDLINE, EMBASE and CINAHL using an economics search strategy developed by ScHARR at the University of Sheffield.

Databases of the results of the searches for each question or topic area were created using the bibliographic management software Reference Manager.

2.4 Identifying the evidence

After the search of titles and abstracts was undertaken, full papers were obtained if they appeared to address the KCQ. The highest level of evidence was sought. Systematic reviews were initially selected. Where systematic reviews had recently been published, the identification of further studies was not done. Where systematic reviews were not available, diagnostic cohort studies were selected for intervention KCQs, and cohort studies were selected for other KCQs. Surveys were not selected. Expert consensus was used when no studies were available that addressed the KCQ. Following a critical review of the full text paper, articles not relevant to the subject in question were excluded. Cohort and diagnostic studies were excluded if they were conducted on an inappropriate patient population. Diagnostic studies were excluded if the test being evaluated was not compared with a reference standard (that would confirm or refute the diagnosis), and if the test and the reference standard were not evaluated in all patients in the study. Diagnostic studies that did not provide test accuracy statistics (for example sensitivity, specificity) were also excluded.

2.5 Critical appraisal of the evidence

From the papers retrieved, the Senior Health Service Research Fellow (SHSRF) synthesised the evidence for each question or questions into a narrative summary. These form the basis of this guideline. Each study was critically appraised using the Institute's criteria for quality assessment and the information extracted for included studies is given in Appendix D. Background papers, for example those used to set the clinical scene in the narrative summaries, were referenced but not extracted.

2.6 Health Economics

2.6.1 Health economic evidence reviews

A broad search of health economics literature was developed based on the original scoping search for the Guideline. The economic literature was identified by conducting searches in NHS Economic Evaluations Database (NHSEED) and also in MEDLINE, EMBASE and CINAHL using an economics search strategy developed by ScHARR at the University of Sheffield. Towards the end of the development of the Guideline, update searches were conducted to search for studies which had been published during the development phase of the Guideline. Databases of the results of the searches for each KCQ or topic area were created using the bibliographic management software Reference Manager™.

Identified titles and abstracts from the economic searches were reviewed by a health economist and full papers obtained as appropriate. Retrieved papers where then reviewed by a health economist, and considered for inclusion in the Guideline. No formal inclusion or exclusion criterion was applied *a priori*. Each paper was considered on its own merit, and in the context of availability of relevant published economic evaluations to inform the KCQs. All valid incremental cost-utility (QALY) analyses (including cost-consequence analyses where the incremental analyses could be calculated from the available study data), taking an NHS costing perspective, were included for all KCQs. In the absence of NHS based cost-utility analyses, incremental cost-effectiveness analyses using alternative outcome measures (e.g. the proportion of patients correctly diagnosed), were considered. For KCQs designated as high priority for economic evaluation (primarily investigations for diagnosis of stable and acute chest pain), if no UK based economic evaluations were found in the literature, then non-UK economic evaluations were considered for inclusion, if it was felt that they would inform the GDG's consideration of the cost-effectiveness for the KCQ under consideration (e.g. where there was dominance which was likely to be replicated in a UK based analysis).

The main reasons for exclusion were that the published study was not an economic evaluation, or that the study population did not meet the inclusion criteria for the review of clinical evidence, as set out in the NICE scope document and as agreed by the GDG. Reasons for exclusion for all requested papers were systematically recorded by the health economist using the reference manager database. A general descriptive overview of the included studies, their quality, and conclusions was presented and summarised in the form of a narrative review (see also Appendix E for the full extractions and reasons for exclusion).

2.6.2 Cost-effectiveness modelling

Having reviewed the health economics literature for this guideline, some de novo economic modelling was undertaken to supplement the available published economic analyses. A summary of the methods is provided here with details presented in Appendix F.

Firstly, with the cooperation of the developers of the model presented in the Mowatt 2008 HTA (Mowatt, G., Cummins, E., Waugh, N. et al, 2008), we have replicated their short-term model for diagnosis of CAD. Outputs from the replicated model include short term costs of diagnosis, the 2*2 true, false, positive, negative matrix, and the incremental cost per correctly diagnosed patient. Only the short term cost of diagnosis was previously available from the data presented in the HTA. Both the original analysis presented in the HTA, and the new analysis produced using the replicated model found heavily in favour of 64-slice CT coronary angiography (e.g. dominance over MPS with SPECT). The GDG, however, had reservations about the existing model, primarily:

- Its relevance for diagnosis of angina (as opposed to coronary artery stenosis assessed by invasive coronary angiography)
- The high sensitivity of 64-slice CT coronary angiography
- Risk of radiation from 64-slice CT coronary angiography.

The latter two reservations were addressed by making revisions to model input assumptions, and by the addition of two new treatment arms respectively. The two new treatment arms explore the health economic impact of using calcium scoring as a pre-cursor to full CT scanning using 64-slice CT. That is, first line testing in the new treatment arm would be by calcium scoring. Patients testing positive or uncertain would then proceed to second line testing using full 64-slice CT coronary angiography. Patients with a negative calcium score would have no further testing, as per the existing model protocol. The difference in the two new treatment arms is inclusion, or exclusion, of invasive coronary angiography as confirmatory third line test.

Because the GDG believed that there was still a role for functional (as opposed to anatomical) testing in chest pain patient populations with moderate likelihood of CAD, a new economic model was built comparing first line functional testing using stress MPS with SPECT compared to first line anatomical testing using invasive coronary angiography. In a sensitivity analysis, invasive coronary angiography was substituted with 64-slice CT coronary angiography.

The economic evaluations presented in the Mowatt et al HTAs of 2004 and 2008, (Mowatt, G., Vale, L., Brazzelli, M. et al, 2004) (Mowatt, G., Cummins, E., Waugh, N. et al, 2008) did build “speculative” longer term cost per QALY Markov models. These models required speculative assumptions to be made about the re-presentations of false-negatives, which of the coronary arteries had significant stenosis, and how these would be treated, as well as the survival and health related quality of life assumptions that would result for treated patients. The results of the longer term model analysis presented in Mowatt 2008 (Mowatt, G., Cummins, E., Waugh, N. et al, 2008), indicated that the difference in QALY outcomes was less than one quarter of one percent. Also, results presented in the MPS HTA of 2004 (Mowatt, G., Vale, L., Brazzelli, M. et al, 2004) (tables 39 and 40) indicate that for all but the lowest CAD prevalence populations, the ICERs of the short term cost per proportion of cases correctly diagnosed and the speculative longer term costs per QALY, have similar values, indicating that the former might be a useful proxy for the

latter. Based on the above, and because of the diagnostic scope of this guideline, the incremental economic analysis from our de novo models has been confined to the short term incremental cost per correct diagnosis. The GDG was consulted during the construction and interpretation of the model to ensure that appropriate assumptions, model structure, and data sources were used. The results of the de novo health economic analysis are presented in Chapter 5 of this Guideline with further detail of the results and methods presented in Appendix F.

2.7 Assigning levels to the evidence

The evidence levels and recommendation are based on the Institute's technical manual 'The guidelines manual'. April 2006. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk/guidelinesmanual. Evidence levels for included studies were assigned based upon details in Table 2.

1

Table 2	
Levels of evidence	
Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytical studies (for example, case reports, case series)
4	Expert opinion, formal consensus

2

3

2.8 Forming recommendations

In preparation for each meeting, the narrative and extractions for the questions being discussed were made available to the GDG one week before the scheduled GDG meeting. These documents were available on a closed intranet site and sent by post to those members who requested it.

GDG members were expected to have read the narratives and extractions before attending each meeting. The GDG discussed the evidence at the meeting and agreed evidence statements and recommendations. Any changes were made to the electronic version of the text on a laptop and projected onto a screen until the GDG were satisfied with these.

Recommendations were also documented in a care pathway which was reviewed regularly by the GDG.

All work from the meetings was posted on the closed intranet site following the meeting as a matter of record and for referral by the GDG members.

2.9 Areas without evidence and consensus methodology

The table of clinical questions in Appendix C1 indicates which questions were searched.

In cases where evidence was sparse, the GDG derived the recommendations via informal consensus methods, using extrapolated evidence where appropriate. All details of how the recommendations were derived can be seen in the ‘Evidence to recommendations’ section of each of the chapters.

2.10 Consultation

The guideline has been developed in accordance with the Institute’s guideline development process. This has included allowing registered stakeholders the opportunity to comment on the scope of the guideline and the draft of the full and short form guideline. In addition, the draft was reviewed by an independent Guideline Review Panel (GRP) established by the Institute.

The comments made by the stakeholders, peer reviewers and the GRP were collated and presented for consideration by the GDG. All comments were considered systematically by the GDG and the development team responded to comments.

2.11 Relationships between the guideline and other national guidance

2.11.1 Related NICE Guidance

It was identified that this guideline intersected with the following NICE guidelines published or in development. Cross reference was made to the following guidance as appropriate.

Published

- Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE clinical guideline 67 (2008). Available from www.nice.org.uk/guidance/CG67
- Secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline 48 (2007). Available from www.nice.org.uk/CG48
- Hypertension: management of hypertension in adults in primary care. NICE clinical guideline 34 (2006). Available from www.nice.org.uk/CG34
- Statins for the prevention of cardiovascular events. NICE technology appraisal guidance 94 (2006). Available from www.nice.org.uk/TA94
- Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction. NICE technology appraisal guidance 73 (2003). Available from www.nice.org.uk/TA73

- **Under development**

NICE is developing the following guidance (details available from www.nice.org.uk):

- Unstable angina and NSTEMI'. NICE clinical guideline. Publication expected March 2010.
- The management of stable angina. NICE clinical guideline. Publication expected July 2011.
- Prevention of cardiovascular disease. NICE public health guideline. Publication date to be confirmed.

2.12 Research Recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future. The Guideline Development Group's full set of research recommendations is detailed in the full guideline (see section 5).

Acute chest pain

2.12.1 Cost-effectiveness of multislice CT coronary angiography for ruling out obstructive CAD in people with troponin-negative acute coronary syndromes

Research question

Is multislice CT coronary angiography a cost-effective first-line test for ruling out obstructive CAD in people with suspected troponin-negative acute coronary syndromes?

Research recommendation

Investigation of the cost-effectiveness of multislice CT coronary angiography as a first-line test for ruling out obstructive CAD in people with suspected troponin-negative acute coronary syndromes.

Why this is important

Current European Society of Cardiology guidelines state that in troponin-negative ACS, with no ST-segment change on the ECG, 'a stress test is recommended… in patients with significant ischaemia during the stress test, coronary angiography and subsequent revascularisation should be considered'. Yet stress testing has relatively low sensitivity and specificity for diagnosing CAD in this group of people. Therefore a significant proportion of at-risk people are missed while others with normal coronary arteries are subjected to an unnecessary invasive coronary angiogram. Multislice CT coronary angiography is highly sensitive and provides a potentially useful

means for early rule-out of CAD in troponin-negative acute coronary disease. We need to know whether it is cost effective compared with exercise ECG as a first test in the diagnostic work up of this group.

2.12.2 Novel cardiac biomarkers in people with acute chest pain

What is the effectiveness and cost effectiveness of new, high-sensitivity troponin assay methods and other new cardiac biomarkers in low, medium, and high risk people with acute chest pain?

Research recommendation

Evaluation of new, high-sensitivity troponin assay methods in low, medium and high risk groups with acute chest pain.

Evaluation of other putative biomarkers compared with the diagnostic and prognostic performance of the most clinically effective and cost-effective troponin assays.

Why this is important

Newer more sensitive troponin assays may offer advantages over previous assays in terms of diagnostic accuracy. They may allow exclusion of myocardial infarction earlier than the 12 hour time frame currently required. Other proposed biomarkers need to be compared to the best available troponin assays.

2.12.3 Refining the use of telephone advice in people with chest pain

Research question

In what circumstances should telephone advice be given to people calling with chest pain? Is the appropriateness influenced by age, sex or symptoms?

Research recommendation

To develop a robust system for giving appropriate telephone advice to people with chest pain.

Why this is important

The telephone is a common method of first contact with healthcare services, and produces a near uniform emergency response to chest pain symptoms. Such a response has considerable economic, social and human costs. Research should be conducted to clarify if an emergency response in all circumstances is appropriate, or if there are identifiable factors such as age, sex, or associated symptoms that would allow a modified response and a more appropriate use of resources.

Stable chest pain

2.12.4 Establishing a national registry for people who are undergoing initial assessment for stable angina

Research question and recommendations

Can a national registry of people presenting with suspected angina be established to allow cohort analysis of treatments, investigations and outcomes in this group? Such a registry would provide a vital resource for a range of important research projects, including:

- development and validation of a new score for assessing the pre-test probability of disease, addressing outstanding uncertainties in the estimation of the pre-test probability of CAD based on simple measures made at initial assessment (history, examination, routine bloods, resting 12-lead ECG)
- assessment of the extent to which new circulating biomarkers add additional information to measures made at initial assessment
- provision of a framework for trial recruitment without significant work-up bias allowing evaluation of the diagnostic and prognostic test performance of CT-based, MR, echocardiography, and radionuclide technologies.

Why this is important

A national prospective registry of consecutive people with suspected stable angina before initial diagnostic testing does not currently exist in the UK or in any other country. Establishing such a registry would offer the following methodological strengths; statistical size, representative patients without work-up bias, contemporary data. This would overcome key problems in much of the existing evidence base.

Accurate assessment of pre-test likelihood of coronary disease is needed to inform the cost-effective choice of investigative technologies such as CT coronary calcium scoring for people with chest pain that may be caused by myocardial ischaemia. The data on which pre-test likelihood is based date from 1979 in a US population and may not be applicable to contemporary UK populations. There remain continuing uncertainties about the initial assessment of people with suspected stable angina. For example, the possible contributions of simple clinical measures such as body mass index, routine blood markers (for example, haemoglobin) or novel circulating biomarkers to estimates of the pre-test likelihood of CAD are not known and require further assessment in the whole population and in predefined subgroups including ethnic minorities.

2.12.5 Cost-effectiveness of multislice CT coronary angiography compared with functional testing in the diagnosis of angina

Research question

What is the clinical and cost effectiveness of multislice CT coronary angiography compared with functional testing in the diagnosis of angina in a population of people with stable chest pain who have a moderate (30–60%) pre-test likelihood of CAD?

Research recommendation

Further research should be undertaken to evaluate the clinical and cost effectiveness of multislice CT coronary angiography compared with functional

testing in the diagnosis of angina in a population of people with stable chest pain who have a moderate pre-test likelihood of CAD.

Why this is important

Multislice CT coronary angiography has developed rapidly in recent years. Published reviews have shown it to be highly effective in the diagnosis of anatomically significant CAD, and costing data indicate that tests can be run at a relatively low cost. However, questions remain about the ability of multislice CT coronary angiography to accurately identify stenoses of functional significance (that is, those that are sufficient to cause angina) in people with stable chest pain. This is especially true for people with a moderate pre-test likelihood of significant CAD.

Cost-effectiveness modelling to date has used the diagnosis of CAD as a short-term outcome, and as such inexpensive anatomical tests like multislice CT coronary angiography fare better than functional testing strategies such as MPS with SPECT, stress perfusion MR imaging and stress echocardiography. Because the diagnosis of angina is the true outcome of interest, health economic modelling is needed to evaluate diagnostic technologies on their ability to diagnose stable angina.

2.12.6 Information about presenting and explaining tests

Research question

All people presenting with chest pain will need to decide whether to accept the diagnostic and care pathways offered. How should information about the diagnostic pathway and the likely outcomes, risks and benefits, with and without treatment, be most effectively presented to particular groups of people, defined by age, ethnicity and sex?

Research recommendation

To establish the best ways of presenting information about the diagnostic pathway to people with chest pain.

Why this is important

Methods of communication (both the content and delivery) will be guided by current evidence-based best practice. Controlled trials should be conducted based on well-constructed randomised controlled clinical trials comparing the effects of different methods of communication on the understanding of the person with chest pain. Such studies might consider a number of delivery mechanisms, including advice and discussion with a clinician or a specialist nurse as well as specific information leaflets or visual data.

Any trials should also investigate the feasibility of introducing a suggested guideline protocol to be used with all people presenting with chest pain when faced with options concerning their clinical pathway.

Only by clearly explaining and then discussing the proposed diagnostic and care pathways can the healthcare professional be reasonably certain that informed consent has been obtained and that a patient's moral, ethical and spiritual beliefs, expectations, and any misconceptions about their condition, have been taken into account. Consideration should be given to any communication problems the person may have.

2.13 Acknowledgements

We gratefully acknowledge the contributions of Beth Shaw as the guideline lead during the scoping phase, Meeta Kathoria for project managing the guideline through the scoping and development phase, Anne Morgan for her work on cost-effectiveness and clinical evidence reviews and Steve Goodacre for information and guidance regarding his published health economic analysis. Thanks to the team from Aberdeen for sharing their short term cost-effectiveness model, which assisted in the development of other cost-effectiveness model developed for this Guideline. Thanks also to Norma O'Flynn for her continued advice during the guideline's development. This guideline should also address Gill Ritchie and Vanessa Nunes for their help and advice with regard to the clinical and cost-effectiveness reviews. In addition, thanks also to Phil Alderson and Joanne Lord for their guidance on NICE related issues. We gratefully acknowledge administrative help from

Tamara Diaz and secretarial support from Lauren Redrup. Finally we are also very grateful to all those who advised the development team and GDG and so contributed to the guideline process.

2.14 Definitions, Glossary and Abbreviations

a) Acute myocardial infarction: The Universal definition of the Joint ESC/ACCF/AHA/WHF Task Force is used in this guideline. When there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia, any one of the following criteria meets the diagnosis for myocardial infarction in patients presenting with acute chest pain or discomfort:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:
- Symptoms of ischaemia
- ECG changes indicative of new ischaemia (new ST-T changes or new left bundle branch block (LBBB)
- Development of pathological Q waves in the ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

b) Unstable angina: This often presents in a comparable way to acute myocardial infarction but without biomarker evidence of myocardial necrosis.

Working definition: new onset chest pain / discomfort, or abrupt deterioration in previously stable angina, with chest pain / discomfort occurring frequently and with little or no exertion, and often with prolonged episodes.

c) Stable angina: Unlike acute coronary syndromes, there are no case definitions of stable angina that have been agreed internationally.

Working definition angina is a symptom of myocardial ischaemia that is recognized clinically by its character, its location and its relation to provocative stimuli.

Relation to CAD: Angina is usually caused by obstructive CAD that is sufficiently severe to restrict oxygen delivery to the cardiac myocytes. Generally speaking angiographic luminal obstruction found during invasive coronary angiography estimated at ≥ 70% is regarded as “severe” and likely to be a cause of angina, but this will depend on other factors listed below that influence ischaemia independently of lesion severity.

Factors intensifying ischaemia. Such factors allow less severe lesions (say ≥ 50%) to produce angina;

- Reduced oxygen delivery: anaemia, coronary spasm
- Increased oxygen demand: tachycardia, left ventricular hypertrophy
- Large mass of ischaemic myocardium: proximally located and longer lesions.

Factors reducing ischaemia. Such factors may render severe lesions (≥70%) asymptomatic;

- Well developed collateral supply
- Small mass of ischaemic myocardium: distally located lesions, old infarction in the territory of coronary supply.

Angina without epicardial CAD. When angina with evidence of ischaemia occurs in patients with angiographically “normal” coronary arteries (syndrome X) pathophysiological mechanisms are often unclear.

Term	Description
Acute Chest Pain	Chest pain / discomfort which has occurred recently and may still be present, is of suspected cardiac origin and which may be due to acute myocardial infarction or unstable angina (see below).
Acute coronary syndrome	A condition in which there is an event in a coronary artery with plaque rupture or erosion, or coronary dissection, with the formation of intra-coronary thrombus. A single term which includes

	both unstable angina and myocardial infarction.
Acute myocardial infarction	The Universal definition of the Joint ESC/ACCF/AHA/WHF Task Force is used in this guideline. (Thygesen, K., Alpert, J. S., and White, H. D., 2007) When there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia, any one of the following criteria meets the diagnosis for myocardial infarction in patients presenting with acute chest pain or discomfort: • Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following: • Symptoms of ischaemia • ECG changes indicative of new ischaemia (new ST-T changes or new left bundle branch block (LBBB) • Development of pathological Q waves in the ECG • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
Annual risk reduction	The difference between the percentage annual incidence of an adverse outcome in a treatment group compared with that in a control group.
Biomarker	An objective measure of an indicator of a normal biologic process, a pathogenic process, or pharmacologic response to a therapeutic intervention.
Cardiovascular event	An acute coronary, cerebrovascular or peripheral arterial event.
Cardiovascular risk	The risk of a cardiovascular event occurring.
Clinical classification	A method of allocating patients into different groups based on clinical characteristics.
Clinical risk stratification	A method of allocating patients to different levels of risk of them suffering an adverse event, based on their clinical characteristics.
Coronary angiography	An invasive diagnostic test which provides anatomical information about the degree of stenosis (narrowing) in a coronary artery. It involves manipulation of cardiac catheters from an artery in the arm or top of the leg. A contrast medium is injected into the coronary arteries, and the flow of contrast in the artery is monitored by taking a rapid series of X-rays. It is considered the 'gold standard' for providing anatomical information and defining the site and severity of coronary artery lesions (narrowing's).
Coronary artery	An artery which supplies the myocardium.
Coronary artery disease	Coronary artery disease is a condition in which atheromatous plaque builds up inside the coronary artery. This leads to narrowing of the arteries which may be sufficient to restrict blood

	flow and cause myocardial ischaemia.
Calcium scoring	Calcium scoring is a technique by which the extent of calcification in the coronary arteries is measured and scored.
Cost-benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment as a net gain results.
Cost-consequences analysis	A type of economic evaluation where various health outcomes are reported in addition to the costs for each intervention under consideration. There is however no formal synthesis of the costs and health effects.
Cost-effectiveness acceptability curve (CEAC)	A CEAC plots the probability of an intervention being cost-effective compared with alternative intervention(s), for a range of maximum monetary values, that decision-makers might be willing to pay, for a particular unit change in outcome.
Cost-effectiveness analysis	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of incremental costs per unit of effectiveness.
Health Economic Model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporates evidence from a variety of sources in order to estimate costs and health outcomes.
Cost-minimisation analysis	An economic evaluation that finds the least costly alternative therapy. This type of analysis implicitly assumes that the health benefits of the competing interventions are equivalent.
Cost-utility analysis	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).
Discounting	Discounting is the process by which economist make allowances for society's time preference for costs and benefits. All else being equal, society places a higher value on the same unit of cost and benefit today than it does for the same unit in the future. For example, society prefers to receive £100 today as opposed to £100 in n years time. The differential is expressed in terms of the discount factor DF, where $DF = 1/ (1+ r)^n$ and where *r* is the discount rate, and *n* is the number of years forward from the current year.
Dominance	A heath intervention is said to be dominant if it is both more effective and less costly than an alternative intervention.
EBCT	Electron Beam Computed Tomography.

Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Emergency	Immediate request leading to an immediate response from the ambulance service with a 'blue light' ambulance.
Equivocal	Where a diagnostic test result is indeterminate because it can be interpreted in one of 2 or more ways.
Exercise ECG (sometimes known as an exercise test or stress ECG)	An investigation which measures the electrical activity from the heart during exercise, usually used to look for signs of myocardial ischaemia.
Extended dominance	Where a combination of two alternative strategies dominates a third.
Evidence statements	A summary of the evidence distilled from a review of the available clinical literature.
Evidence-based questions (EBQs)	Questions which are based on a conscientious, explicit and judicious use of current best evidence.
Health economics	The branch of economics concerned with the allocation of society's scarce health resources, between alternative healthcare treatments/programmes, in an attempt to improve the health of the population.
Health related quality of life	An attempt to summarise an individual's or the population's quality of life resulting from the combined effect of their physical, mental, and social well-being.
Haemodynamic instability	A clinical state of perfusion failure with clinical features of circulatory shock and or severe heart failure, and requiring pharmacological or mechanical support to maintain normal blood pressure and or adequate cardiac output. It may also be used to describe a clinical state when one or more physiological measurements, for example blood pressure and or pulse, are outside the normal range.
Incremental cost-effectiveness ratio (ICER)	The difference in the costs of two alternative treatment strategies/programmes, divided by the difference in the effectiveness outcomes of the treatment strategies/programmes for a defined population of interest. That is; $\frac{\text{Cost treatment B – Cost treatment A}}{\text{Effectiveness treatment B - Effectiveness treatment B}}$
Killip classification	The Killip classification is a system used in people with acute myocardial infarction to stratify them according to whether there are signs of heart failure and haemodynamic compromise.
Life years	The number of years lived by an individual or a population. For example, if a population of 50 patients live for an average addition 2 years each as the result of receiving a healthcare intervention,

	then the intervention has provided 100 life years gained.
Meta regression analysis	An approach for aggregating data from different clinical trials which examine the same question and report the same outcomes, and relating sources of variation in treatment effects to specific study characteristics.
Multiple logistic regression analysis	In a clinical study, an approach to examine which variables independently explain an outcome.
Multislice CT coronary angiography	Multi-slice CT coronary angiography is a non-invasive investigation which provides coronary calcium scoring and anatomical information about the degree of stenosis (narrowing) in the coronary arteries. The scanner has a special X-ray tube and rotation speed and as the technology has advanced the number of slices in each rotation has increased. A dual source scanner has two pairs of X-ray sources and multi-slice detectors mounted at 90 degrees to each other.
Myocardial infarction	See Acute Myocardial Infarction.
Myocardial perfusion scintigraphy with SPECT (MPS)	MPS involves injecting small amounts of radioactive tracer to evaluate perfusion of the myocardium via the coronary arteries at stress and at rest. The distribution of the radioactive tracer is imaged using a gamma camera. In SPECT the camera rotates round the patient and the raw data processed to obtain tomographic images of the myocardium. Cardiovascular stress may be induced by either pharmacological agents or exercise.
Opioid	An opioid is a chemical that works by binding to opioid receptors, and has pain killing properties. The term opiate is sometimes used as synonym, but this is natural opium alkaloids occurring in the resin of the opium poppy and the semi-synthetic opioids derived from them, and should be restricted to this.
Opportunity cost	The cost in terms of health benefits foregone by allocating resources to one intervention over an alternative intervention. The definition implicitly acknowledges the concept of scarcity of healthcare resources.
Probabilistic sensitivity analysis (PSA)	The process of measuring the degree of uncertainty around outcomes in an economic evaluation by assigning probability distributions to all of the key parameters in the evaluation, and then simultaneously generating values from each of these distributions using techniques of random number generation such as Monte Carlo methods.
Quality adjusted life year (QALY)	An index of survival weighted to account for quality of life. The year of life is weighted by a utility value U (where $0 \leq U \leq 1$). U reflects the health related quality of life, such that a U of zero represents the worst possible quality of life (equivalent to being dead), and a U of 1 represents perfect health. For example, 1 QALY is achieved if one patient lives in perfect health for one year, or alternatively if 2 people live in perfect health for 6 months each. Alternatively, a person living with a quality of life represented by a U value of 0.5 for 2 years is also representative of 1 QALY value. QALYs have the advantage of incorporating changes in both quantity (longevity/survival) and quality of life (morbidity as represented by psychological, physical and social

	functioning for example). QALYs are core to cost-utility analysis where the QALY is used as the measure of effectiveness in the economic evaluation.
Relative risk reduction	The ratio of the probability of an event occurring in the treatment group compared to the control group.
Sensitivity	Sensitivity is the proportion of people with the disease who have a positive test. Sensitivity reflects how good the test is at identifying people with the disease. A measure of the diagnostic accuracy in including individuals with the condition. Number of True Positives divided by (Number of True Positives + Number of False Negatives) • True positive: People correctly diagnosed with the condition • False positive: Healthy people wrongly diagnosed with the condition • True negative: Healthy people correctly identified as healthy • False negative: People wrongly identified as healthy
Sensitivity analysis	A means of exploring the uncertainty in the results of an economic evaluation/model by varying the parameter values of the included variables one at a time (univariate sensitivity analysis) or simultaneously (multi-variate sensitivity analysis).
Significant coronary artery disease	Significant CAD found during invasive coronary angiography is ≥ 70% diameter stenosis of at least one major epicardial artery segment or 50% ≥ diameter stenosis in the left main coronary artery a). Factors intensifying ischaemia. Such factors allow less severe lesions (say ≥ 50%) to produce angina □ Reduced oxygen delivery: anaemia, coronary spasm □ Increased oxygen demand: tachycardia, left ventricular hypertrophy □ Large mass of ischaemic myocardium: proximally located lesions □ and longer lesion length b). Factors reducing ischaemia. Such factors may render severe lesions (≥ 70%) asymptomatic □ Well developed collateral supply □ Small mass of ischaemic myocardium: distally located lesions, old infarction in the territory of coronary supply. c). Angina without epicardial coronary artery disease. When angina occurs in patients with angiographically “normal” coronary arteries (syndrome X) pathophysiological mechanisms are often unclear.
Specialist	A healthcare professional who has expert knowledge of and skills in a particular clinical area, especially one who is certified by a higher medical educational organization.
Specificity	Specificity is the proportion of people free of disease who have a negative test. Specificity reflects how good the test is at identifying

	people without the disease. A measure of the diagnostic accuracy in excluding individuals without the condition. Number of True Negatives divided by (Number of True Negatives + Number of False Positives) • True positive: People correctly diagnosed with the condition • False positive: Healthy people wrongly diagnosed with the condition • True negative: Healthy people correctly identified as healthy • False negative: People wrongly identified as healthy
Stable angina	Unlike acute coronary syndromes, there are no case definitions of stable angina that have been agreed internationally. Working definition angina is a symptom of myocardial ischaemia that is recognized clinically by its character, its location and its relation to provocative stimuli. Relation to coronary artery disease: Angina is usually caused by obstructive coronary artery disease that is sufficiently severe to restrict oxygen delivery to the cardiac myocytes. Generally speaking angiographic luminal obstruction estimated at ≥70% is regarded as "severe" and likely to be a cause of angina, but this will depend on other factors listed below that influence ischaemia independently of lesion severity. *Factors intensifying ischaemia.* Such factors allow less severe lesions (say ≥50%) to produce angina Reduced oxygen delivery: anaemia, coronary spasm Increased oxygen demand: tachycardia, left ventricular hypertrophy Large mass of ischaemic myocardium: proximally located and longer lesions *Factors reducing ischaemia.* Such factors may render severe lesions (≥ 70%) asymptomatic Well developed collateral supply Small mass of ischaemic myocardium: distally located lesions, old infarction in the territory of coronary supply. *Angina without epicardial coronary artery disease.* When angina with evidence of ischaemia occurs in patients with angiographically "normal" coronary arteries (syndrome X) pathophysiological mechanisms are often unclear.
Stable chest pain	Chest pain occurring intermittently, whose frequency and intensity does not vary significantly day to day and which often occurs with a predictable pattern. May also be described as a chest discomfort.
Stress echocardiograph	Echocardiography is an ultrasound examination of the heart. Exercise or pharmacological stress may be used to look for reversible systolic regional wall motion abnormalities consistent

	with the development of myocardial ischaemia.
Stress ECG	See exercise ECG above.
Stress magnetic resonance imaging (stress MRI)	MRI is a diagnostic procedure that uses radio waves in a strong magnetic field. The pattern of electromagnetic energy released is detected and analysed by a computer to generate detailed images of the heart. Stress MRI is a specific application in which a contrast agent is used to detect myocardial blood flow at stress and at rest. Pharmacological stress is used to induce cardiovascular stress.
Technology appraisal	Formal ascertainment and review of the evidence surrounding a health technology, which in this publication refers to technology appraisals undertaken by NICE only.
TAG	Technology Appraisal Guidance (see Technology Appraisal)
Troponin	A complex of three regulatory proteins that is integral to muscle contraction in skeletal and cardiac muscle. The presence of the subtypes, troponin I and troponin T, in peripheral blood is very sensitive and specific for detecting myocardial damage.
Unstable angina	This often presents in the same way as myocardial infarction but without biomarker evidence of myocardial necrosis. The working definition for this guideline is: new onset chest pain / discomfort, or abrupt deterioration in previously stable angina, with chest pain / discomfort occurring frequently and with little or no exertion, and often with prolonged episodes.
Unstable chest pain	Chest pain which occurs with increasing frequency, often with increasing intensity, and which occurs with no predictable pattern. May also be described as a chest discomfort.
Urgent	Requiring an early action on the same day, but not as an emergency. Usually includes additional clarification of the timescale using clinical judgement.
Utility	A variable usually taking a value between zero (death) and unity (perfect health) which reflects health related quality of life, and which is used in the calculation of QALYs.
Willingness to pay (WTP)	The amount of money that an individual or society is willing to pay in order to achieve a specified level of health benefit. For example, it is generally recognised that the current willingness to pay for an incremental QALY gain in the NHS is somewhere between £20,000 and £30,000.

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Abbreviations

Abbreviation	Description
2VD	two-vessel disease
3VD	three-vessel disease
AC	attenuation-corrected
ACER	average cost-effectiveness ratio
AMI	acute myocardial infarction
BMJ	British Medical Journal
CA	coronary angiography
CABG	coronary artery bypass graft
CAD	coronary artery disease
CHD	coronary heart disease
CI	confidence interval
CRD	Centre for Reviews and Dissemination
DTM	decision tree model
EBCT	electron beam computed tomography
ECG	electrocardiography
ECHO	echocardiography
ExECG	exercise ECG
FN	false negative
FP	false positive
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
LAD	left anterior descending
LBBB	left bundle branch block
LMS	left main stem
LR	likelihood ratio
MI	myocardial infarction
MIBI	technetium-99m sestamibi
MPI	myocardial perfusion imaging
MPS	myocardial perfusion scintigraphy
MRI	magnetic resonance imaging
MVD	multivessel disease
NICE	National Institute for Health and Clinical Excellence
NIDDM	Non-insulin dependent diabetes mellitus
NSF	National Service Framework
OR	odds ratio
PET	positron-emission tomography
PTCA	percutaneous transluminal coronary angioplasty
QALY	quality-adjusted life-year
QoL	quality of life
QUADAS	quality assessment of diagnostic accuracy studies
RCT	randomised controlled trial
ROC	receiver operating characteristic
RR	relative risk
SA	sensitivity analysis
SPECT	single photon emission computed tomography

SRS	summed rest score
SVD	single-vessel disease
TN	true negative
TP	true positive
BB	beta-blocker
CAD	coronary artery disease
CCB	calcium-channel blocker
CFR	coronary flow reserve ratio
LDL	low-density lipoprotein
MBF	myocardial blood flow
MPI	myocardial perfusion imaging
PCI	percutaneous coronary intervention
PET	positron emission tomography
Stable Angina	A symptom of myocardial ischaemia that is recognized clinically by its character, its location and its relation to provocative stimuli.
Unstable Angina	New (within 24 hours) onset angina or abrupt deterioration in previously stable angina, often with prolonged episodes of rest pain.

1

3 Information for Patients Chapter

Return to Recommendations

3.1.1 Introduction

In general conveying information to the patient requires good communication skills, assessment of prior knowledge and readiness to learn, and effective teaching strategies. Information giving to an acutely ill patient such as a patient with acute chest pain in the emergency department poses a number of challenges, for example; disorientation due to unfamiliarity of setting, technical complexity of procedures and conveying the findings particularly if the results are indeterminate and further diagnostic testing is required, patients preconceptions of the outcome of their acute chest pain, and the capacity of the patient with acute symptoms to engage with the physician.

Patient information giving should be viewed as a continuous process that should be part of every patient encounter i.e. on hospital arrival, and thereafter before each investigative procedure with subsequent follow up with an explanation of the results. It may also be appropriate to convey information to carers and family members.

Despite the importance of information giving in the patient with acute chest pain in the emergency department, literature on this area is particularly sparse. Almost exclusively studies on information giving / education are in patients with a diagnosis of acute MI, ACS, angina or non cardiac chest pain and these populations are not part of this guideline. Once a diagnosis is made in a patient with either acute chest pain, stable angina, or the patient is diagnosed with non cardiac chest pain, the patient exits the care pathway of this guideline. One randomised controlled trial was identified that examined the use of an information sheet in the education of patients with acute chest pain of suspected cardiac origin.

3.1.2 Evidence statements

A non blinded randomised controlled trial that compared standard verbal advice or verbal advice followed by an information sheet in patients with acute

chest pain of suspected cardiac origin (700 patients) found that an information sheet reduced anxiety and depression, and improved mental health and perception of general health at 1 month follow up. There was no difference between the patients who received the information sheet compared with those who did not for the following outcomes; satisfaction with care, severity of pain, prevalence of further pain, patient modification of lifestyle factors, seeking additional information, and altered planned action in the event of recurrent pain (Arnold, J., Goodacre, S., Bath, P. et al, 2009).

3.1.3 Evidence

A non-blinded randomised controlled trial examined the use of an information sheet in patients with acute chest pain in the emergency department. The study population of 700 patients was divided into an intervention group (346 patients) and a control group (351 patients) (Arnold, J., Goodacre, S., Bath, P. et al, 2009). Patients with acute chest pain were recruited if they were aged over 25 years, had no changes for ACS on resting ECG, had no suspected life threatening non-cardiac disease and did not have known CAD presenting with recurrent or prolonged episodes of cardiac type chest pain. Patients were excluded if they were unable to read or comprehend the trial documentation. The study population had a mean age of 48.6 years, and 61.6% were men (Arnold, J., Goodacre, S., Bath, P. et al, 2009).

Four separate information sheets were developed for patients in the following categories after diagnostic assessment; definite angina, definite benign non-cardiac chest pain, uncertain cause requiring further cardiology investigation, and uncertain cause suitable for expectant management where no further action was to be taken unless there was a change in the patient signs and symptoms. Information sheets were deemed suitable for 19 patients with a diagnosis of angina (mean age 69 years, 58% men), 162 patients with a diagnosis of definite benign non cardiac pain (mean age 43 years, 65% men), 61 patients with a diagnosis of uncertain cause requiring further cardiology investigation (mean age 52 years, 49% men), and 458 patients with a diagnosis of uncertain cause suitable for expectant management (mean age 49 years, 62% men) (Arnold, J., Goodacre, S., Bath, P. et al, 2009).

Intervention took place after diagnostic assessment was complete and the patient's management plan had been formulated. The chest pain nurses determined which of the 4 information sheets was most appropriate for each patient and they were then randomised to either intervention or control groups. After verbal advice, all patients in the intervention group were given the appropriate information sheet to read and take away. One month after recruitment all patients were sent a questionnaire by post. Questionnaires were re-sent to non-responders at six and eight weeks (Arnold, J., Goodacre, S., Bath, P. et al, 2009).

The primary outcome was patient score on the anxiety subscale of the hospital anxiety and depression scale. This self screening scale was developed and validated for measuring symptoms of anxiety and depression in the outpatient setting. Secondary outcomes included the following; patient depression score and SF-36 score for quality of life, patient satisfaction as measured by a consumer satisfaction survey developed by the Group Health Association of America, evidence of further symptoms, and planned health seeking behaviours in response to further pain (Arnold, J., Goodacre, S., Bath, P. et al, 2009).

There was a 70.6% response rate to the questionnaire. Compared with patients receiving standard verbal advice, patients receiving advice and an information sheet had significantly lower anxiety scores 7.61 versus 8.63 (95%CI 0.20 to 1.84, $P = 0.015$) and depression scores 4.14 versus 5.28 (95%CI 0.41 to 1.86, $P = 0.002$). On the anxiety subscale, intervention was associated with a shift from mild or moderate anxiety to no anxiety. On the depression subscale the intervention was associated with a shift towards lower scores among those with no depression and also a reduction in the proportion with moderate depression. The number needed to treat (NNT) to avoid one case of anxiety was 9.0 and the NNT for depression was 13.1. Patients in the intervention group had significantly higher scores for mental health ($P < 0.007$) and general health perception ($P < 0.006$) on the SF-36 than those in the control group. There were no other significant differences between the two groups (Arnold, J., Goodacre, S., Bath, P. et al, 2009).

There are some limitations which may have biased the outcome of this study. The study was not blinded, and there was a 30% non response rate to the questionnaire hence there may be significant attrition bias. There was potential for contamination between groups by the nurses giving the information on the information sheet verbally to the control group. The results from the questionaire were pooled across all four patient groups, and there is a question of the transferability of the findings given that some of the patients had chest pain of non cardiac origin (Arnold, J., Goodacre, S., Bath, P. et al, 2009).

Despite these limitations however, the authors concluded that as the information sheets are simple to administer and outcomes of the study were on balance positive, the use of these sheets should be recommended in patients receiving diagnostic assessment for acute chest pain (Arnold, J., Goodacre, S., Bath, P. et al, 2009).

3.1.4 Evidence to recommendations

Very little evidence was found about providing information for unselected patients with acute chest pain. This contrasts with that for patients with acute myocardial infarction for which there is far more evidence. However, the GDG recognised that the time before a diagnosis is confirmed is an anxious one for many patients and their families / carers, and that providing information which helps people cope with the uncertainty is important. The available evidence was that information should be given verbally, supported by written information sheets.

4 People Presenting with Acute Chest Pain Chapter

4.1 Introduction

This section 4.1 examines the assessment of patients presenting with acute chest pain of suspected cardiac origin and is intended for patients presenting in both the primary and secondary healthcare settings. Importantly the initial assessment is aimed at identifying those patients with acute MI or ACS and in whom very early therapeutic interventions will make a substantial difference to patient outcomes. This encompasses determining risk factors for CAD, obtaining a clinical history, physical examination, resting ECG recording, and cardiac biomarker measurement. In reviewing this evidence and making recommendations the GDG emphasized the importance of early recognition of patients with acute MI or ACS, and adopted a high threshold for ruling out these diagnoses. If an acute MI or ACS has been ruled out, patients may still have chest pain of cardiac origin (for example patients with risk factors for CAD and troponin negative results), and these patients have been identified for further assessment according to the stable chest pain recommendations in Chapter section 1.3.

Other life threatening conditions may also present with acute chest pain. The GDG recognised the importance of diagnosing these and that these patients may need further early diagnostic testing. However, the purpose of this guideline is to identify patients with chest pain due to myocardial ischaemia / infarction and it was beyond the scope of the guideline to search for the evidence and make detailed recommendations for making these other diagnoses.

4.2 Assessment

4.2.1 Initial assessment and referral to hospital; history, risk factors and physical examination

Return to Recommendations

4.2.1.1 Evidence statements for initial assessment and referral to hospital

1 There is considerable heterogeneity in the patient characteristics and study settings between cohort studies and within the studies selected for meta-analyses in the systematic reviews for the diagnosis of acute MI / ACS.

2 The majority of studies on history, risk factors and physical examination in patients with acute chest pain are in the emergency department setting rather than in primary care.

3 In patients presenting with acute chest pain, there were chest pain characteristics and associated symptoms which increased or decreased the likelihood of acute MI / ACS, but none either alone or in combination were identified which reliably confirmed or excluded a diagnosis of acute MI / ACS. (Swap, Clifford J. and Nagurney, John T., 2005) (Bruyninckx, R., Aertgeerts, B., Bruyninckx, P. et al, 2008) (Mant, J., McManus, R. J., Oakes, R.-A. L. et al, 2004)

4 One systematic review in patients with suspected acute MI / ACS found that if pain radiates to one shoulder or both shoulders or arms, or is precipitated by exertion, it is more likely that the patient has an acute MI or ACS. If the pain is stabbing, pleuritic, positional or reproducible by palpation it is less likely the patient has acute MI or ACS. (Swap, Clifford J. and Nagurney, John T., 2005)

5 One systematic review in patients with suspected acute MI / ACS found that the presence of chest wall tenderness (pain on palpitation) reduced the likelihood of acute MI or ACS. (Bruyninckx, R., Aertgeerts, B., Bruyninckx, P. et al, 2008)

6 One systematic review in patients with suspected acute MI / ACS found that right sided radiation of chest pain, the presence of pulmonary crackles, systolic blood pressure under 80 mmHg or a third heart sound increased the likelihood of acute MI or ACS. The presence of pain on palpation, pleuritic pain or positional thoracic pain reduced the likelihood of acute MI or ACS. (Mant, J., McManus, R. J., Oakes, R.-A. L. et al, 2004)

7 One cohort study used seven predefined criteria based on clinical symptoms, history and risk factors to evaluate patients with acute chest pain and categorised the criteria as typical or atypical of myocardial ischemia as follows;

- location of chest pain; typical left sided, substernal, atypical; right sided
- character of chest pain; typical; squeezing or crushing, burning, tightness, heaviness or deep, atypical; stabbing, single spot, superficial
- radiation of chest pain; typical; to the left or both arms, neck and back, atypical; not radiating
- appearance of chest pain; typical; exercise induced, undulating, relieved with rest or nitroglycerin, atypical; inducible by local pressure, abrupt palpitations, sustained, position dependent, respiration dependent, cough dependent
- vegetative signs; typical; dyspnoea, nausea, diaphoresis, atypical; absence of vegetative signs)
- history of CAD; typical MI, percutaneous coronary interventions (PCI), coronary artery bypass graft (CABG), angiographic CAD, atypical; absence of CAD history
- risk factors of CAD (having 2 or more) typical; smoking obesity, hypertension, diabetes, hyperlipidaemia, family history, atypical absence or only 1 risk factor.

The study found that typical criteria had limited use in the identification of patients with acute MI and adverse events at 6

months, and increased numbers of typical criteria were diagnostically unhelpful. Increasing numbers of atypical criteria were associated with increasing positive predictive values for excluding acute MI and major coronary adverse events at six months. (Schillinger, Martin, Sodeck, Gottfried, Meron, Giora et al, 2004)

4.2.1.2 Clinical evidence for clinical history, risk factors and physical examination

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

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

Three systematic reviews (Swap, Clifford J. and Nagurney, John T., 2005) (Bruyninckx, R., Aertgeerts, B., Bruyninckx, P. et al, 2008) (Mant, J., McManus, R. J., Oakes, R.-A. L. et al, 2004), and one cohort study (Schillinger, Martin, Sodeck, Gottfried, Meron, Giora et al, 2004) 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 past medical history and other factors such as age, gender and family history. Physical examination is defined as the patient's signs elicited when they present with chest pain.

The first systematic review identified 28 studies on the value and limitations of clinical history in the evaluation of patients with suspected MI or ACS (search

date 2005) (Swap, Clifford J. and Nagurney, John T., 2005). Prior systematic reviews and prospective and retrospective cohort studies were included in the analyses. The characteristics of the chest pain examined were as follows; the quality, location, radiation, size of area or distribution, severity, time of onset (and ongoing), duration, first occurrence frequency, and similarity to previous cardiac ischaemic episodes. The following factors that precipitated or aggravated chest pain were also examined; pleuritic, positional, palpable, exercise, emotional stress, relieving factors, and associated symptoms (Swap, Clifford J. and Nagurney, John T., 2005).

Analyses found that there was an increased likelihood of acute MI or ACS if the chest pain radiated to one shoulder or both shoulders or arms, or was precipitated by exertion. Conversely, there was a decreased likelihood of acute MI or ACS if the pain was stabbing, pleuritic, positional, or reproducible by palpation. Table 3 details the calculated positive likelihood ratio(s) (PLR(s)) for the components of the clinical history that were assessed. No single component was sufficiently predictive to rule out a diagnosis of acute MI or ACS. The systematic review identified a number of studies that examined combinations of the clinical history as a rule out for cardiac chest pain. No combination of elements of the chest pain history was found to be sufficiently predictive as a rule out (Swap, Clifford J. and Nagurney, John T., 2005).

Table 3			
Value of specific components of chest pain history for the diagnosis of acute MI			
	Pain Descriptor	Number of patients	PLR (95%CI)
Increased likelihood of acute MI			
	Radiation to right arm or shoulder	770	4.7 (1.9-12)
	Radiation to both arms or shoulders	893	4.1 (2.5-6.5)
	Associated with exertion	893	2.4 (1.5-3.8)
	Radiation to left arm	278	2.3 (1.7-3.1)
	Associated with diaphoresis	8426	2.0 (1.9-2.2)
	Associated with nausea or vomiting	970	1.9 (1.7-2.3)
	Worse than previous angina or similar to previous MI	7734	1.8 (1.6-2.0)
	Described as pressure	11504	1.3 (1.2-1.5)
Decreased likelihood of acute MI			
	Described as pleuritic	8822	0.2 (0.1-0.3)
	Described as positional	8330	0.3 (0.2-0.5)
	Described as sharp	1088	0.3 (0.2-0.5)
	Reproducible with palpation	8822	0.3 (0.2-0.4)
	Inflammatory location	903	0.8 (0.7-0.9)
	Not associated with exertion	893	0.8 (0.6-0.9)
Permissions granted from original source (Swap, Clifford J. and Nagurney, John T., 2005).			

The second systematic review on the accuracy of 10 elements of the clinical history identified 28 prospective and retrospective cohort studies (search date 2006) (Bruyninckx, R., Aertgeerts, B., Bruyninckx, P. et al, 2008). The following individual components were examined; pain in left arm and / or shoulder, pain in right arm and / or shoulder, pain in both arms, pain in neck, pain in back, epigastric pain, oppressive pain, vomiting and / or nausea, sweating, and absence of chest wall tenderness. The 28 studies identified by the systematic review had a combined total of 46,908 patients, with a mean age of 50 to 71 years, and 40% to 71% were male. Of the 28 studies, 16 were of non selected patients (patients presenting to their general practitioners, patients presenting to the emergency department or those selected by paramedics), 11 were of selected patients recruited by coronary care units and cardiologists and 1 was in a chest pain observation unit. Eleven studies were set in the emergency department, 10 studies were set in a coronary care unit, 3 studies were set in the ambulance, 3 in primary care, and 1 was in a chest pain observational unit (Bruyninckx, R., Aertgeerts, B., Bruyninckx, P. et al, 2008).

Table 4 and Table 5 detail the results of meta-analyses for the utility of components of the clinical history in the diagnosis of acute MI and ACS, respectively. The results are from studies on unselected patients presenting with chest pain. For acute MI there was homogeneity in the PLR for oppressive pain, and in the negative likelihood ratio (NLR) for chest wall tenderness. For ACS, there was homogeneity in the PLR of left arm pain and the NLR for sweating and tenderness. For all other analyses there was a moderate to high level of heterogeneity, indicating that these results must be carefully interpreted. It is probable that the heterogeneity was due to different settings, inclusion criteria and reference standards. The absence of chest wall tenderness was highly sensitive for acute MI and ACS (92% and 94% respectively), although it was not specific (36% and 33%, respectively). Oppressive chest pain with a pooled sensitivity of 60% and specificity of 58% had almost no influence predicting the likelihood of an acute MI. Other symptoms had even less influence on predicting the likelihood of an acute MI indicating that they could not be used to exclude an acute MI or ACS. Presentation with presence of chest wall tenderness (pain on palpitation) was found to be the only symptom that may rule out the probability of an acute MI or ACS, as indicated by NLRs of 0.23 and 0.17, respectively). However, as found with (Swap, Clifford J. and Nagurney, John T., 2005), overall the results of the meta-analyses suggest that in isolation components of the clinical history and signs and symptoms are not helpful in the diagnosis of acute MI and ACS. Differences in PLRs and NLRs for the individual components between the two systematic reviews may have resulted from different selection criteria for study inclusion. For example, one systematic review excluded studies with less than 80 patients, and included studies that recruited patients with acute MI and / or ACS (Swap, Clifford J. and Nagurney, John T., 2005). The second systematic review differentiated the data from those studies in selected patients (recruited by cardiologists or in the coronary care unit) and unselected patients (selected by general practitioners, paramedic or emergency department staff). No information was given on the minimum number of patients required for inclusion, and studies that were only

in patients with acute MI were excluded (Bruyninckx, R., Aertgeerts, B., Bruyninckx, P. et al, 2008)

Table 4

Pooled sensitivity, specificity, PLRs and NLRs odds ratios of signs and symptoms for acute MI

Symptom					*Non-selected patients*
	Sensitivity (95%CI)	Specificity (95%CI)	PLR (95%CI)	NLR (95%CI)	OR (95%CI)
Pain in left arm and / or shoulder	33 (25.4 to 41.8)	76.3 (74.5 to 78.2)	1.42 1.10 to 1.83	0.87 0.77 to 0.99	1.631 1.20 to 2.39
Pain in right arm and / or shoulder	15 (5.0 to 23.7)	95 (92.8 to 97.0)	2.89 (1.40 to 5.98)	0.90 (0.81 to 1.00)	3.22 (1.41 to 7.36)
Pain in neck	14 (8.2 to 20.4)	90 (89.0 to 91.6)	1.48 (0.94 to 2.31)	0.95 (0.88 to 1.02)	1.55 (0.92 to 2.61)
Epigastric pain	10 (3.9 to 15.3)	93 (91.1 to 95.2)	1.44 (0.73 to 2.83)	0.97 (0.91 to 1.04)	1.49 (0.71 to 3.12)
Oppressive pain	60 53.7 to 66.0	58 (55.0 to 60.2)	1.42 (1.32 to 1.53)	0.69 (0.61 to 0.80)	2.06 1.60 to 2.53
Vomiting and/or nausea	34 (25.3 to 44.1)	77 (71.1 to 81.3)	1.41 (1.17 to 1.72)	0.83 (0.83 to 0.96)	1.62 (1.22 to 2.14)
Sweating	45 (36.0 to 54.0)	84 (78.6 to 88.0)	2.92 (1.97 to 4.32)	0. 69 (0.60 to 0.78)	4.54 (2.47 to 8.36)
Absence of chest wall tenderness	92 (85.5 to 96.4)	36 (20.5 to 51.8)	1.47 (1.23 to 1.75)	0.23 (0.18 to 0.29)	0.17 (0.12 to 0.23)

= number of studies, LR = likelihood ratio, OR = odds ratio
Permissions granted from original source (Bruyninckx, R., Aertgeerts, B., Bruyninckx, P. et al, 2008).

Table 5

Pooled sensitivity, specificity, positive and negative likelihood ratios, and odds ratios of signs and symptoms for ACS in patient groups

				ACS					ACS	
Symptom				Non-selected patients					Selected patients	
		#		95%CI	I^{2a} (%)		#		95%CI	I^{2a} (%)
Pain in left arm and/or shoulder	Sensitivity	3	38	18.6 to 59.5	95		0		No studies	
	Specificity		71	56.9 to 82.6	97					
	PLR		1.3	1.13 to 1.47	0					
	NLR		0.88	0.78 to 1.00	58					
	OR		1.5	1.19 to 1.9	0					
Pain in right arm and/or shoulder	Sensitivity	1	18	9.6 to 26.2	Only one study		1	23	10.6 to 35.9	Only one study
	Specificity		95	93.8 to 96.1				94	87.2 to 100	
	PLR		3.78	2.17 to 6.60				3.8	1.12 to 12.91	
	NLR		0.86	0.77 to 0.96				0.82	0.98 to 0.98	
	OR		4.4	2.29 to 8.48				46.5	1.19 to 18.20	
Pain in neck	Sensitivity	1	35	27.9 to 42.4	Only one study		0		No studies	
	Specificity		76	72.2 to 79.1						
	PLR		1.44	1.12 to 1.86						
	NLR		0.86	0.76 to 0.97						
	OR		1.69	1.16 to 2.44						
Pain in back	Sensitivity	2	13	2.8 to 34.3	86		1	29	15.3 to 43.2	Only one study
	Specificity		76	26.7 to 98.6	98			49	35.0 to 63.0	
	PLR		1.49	0.62 to 3.56	80			0.57	0.33 to 0.99	
	NLR		0.93	0.77 to 1.13	87			1.44	1.02 to 2.04	
	OR		1.59	0.58 to 4.37	80			0.4	0.17 to 0.90	
Epigastric pain	Sensitivity	4	12	5.4 to 20.8	97		0		No studies	
	Specificity		89	82.9 to 94.1	98					
	PLR		1.05	0.35 to 3.20	97					
	NLR		0.98	0.88 to 1.08	97					
	OR		1.08	0.31 to 3.74	97					
Oppressive pain	Sensitivity	1	56	49.7 to 62.1	Only one study		1	79	66.9 to 91.2	Only one study
	Specificity		67	61.8 to 71.1				39	25.1 to 52.4	
	PLR		1.68	1.40 to 2.02				1.29	0.99 to 1.69	
	NLR		0.66	0.56 to 0.77				0.54	0.27 to 1.06	
	OR		2.54	1.82 to 3.56				2.39	0.94 to 6.08	
Vomiting and/or nausea	Sensitivity	6	26	20.7 to 32.2	91		0		No studies	
	Specificity		82	74.1 to 88.4	98					
	PLR		1.32	1.09 to 1.65	68					
	NLR		0.93	0.89 to 0.96	35					
	OR		1.43	1.14 to 1.81	63					

Table 5

Pooled sensitivity, specificity, positive and negative likelihood ratios, and odds ratios of signs and symptoms for ACS in patient groups

				ACS					ACS	
Symptom				Non-selected patients					Selected patients	
		#		95%CI	I^{2a} (%)		#		95%CI	I^{2a} (%)
Sweating	Sensitivity	4	43	32.2 to 64.9	98		0		No studies	
	Specificity		68	44.0 to 86.5	99					
	PLR		1.34	1.09 to 1.65	76					
	NLR		0.85	0.79 to 0.92	40					
	OR		1.65	1.39 to 1.95	0					
				Acute MI					Acute MI	
Sweating	Sensitivity	6	45	36.0 to 54.0	91		4	41	22.9 to 60.5	95
	Specificity		84	78.6 to 88.0	97			85	69.2 to 94.7	98
	PLR		2.92	1.97 to 4.32	95			2.44	1.42 to 4.20	81
	NLR		0.69	0.60 to 0.78	81			0.72	0.56 to 0.91	90
	OR		4.54	2.47 to 8.36	94			3.81	1.88 to 7.70	83
Absence of chest	Sensitivity	2	94	91.4 to 96.1	0		0		No studies	
wall tenderness	Specificity		33	19.7 to 47.9	96					
	PLR		1.41	1.12 to 1.78	94					
	NLR		0.17	0.11 to 0.26	0					
	OR		0.12	7.0 to 21.0	34					

= number of studies
Selected patients = patients recruited by coronary care units and cardiologists
LR = likelihood ratio
OR = odds ratio
I^{2a} = test for heterogeneity
Permissions granted from original source (Bruyninckx, R., Aertgeerts, B., Bruyninckx, P. et al, 2008).

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The third systematic review was a Health Technology Appraisal that examined the diagnostic value of components of the clinical history or the physical examination in patients with suspected acute MI or ACS (Mant, J., McManus, R. J., Oakes, R.-A. L. et al, 2004). Twenty one papers were identified that examined 16 individual components rather than combinations for diagnosis. These were; pleuritic pain, sharp pain, positional pain, pain on palpation, crushing pain, central pain, left-sided radiation pain, right-sided radiation pain, any radiation of pain, pain duration of longer than 1 hour, previous MI / angina, nausea / vomiting, sweating, pulmonary crackles, systolic blood pressure under 80 mmHg and a third heart sound. The studies identified had a combined total of 38 638 patients, with a mean age of 50 to 73 years, and 50% to 71% of the participants were male. Of the 21 papers, 8 were set exclusively in secondary care, 10 in the emergency department, and 3 in both primary and secondary care (Mant, J., McManus, R. J., Oakes, R.-A. L. et al, 2004).

Meta-analysis of the 16 components of the clinical assessment from the 21 studies found that no individual component was useful in the diagnosis of acute MI in isolation; no symptom achieved a statistically significant LR of either < 0.1 or >10 (Table 6). The presence of a third heart sound, systolic hypotension and right sided radiation of chest pain had the highest PLRs for the diagnosis of acute MI, although these values were not significant (PLRs: 3.21, 3.06, 2.59, respectively). Signs and symptoms that were most helpful in ruling out a diagnosis were the presence of pleuritic, sharp or positional pain, and pain produced by physical palpitation, although these did not achieve statistical significance (NLR; 1.17, 1.36, 1.12 and 1.18 respectively) (Mant, J., McManus, R. J., Oakes, R.-A. L. et al, 2004).

Table 6

Positive and negative likelihood ratios for individual components of the clinical history and signs and symptoms for the assessment of acute chest pain

Symptom		*Number of studies*	*LR*	*95%CI*	*P for heterogeneity*
Pleuritic pain	PLR	3	0.19	0.14 to 0.25	0.5
	NLR		1.17	1.15 to 1.19	0.003
Sharp pain	PLR	2	0.32	0.21 to 0.50	0.3
	NLR		1.36	1.26 to 1.46	0.4
Positional pain	PLR	2	0.27	0.21 to 0.36	0.3
	NLR		1.12	1.11 to 1.14	0.09
Pain on palpation	PLR	3	0.23	0.08 to 0.30	0.15
	NLR		1.18	1.16 to 1.20	0.001
Crushing pain	PLR	6	1.44	1.39 to 1.49	0.14
	NLR		0.63	0.60 to 0.67	0.9
Central pain	PLR	3	1.24	1.2 to 1.27	0.01
	NLR		0.49	0.43 to 1.56	0.002
Left-sided radiation of pain	PLR	2	1.45	1.36 to 1.55	0.004
	NLR		0.78	0.73 to 0.82	0.02
Right-sided radiation of pain	PLR	2	2.59	1.85 to 3.70	0.7
	NLR		0.8	0.72 to 0.88	0.01
Any radiation of pain	PLR	2	1.43	1.33 to 1.55	0.7
	NLR		0.8	0.75 to 0.84	0.01
Pain duration > 1 h	PLR	1	1.3	1.15 to 1.47	only one study
	NLR		0.35	0.19 to 0.64	
Previous MI/angina	PLR	4	1.29	1.22 to 1.36	0.001
	NLR		0.84	0.81 to 0.88	0.001
Nausea/vomiting	PLR	4	1.88	1.58 to 2.23	0.5
	NLR		0.77	0.71 to 0.84	0.001
Sweating	PLR	5	2.06	1.96 to 2.16	0.7
	NLR		0.65	0.62 to 0.67	0.001
Pulmonary crackles	PLR	1	2.08	1.42 to 3.05	only 1 study
	NLR		0.76	0.62 to 0.93	
Systolic blood pressure < 80 mmHg	PLR	1	3.06	1.80 to 5.22	only 1 study
	NLR		0.97	0.95 to 0.99	

PLR = positive likelihood ratio, NLR = negative likelihood ratio.
Permissions granted from original source (Mant, J., McManus, R. J., Oakes, R.-A. L. et al, 2004).

There was considerable heterogeneity in the results, particularly (although not exclusively) for the NLRs, indicating that the pooled summary statistics should be interpreted with caution. Nevertheless, there is no evidence that any single

symptom or sign taken in isolation is of much value in the diagnosis of acute chest pain (Mant, J., McManus, R. J., Oakes, R.-A. L. et al, 2004).

The cohort study assessed the predictive value of the combination of components of the clinical history and risk factors in the identification of patients with suspected acute MI (Schillinger, Martin, Sodeck, Gottfried, Meron, Giora et al, 2004). The study recruited consecutive patients with chest pain (onset in previous 24 hours) at a non-trauma emergency department during an 8 month period. A total of 1288 patients were included in the study, the mean age was 49(SD 17) years and 59% were men (Schillinger, Martin, Sodeck, Gottfried, Meron, Giora et al, 2004).

Seven pre-defined factors were evaluated and designated as either typical or atypical, location of chest pain (typical: left sided, atypical: right sided), character of pain (typical: crushing / squeezing / burning / tightness, atypical: stabbing / single spot / superficial), radiation (typical to the left or both arms, neck, back, atypical: not radiating), appearance of chest pain (typical: exercise induced / undulating / relieved with rest or nitroglycerin, atypical: inducible by pressure / abrupt palpitations / sustained / position dependent / respiration dependent / cough dependent), vegetative signs (typical dyspnoea / nausea / diaphoresis, atypical: absence of vegetative signs), history of CAD (typical: MI / PCI / CABG, atypical: none) and risk factors for CAD namely; smoking, obesity, hypertension, diabetes, hyperlipidemia, and family history all typical, atypical was defined as absence or only one risk factor (Schillinger, Martin, Sodeck, Gottfried, Meron, Giora et al, 2004).

Thirteen percent of patients (168 patients) had an acute MI and 19% (240 patients) had a major adverse event at 6 month follow up (defined as either cardiovascular death, PCI, CABG or MI (Schillinger, Martin, Sodeck, Gottfried, Meron, Giora et al, 2004).

The LRs to predict an acute MI up to 6 months according to symptoms and / or history were as follows; 1 typical symptom or history: 1.15, 2 typical symptoms and / or history: 1.32, 3 typical symptoms and / or history: 1.48, 4 typical symptoms and / or history: 1.77, 5 typical symptoms and / or history:

1.88, 6 typical symptoms and / or history: 1.85. The LRs to predict a major cardiac adverse event up to 6 months were as follows; 1 typical symptom or history: 1.15, 2 typical symptoms and / or history: 1.34, 3 typical symptoms and / or history: 1.58, 4 typical symptoms and / or history: 1.87, 5 typical symptoms and / or history: 2.11, 6 typical symptoms and / or history: 1.54 (Schillinger, Martin, Sodeck, Gottfried, Meron, Giora et al, 2004).

The LRs to exclude an acute MI up to 6 months according to symptoms and / or history were as follows; 1 typical symptom or history: 1.05, 2 typical symptoms and / or history: 1.24, 3 typical symptoms and / or history: 1.76, 4 typical symptoms and / or history: 2.22, 5 typical symptoms and / or history: 3.99, 6 typical symptoms and / or history: 3.34. The LRs to exclude a major cardiac adverse event up to 6 months were as follows; 1 typical symptom or history: 1.04, 2 typical symptoms and / or history: 1.29, 3 typical symptoms and / or history: 1.85, 4 typical symptoms and / or history: 3.02, 5 typical symptoms and / or history: 4.87, 6 typical symptoms and / or history: 4.58 (Schillinger, Martin, Sodeck, Gottfried, Meron, Giora et al, 2004).

Based upon the calculated LRs, the typical characteristics defined in the study appear to have little use in the in the identification of patients with acute MI. Atypical characteristics may have greater use in excluding a diagnosis of acute chest pain, although the proportion of a chest pain population presenting with 6 atypical symptoms may be small (Schillinger, Martin, Sodeck, Gottfried, Meron, Giora et al, 2004).

4.2.1.3 Health economic evidence

This clinical question was designated as low priority for economic evaluation, and so no specific search of the economic literature was undertaken. No relevant health economic evaluations were found, relating to this question, in either the scoping, or the update searches, undertaken for this Guideline.

4.2.1.4 Evidence to recommendations

Methodologically all three systematic reviews were of high quality with a low risk of study incorporation bias, and a low risk of study selection bias with respect to study design. Although certain elements of the chest pain history

and symptoms were associated with an increased or decreased likelihood of a diagnosis of acute MI or ACS in the analyses conducted in the systematic reviews, none of elements alone or in combination identified a group of patients who could be safely discharged without further diagnostic investigation. The one cohort study was well conducted with a low risk of bias. It demonstrated that some risk factors and symptoms were associated with an increased probability of acute MI; however, the study demonstrated that risk factors and symptoms in isolation were of limited use in the diagnosis of acute MI.

The studies examining the effectiveness of a clinical history, risk factor assessment and physical examination to determine if patients with acute chest pain of suspected cardiac origin have an acute MI/ACS are largely confined to emergency departments making their generalisability to primary care limited. There was little evidence in patients presenting to primary care. However, whilst the results of the systematic reviews, further supported by the one cohort study, found that the characteristics of the chest pain and associated symptoms, the presence of risk factors and a past history of coronary disease influence the likelihood of whether a patient with chest pain is suffering an acute MI / ACS, and the GDG agreed that this was insufficient from which to reach a definitive diagnosis. Irrespective of whether a patient presents to emergency services, an emergency department, primary care or other healthcare settings, additional testing is always necessary if an acute MI / ACS is suspected.

The GDG also recognised that patients with acute chest pain of suspected cardiac origin might also have other causes for their symptoms. In some cases, these may be due to other life threatening conditions and early diagnosis is important and potentially life saving. Searching for the evidence for symptoms associated with these was not part of this guideline, but the GDG felt it was important to emphasise the importance of considering other possible diagnoses during a clinical assessment (see section 4.2.6.1).

4.2.2 Gender differences in symptoms

Return to Recommendations

4.2.2.1 Evidence statements for differences in presentation by gender

1 Two systematic reviews on gender differences in acute MI and ACS symptom presentation found that there was considerable heterogeneity in identified studies with respect to patient characteristics and that there was a lack of standardisation on data collection and symptom reporting. (Canto, J. G., Goldberg, R. J., Hand, M. M. et al, 2007), (Patel, H., Rosengren, A., and Ekman, I., 2004)

2 One systematic review found that women presenting with ACS were more likely to experience back and jaw pain, nausea and / or vomiting, dyspnoea, indigestion, palpitations compared with men. (Patel, H., Rosengren, A., and Ekman, I., 2004)

3 One systematic review found that women presenting with ACS were more likely to experience middle or upper back pain, neck pain, jaw pain, shortness of breath, nausea or vomiting, loss of appetite, weakness and fatigue, cough, paroxysmal nocturnal dyspnoea, indigestion and dizziness. (Canto, J. G., Goldberg, R. J., Hand, M. M. et al, 2007)

4 One systematic review found that women presenting with acute MI were more likely to experience; back, jaw, and neck pain, and nausea and / or vomiting, dyspnoea, palpitations, indigestion, dizziness, fatigue, loss of appetites and syncope compared with men. (Patel, H., Rosengren, A., and Ekman, I., 2004)

5 One cohort study in patients presenting with acute MI found that women under 65 years more often experienced atypical pain as defined as < 20 minutes, intermittent, or pain at an unusual site such as upper abdomen, arms, jaw and / or neck compared with men. (Isaksson, R. M., Holmgren, L., Lundblad, D. et al, 2008)

6 One cohort study in patients presenting with acute MI found that women compared with men were more likely to experience pain in sites other than the chest as defined as pain in the jaw, throat and neck, left shoulder, left arm and / or hand and back. Women were also more likely to experience nausea, vomiting and shortness of breath. (Kosuge, M., Kimura, K., Ishikawa, T. et al, 2006)

7 One cohort study in patients presenting with acute MI found that women compared with men were older and more likely to have hypertension, diabetes and hyperlipidaemia. (Kosuge, M., Kimura, K., Ishikawa, T. et al, 2006)

8 One cohort study in patients presenting with acute MI or unstable angina found that women compared with men were more likely to have hypertension, whereas men were more likely than women to have hypercholesterolaemia and a family history of CAD. (Chrysohoou, C., Panagiotakos, D. B., Pitsavos, C. et al, 2003)

9 One cohort study in patients presenting with acute MI or unstable angina found that women compared with men were more likely to have hypertension and diabetes, whereas men were more likely than women to have a past history of MI, previous CABG surgery and history of smoking. (Chua, T. P., Saia, F., Bhardwaj, V. et al, 2000),

4.2.2.2 Clinical evidence

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

Introduction

Historically, the descriptions of chest pain symptoms associated with acute MI / ACS have been based on the presentation characteristics of men. 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 may differ between men and women is important in the initial assessment of chest pain to determine the need for further evaluation.

Two systematic reviews (Canto, J. G., Goldberg, R. J., Hand, M. M. et al, 2007) (Patel, H., Rosengren, A., and Ekman, I., 2004), three cohort studies (Isaksson, R. M., Holmgren, L., Lundblad, D. et al, 2008) (Kosuge, M., Kimura, K., Ishikawa, T. et al, 2006) (Chua, T. P., Saia, F., Bhardwaj, V. et al, 2000), and one case controlled study were reviewed (Chrysohoou, C., Panagiotakos, D. B., Pitsavos, C. et al, 2003).

The first systematic review (search date 2002) examined the gender differences in the presentation of acute MI and ACS (Patel, H., Rosengren, A., and Ekman, I., 2004). The systematic review identified 15 cohort studies that recruited both men and women, 11 cohort studies were in patients presenting with acute MI and 4 cohort studies were in patients presenting with all types of ACS. The systematic review did not however provide a definition of ACS in their study, nor detail the definitions used in their selected studies (Patel, H., Rosengren, A., and Ekman, I., 2004).

As shown in Table 7 that details the proportion of studies reporting gender differences compared with total number of studies, analysis of the 4 studies in patients presenting with ACS found that women were more likely to experience back pain, indigestion and palpitations compared with men. No gender differences were reported for the following symptoms; presence of chest pain (2 studies), arm and shoulder pain (2 studies), neck pain (2 studies), dizziness (3 studies) (Patel, H., Rosengren, A., and Ekman, I., 2004).

As detailed in Table 7, analysis of the 11 studies in patients presenting with acute MI found that women are more likely to have back, jaw, and neck pain,

and nausea and / or vomiting, dyspnoea, palpitations, indigestion, dizziness, fatigue, loss of appetite and syncope. The following symptoms were not associated with gender differences in the presentation of acute MI in some of the studies; arm and shoulder pain (4 studies), epigastric discomfort, heartburn or abdominal pain (7 studies), throat pain (2 studies) (Patel, H., Rosengren, A., and Ekman, I., 2004).

Table 7

Summary of sex differences in the symptoms in the ACS and acute MI

ACS		Acute MI	
Symptom	Number studies identifying symptom greater in women versus men / total studies	Symptom	Number studies identifying symptom greater in women versus men / total studies
Back pain	3/4	Back pain	3/4
Dyspnoea	1/4	Dyspnoea	5/8
Indigestion	1/4	Indigestion	2/2
Nausea / vomiting	2/4	Nausea / vomiting	4/6
Palpitations	2/2	Palpitations	1/2
Fatigue	1/1	Fatigue	2/4
Cough	1/1	Next Pain	3/5
		Jaw pain	1/5
		Sweating	2/6
		Dizziness	1/5
		Loss of appetite	1/1

Table produced from data extracted in text of study

There was inconsistency in the gender-specific symptoms reported, in that no individual symptom was identified by all studies that examined the symptom. It is likely that the baseline characteristics of the populations varied, and the sex differences may disappear after controlling for variables such as age and co-morbid conditions. Some studies evaluated only a small number of symptoms, and may have missed other statistically significant symptoms (Patel, H., Rosengren, A., and Ekman, I., 2004).

The second systematic review (search date 2005) examined the gender differences in the presenting symptoms of ACS (Canto, J. G., Goldberg, R. J., Hand, M. M. et al, 2007). Large cohorts and registries, single studies and studies based on personal interviews were included in the systematic review.

In total 69 studies were included, of which 6 cohort studies were identified that were subsequent to the first systematic review (Patel, H., Rosengren, A., and Ekman, I., 2004). Typical symptoms of MI were described in the review as broadly including (1) precordial chest discomfort, pain heaviness, or fullness, possibly radiating to the arm, shoulder, back, neck, jaw, epigastrum, or other location, (2) symptoms exacerbated by exertion or by stress, (3) symptoms that may be relieved by rest or the use of nitroglycerin, (4) symptoms associated with shortness of breath, diaphoresis, weakness, nausea or vomiting, and light headedness. The review stated that symptoms occurring in the ACS setting (defined in the systematic review as symptom presentation setting) without chest pain are frequently labeled as ‘atypical’ and included pain or discomfort in locations other than the chest, such as pain localised to the arm(s), shoulder, middle back, jaw or epigastrum. Atypical chest pain has also been described as not severe, not prolonged, and not classic in presentation, where classic cardiac chest pain is described as burning, sharp, pleuritic, positional pain or discomfort that is reproducible on palpitation of the chest wall.

The review included studies from large cohorts or registries, single-centre reports, or studies based on personal interviews that compared symptom presentation in men versus women. In the studies identified there was a lack of standardisation on data collection and reporting on principal or associated symptoms. Given the considerable heterogeneity of the studies analysed, there were no formal meta-analyses performed, and results were reported as a descriptive narrative with simple descriptive statistics (Canto, J. G., Goldberg, R. J., Hand, M. M. et al, 2007).

The review identified 9 large cohort studies, and 20 smaller cohort studies or personal interview studies that provided information on ACS presentation with and without typical chest pain or discomfort according to sex (Canto, J. G., Goldberg, R. J., Hand, M. M. et al, 2007).

Analysis of the nine large cohort studies found that approximately one third of all patients presented without acute chest pain / discomfort (32%, 149 039 of

471 730 patients), and the absence of chest pain was more common in women than in men (38%, 73 003 of 19 4797 women versus 27%, 76 036 of 27 6933 men). One of the large studies had significantly greater patient numbers (National Registry of MI Report) (Canto, J. G., Shlipak, M. G., Rogers, W. J. et al, 2000) which could have dominated the results, hence the analysis was repeated excluding this study and showed that almost one quarter of women with ACS did present with typical chest pain (Canto, J. G., Goldberg, R. J., Hand, M. M. et al, 2007).

Analysis of the twenty smaller cohort or personal interview studies found that one quarter of all patients presented without typical acute chest pain / discomfort (25%, 1333 of 5324 patients), and the absence of chest pain was more common in women than in men (30%, 499 of 1644 women versus 17%, 346 of 2031 men). In re-analysing only those studies that included both women and men, the sex differences noted in the single centre and small reports or interviews were attenuated (24% women versus 20% men), while for the large cohort studies the cumulative summary did not change (Canto, J. G., Goldberg, R. J., Hand, M. M. et al, 2007).

The review identified a number of studies that demonstrated that the frequency of other ACS-associated symptoms differed according to sex. Compared with men, 8 studies found that women are more likely to experience middle or upper back pain, 4 studies found that women are more likely to have neck pain, and 2 studies found that women are more likely to have jaw pain. Five studies found that women are more likely to have shortness of breath and 5 studies showed women are more likely to have nausea or vomiting. Loss of appetite, weakness and fatigue, and cough were identified as more common in women versus men in 2 studies each. Paroxysmal nocturnal dyspnoea, indigestion and dizziness were reported as more common in women versus men in 1 study each (Canto, J. G., Goldberg, R. J., Hand, M. M. et al, 2007).

The first cohort study compared symptoms of acute MI in women versus men (Isaksson, R. M., Holmgren, L., Lundblad, D. et al, 2008). The study was part

of the Multinational Monitoring of Trends and Determinants in Cardiovascular disease (MONICA), a population-based registry which included all acute events rather than only events recorded in hospital. According to the MONICA criteria (based on the World Health Organization (WHO) definitions) typical symptoms of MI were defined as the presence of typical chest pain and characterised by duration of more than 20 minutes, and any synonym for pain was acceptable such as pressure, discomfort or ache. Atypical symptoms meant symptoms that were not typical, but that there was one or more of the following present; atypical pain, acute left ventricular failure, shock and / or syncope. Atypical pain was recorded if the pain was short in duration or intermittent with each bout lasting less than 20 minutes, or pain at an unusual site such as the upper abdomen, arms, jaw and / or neck. A total of 6342 patients (5072 men and 1470 women) were included in the registry which collected patients over a 15 year period. The mean age was 56(SD 6.8) years for men and 56.6(SD 6.68) years for women (Isaksson, R. M., Holmgren, L., Lundblad, D. et al, 2008).

The study found that men were more likely to experience typical pain based on the MONICA criteria compared with women (86.3% versus 80.8%, respectively), and this was found for all age groups. For women, a lower proportion experienced typical symptoms compared with men in all age ranges. However in the age range 65 to 74 years the difference in proportion of men versus women with typical symptoms was less marked (79.8% versus 78.0%), and hence in the oldest age group the frequency of atypical pain was found to be similar in men and women (Isaksson, R. M., Holmgren, L., Lundblad, D. et al, 2008).

The second cohort study examined sex-related differences in the clinical history and risk factors associated with ST-segment elevation acute MI (Kosuge, M., Kimura, K., Ishikawa, T. et al, 2006). Five hundred and ten consecutive patients admitted to a coronary care unit were identified, and of these, 457 patients (351 men and 106 women) were studied as they had a detailed clinical history within 48 hours of admission. All recruited patients had symptom onset within 24 hours of admission. Acute MI was diagnosed on the

basis of typical chest pain lasting ≥ 30 minutes, ST-segment elevation of ≥ 2 mm at least 2 contiguous precordial leads or ST-segment elevation of ≥ 1 mm in at least 2 inferior leads (II, III, or a VF), and a typical increase in serum creatine kinase (Kosuge, M., Kimura, K., Ishikawa, T. et al, 2006).

The study found that women were older than men (72 versus 62 years, respectively, *P* < 0.001), had higher rates of hypertension (51% versus 38%, respectively, *P* = 0.017), diabetes (36% versus 26%, respectively, *P* = 0.047) and hyperlipidaemia (51% versus 38%, respectively, *P* = 0.019). Women were also more likely to experience atypical symptoms compared with men. For women versus men, pain was more common in the jaw (9% versus 3%, respectively, *P* = 0.047) throat and neck (13% versus 5%, respectively, *P* = 0.007), left shoulder, left arm, forearm and / or hand (12% versus 5%, respectively, *P* = 0.024) and back (24% versus 12%, respectively *P* = 0.047). Women were also more likely to experience milder pain compared with men (20% versus 7%, respectively, *P* < 0.001), and nausea (49% versus 36%, respectively, *P* = 0.047), vomiting (25% versus 15%, respectively *P* = 0.08), and shortness of breath (62% versus 52%, respectively, *P* = 0.07). Coronary angiography showed that there was no difference in the severity of coronary artery lesions between men and women, although in-hospital mortality was significantly higher in women than in men (6.6% versus 1.4%, respectively, *P* = 0.003) (Kosuge, M., Kimura, K., Ishikawa, T. et al, 2006).

The third study was a multicentre case-control study, the CAD Offspring of Year 2000 CARDIO2000 study, and examined cardiovascular risk factors and their relationship with gender (Chrysohoou, C., Panagiotakos, D. B., Pitsavos, C. et al, 2003). The study randomly selected patients who were admitted to a hospital with a first acute MI or unstable angina event. After selection of cardiac patients, 1078 cardiovascular disease-free subjects (controls) were randomly selected and matched to the patients by age (±3 years), gender and region. Controls were mainly individuals who visited the outpatient clinics of the same hospital in the same time period as the coronary patients for routine examinations or minor surgical operations. All control subjects had no clinical symptoms or evidence of cardiovascular disease in their medical history. A

total of 848 cardiac patients were included in the study and 1078 controls (Chrysohoou, C., Panagiotakos, D. B., Pitsavos, C. et al, 2003).

The study examined the following risk factors; hypertension, hypercholesterolemia, diabetes, family history of premature CAD, smoking, in addition to body mass index, diet and alcohol consumption. Medical records were reviewed and questionnaires were conducted on lifestyle (carried out on the second day of hospitalisation) and on nutrition (according to the Department of Nutrition of the National School of Public Health). Seven hundred and one (82%) of the cardiac patients were men with a mean age 59(SD 10) years, and 147 (18%) of cardiac patients were women with a mean age of 65.3(SD 8) years. Similarly for the controls 80% were men and 20% were women with mean ages of 58.8(SD 10) years and 64.8(SD 10) years, respectively. Women experiencing their first cardiac event were significantly older than men ($P < 0.01$) (Chrysohoou, C., Panagiotakos, D. B., Pitsavos, C. et al, 2003).

When adjusting for age, multivariate analysis found that for women hypertension was associated with a higher risk of CAD compared with men (OR 4.86 versus 1.66 $P < 0.01$, respectively) (Chrysohoou, C., Panagiotakos, D. B., Pitsavos, C. et al, 2003).

Family history of CAD and hypercholesterolemia were associated with a higher risk of CAD in men than in women with ORs of 5.11 versus 3.14 for family history, respectively ($P < 0.05$), and ORs of 3.77 versus 2.19 for hypercholesterolemia, respectively ($P < 0.05$). Details of the results of the multivariate analysis are given in Table 8 (Chrysohoou, C., Panagiotakos, D. B., Pitsavos, C. et al, 2003).

Table 8

Results from the multivariate analysis performed to evaluate the effect of several risk factors on the CAD risk, separately in men and women, with respect to age

	Men		Women		
	OR	95%CI	OR	95%CI	*P* value †
Smoking habit (per 1 – pack year)	1.019	1.001-1.03	1.018	1.001-1.04	NS
Hypertension (yes/no)	1.66	1.16-2.38	4.96	2.56-9.53	<0.01
Hypercholesterolemia (yes/no)	3.77	2.68-5.27	2.19	1.80-2.66	<0.05
Diabetes mellitus (yes/no)	2.04	1.25-3.35	2.18	1.02-4.69	NS
Family history of CHD (yes/no)	5.11	3.77-7.01	3.14	2.68-3.67	<0.05
Body mass index (per 1 kg/m^2)	1.002	0.98-1.01	1.001	0.92-1.02	NS
Physical activity (yes/no)	0.91	0.80-0.98	0.84	0.61-1.14	NS
Alcohol consumption (w/day)**	1.23	1.10-1.37	1.03	0.78-1.46	NS

OR = odds ratio; CI = confidence interval; CHD = coronary heart disease; **p* value for the different effect (men vs. women) of the investigated factor on coronary risk; ** alcohol intake was measured in wine glasses (100ml, concentration 12%) per day.
Permissions granted from original source (Chrysohoou, C., Panagiotakos, D. B., Pitsavos, C. et al, 2003).

The fourth study was a retrospective cohort study that reviewed patients' case notes to assess risk factors and gender differences in patients presenting with unstable angina (Chua, T. P., Saia, F., Bhardwaj, V. et al, 2000). The study included 313 patients who were referred for coronary angiography and further management during a 42 month period. Two hundred and ten (67%) were men (184 men were Caucasian, 23 were Asian (Indian subcontinent) and 3 had other ethnic origin) and 103 (33%) were women (83 women were Caucasian, 15 were Asian (Indian subcontinent) and 5 had other ethnic origin, no difference in ethnicity and gender). The mean age for men was 61.6(SD 11) years and for women 63.5(SD 10.5) years (*P* = 0.14) (Chua, T. P., Saia, F., Bhardwaj, V. et al, 2000).

The results for the differences in risk factors showed that women were more likely to have diabetes mellitus (23% in women versus 11% in men, *P* = 0.007), and a history of hypertension (52% in women versus 32% in men, *P* =

0.001). Men were more likely to have a history of prior MI (51% in men versus 39% in women *P* = 0.06), history of previous cornary artery bypass graft (CABG) (17% in men versus 6% in women, *P* = 0.013) and a history of smoking (73% in men versus 46% in women, *P* = 0.00001). There was no significant difference between men and women in age, the ratio of Caucasian to non-Caucasian patients, past history of angina pectoris, the duration of time before seeking medical help, mean total serum cholesterol level, family history of ischaemic heart disease. There was also no difference in the number of men and women who underwent cardiac catheterization (94% in men and 95% in women). It should be noted that the study was analysis of a survivor cohort and as such may be susceptible to population bias. Further, this study recruited a highly selected population that was transferred to a tertiary centre; the results should be interpreted with caution due to generalisability to all patients presenting with unstable angina (patients with unstable angina may present in primary care or the emergency department) (Chua, T. P., Saia, F., Bhardwaj, V. et al, 2000).

4.2.2.3 Health economic evidence

This clinical question did not readily lend itself to health economic evaluation. As such, no specific search of the economic literature was undertaken for this question. No relevant health economic evaluations were found, relating to this question, in either the scoping, or the update searches, undertaken for this Guideline.

4.2.2.4 Evidence to recommendations

The GDG review of the evidence found methodologically the two systematic reviews were well conducted with a low risk of bias. However, there was general inconsistency in the gender-specific symptoms reported in the studies included in the reviews, baseline characteristics of the studies might have varied and there was a lack of standardization in data collection. The results of the systematic reviews suggest that women presenting with ACS compared with men are more likely to experience atypical symptoms such as back and jaw pain, nausea and / or vomiting, shortness of breath, indigestion and palpitations. However, these differences were small. This was supported by

evidence in two well conducted cohort studies with a low risk of bias in patients presenting with acute MI. Two well conducted cohort studies and one study with a high probability of bias found that women presenting with acute MI are more likely to have hypertension compared with men, two of these studies also reported that women were more likely than men to have diabetes, and in one study that women were older than men.

4.2.3 Ethnic differences in symptoms

Return to Recommendations

4.2.3.1 Evidence statements for differences in presentation by ethnicity

1 Two cohort studies in patients presenting with acute chest pain found that African American patients had similar presenting signs and symptoms compared with Caucasian patients. (Johnson, P. A., Lee, T. H., Cook, E. F. et al, 1993) (Klingler, Diane, Green, Weir Robbya, Nerenz, David et al, 2002)

2 One cohort study in patients presenting with acute chest pain found no difference in the number of male African Americans and Caucasians reporting chest pain as a primary symptom, while a higher number of African American female patients had chest pain as a primary symptom compared with Caucasian female patients. (Maynard, C., Beshansky, J. R., Griffith, J. L. et al, 1997)

3 One cohort study in patients presenting with acute chest pain found that African American patients were more likely to report additional symptoms of shortness of breath, abdominal pain, nausea, vomiting and dizziness compared with Caucasians. (Maynard, C., Beshansky, J. R., Griffith, J. L. et al, 1997)

4 One cohort study in patients presenting with acute chest pain found that African Americans were more likely to smoke and have hypertension compared with Caucasians. (Maynard, C., Beshansky, J. R., Griffith, J. L. et al, 1997)

5 One cohort study in patients presenting with acute chest pain found that African American women were more likely to have diabetes compared with Caucasian women. (Maynard, C., Beshansky, J. R., Griffith, J. L. et al, 1997)

6 One cohort study in patients presenting with acute chest pain found that acute MI and angina was less likely to be diagnosed in African American patients compared with Caucasians. (Maynard, C., Beshansky, J. R., Griffith, J. L. et al, 1997)

7 One cohort study in patients presenting with ACS found that Asian patients were younger and more likely to be diabetic compared with Caucasians. (Teoh, M., Lalondrelle, S., Roughton, M. et al, 2007)

8 One cohort study in patients presenting with ACS found that Asian patients were more likely to report frontal upper body discomfort, pain on the rear of their body and greater intensity of pain over greater area of body than Caucasians. (Teoh, M., Lalondrelle, S., Roughton, M. et al, 2007)

9 One cohort study in patients presenting with ACS found that Bangladeshi patients were younger, more often male, and more likely to be diabetic and to report a previous MI compared with Caucasians. (Barakat, K., Wells, Z., Ramdhany, S. et al, 2003).

10 One cohort study in patients presenting with acute MI found that Bangladeshi patients were less likely to report central pain, less likely to report classic descriptions of the character of the pain (heaviness, tightness, weight, pressure, band-like, gripping) and more likely to offer non-classic descriptions of the character of the pain (sharp, stabbing, pinching, burning) compared with Caucasians. (Barakat, K., Wells, Z., Ramdhany, S. et al, 2003).

11 No health economic evidence was identified.

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4.2.3.2 Clinical evidence

Are the symptoms and description of the symptoms different in Black and Ethnic Minorities presenting with acute chest pain compared with Caucasians?

Introduction

People of South Asian origin have higher rates of CAD compared with the general UK population estimated at a 1.5 fold increase in susceptibility. According to the British Heart Foundation South Asian men have an age standardised mortality rate from coronary heart disease that is about 40% higher than the whole population, and for women the figure is 51%. Some studies have suggested that South Asians have less access to cardiac investigation and treatment (Lear, J. T., Lawrence, I. G., Burden, A. C. et al, 1994) (Barakat, K., Wells, Z., Ramdhany, S. et al, 2003) although other reports conflict with these findings (Wilkinson, P., Sayer, J., Laji, K. et al, 1996) (Britton, A., Shipley, M., Marmot, M. et al, 2004). There may be different beliefs about care-seeking appropriateness and also in health seeking behaviour in South Asians compared with the general population; a recent prospective cohort study found that South Asians are less likely to arrive by ambulance than the general population irrespective of admission diagnosis (Ben-Shlomo, Y., Naqvi, H., and Baker, I., 2008). The same study found that physicians had a lower threshold for giving thrombolytic therapy to South Asians with acute chest pain, which may reflect the perceived increased risk of CAD in this group.

Many studies have shown that African American patients with acute MI and ACS are less like to receive invasive coronary interventions compared with Caucasians (Sonel, A. F., Good, C. B., Mulgund, J. et al, 2005) (Chen, J., Rathore, S. S., Radford, M. J. et al, 2001) (Conigliaro, J., Whittle, J., Good, C. B. et al, 2000). However, these studies have been conducted in the USA, and it is unclear whether the disparities would be reflected in the UK due to differing healthcare provision; African Americans have been shown to be more likely to be self-insured or uninsured compared with Caucasians in

some studies, and some studies have reported that the differences remained after adjustment. A number of studies have shown that African Americans have different attitudes about procedural risk and may be less willing to undergo invasive procedures. The treatment disparities identified could be partially a result of clinical factors because African Americans are more likely to have renal insufficiency and congestive heart failure (CHF).

Cultural differences in descriptors of pain, perceived severity and attribution of symptoms, and unique genetic susceptibilities to artery disease risk factors such as hypertension and diabetes may have an impact on the initial clinical evaluation of Black and Ethnic Minority patients. Most studies that have evaluated the clinical presentation of patients with acute chest pain of suspected cardiac origin have been conducted in Caucasian populations. There is a perception in the literature that patents from other ethnic backgrounds may exhibit atypical chest pain symptoms, rather than typical chest pain symptoms associated with cardiac chest pain. However it should be noted that there are surprising few studies that have investigated this perception and studies in non-Caucasian populations often have very low patient numbers relative to other larger studies in the general population.

Five cohort studies in patients with acute chest pain were reviewed of which three studies compared African American patients with Caucasian patients (Johnson, P. A., Lee, T. H., Cook, E. F. et al, 1993) (Klingler, Diane, Green, Weir Robbya, Nerenz, David et al, 2002) (Maynard, C., Beshansky, J. R., Griffith, J. L. et al, 1997) and two studies compared Asian patients with Caucasian patients (Teoh, M., Lalondrelle, S., Roughton, M. et al, 2007) (Barakat, K., Wells, Z., Ramdhany, S. et al, 2003).

The first cohort study examined racial differences in symptom presentation in African American or Caucasian patients aged 30 years or older presenting to the emergency department with a chief complaint of anterior, precordial, or left lateral chest pain that could not be explained by obvious local trauma or abnormalities on a chest X ray (Johnson, P. A., Lee, T. H., Cook, E. F. et al, 1993). The emergency department physician recorded clinical data of all

patients attending the emergency department at the time of presentation, including the patient's age, sex, and findings from history, physical examination and ECG recording. Results were recorded on a standardized form. Patients who experienced cardiac arrest in the emergency department were excluded from the study. During the study period, 4173 potentially eligible patient visits occurred, and the final study population was 3031 after exclusions (11 due to incomplete data, 531 consent not obtained, 204 inadequate follow-up, 158 race not identified, and 238 as race was Asian or Hispanic). A final diagnosis of acute MI was made on the basis of one of the following; (1) characteristic evolution of serum enzyme levels (creatine kinase) (2) ECG showing development of pathological Q waves and at least a 25% decrease in the amplitude of the following R wave compared with that of the emergency department ECG (3) sudden unexpected death within 72 hours of presentation (Johnson, P. A., Lee, T. H., Cook, E. F. et al, 1993).

Of 3031 patients included, 1374 (45%) were African American and 1657 (55%) were Caucasian with mean age of 53 years and 58 years, respectively ($P < 0.001$). For the initial study patients recruited, African American patients were significantly more likely to be female compared with Caucasian patients (68% versus 47%, respectively $P < 0.0001$), and less likely to have a past history of the following; CAD (30% versus 47%, respectively, $P < 0.0001$), cardiac catheterization (6% versus 11%, respectively $P < 0.0001$), and CABG (3% versus 11%, respectively, $P < 0.0001$). African Americans compared with Caucasians were less likely to have a final diagnosis of acute MI (6% versus 12%, respectively, $P < 0.0001$), and this result was consistent with the prior history findings of African American patients versus Caucasian patients (Johnson, P. A., Lee, T. H., Cook, E. F. et al, 1993).

Sub group analysis of patients with a final diagnosis of acute MI found that African American patients had similar presenting signs and symptoms compared with the Caucasian patients. The ORs were all > 1.0 for all symptoms examined in both Caucasians and African Americans, and there was no significant difference in the ORs in two groups for the following; chest pain $\geq$ 30 minutes (Caucasian OR 4.2 (95%CI 1.9 to 9.3) versus African

American OR 6.2 (95%C 3.4 to 11.3), *P* > 0.2), pressure type chest pain (Caucasian OR 2.7 (95%C 1.7 to 4.4) versus African American OR 1.7 (95%C 1.2 to 2.8), *P* > 0.10), radiation of pain to left arm, left shoulder, neck or jaw (Caucasian OR 2.0 (95%C 1.3 to 3.1) versus African American OR 1.9 (95%C 1.4 to 2.6), *P* > 0.2), diaphoresis (Caucasian OR 2.4 (95%C 1.5 to 3.9) versus African American OR 3.2 (95%C 2.4 to 4.4) *P* > 0.2) and rales on physical examination (Caucasian OR 3.8 (95%C 2.3 to 6.4) versus African American OR 2.4 (95%C 1.8 to 3.4), *P* > 0.15) (Johnson, P. A., Lee, T. H., Cook, E. F. et al, 1993).

While it was found that African American patients were less likely to have a final diagnosis of acute MI in the whole study population (*P* < 0.0001), there was no longer a statistical association with race and acute MI after adjustments were made for presenting signs and symptoms using logistical regression analysis. The OR for acute MI outcome for African Americans compared with Caucasians was 0.77 (95%CI 0.54 to 1.1) (Johnson, P. A., Lee, T. H., Cook, E. F. et al, 1993).

The second cohort study assessed the causes of chest pain and presenting symptoms in African American patients and Caucasian patients presenting to the emergency department (Maynard, C., Beshansky, J. R., Griffith, J. L. et al, 1997). Patients were included if they presented with chest or left arm pain, shortness of breath or other symptoms suggestive of acute cardiac ischemia. A total of 10 001 patients were included, of which 3401 were African American and 6600 were Caucasian. The mean age for male African Americans was 52(±14 (not defined as either SD or SE)) years and was 55(±15 (not defined as either SD or SE)) years for female African Americans. The mean age for Caucasian males was 60(±15 (not defined as either SD or SE)) years and for Caucasian females the mean age was 65(±16 (not defined as either SD or SE)) years. The study compared risk factors and signs and symptoms of the patients and these are detailed in Table 9 (Maynard, C., Beshansky, J. R., Griffith, J. L. et al, 1997).

Table 9
Medical history and clinical characteristics of patients on admission

	Men			Women		
Variable	% Caucasian*	% African American†	*P*	% Caucasian ‡	% African American§	*P*
Medical history						
Ulcer	16	16	0.74	14	14	0.73
Hypertension	44	57	<0.0001	51	64	<0.0001
Angina	42	29	<0.0001	39	32	<0.0001
MI	35	20	<0.0001	26	18	<0.0001
Stroke	8	9	0.47	9	9	0.85
Diabetes	20	20	0.88	23	32	<0.0001
Current Smoker	30	56	<0.0001	24	34	<0.0001
Cardiac medications	59	47	<0.0001	64	60	0.01
Signs and Symptoms						
Chest pain	75	77	0.20	72	79	<0.0001
Chest pain as primary symptom	70	69	0.49	64	69	0.0002
Shortness of breath	51	62	<0.0001	55	61	<0.0001
Abdominal pain	12	20	<0.0001	13	17	<0.0001
Nausea	24	28	0.01	29	35	<0.0001
Vomiting	7	13	<0.0001	10	14	<0.0001
Dizziness	26	35	<0.0001	26	33	<0.0001
Fainting	7	6	0.32	7	5	0.0001
Rales	20	19	0.14	25	19	<0.0001
S3 sound	3	4	0.13	3	3	0.74
Congestive heart failure	16	16	0.65	18	15	0.019
Systolic blood pressure >160 mmHg	23	21	0.29	28	28	0.45
Diastolic blood pressure > 90 mmHg	28	36	<0.0001	23	34	<0.0001

*n = 3655
†n = 1391
‡n = 2944
§n = 1910
Permissions granted from original source (Maynard, C., Beshansky, J. R., Griffith, J. L. et al, 1997)

The study found that there were differences in patients' medical history dependent upon racial background. African Americans were more likely to smoke and have hypertension compared with Caucasians, and African American women were more likely to have diabetes than Caucasian women. Caucasian patients were more likely to have a history of angina or MI and to take cardiac medications. There was no difference in the number of African

Americans and Caucasian male patients who had chest pain as a primary symptom. There were a higher number of African American female patients than Caucasian female patients who had chest pain as a primary symptom. African American patients were more likely to report additional symptoms of shortness of breath, abdominal pain, nausea, vomiting and dizziness. African Americans were more likely to have a diastolic blood pressure of > 90mmHg when admitted to hospital compared to Caucasian patients (Maynard, C., Beshansky, J. R., Griffith, J. L. et al, 1997).

Acute MI and angina was less likely to be diagnosed in African American men compared with Caucasian men (acute MI; 6% versus 12%, respectively; angina 8% compared to 20%). Non cardiac diagnoses were confirmed in almost half of African American men compared with one third of Caucasian men. Similarly only 4% of African American women had a final diagnosis of acute MI compared with 8% of Caucasian women, and angina was diagnosed in 12% of African American women compared with 17% of Caucasian women. Non cardiac diagnoses were confirmed in almost half of African American women compared with 39% of Caucasian women (Maynard, C., Beshansky, J. R., Griffith, J. L. et al, 1997).

Logistic regression in 74% of the patients examined the racial differences in the diagnoses, using the following variables; medical history, sociodemographic factors, signs and symptoms, and the hospital the patient was admitted to. African American patients compared to Caucasian patients were half as likely to have had an acute MI (OR 0.54, 95%CI 0.41 to 0.68) (Maynard, C., Beshansky, J. R., Griffith, J. L. et al, 1997).

The third cohort study compared the medical history and the risk factors of African Americans with Caucasian patients admitted with suspected acute MI to an emergency department chest pain unit within 48 hours of pain onset (Klingler, Diane, Green, Weir Robbya, Nerenz, David et al, 2002). The study also examined patient perception of chest pain by race. The study identified patients through a floor census and screened through a brief review of their medical charts. Patients were approached to participate based on their

medical record number. Five hundred patients were approached and 215 met the inclusion criteria. Patients were included if English was their primary language and they could recall pre-hospital events. Patients were excluded if they were of a race other than African American or Caucasian, were aged < 18 years, had known mental impairment, were pregnant, had a MI subsequent to admission, had a previous interview prior to admission, or had significant emergency data missing from their medical records. The study recruited 157 African American patients (73%) and 58 Caucasian patients (27%). The mean age for African American patients was 59(SD 14) years and for Caucasian patients was 62(SD 15) years, 46% of the African American patients were male compared to 57% of the Caucasian patients (Klingler, Diane, Green, Weir Robbya, Nerenz, David et al, 2002).

A structured questionnaire was developed to assess the contextual, emotional and behavioural factors in patients seeking medical help. The questionnaire was adapted from existing questionnaires, after external validation by a group of experts it was piloted on 10 patients and altered accordingly (Klingler, Diane, Green, Weir Robbya, Nerenz, David et al, 2002).

The study examined the demographics and medical history of the two groups, and there were no significant differences between the two groups' age, sex and insurance status (suggestive of socioeconomic status). African Americans were marginally more likely to have diabetes ($P = 0.05$) and to be more likely to be taking calcium-channel blockers ($P = 0.005$). Caucasian patients were more likely to have had CABG ($P = 0.01$) and to have had a previous stomach complaint ($P = 0.03$) (Klingler, Diane, Green, Weir Robbya, Nerenz, David et al, 2002).

Symptoms were assessed through open ended questions and a close ended check off of symptoms. Patients answered yes or no. The patients had no differences in frequency of symptoms according to race. No significant differences were found between African American and Caucasian patients in the subjective (chest pain, chest pressure, chest tightness, chest discomfort, palpitations, nausea, arm / shoulder pain, back pain, jaw pain, neck pain,

headache, numbness / tingling, shortness of breath, cough, dizziness, sweating, weakness). There was no significant difference in the one worst reported symptom (respiratory, cardiac, gastrointestinal, other, unable to identify) between African American and Caucasian patients. There was also no significant difference in the location of pain (above diaphragm, below diaphragm, both, other), the timing of the pain (constant, intermittent, wax/wane) and the median discomfort and control of pain between African American and Caucasian patients. African Americans were as likely as Caucasian patients to report typical subjective symptoms but were marginally more likely to attribute their symptoms to a gastrointestinal source rather than a cardiac source ($P = 0.05$). Of 157 African American patients, 11 patients were diagnosed as having had an acute MI (11%), while 27 out of 58 Caucasian patients (47%) were diagnosed with acute MI ($P < 0.001$). However of those patients with a final diagnosis of MI, 61% of African Americans attributed their symptoms to a gastrointestinal source and 11% to a cardiac source versus 26% and 33%, respectively for Caucasian patients. Hence although the proportion of objectively defined typical symptoms were similar, self attribution was more likely to be non cardiac in African American patients compared with Caucasian patients (Klingler, Diane, Green, Weir Robbya, Nerenz, David et al, 2002).

The fourth cohort study compared the symptom presentation in Asian and Caucasian patients with ACS (Teoh, M., Lalondrelle, S., Roughton, M. et al, 2007). Consecutive patients requiring hospital admission for ACS were recruited by a senior cardiac nurse. The final diagnosis was decided by a cardiologist based upon the results of ECG, exercise ECG and troponin T testing. The patients were asked to complete a brief question survey asking for the location of their symptoms on a schematic diagram of the front and back views of the upper body. Additional volunteered symptoms were also recorded, and patients were asked to rank these. Intensity of pain was also recorded on a scale of 0 to 10 where 10 equated to worst pain ever experienced. ACS were divided into 3 categories; ischaemic events due to angina, non-ST-segment elevation MI, and MI associated with ST-segment elevation (Teoh, M., Lalondrelle, S., Roughton, M. et al, 2007).

Of 3000 patients surveyed, 95 (3.2%) were of neither Caucasian nor Asian race, or were of mixed racial origins. Of the remaining 2905 patients, 604 (21%) were Asian and 2301 (79%) were Caucasian. The demographic details and type of ACS are detailed in Table 10. Compared with Caucasian patients, Asian patients were younger and more likely to have diabetes. Proportionally, more Asians had angina compared with Caucasians (51% versus 37%, respectively, $P < 0.001$), while proportionally more Caucasians compared with Asians had acute MI (63% versus 49%, respectively, $P < 0.001$), which was attributable to a higher incidence of non-ST-segment elevation MI (40% versus 29%, respectively, $P < 0.001$), and there was no statistically significant difference in the proportion of Caucasians (21%) versus Asians (18%) being diagnosed with ST-segment elevation MI (Teoh, M., Lalondrelle, S., Roughton, M. et al, 2007).

Table 10

Demographics and cardiac diagnosis of presentation in the Asian and Caucasian groups

	Asian patients, n=604	Caucasian patients, n=2301	*P* Value
Age (years) mean (SD)	60.6 (12.7)	68.9 (13.9)	<0.001
Male, n (%)	396 (66)	1431 (62)	0.13
Diabetic, n (%)	262 (43)	398 (17)	<0.001
MI, n (%)	294 (49)	1439 (63)	<0.001
ST-segment elevation MI, n (%)	109 (18)	482 (21)	0.12
Anterior ST-segment elevation MI, n (%)	54 (9)	206 (9)	0.99
Non ST-segment elevation MI, n (%)	173 (29)	917 (40)	<0.001
Left bundle branch block, n (%)	12 (2)	40 (2)	0.68
Angina, n (%)	310 (51)	851 (37)	<0.001

Permissions granted from original source (Teoh, M., Lalondrelle, S., Roughton, M. et al, 2007).

The distribution of reported discomfort for Asians and Caucasians is detailed in Table 11 for all patients admitted to the emergency department. Frontal upper body discomfort was reported by 94% of Asian patients versus 89% of Caucasian patients ($P < 0.001$), while almost twice as many Asian patients reported pain on the rear of their body compared with Caucasian patients (46% versus 25%, respectively, $P < 0.001$) (Teoh, M., Lalondrelle, S., Roughton, M. et al, 2007).

Table 11

Comparison of pain characteristics between Asian and Caucasian groups

	Asian patients, n=604	Caucasian patients, n=2301	*P* Value
Frontal discomfort, n (%)	565 (94)	1975 (86)	<0.001
Posterior discomfort, n (%)	278 (46)	562 (25)	<0.001
Classical distribution of discomfort, n (%)	545 (90)	1887 (82)	<0.001
Silent pain, n (%)	35 (6)	299 (13)	<0.001
Intensity of discomfort, median (range)	7.5 (0-10)	7 (0-10)	0.002
Maximum discomfort intensity of 10, n (%)	148 (25)	459 (20)	0.02
Area of discomfort, median (range)	5 (0-19)	4 (0-24)	<0.001

Permissions granted from original source (Teoh, M., Lalondrelle, S., Roughton, M. et al, 2007).

The character of the discomfort as described by the Asian patients was 'weight' (34%), followed by 'squeeze' (28%), and 'ache' (14%). For Caucasian patients the most common term was 'weight' (28%), followed by 'ache' (23%), and 'squeeze' (20%) (Teoh, M., Lalondrelle, S., Roughton, M. et al, 2007).

There was a small but statistically significant difference in the intensity of discomfort reported, with Asian patients reporting a median pain rating of 7.5 compared with 7.0 in Caucasian patients ($P < 0.002$). Twenty four percent of Asian patients rated their discomfort at the maximum value of 10 compared with 19% of Caucasian patients. A smaller percentage of Asian patients (6%) reported feeling no discomfort at presentation (silent MI) compared with Caucasian patients (13%) ($P = 0.002$). These patients were identified by a combination of symptoms, including fatigue, shortness of breath, collapse and resuscitation following cardiac arrest. Logistic regression analysis was performed to determine which factors contributed to patients reporting a silent episode, and the most significant factor was a patient's diabetic status, such patients were more than twice as likely to report that they felt no pain during presentation compared with non-diabetics (OR 2.08, 95%CI 1.56 to 2.76). Analysis showed that Caucasian patients were also more likely to experience no discomfort compared with Asian patients (OR 1.61, 95%CI 1.08 to 1.10).

Analysis with age as a continuous variable was also associated with silent episodes. Overall Asian patients were younger, more likely to be diabetic and they tended to report greater intensity of pain over a greater area of the body, and more frequent discomfort over the rear of their upper thorax compared with Caucasian patients (Teoh, M., Lalondrelle, S., Roughton, M. et al, 2007).

The fifth cohort study assessed the differences in presentation of acute MI between Bangladeshi patients and Caucasian patients (Barakat, K., Wells, Z., Ramdhany, S. et al, 2003). Inclusion criteria were acute MI as defined by the presence of cardiac chest pain with ST-segment elevation > 1 mm in two consecutive leads, Q wave development, and a creatine kinase rise greater than twice the upper limit of normal (400 IU/ml). A total of 371 patients were included in the study, 108 were Bangladeshi and 263 were Caucasian. The study compared the risk factors and presenting symptoms of the two groups of patients. The mean age for Bangladeshi patients was 63(±12 (not defined as either SD or SE)) years and for Caucasian patients was 68(±19 (not defined as either SD or SE)) years, 87% of the Bangladeshi group were male compared to 70% of the Caucasian group. One third of the Bangladeshi patients were fluent in English (Barakat, K., Wells, Z., Ramdhany, S. et al, 2003).

The study examined the patients' age, sex, smoking status, history of hypertension, diabetes, family history of ischaemic heart disease, previous MI, the nature of the chest pain (central pain, left sided pain or other pain) the character of the pain typical (heaviness, tightness, weight, pressure, band-like, gripping) or non-classical (sharp, stabbing, pinching, burning), how the pain was interpreted and what the patients initial response was. The study also adjusted any significant results with respect to the patients age, sex, risk factors and proficiency in English (Barakat, K., Wells, Z., Ramdhany, S. et al, 2003).

The study found that the Bangladeshi patients were younger, more often male, and more likely to be diabetic and to report a previous MI compared with Caucasian patients. However Caucasian patients were more likely to

report a family history of ischaemic heart disease compared with Bangladeshi patients. The study also found that Bangladeshi patients were significantly less likely to report central chest pain (OR 0.11, 95%CI 0.03 to 0.38; *P* = 0.0006) than Caucasian patients. This significant difference remained after adjustment for the patients' age, sex, risk factor profiles and fluency in English. Bangladeshi patients were also were more likely to offer non-classic descriptions of the character of the pain (sharp, stabbing, pinching, burning) and less likely to report classic descriptions of the character of the pain (heaviness, tightness, weight, pressure, band-like, gripping) (OR 0.25, 95%CI 0.09 to 0.74; *P* = 0.0118). Again these differences remained after adjustment for the patients' age, sex, risk factor profiles and fluency in English (Barakat, K., Wells, Z., Ramdhany, S. et al, 2003).

4.2.3.3 Health economic evidence

This clinical question did not readily lend itself to health economic evaluation. As such, no specific search of the economic literature was undertaken for this question. No relevant health economic evaluations were found, relating to this question, in either the scoping, or the update searches, undertaken for this Guideline.

4.2.3.4 Evidence to recommendations

The review of the evidence found two well conducted cohort studies with a low risk of bias which found that African Americans had a similar clinical presentation of acute MI compared with Caucasians, while one well conducted cohort study reported that African American patients were more likely to report additional symptoms of shortness of breath, abdominal pain, nausea, vomiting and dizziness compared with Caucasians. One well conducted cohort study and a second study that may have spectrum bias (because recruited patients had been selected as those with Q wave acute MI (Barakat, K., Wells, Z., Ramdhany, S. et al, 2003) indicated that Asian patients may present with more atypical symptoms compared with Caucasian patients, and that Asian patients are more likely to be younger, to be diabetic and to have had a prior MI. The GDG concluded that whilst there may be

differences between different ethnic groups in the symptomatic presentation of ACS / MI, these are small.

4.2.4 Use of nitrates in the diagnosis of acute chest pain

4.2.4.1 Evidence statements for nitrates

1 In 3 prospective cohort studies and one retrospective cohort studies, nitrates were of no diagnostic value in patients with acute chest pain. (Steele, R., McNaughton, T., McConahy, M. et al, 2006) (Diercks, D. B., Boghos, E., Guzman, H. et al, 2005) (Henrikson, C. A., Howell, E. E., Bush, D. E. et al, 2003) (Shry, E. A., Dacus, J., Van De Graaff, E. et al, 2002)

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4.2.4.2 Clinical evidence

What is the diagnostic utility of pain relief with nitrates in the identification of patients with acute chest pain of cardiac origin?

Three cohort studies (Steele, R., McNaughton, T., McConahy, M. et al, 2006) (Diercks, D. B., Boghos, E., Guzman, H. et al, 2005) (Henrikson, C. A., Howell, E. E., Bush, D. E. et al, 2003) and one retrospective cohort study (Shry, E. A., Dacus, J., Van De Graaff, E. et al, 2002) were reviewed.

The first prospective cohort study examined the utility of pain relief with sublingual nitroglycerin as a diagnostic test to differentiate cardiac chest pain from non cardiac chest pain (Steele, R., McNaughton, T., McConahy, M. et al, 2006). The inclusion criteria were as follows; admission to the emergency department with a chief complaint of chest pain and sublingual nitroglycerin administration by a healthcare professional. The exclusion criteria were as follows; obvious diagnosis of myocardial ischaemia (e.g. cardiogenic shock), patients with ECG evidence of acute MI on initial ECG, patients urgently referred for cardiac catheterisation, patients who could not quantify their chest pain, and those that did not complete a standard cardiac work-up (at least 2 ECGs, 2 troponin tests, and chest X ray) (Steele, R., McNaughton, T., McConahy, M. et al, 2006).

The treating healthcare professional was not blinded to the patient's response to nitroglycerin, while the study investigator was not involved in the patient care. The standard protocol for nitroglycerin administration to patients with suspected cardiac chest pain was 1 dose of 400 μg every 5 minutes up to 3 doses or until pain was resolved. The investigator recorded the pain before and after each dose of nitroglycerin. The patient reported pain on a 1 to 10 scale (1 = very mild; 10 = severe), and an analogue scale with happy to sad faces was also used. A positive response to nitroglycerin was defined *a priori* as a reduction in 3 points or more, or complete relief if the initial score was 3 or less. A negative response to nitroglycerin was defined as a failure to achieve the defined positive response. Cardiac chest pain as the outcome was defined as chest pain associated with 1 of the following; new ECG changes of 1 mm in 2 contiguous leads, positive cardiac troponin T > 0.3 μg /l, cardiac catheterisation showing > 70% stenosis, or a positive provocative test (myocardial perfusion scintigraphy, dobutamine or exercise stress echocardiography). Non cardiac chest pain was defined as no positive findings on the cardiac work up (results of 2 ECGs had to be normal and all patients received 2 troponin tests) (Steele, R., McNaughton, T., McConahy, M. et al, 2006).

Of a total of 278 patients who were initially enrolled, 8 patients were excluded and discharged from the emergency department; 5 had non cardiac chest pain, and 3 had a diagnosis of stable chest pain, and they were not admitted to hospital and required medical management only. The final 270 patients were followed up for 4 weeks after hospital discharge to determine repeat hospitalisations, cardiac events, death, new medical diagnoses after discharge and other cardiac testing. Twelve patients (4.4%) were lost to follow up (Steele, R., McNaughton, T., McConahy, M. et al, 2006).

Of the 270 patients studied, 177 patients (66%) showed a positive response to nitroglycerin. In the positive pain relief with nitroglycerin group, 60 out of 177 patients (34%) had defined cardiac chest pain. In the negative pain relief group 23 out of 93 patients (25%) had cardiac chest pain. For patients diagnosed with acute MI, 20 were in the pain relief with nitroglycerin group,

and 15 were in the no pain relief group. There were 3 deaths in the group which experienced pain relief and 6 deaths in the group with no pain relief (Steele, R., McNaughton, T., McConahy, M. et al, 2006).

The mean age in the positive nitroglycerin responsive group versus the negative groups was 52 years and 53 years, respectively. The percentage of men in the negative nitroglycerin responsive group was higher compared with the positive response group (55% versus 27%). There was no statistical difference in the following variables of the patient history between the positive response group compared with the negative response group; hypertension 65% versus 63%, respectively, prior CAD 36% versus 45%, respectively, diabetes 28% versus 26%, respectively, MI 11% versus 16%, respectively, hypercholesterolemia 37% versus 43%, respectively, and family history of CAD 36% versus 40%, respectively (Steele, R., McNaughton, T., McConahy, M. et al, 2006).

The sensitivity of nitroglycerin as a diagnostic test was 72% (95%CI 64% to 80%) and the specificity was 37% (95%CI 34% to 41%). The positive likelihood was 1.1 (95%CI 0.96 to 1.34). Sublingual nitroglycerin as a diagnostic tool was not found to be statistically significant in differentiating between patients with and without acute cardiac chest pain using Pearson χ^2 statistic, $P = 0.12$ (Steele, R., McNaughton, T., McConahy, M. et al, 2006).

The second cohort study examined the change in numeric description of pain after sublingual nitroglycerin administration to patients presenting to the emergency department with suspected cardiac chest pain (Diercks, D. B., Boghos, E., Guzman, H. et al, 2005). An 11 point numeric descriptive scale was used to assess pain before and 5 minutes after sublingual nitroglycerin administration (tablet or spray), and a zero score indicated no pain while 10 was the worst possible pain imaginable. Pain description was divided into 4 categories; (1) significant / complete relief, 85% to 100% relief if initial pain score > 5, or 29% to 100% reduction if pain score was $\leq$ 5, (2) moderate reduction, 34% to 84% relief if initial pain score > 5, or 25% to 28% reduction if initial pain score was $\leq$ 5, (3) minimal reduction, 1% to 34% relief if initial

pain score > 5, or 1% to 25% reduction if initial pain score was ≤ 5, (4) no change. Analysis was limited to the change in numeric description after the first dose only. Patients were excluded if the numeric descriptive scale was incomplete, or the data were obtained more than 10 minutes after administration of nitroglycerin (Diercks, D. B., Boghos, E., Guzman, H. et al, 2005).

The primary outcome was the presence or absence of ischaemic chest pain. Patients were followed up daily during hospitalisation to determine if the cause of their chest pain was cardiac-related. Chest pain was considered ischaemic, and therefore cardiac-related if any of the following events occurred; all cause mortality, MI, or diagnostic testing confirming the presence of CAD. Patients were also followed up for a further 30 days (Diercks, D. B., Boghos, E., Guzman, H. et al, 2005).

Of 715 patients initially identified, 51 were excluded due to incomplete data leaving 664 patients, including 345 women (52%) and 319 men (48%). The mean age was 54(SD 12) years. There was no difference in chest pain descriptors (e.g. pressure, stabbing, dullness) or associated symptoms (e.g. nausea, vomiting, shortness of breath) between those patients with and without cardiac-related chest pain. Complete 30 day follow up was obtained in 591 out of 664 patients (89%) (Diercks, D. B., Boghos, E., Guzman, H. et al, 2005).

The primary outcome of cardiac-related chest pain was found in 122 patients (18%), of which 68 had acute MI and 54 had unstable angina. An initial pain score of > 5 was documented in 478 patients (71%), and in this group the primary outcome of cardiac-related chest pain was found in 82 patients (17%). An initial pain score of ≤ 5 was documented in 186 patients (29%), and in this group the primary outcome of cardiac-related chest pain was found in 40 patients (17%) (Diercks, D. B., Boghos, E., Guzman, H. et al, 2005).

In the total patient population, 125 (19%) patients had no change in pain, 206 (31%) patients had minimal pain reduction, 145 (22%) had moderate pain reduction, and 188 (28%) patients had significant or complete pain reduction.

A change in the numeric descriptive scale score was not associated with a diagnosis of cardiac-related chest pain (as defined as all cause mortality, MI, or diagnostic testing confirmed the presence of CAD) in any of these 4 subgroups using Pearson χ^2 statistic $P = 0.76$) (Diercks, D. B., Boghos, E., Guzman, H. et al, 2005).

The third cohort study examined the diagnostic and prognostic value of chest pain relief with sublingual nitroglycerin in patients with suspected chest pain of cardiac origin in the emergency department (Henrikson, C. A., Howell, E. E., Bush, D. E. et al, 2003). To be included patients had to have documented chest pain while under medical supervision, and had to be given sublingual nitroglycerin. Patients were excluded if their chest pain developed before being under medical supervision or they were unable to quantify their pain (Henrikson, C. A., Howell, E. E., Bush, D. E. et al, 2003).

Chest pain was rated on a score from 1 (mild pain) to 10 (severe pain), and the pain score was recorded immediately before and approximately 5 minutes after nitroglycerin administration. Although further pain relief may have been required following the initial dose, assessment of the response to nitroglycerin was determined after the first dose. Positive nitroglycerin pain relief was defined as 50% or greater reduction in chest pain intensity within approximately 5 minutes of administration of 0.4 mg sublingual nitroglycerin either as a tablet or a spray (Henrikson, C. A., Howell, E. E., Bush, D. E. et al, 2003).

The outcome was CAD as defined as typical chest pain with one of the following during the index hospitalisation or during the follow up period; elevated serum troponin T level (≥ 0.1 µg/l), coronary angiography demonstrating ≥ 70% stenosis, or positive stress exercise test. No active CAD was defined as no elevation in troponin T levels during index visit or during follow up and at least on of the following; coronary angiography without flow limiting stenosis, negative exercise stress test. Patients were also defined as having no active coronary disease in the following circumstances; no history of CAD, no cardiac testing at index visit and follow up, and no cardiac events,

or, known history of CAD but atypical chest pain, no events during follow up, and other clinical explanations for symptoms (Henrikson, C. A., Howell, E. E., Bush, D. E. et al, 2003).

The study participants were followed up at approximately 4 months to determine their clinical status, health care seeking behaviour, clinical events, hospitalisations, cardiac testing and medication use (Henrikson, C. A., Howell, E. E., Bush, D. E. et al, 2003).

Of 459 patients, 181 (39%) had at least a 50% reduction in chest pain with nitroglycerin, while 278 patients (61%) did not. Of the 459 patients, 4 month follow up was completed in 389 patients (85%). The mean follow-up was 176(SD 56) days. There was no statistical difference in the incidence of death, subsequent MI or coronary revascularisation either individually or as a combined endpoint in the nitroglycerin responsive group versus the nitroglycerin non responsive group (Henrikson, C. A., Howell, E. E., Bush, D. E. et al, 2003).

A total of 141 (31%) of patients were determined to have active CAD as a cause of their index visit. Two hundred and seventy five patients (59%) did not have active coronary disease. A total of 58 patients without testing were classified as not having active CAD because they had no history of CAD and no events during follow up (53 patients), or, had an obvious other explanation of their chest pain (5 patients). The cause of chest pain could not be determined in 43 of 459 patients (9%), and they were omitted from the sensitivity and specificity analysis. None of these 43 patients had testing and 31 could not be located for follow up. The remaining 12 had no events in follow up events, but had a known history of CAD, and a non diagnostic index hospitalisation (Henrikson, C. A., Howell, E. E., Bush, D. E. et al, 2003).

The sensitivity and specificity of chest pain relief with nitroglycerin for the presence of active CAD were 35% and 58%, respectively. The PLRs and NLRs were 0.85 and 1.4, respectively. Further analysis was conducted in 3 pre-specified subgroups for chest pain relief with nitroglycerin for the presence of active CAD. For troponin negative patients the sensitivity,

specificity, PLR and NLR were 39%, 58%, 0.88 and 1.1, respectively. For patients with a history of CAD the sensitivity, specificity, PLR and NLR were 30%, 63%, 0.84 and 1.3, respectively. For patients with no history of CAD, the sensitivity, specificity, PLR and negative likelihoods were 40%, 56%, 0.87 and 1.1, respectively. ROC curves were constructed for chest pain relief by nitroglycerin and active CAD. For ROC curves of both reduction in pain intensity and absolute changes in pain intensity the plotted points closely approximated to a likelihood of 1.0. Hence regardless of which definition is used, either percentage chest pain reduction or absolute pain reduction, the test of chest pain relief by nitroglycerin was found to have no value in determining the presence or absence of CAD (Henrikson, C. A., Howell, E. E., Bush, D. E. et al, 2003).

The fourth cohort study evaluated the pain response to nitroglycerin as a diagnostic tool in patients with chest pain of suspected cardiac origin based upon patient recall of their pain (Shry, E. A., Dacus, J., Van De Graaff, E. et al, 2002). Patients were included if they presented to the emergency department with ongoing chest pain and they received sublingual nitroglycerin and no other treatment within 10 minutes of nitroglycerin administration (other than aspirin). In addition the patient's pain response had to have been recorded, and follow up had to be available (Shry, E. A., Dacus, J., Van De Graaff, E. et al, 2002).

Cardiac chest pain was defined as including any of the following; dynamic or new wave ECG changes (0.1 mV ST-segment elevation or depression or T wave inversion during pain), myocardial necrosis (cardiac specific enzyme elevation), abnormal stress test, abnormal cardiac catheterisation ($\geq$ 50% stenosis of the left main artery or $\geq$ 70% of any other epicardial coronary artery) or a diagnosis of cardiac aetiology (in absence of previous mentioned criteria) by a cardiologist. The patient's subjective pain level at presentation and after nitrate therapy was determined using a pain score of 0 to 10, with 0 representing no pain and 10 denoting maximal pain. A response to pain was defined as a reduction in pain by at least 2 units, and complete relief was defined as absence of chest pain. Pain responses that occurred > 10 minutes

after nitroglycerin administration were excluded (Shry, E. A., Dacus, J., Van De Graaff, E. et al, 2002).

Of 251 patients, 223 patients met enrolment criteria, 23 patients were excluded for simultaneous medication and 5 were excluded due to hospital transfer. The mean age of the included patients was 60(SD 14) years, 53% were men, 38% had a history of CAD, 61% had hypertension, 23% had diabetes, and 43% had prior hypercholesterolaemia. Diagnostic evaluation included ECG (99%), cardiac enzymes (97%), exercise stress testing (45%) and cardiac catheterisation (29%). After testing, 67% patients were discharged due to a diagnosis of non cardiac chest pain, and the remaining 33% had suspected CAD. Of these, 82% had objective findings of CAD, and the remaining were diagnosed with CAD based on prior history and reoccurrence of index symptoms (Shry, E. A., Dacus, J., Van De Graaff, E. et al, 2002).

Ninety percent, 199 out of 223 patients responded to nitroglycerin (at least a 2 unit reduction in chest pain score based on the 10 point scale). Of the patients diagnosed with chest pain attributable to CAD, 88% responded to nitroglycerin, while 92% of the non cardiac chest pain group responded to nitroglycerin. Seventy percent of patients (52 out of 74 patients) with cardiac chest pain had complete pain resolution with nitroglycerin versus 73% of patients (108 out of 149 patients) with non cardiac chest pain had complete resolution (P = 0.85) (Shry, E. A., Dacus, J., Van De Graaff, E. et al, 2002).

4.2.4.3 Health economic evidence

This clinical question was designated as low priority for economic evaluation, and so no specific search of the economic literature was undertaken. No relevant health economic evaluations were found, relating to this question, in either the scoping, or the update searches, undertaken for this Guideline.

4.2.4.4 Evidence to recommendations

Three well conducted cohort studies with a low risk of bias found that patients with acute cardiac chest pain had equivalent rates of pain relief compared with patients with non cardiac causes of their pain. The results of the

retrospective study were similar to the other studies, although it had a high risk of patient re-call bias. The GDG concluded that response to nitroglycerin is not helpful as a diagnostic tool in differentiating cardiac chest pain, from non cardiac chest pain, but may nevertheless be useful as a therapeutic agent for pain relief.

4.2.5 Resting 12 lead ECG

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4.2.5.1 Evidence statements for ECG

1 One systematic review in patients presenting with acute chest pain in primary care found that the presence of ST-segment elevation was the most discriminating single ECG change for ruling in a diagnosis of acute MI. The two next best changes were the presence of Q waves and ST-segment depression. The combination of a number of features for example ST-segment elevation, ST-segment depression, Q waves and or T wave changes gave reasonable discrimination in the identification of patients with acute MI. A completely normal ECG was reasonably useful at ruling out a MI, although was not definitive. Heterogeneity was found in the studies identified. (Mant, J., McManus, R. J., Oakes, R.-A. L. et al, 2004)

2 One systematic review in patients with acute chest pain of suspected cardiac origin, found that ECG changes were the most discriminating criteria for the diagnosis of acute MI compared with signs and symptoms, and risk factors. ST-segment elevation gave the best diagnostic performance compared with other ECG changes. There was heterogeneity in the studies identified. (Chun, Andrea Akita and McGee, Steven R., 2004)

3 One systematic review that examined the use of a pre-hospital ECG and advanced notification of the ECG found that the door to treatment interval decreased with use of a pre-hospital ECG and advanced notification compared with no pre-hospital notification of

ECG. There was heterogeneity in the studies identified. (Morrison, L. J., Brooks, S., Sawadsky, B. et al, 2006)

4 One systematic review in patients with acute chest pain found that an out-of-hospital ECG had excellent diagnostic performance for the identification of acute MI and good diagnostic performance for ACS. There was heterogeneity in the studies. (Ioannidis, J. P., Salem, D., Chew, P. W. et al, 2001)

5 One cohort study of limited power in patients with acute chest pain of suspected cardiac origin and normal serial troponin levels found that ST-segment depression was a significant predictor of both acute MI and major adverse cardiac events (acute MI / and or cardiac death). (Sanchis, J., Bodí, V., Llácer, A. et al, 2005)

6 One cohort study in patients with acute chest pain found that the results of an ECG in addition to a chest pain score derived from the clinical history could identify patients at very low risk who could be safely discharged following a first line negative evaluation that included negative serum biomarkers. (Conti, Alberto, Paladini, Barbara, Toccafondi, Simone et al, 2002)

7 One cohort study in chest pain patients found that in patients at moderate and high risk of acute MI or unstable angina continuous 12-lead ST-segment monitoring with automated serial ECG may be beneficial in their early management. (Fesmire, F. M., 2000)

8 One cohort study found that access to a previous ECG from the same patient improved diagnostic performance of an artificial neural network and also of an intern in detecting acute MI, but not that of a cardiologist. (Ohlsson, M., Ohlin, H., Wallerstedt, S. M. et al, 2001)

9 One retrospective cohort study in patients with suspected acute MI, that compared automated QT dispersion and ST-segment measurements to that of physician interpretation of ECG found that independent classification by QT-end and QT-peak dispersions was

not superior to physician consensus. Automated assessment of ST-segment deviation gave a higher sensitivity but a lower specificity for the diagnosis of acute MI compared with the physicians' interpretation. The combination of the physicians consensus and the automated classification of ST-segment deviations increased the sensitivity compared with the physician consensus alone by 88%, while the specificity decreased substantially The combination of automated QT- end dispersion, QT- peak dispersion and ST deviations measurements with physicians' consensus increased sensitivity gave optimal classification for the diagnosis of acute MI. (Aufderheide, T. P., Xue, Q., Dhala, A. A. et al, 2000)

10 A study that examined data from a large registry of acute ST-segment elevation MI patients found that pre-hospital ECG recording reduced door to needle times for patients receiving fibrinolytic therapy and reduced door to balloon time for patients undergoing primary percutaneous coronary intervention compared with patients who received an in-hospital ECG. One quarter of patients transported by the emergency services received a pre-hospital ECG. There was a trend for a reduction in mortality in patients who received a pre-hospital ECG compared with patients who received an in-hospital ECG. (Diercks, D. B., Kontos, M. C., Chen, A. Y. et al, 2009)

4.2.5.2 Clinical evidence

What is the utility and cost-effectiveness of the resting ECG in evaluation of individuals with chest pain of suspected cardiac origin?

Four systematic reviews (Ioannidis, J. P., Salem, D., Chew, P. W. et al, 2001) (Morrison, L. J., Brooks, S., Sawadsky, B. et al, 2006) (Chun, Andrea Akita and McGee, Steven R., 2004) (Mant, J., McManus, R. J., Oakes, R.-A. L. et al, 2004), and six cohort studies (Sanchis, J., Bodí, V., Llácer, A. et al, 2005) (Conti, Alberto, Paladini, Barbara, Toccafondi, Simone et al, 2002) (Fesmire, F. M., 2000) (Ohlsson, M., Ohlin, H., Wallerstedt, S. M. et al, 2001)

(Aufderheide, T. P., Xue, Q., Dhala, A. A. et al, 2000) (Diercks, D. B., Kontos, M. C., Chen, A. Y. et al, 2009) were identified in patients with acute chest pain. Two of the systematic reviews examined studies in both acute and stable patients with chest pain (Chun, Andrea Akita and McGee, Steven R., 2004) (Mant, J., McManus, R. J., Oakes, R.-A. L. et al, 2004). One systematic reviewed out of hospital ECG (Ioannidis, J. P., Salem, D., Chew, P. W. et al, 2001), a second systematic reviewed pre-hospital ECG and advanced notification of the ECG, and one cohort study examined the use and impact of pre-hospital ECG (Diercks, D. B., Kontos, M. C., Chen, A. Y. et al, 2009). Two cohort studies assessed the use of ECG and chest pain scores (Sanchis, J., Bodí, V., Llácer, A. et al, 2005), (Conti, Alberto, Paladini, Barbara, Toccafondi, Simone et al, 2002), one cohort examined the use of serial ECG (Fesmire, F. M., 2000) and two cohorts examined computer assessment of ECG (Ohlsson, M., Ohlin, H., Wallerstedt, S. M. et al, 2001) (Aufderheide, T. P., Xue, Q., Dhala, A. A. et al, 2000).

The first systematic review examined the utility of ECG changes in patients with acute chest pain presenting in primary care, rapid access chest pain units and / or the emergency department (Mant, J., McManus, R. J., Oakes, R.-A. L. et al, 2004). The reference standards used for MI were combinations of ECG changes, enzyme changes and typical clinical features and in some cases radionucleotide scanning results. The WHO criteria were most commonly used. The diagnosis of unstable angina is not possible with ECG and hence only studies relating to acute MI were included. It should be noted that the diagnostic utility of ECG changes was compared a reference standard (WHO criteria) that was not independent of ECG changes. The WHO criteria require the presence of two of the following three features: symptoms of myocardial ischaemia, elevation of cardiac marker concentrations in the blood, and a typical ECG pattern involving the development of Q waves or persistent T wave changes. Fifty three papers were identified that examined the use of one or more features of an ECG. LRs were calculated from each study, and pooled LRs were generated with 95% confidence intervals (Mant, J., McManus, R. J., Oakes, R.-A. L. et al, 2004).

As detailed in Table 12, the presence of ST-segment elevation (commonly defined as 1 mm in at least two contiguous limb leads or 2 mm in two contiguous precordial leads) was the most discriminating single ECG change for ruling in a diagnosis of acute MI in patients with acute chest with a positive LR of 13.1 (95%CI 8.28 to 20.60, $P < 0.001$). The two next best changes were the presence of Q waves (PLR 5.01 95%CI 3.56 to 7.06) and ST depression (PLR 3.13, 95%CI 2.50 to 3.92). Reasonable discrimination of MI was possible when a number of features were combined, for example ST-segment elevation, depression, Q waves and/ or T wave changes. A completely normal ECG was reasonably helpful at ruling out a MI (PLR 0.14, 95%CI 0.11 to 0.20, $P = 0.007$) in patients with acute chest pain. There was significant heterogeneity in the studies, nevertheless, the results indicated that a single ECG gave important diagnostic information in the evaluation of patients with acute chest pain (Mant, J., McManus, R. J., Oakes, R.-A. L. et al, 2004).

Table 12					
Resting ECG for acute chest pain					
				MI only	
		Studies	LR	95%CI	P for heterogeneity
Normal ECG	PLR	11	0.14	0.11 to 0.20	0.007
	NLR		1.58	1.42 to 1.76	<0.001
Sinus rhythm	PLR	0			
	NLR				
AF	PLR	1	0.57	0.13 to 2.49	
	NLR		1.02	0.98 to 1.05	
ST elevation (STe)	PLR	17	13.1	8.28 to 20.6	<0.001
	NLR		0.47	0.42 to 0.54	<0.001
ST depression (STd)	PLR	2	3.13	2.50 to 3.92	0.6
	NLR		0.60	0.25 to 1.43	
T waves	PLR	1	1.87	1.41 to 2.48	
	NLR		0.66	0.50 to 0.87	
Q waves	PLR	1	5.01	3.56 to 7.06	
	NLR		0.45	0.32 to 0.64	
Left BBB	PLR	1	0.49	0.15 to 1.60	
	NLR		1.03	0.99 to 1.08	
Right BBB	PLR	1	0.28	0.04 to 2.12	
	NLR		1.03	1.00 to 1.06	
STe/STd/Q/T	PLR	5	5.30	3.66 to 7.70	<0.001
	NLR		0.38	0.21 to 0.65	<0.001
STe/STd/Q/T/BBB	PLR	3	4.34	2.46 to 7.67	0.08
	NLR		0.36	0.33 to 0.38	0.7
STe/STd/Q/T/BBB or other rhythms	PLR	2	2.11	1.17 to 3.78	<0.001
	NLR		0.28	0.16 to 0.50	0.003
Permissions granted from original source (Mant, J., McManus, R. J., Oakes, R.-A. L. et al, 2004).					

A further number of studies were identified that examined an ECG in addition to some or all of the following evaluations that had been used in the emergency department: signs, symptoms, and investigations. These were defined as ‘black box’ studies. There were fifteen studies evaluating real time decision making on the initial information available to physicians. Analysis of black box studies was divided into 4 subgroups; interpretation of admission ECG for MI and ACS, interpretation of clinical data other than ECG, A&E initial diagnoses for MI and ACS, and A&E decisions to admit for MI and ACS. Clinical interpretation of admission ECG studies showed that there was a very high PLR (145 in the best quality paper) for ruling in an MI, however the sensitivity was low (NLR 0.58). The one study that examined the exclusive use of signs and symptoms in diagnosis found that clinical evaluation was not

helpful. The studies evaluating A&E initial diagnoses for MI found a PLR of 4.48 (95%CI 2.82 to 7.12) and a NLR of 0.29 (95%CI 0.18 to 0.49). Studies evaluating A&E decisions to admit for MI found a PLR of 2.55 (95%CI 1.87 to 3.47) and a NLR of 0.08 (95%CI 0.05 to 0.18). Full details are shown in Table 13 (Mant, J., McManus, R. J., Oakes, R.-A. L. et al, 2004).

Table 13

Black box studies

	Studies	Sensitivity	Specificity	PLR	NLR
ECG		diagnosis			
AMI: adequate quality	1	0.42 (95%CI 0.32 to 0.52)	0.997 (95%CI 0.98 to 0.99)	14 (95%CI 20.2 to 1044)	0.58 (95%CI 0.49 to 0.70)
AMI: all studies	3	0.25 (95%CI 0.23 to 0.28)	0.995 (95%CI 0.991 to 0.998)	52 (95%CI 7.97 to 339.5)	0.60 (95%CI 0.43 to 0.82)
ACS: adequate quality	1	0.42 (95%CI 0.37 to 0.49)	0.87 (95%CI 0.82 to 0.91)	3.28 (95%CI 2.23 to 4.84)	0.66 (95%CI 0.58 to 0.74)
ACS: all studies	1	0.42 (95%CI 0.37 to 0.49)	0.87 (95%CI 0.82 to 0.91)	3.28 (95%CI 2.23 to 4.84)	0.66 (95%CI 0.58 to 0.74)
Signs and history					
AMI: adequate quality	1	0.94 (95%CI 0.89 to 0.96)	0.23 (95%CI 0.18 to 0.30)	1.22 (95%CI 1.12 to 1.33)	0.28 (95%CI 0.16 to 0.50)
AMI: all studies	1	0.94 (95%CI 0.89 to 0.96)	0.23 (95%CI 0.18 to 0.30)	1.22 (95%CI 1.12 to 1.33)	0.28 (95%CI 0.16 to 0.50)
ACS: adequate quality	0				
ACS: all studies	0				
A&E		diagnosis			
AMI: adequate quality	1	0.45 (95%CI 0.35 to 0.55)	0.95 (95%CI 0.92 to 0.97)	9.22 (95%CI 5.50 to 15.5)	0.58 (95%CI 0.48 to 0.70)
AMI: all studies	6	0.64 (95%CI 0.62 to 0.66)	0.78 (95%CI 0.77 to 0.79)	4.48 (95%CI 2.82 to 7.12)	0.29 (95%CI 0.18 to 0.49)
ACS: adequate quality	3	0.84 (95%CI 0.81 to 0.87)	0.72 (95%CI 0.69 to 0.74)	4.01 (95%CI 1.55 to 10.4)	0.23 (95%CI 0.07 to 0.75)
ACS: all studies	4	0.81 (95%CI 0.79 to 0.83)	0.73 (95%CI 0.72 to 0.75)	3.54 (95%CI 1.97 to 6.38)	0.25 (95%CI 0.14 to 0.45)
Admission					
AMI: adequate quality	1	0.92 (95%CI 0.90 to 0.95)	0.69 (95%CI 0.66 to 0.72)	3.01 (95%CI 2.73 to 3.31)	0.11 (95%CI 0.08 to 0.16)
AMI: all studies	3	0.95 (95%CI 0.94 to 0.96)	0.55 (95%CI 0.54 to 0.56)	2.55 (95%CI 1.87 to 3.47)	0.08 (95%CI 0.05 to 0.13)

Table 13

Black box studies

	Studies	Sensitivity	Specificity	PLR	NLR
ACS: adequate quality	1	0.85 (95%CI 0.82 to 0.88)	0.74 (95%CI 0.71 to 0.77)	3.24 (95%CI 2.89 to 3.64)	0.20 (95%CI 0.16 to 0.25)
ACS: all studies	4	0.90 (95%CI 0.88 to 0.91)	0.67 (95%CI 0.66 to 0.68)	3.01 (95%CI 2.55 to 3.56)	0.13 (95%CI 0.09 to 0.20)

[a]Studies of 'adequate quality' included a realistic decision being tested (i.e. a decision by a front-line physician, not an outside expert) and adequate follow up.
AMI, acute MI.
Permissions granted from original source (Mant, J., McManus, R. J., Oakes, R.-A. L. et al, 2004).

The second systematic review identified 9 studies that examined the use of an ECG in the identification of acute MI in patients presenting to the emergency department with chest pain (Chun, Andrea Akita and McGee, Steven R., 2004). Seven out of 9 studies were identified in this systematic review were identified in (Mant, J., McManus, R. J., Oakes, R.-A. L. et al, 2004). Pooled estimates were calculated for PLRs and NLRs. Based on the PLR and its 95%CI, ST-segment elevation was the most useful ECG change for the diagnosis of acute MI (sensitivity range 31% to 49%, specificity range 97% to 100%, PLR 22 (95%CI 16 to 30) and NLR 0.6 (95%CI 0.6 to 0.6)) The second most useful was the presence of Q wave (sensitivity of 10% to 34%, and a specificity of 96% to 100%, PLR 22 (95%CI 7.6 to 62) and NLR 0.8 (95%CI 0.8 to 0.9)). For ST-segment depression the sensitivity was 20% to 62%, specificity was 88% to 96%, PLR 4.5 (95%CI 3.6 to 5.6) and NLR 0.8 (95%CI 0.7 to 0.9). T wave inversion had a sensitivity of 9% to 39%, specificity of 84% to 94%, PLR 2.2 (95%CI 1.8 to 2.6) and NLR 0.9 (95%CI 0.8 to 1.0) (Chun, Andrea Akita and McGee, Steven R., 2004).

The diagnostic utility of the ECG was compared with other assessments including classification of chart pain, associated symptoms (nausea, diaphoresis, dyspnoea), risk factors (gender, age, hypertension, diabetes, smoking status, family history of CAD, hypercholesterolaemia, prior MI, angina, obesity). A normal ECG was by far the most discriminatory feature for ruling out a diagnosis of acute MI (sensitivity from 1% to 13%, specificity from

48% to 77%, PLR 0.20 (95%CI 0.1 to 0.3) and NRL 1.4 (95%CI 1.4 to 1.6)) (Chun, Andrea Akita and McGee, Steven R., 2004).

The third systematic review examined the use of pre-hospital ECG (PHECG) and the advanced notification of the ECG to improve outcome in acute MI (Morrison, L. J., Brooks, S., Sawadsky, B. et al, 2006). Five studies were identified with a total patient number of 519). The pre-hospital on scene time for acute MI was not significantly different when comparing the 5 studies with a pool weighted mean difference of 1.19 minutes (95%CI -0.84 to 3.21). The door to treatment interval was compared in 181 patients and decreased with PHECG and advanced notification compared with no PHECG (mean weighted difference of 36.1 minutes (95%CI -63.0 to -9.327). However there was heterogeneity in these studies (Q statistic 10.9, $P < 0.01$). Only one study examined all cause mortality. There was no difference in all cause mortality when PHECG was compared with standard management (PHECG: 8.4% versus standard management: 15.5%, $P = 0.22$) (Morrison, L. J., Brooks, S., Sawadsky, B. et al, 2006).

The fourth systematic review investigated the accuracy and clinical effect of out-of-hospital ECG in the diagnosis of acute MI and acute cardiac ischemia (defined in the publication as both unstable angina and acute MI) (Ioannidis, J. P., Salem, D., Chew, P. W. et al, 2001). Eleven studies were identified. Eight studies examined the diagnostic accuracy for acute MI and 5 of the studies considered the diagnostic accuracy for acute cardiac ischemia, some studies overlapped in the populations. Diagnostic performance was assessed by estimates of sensitivity, specificity and diagnostic OR (which compared an out of hospital ECG with a hospital ECG) (Ioannidis, J. P., Salem, D., Chew, P. W. et al, 2001).

Analysis of the diagnostic performance for acute MI in the eight studies evaluating an out of hospital ECG found that the diagnostic OR was 104 (95%CI 48 to 224) with a sensitivity of 68% (95%CI 59% to 76%) and a specificity of 97% (95%CI 89% to 92%). For the five studies diagnosing acute coronary ischaemia, the diagnostic OR was 23 (95%CI 6.3 to 85) with a

sensitivity of 76% (95%CI 54% to 89%) and a specificity of 88% (95%CI 67% to 96%). There was heterogeneity in the sensitivity and specificity for both the acute MI studies (possibly due to the difference in the definition of an abnormal ECG) and the acute coronary ischaemia studies (possibly due to the difference in definition of an abnormal ECG and the difference in the definition of ACS). However, the results indicated that an out of hospital ECG had excellent diagnostic performance for acute MI and good diagnostic performance for acute coronary ischaemia. The time to thrombolysis and angioplasty were compared with use of an out of hospital ECG versus a hospital ECG. The median time was shortened for an out of hospital ECG for both thrombolysis (median 10 versus 40 minutes) and angioplasty (92 versus 115 minutes) compared with an in hospital ECG (Ioannidis, J. P., Salem, D., Chew, P. W. et al, 2001).

The first cohort study assessed the risk stratification of patients with acute chest pain presenting to the emergency department with normal serial troponin I concentrations (Sanchis, J., Bodí, V., Llácer, A. et al, 2005). A total of 609 patients were consecutively recruited; the mean age was 64(SD 12) years and 67% were men (Sanchis, J., Bodí, V., Llácer, A. et al, 2005).

Patients underwent an ECG in the emergency department, a chest pain score assessment, clinical history and an exercise test. Of 609 patients with a normal troponin test, 70 (12%) had ST-segment depression and 54 (9%) had T wave inversion. During a 6 month follow up, 25 patients (4.1%) had an acute MI, 9 (1.5%) died of cardiac causes and 29 (4.8%) had a major event (acute MI or cardiac death). Univariate analysis found that ST-segment depression was an independent factor in predicting an acute MI ($P < 0.004$), and also in predicting major adverse cardiac events (acute MI and / or cardiac death) ($P = 0.003$). Multivariate analysis found that ST-segment depression was an independent factor in predicting an acute MI ($P = 0.02$), and also in major events (acute MI and / or cardiac death) ($P = 0.003$). T wave inversion was not an independent predictor. Comparison with other predictors including a pain score and components of the clinical history found that ST-segment depression was the second most significant factor related to acute MI, with

gender being the most predictive (Table 14). Multivariate analysis for T wave inversion was not applicable as univariate analysis found that it was not significant (*P* = 0.5) for acute MI and major events (*P* = 0.7) (Sanchis, J., Bodí, V., Llácer, A. et al, 2005).

Table 14

Predictors of acute myocardial infarction by univariate and multivariate analyses

	Univariate *P* value	Multivariate *P* value	OR	95%CI
Clinical history				
Pain score (per point)	0.003	0.009	1.2	1.1 to 1.4
Age (per year)	0.02	0.04	1.04	1.01 to 1.09
Men	0.008	0.02	3.7	1.2 to 11.1
Smoking	0.4	NA	NA	NA
Hypertension	0.3	NA	NA	NA
Hypercholesterolaemia	0.7	NA	NA	NA
Diabetes	0.03	0.02	2.5	1.1 to 5.7
Family History of IHD	0.3	NA	NA	NA
History of IHD	0.02	NS	NA	NA
Coronary surgery	0.09	NS	NA	NA
ECG				
ST depression	0.004	0.02	2.9	1.2 to 6.8
T Wave inversion	0.5	NA	NA	NA

CI, confidence interval; NA, not applicable; NS, not significant; OR, odds ratio
Permission granted from original source (Sanchis, J., Bodí, V., Llácer, A. et al, 2005).

The second cohort study examined the use of a chest pain score which included the results of ECG in the identification of patients with acute MI and ACS (Conti, Alberto, Paladini, Barbara, Toccafondi, Simone et al, 2002). The study recruited consecutive patients with chest pain who underwent screening and prospective evaluation during a 33 month. Patients were included if they were over 18 years old, and had chest pain defined as pain in the thoracic region, independent of duration, radiation, or relation to exercise, occurring in the last 24 hours, and lasting minutes to hours. A total of 13 762 patients were recruited; the mean age was 65(SD 18) years, and 57% were men (Conti, Alberto, Paladini, Barbara, Toccafondi, Simone et al, 2002).

The chest pain score was based on the elements of the clinical history, each of which was given a value. These included; location of pain (substernal or precordial) = +3, left chest, neck, lower jaw or epigastrium)= +1, apex = -1; radiation of pain (arm, shoulder, back, neck or lower jaw) = +1; character of

pain (crushing, pressing or heaviness) = +2, character of pain (sticking, pleuritic or pinprick) = -1; associated symptoms (dyspnoea, nausea or diaphoresis) = +2; history of angina = +3 (Conti, Alberto, Paladini, Barbara, Toccafondi, Simone et al, 2002).

A score of < 4 with a normal ECG was considered to indicate a very low probability of CAD, a score of ≥ 4 with a normal ECG a low probability of CAD and a score of ≥ 4 with an abnormal ECG an intermediate probability. A high probability was indicated by an ECG suggestive of acute MI. The mean age for high, intermediate and low probability was 63(SD 10), 64(SD 11) and 38(SD 15) years, respectively. The proportion of men in the high, intermediate and low probability groups was 67%, 62% and 66%, respectively (Conti, Alberto, Paladini, Barbara, Toccafondi, Simone et al, 2002).

Patients at very low probability (score < 4) with a normal ECG were sent home in 6 hours or less following first line negative evaluation that included negative serum biomarkers (2672 patients). At six month follow up 0.2% of these patients were identified as having non fatal coronary disease (3 patients with acute MI, 1 patient with unstable angina, and 3 patients with CAD). The negative predictive value (NPV) of a chest pain score of < 4 and normal ECG was > 99% (Conti, Alberto, Paladini, Barbara, Toccafondi, Simone et al, 2002).

Of the patients at low probability with a chest pain score > 4 and a normal ECG (1755 patients, 40%), 885 patients (20%) had documented CAD. There were 9335 intermediate or high probability patients, of which 2420 patients (26%) had an acute MI and 3764 patients (40%) had unstable angina. Other diagnoses were as follows; 129 patients (1.4%) aortic dissection, 408 patients (5%) pulmonary embolism, 268 patients (3%) pneumothorax, 90 patients (1%) acute pericarditis, and 2256 (24%) patients had either stable angina, previous MI, and or angiographically documented CAD (Conti, Alberto, Paladini, Barbara, Toccafondi, Simone et al, 2002).

The third cohort study examined which patients with acute chest pain could potentially benefit from continuous 12-lead ST-segment monitoring with

automated serial ECG (Fesmire, F. M., 2000). The study included 706 consecutive patients from a convenience population who presented to an emergency department. Patients had an initial history, physical examination and ECG, and were subsequently classed in four different categories. Category I were patients with ACS with clinical and ECG criteria for emergency reperfusion therapy, category II were patients with probable ACS but without clinical and ECG criteria for emergency reperfusion therapy, category III were patients with possible ACS, and category IV were patients with probable non-ACS chest pain but with the presence of pre-existing disease or significant risk factors for CAD. Twenty eight patients were in category I, 137 patients in category II, 333 patients in category III and 208 patients in category IV. Category I patients were excluded from the study. For the patients in category II to IV, serial ECGs were obtained at least every 10 minutes until the patient was taken for PCI or alternatively for a maximum of 2 hours. The average age for category II was 57.3(SD 11.3) years, 67.2% were men, 89.8% were Caucasian, 10.2% were African American, 62% had prior MI, and 52.3% had prior PCI / CABG. The average age for category III was 54.6 (SD 12.9) years, 61% were men, 76.6% were Caucasian, 22.8% were African American, 31.5% had prior MI, and 25.2% had prior PCI / CABG. The average age for category IV was 52.6 (SD 14.4) years, 49% were men, 67.9% were Caucasian, 29.8% were African American, 21.6% had prior MI, and 15.4% had prior PCI / CABG (Fesmire, F. M., 2000).

Patients were diagnosed with acute MI if they met WHO diagnostic criteria (Gillum, R. F., Fortmann, S. P., Prineas, R. J. et al, 1984). Unstable angina was diagnosed if the admitted patient received that discharge diagnosis by the physician, or if the patient had a 30 day adverse event outcome (death, PCI, CABG, post emergency department acute MI, cardiogenic shock, ventricular fibrillation, sustained ventricular tachycardia, third degree AV block, bradycardic or asystolic arrest). The final diagnosis according to initial category was as follows; category II acute MI 24.1%, completed acute MI 1.5%, unstable angina 46.0% and non cardiac chest pain 28.5%; category III acute MI 3.9%, completed acute MI 0.3%, unstable angina 19.2% and non cardiac chest pain 76.6%; category IV acute MI 1.0%, completed acute MI

1.9%, unstable angina 2.4% and non cardiac chest pain 94.7% (Fesmire, F. M., 2000).

Sensitivity and specificity of serial ECG diagnostic for acute MI was 41.7% (95%CI 27.6 to 58.6) and 98.1% (95%CI 96.7 to 99) (PLR of 21.9, and a NLR of 0.59). Sensitivity and specificity of serial ECG diagnostic for ACS 15.5% (95%CI 10.6% to 21.5%) and 94.4% (95%CI 98.2% to 99.9%), respectively for ACS (PLR of 25.4, and a NLR of 0.85) (Fesmire, F. M., 2000).

The study also evaluated if serial ECG monitoring resulted in significant changes in therapy. Change in therapy was considered significant if the evaluating physician determined that the decision to alter therapy was based on findings on serial ECGs independent of results of clinical findings or laboratory results. Therapies examined were fibrinolytic drug administration, emergent PCI, and intensive anti-ischaemic therapy with intravenous nitroglycerin and intravenous heparin or subcutaneous enoxaparin. As a result of the serial ECG 26 patients had their treatment changed, 20 of these were in category II (out of 137 patients), 5 in category III (out of 333 patients) and 1 in category IV (out of 208 patients). Patients in the high risk II category had a 15.2 increased odds of a change in therapy compared with those in categories of III and IV (14.6% versus 1.1%, 95%CI 6.0 to 38.3%, $P < 0.001$) (Fesmire, F. M., 2000).

The serial ECG finding leading to change in therapy consisted of 22 patients (84.6%) with new injury and 4 patients (15.4%) with new ischaemia. Predictive values of new injury or new ischaemia for change in treatment was 91.7% and 50%, respectively. The mean time from onset of ECG monitoring to change in therapy was 21(SD 31) minutes (Fesmire, F. M., 2000).

The fourth cohort study was a retrospective study that examined whether the utilization of artificial neural networks in the automated detection of an acute MI was improved by using a previous ECG in addition to the current ECG (Ohlsson, M., Ohlin, H., Wallerstedt, S. M. et al, 2001). In total 902 ECG-confirmed acute MIs were reviewed. If a patient presented more than once to the emergency department and had an ECG, the final ECG was used in the

study. For each ECG included, a previous ECG for the same patient was selected from the clinical electrocardiographic database. Artificial neural networks were then programmed to detect the acute MI based on either the current ECG only or on the combination of the previous and current ECG if available. The average age of the patients was 74(SD 11) years, and 60% were men (Ohlsson, M., Ohlin, H., Wallerstedt, S. M. et al, 2001).

The study analysed a 12 lead ECG by the use of the computerized ECGs during which the QRS duration, QRS area, Q, R and S amplitudes and 6 ST-T measurements (ST-J amplitude, ST slope, ST amplitude 2/8, ST amplitude 3/8, positive T amplitude and negative T amplitude) were recorded. For each measurement of the new ECG the same measurement was recorded from the previous ECG. The artificial neutral network used standard feed forward, multilayer, perceptron architecture, which consisted of 1 input layer, 1 hidden layer and 1 output layer with 16 or 32 nodes. The ECGs were independently interpreted by two physicians (one cardiologist and one intern) on two occasions, the first occasion only the new ECG was shown and on the second occasion both ECGs were shown (Ohlsson, M., Ohlin, H., Wallerstedt, S. M. et al, 2001).

The study used ROC curves to evaluate the difference in interpretation and diagnosis of the acute MI when both ECGs were analysed compared to only the current ECG. The ROC curve showed that the neural network performance in the diagnosis of an acute MI was improved when both ECGs were present (area under ROC with current ECG only = 0.85, area under ROC with both ECGs = 0.88; $P = 0.02$). The intern performed better when both ECGs were present (area under ROC with current ECG = 0.71, area under ROC with both ECGs = 0.78; $P < 0.001$) and made a diagnosis of acute MI more frequently when both ECGs were analysed, compared with the current ECG only. In contrast, the cardiologists performance was not significantly improved when both ECGs were analysed (area under ROC with current ECG = 0.79, area under ROC with both ECGs = 0.81; $P = 0.36$). The study indicated the diagnostic performance of an artificial neural network and

that of an intern was improved when there was access to a previous ECG from the same patient (Ohlsson, M., Ohlin, H., Wallerstedt, S. M. et al, 2001).

The fifth cohort study examined the added diagnostic value of automated QT-dispersion measurements and automated measurements of ST-segment deviation in the interpretation of the ECG by emergency department physicians who did not have cardiology training or expertise in the electrocardiographic diagnosis of acute cardiac ischemia (Aufderheide, T. P., Xue, Q., Dhala, A. A. et al, 2000). The study included 1568-patient ECGs. Patients were included if they were aged over 18 years, sought paramedic evaluation for suspected cardiac chest pain and their chest pain was classed as stable (a systolic blood pressure of 90 mmHg or more, absence of second- or third-degree heart block, ventricular fibrillation or ventricular tachycardia on initial examination). Patients were excluded if the paramedic thought a pre-hospital ECG would affect treatment, if they had atrial fibrillation or flutter, heat block, or fully paced rhythms, and based on QRS duration criteria although the study did not specify the duration. The pre-hospital ECGs were sent by mobile phone and were interpreted by a physician. The median age of patients was 62 years and 55% were men (Aufderheide, T. P., Xue, Q., Dhala, A. A. et al, 2000).

The study assessed the sensitivity and specificity for diagnosing an acute MI by two physicians examining the ECG recording and the automated independent classification of ST-segment changes (both elevation and depression), QT-end dispersion and QT-peak dispersion measurements (Aufderheide, T. P., Xue, Q., Dhala, A. A. et al, 2000).

The study found that for physician interpretation of the ECG the average sensitivity was 48% and specificity was 99%. Independent assessment of ST-segment deviation using the automated computer gave a higher sensitivity of 90% but a lower specificity of 56% compared with the physician interpretation. Independent QT-end dispersion classification for the diagnosis of acute MI gave a sensitivity of 44% and specificity of 91%, and for QT-peak dispersion the sensitivity was 44% and the specificity was 91%. The combination of the

physician consensus and the automated classification of ST-segment deviations increased the sensitivity compared with the physician consensus 88% (90% versus 48%, respectively, $P < 0.001$), while the specificity decreased substantially (55% versus 99%, respectively, $P < 0.001$). The combination of physician consensus and QT-end dispersion classification gave a sensitivity of 60% and a specificity of 90% for the diagnosis of acute MI, and likewise the combination of physician consensus and QT-peak dispersion classification gave a sensitivity of 60% and a specificity of 90%. The combination of automated QT- end dispersion, QT- peak dispersion and ST deviations measurements with physicians' consensus increased sensitivity compared with physician consensus alone (65% versus 48%, respectively $P <$ 0.001) and the specificity remained comparable (96% versus 99%, respectively). This study suggests that the addition of automated computer interpretation of the ECG to physicians' interpretation of the ECG may improve the identification of patients with acute MI (Aufderheide, T. P., Xue, Q., Dhala, A. A. et al, 2000).

The sixth cohort study examined the use and impact of pre-hospital ECG for patients with acute ST-segment elevation MI (Diercks, D. B., Kontos, M. C., Chen, A. Y. et al, 2009). Data was analysed from the NCDR (National Cardiovascular Registry) ACTION (Acute Coronary Treatment and Intervention Outcomes Network). The study enrolled 19 481 patents with ST-segment elevation MI (defined as persistent ST-segment elevation or new left bundle block and presenting within 24 hours of ischaemic symptom onset. Patients were excluded for the following; clinical evaluation not performed in the emergency department or cardiac catheterization laboratory, missing information on transport by emergency medical services (EMS), missing data on pre-hospital ECG, not listed as transported by EMS, transferred to an ACTION-participating hospital because the structure of the data collection form prevented delineation of location of first ECG obtained (pre-hospital versus in-outside hospital emergency department) (Diercks, D. B., Kontos, M. C., Chen, A. Y. et al, 2009).

The final study population was 12 097 patients, of which 7098 patients (58.7%) were transported to ACTION-participating hospitals by the EMS. EMS transported patients were older, less commonly male, and more commonly had prior MI, prior CHF or signs of CHF. They also had shorter times from symptom onset to hospital presentation compared with patients who self presented to ACTION-participating hospitals. A pre-hospital ECG was recorded in 1941 (24.7%) of patients, and pre-hospital ECG patients were more commonly male, less commonly had diabetes and LBBB or signs of CHF on presentation compared with patients with an in-hospital ECG (Diercks, D. B., Kontos, M. C., Chen, A. Y. et al, 2009).

The study found that patients with a pre-hospital ECG were more likely to undergo PCI, less likely to receive no reperfusion therapy, and more likely to receive aspirin, clopidogrel, and glycoprotein IIb/IIIa inhibitors within the first 24 hours compared with patients with an in-hospital ECG (Diercks, D. B., Kontos, M. C., Chen, A. Y. et al, 2009).

The door to needle time (DNT) and the door to balloon time (DTB) were faster in patients with a pre-hospital ECG compared with patients with an in-hospital ECG, which persisted after adjustment for confounders (DNT; pre-hospital ECG 19 minutes versus in-hospital ECG 29 minutes (P = 0.003), adjusted decrease time of 24.9%, 95%CI -38.1% to -9.0%, and DTB pre-hospital ECG 61 minutes versus in-hospital ECG 75 minutes (P < 0.001), adjusted decrease time of 19.3%, 95%CI -23.1% to -15.2% (P = 0.003) (Diercks, D. B., Kontos, M. C., Chen, A. Y. et al, 2009).

With respect to clinical outcomes in the total population, there was a trend for a decrease in mortality for pre-hospital ECG patients versus in-hospital ECG, 6.7% versus 9.5%, respectively, adjusted OR 0.80 95%CI 0.63 to 1.01 (P = 0.06). However, in patients who received any reperfusion therapy, there was no difference in the adjusted risk of mortality of pre-hospital ECG versus in-hospital ECG (4.6% versus 5.2%, respectively, P = 0.82). There was no significant difference for the clinical outcomes of CHF and cardiogenic shock comparing pre-hospital ECG patients versus in-hospital ECG patients in the

total population, nor for cardiogenic shock in the reperfusion population. There was a trend for a decrease in the incidence of CHF in pre-hospital ECG patients who received any reperfusion therapy versus those with an in-hospital ECG who received any reperfusion therapy (5.3% versus 6.4%, respectively, adjusted OR 0.75, 95%CI 0.56 to 1.01, *P* = 0.06) (Diercks, D. B., Kontos, M. C., Chen, A. Y. et al, 2009).

4.2.5.3 Health economic evidence

This clinical question was designated as low priority for economic evaluation, and so no specific search of the economic literature was undertaken. No relevant health economic evaluations were found, relating to this question, in either the scoping, or the update searches, undertaken for this Guideline. The GDG were of the opinion that an ECG was mandatory in all patients with acute chest pain of suspected cardiac origin, and did not request further economic analysis.

4.2.5.4 Evidence to recommendations

Two high quality systematic reviews with a low risk of study selection bias found that ST-segment elevation had the greatest diagnostic utility for the detection of acute MI in patients presenting with acute chest pain compared with other ECG changes. Reasonable diagnostic performance was found when a number of ECG changes were combined. A normal ECG appeared to be useful in ruling out a diagnosis of acute MI, but was not definitive. However in many of the studies included in the systematic reviews the reference standard used for diagnosis (for example the WHO classification) was applied retrospectively at discharge, which may have made incorporation bias more likely because the result of the ECG could have influenced whether or not the reference standard diagnosis was positive or negative. One high quality systematic review found that a pre-hospital ECG and advanced notification of the ECG improved the door to treatment interval compared with an emergency department ECG. One well conducted cohort study in acute chest pain patients with normal troponin concentrations found that ST-segment depression was a significant predictor of major cardiac events of acute MI and / or death at 6 months. One well conducted study in patients with acute chest

pain found that an ECG together with a chest pain score derived from the clinical history identified a subgroup of patients at very low risk who following a first line negative evaluation that included negative serum biomarkers could be discharged. One well conducted cohort study in patients with acute chest pain indicated that the diagnostic utility of the ECG was improved when there was access to a previous ECG from the same patient, unless the ECG was interpreted by a cardiologist. One well conducted cohort study suggested that serial ECGs may improve the management of patients with acute chest pain without initial ECG criteria for emergency reperfusion therapy. One well conducted cohort study in patients with acute chest pain indicate that the use of automated computers may aid the healthcare professional in the diagnosis of patients with acute chest pain.

The GDG concluded that an ECG was mandatory in all patients with acute chest pain of suspected cardiac origin and that this should be performed and interpreted as soon as possible. A pre-hospital ECG, ideally with advanced notification to hospital, was preferred providing this did not delay transfer of the patient to hospital. The GDG further noted that there was a very high likelihood of an acute MI when ST-segment elevation was present on the ECG and such patients with a suspected MI, and those with presumed new LBBB, should have their further management informed by guidelines for management of ST-segment elevation MI, pending confirmation. Similarly, ST-segment depression was very predictive of an acute MI / ACS and management of these patients should be informed by guidelines for management of non ST-segment elevation MI, pending confirmation of the diagnosis. Other ECG abnormalities are less diagnostic, but may be useful when part of the initial assessment, which includes the clinical history, to reach a provisional diagnosis pending confirmation. A normal ECG makes the diagnosis of an acute MI / ACS less likely, but is not definitive and the GDG emphasized that a normal ECG alone should not be used to exclude a diagnosis of MI / ACS without further evaluation and testing. In patients with normal or equivocal ECG findings on presentation, serial ECG testing may be helpful.

The GDG also discussed interpretation of the ECGs, and were of the opinion that whilst automated interpretation may be a useful adjunctive tool, particularly when the ECG was reported as normal, it should not be the sole method of interpretation. They recommended that when this is used it should be combined with interpretation by a suitably qualified health professional. Access to a previous ECG from the same patient may also aid diagnostic performance.

4.2.6 Early assessment in hospital

4.2.6.1 Other causes of chest pain

The differential diagnosis of patients presenting with chest pain is extensive, ranging from relatively benign musculoskeletal etiologies and gastro-oesophageal reflux to life-threatening cardiac and pulmonary disorders. The symptoms of potentially life threatening conditions such as aortic dissection, pulmonary embolism, pneumothorax, pericarditis with impending tamponade or serious gastrointestinal pathology may closely mimic the presentation of acute MI or ACS. For example pulmonary embolism may present with acute onset of dyspnoea, pleuritic chest pain and severe hypoxia, aortic dissection with severe chest pain that is nature, or stabbing or sharp in character, pneumothorax may present with dyspnoea and pain in the chest, back and / or arms and pericarditis with chest pain radiating to the back. Early diagnosis of these and other life-threatening conditions is important, and a careful medical history and physical examination is essential for their detection. Suspected serious conditions should be urgently investigated and treated according to relevant guidelines or local protocols. The diagnosis of other causes of chest pain is beyond the scope of this guideline. Table 15 details the symptoms of some of the causes of non ischamic cardiac chest pain as published by The European Society of Cardiology Task Force Report (Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction, 2000). Note that for some

diseases, the differentiating symptoms and signs include diagnostic interventions.

Table 15

Non-ischaemic causes of chest pain
Taken from Eur Heart J, vol. 23, issue 15, August 2002

Disease	Differentiating symptoms and signs
Reflux oesophagitis, oesophageal spasm	No ECG changes Heartburn Worse in recumbent position, but also during strain, such as angina pectoris A common cause of chest pain
Pulmonary embolism	Tachypnoea, hypoxaemia, hypocarbia No pulmonary congestion on chest X ray May resemble inferior wall infarction: ST elevation (II, III, aVF) Hyperventilation PaO_2 and $PaCO_2$ decreased
Hyperventilation	The main symptom is dyspnoea, as in pulmonary embolism Often a young patient Tingling and numbness of the limbs, dizziness $PaCO_2$ decreased, PaO_2 increased or normal An organic disease may cause secondary hyperventilation
Spontaneous pneumothorax	Dyspnoea is the main symptom Auscultation and chest X ray One sided pain and bound to respiratory movements
Aortic dissection	Severe pain with changing localization In type A dissection sometimes coronary ostium obstruction, usually right coronary with signs of inferoposterior infarction Sometimes broad mediastinum on chest X ray New aortic valve regurgitation
Pericarditis	Change of posture and breathing influence the pain Friction sound may be heard ST-elevation but no reciprocal ST depression
Pleuritis	A jabbing pain when breathing A cough is the most common symptom Chest X ray
Costochondral	Palpation tenderness Movements of chest influence the pain
Early herpes zoster	No ECG changes Rash Localized paraesthesia before rash
Ectopic beats	Transient, in the area of the apex
Peptic ulcer, cholecystitis, pancreatitis	Clinical examination (inferior wall ischaemia may resemble acute abdomen)
Depression	Continuous feeling of heaviness in the chest No correlation to exercise ECG normal
Alcohol-related	Young man in emergency room, inebriated

Permissions granted from (Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction, 2000).

Use of chest X ray

4.2.6.2 Evidence statements for chest X ray

1 No studies were found that examined the use of a chest X ray in the diagnosis of acute MI and ACS.

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4.2.6.3 Clinical evidence for chest X ray

What is the utility and cost-effectiveness of the chest X ray in evaluation of individuals with chest pain of suspected cardiac origin?

Literature searching did not identify any studies that examined the use of a chest X ray for the diagnosis of acute MI and ACS. Studies on the use of chest X rays for other diagnoses were not appraised.

4.2.6.4 Health economic evidence

This clinical question was designated as low priority for economic evaluation, and so no specific search of the economic literature was undertaken. No relevant health economic evaluations were found, relating to this question, in either the scoping, or the update searches, undertaken for this Guideline.

4.2.6.5 Evidence to recommendations

The GDG recognised that a chest X ray may be of value in the diagnosis of other conditions which might cause chest pain, but no studies were found that examined the performance of a chest X ray in the diagnosis of acute MI and ACS in patients presenting to the emergency department.

4.3 Early Management

4.3.1 Introduction

This section considers evidence for the early treatment of patients with acute chest pain of suspected cardiac origin. It is not intended to address the early

management of patients who have a very high likelihood of an acute MI or ACS, nor patients diagnosed with acute MI or ACS as these patients are not part of this guideline. Such patients should be managed according to other relevant guidelines. Studies in unselected acute chest pain populations were selected, with the exception of aspirin for which no literature was identified in patients with acute chest pain and a study in patients with acute MI in the emergency department was reviewed. There was a paucity of literature in patients with acute chest pain, and the studies in this population had very low patient numbers relative to the many studies in patients with acute MI and ACS.

4.3.2 Oxygen

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4.3.2.1 Evidence statements for oxygen

1 One systematic review in patients with acute MI found that oxygen administration resulted in; an unchanged heart rate but a fall in stroke volume and cardiac volume, a rise in systemic vascular resistance, and either a slight rise or no change in arterial blood pressure. The results of lactate level, ST-segment elevation and ST-segment depression changes were inconclusive. There was some evidence that oxygen administration increased the cardiac enzyme aspartate aminotransferase. No respiratory side effects were reported. (Nicholson, Christopher, 2004)

2 One randomised controlled trial in patients with acute MI found that oxygen administration did not reduce mortality compared with air, although the trial was not powered to detect this outcome. There was significantly greater rise in the serum myocardial enzyme aspartate aminotransferase in the oxygen treatment group compared with the air group. Oxygen administration did not reduce the incidences of arrhythmias. (Rawles, J. M. and Kenmure, A. C., 1976)

3 One small randomised controlled trial in patients with acute MI found that there were no differences between the oxygen group and no oxygen group in the incidence or type of arrhythmias or ST-segment changes. (Wilson, A. T. and Channer, K. S., 1997)

4 No studies evaluating the cost-effectiveness of oxygen use in the early management of the relevant patient group were identified.

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4.3.2.2 Clinical evidence

In adults presenting with acute chest pain of suspected cardiac origin, what is the clinical and cost-effectiveness of giving oxygen compared with a placebo?

One systematic review was reviewed (Nicholson, Christopher, 2004). A second more recent systematic review (Wijesinghe, M., Perrin, K., Ranchord, A. et al, 2009) identified 2 randomised controlled trials in addition to the studies identified by the first systematic review (Nicholson, Christopher, 2004). Rather than appraise the second systematic review it was decided to appraise the 2 randomised controlled trials individually (Wilson, A. T. and Channer, K. S., 1997) (Rawles, J. M. and Kenmure, A. C., 1976).

The systematic review (search date not specified) on the effectiveness of oxygen in reducing acute myocardial ischaemia identified 9 studies; 2 randomised controlled trials and 7 case control studies (Nicholson, Christopher, 2004). The intervention was oxygen of any flow rate or delivery method (excluding hyperbaric oxygen). The studies identified had a combined total of 463 patients, of which 350 were male, and 37 of which had no gender stated. Of the 7 studies that reported age, the ranges and the means were comparable. Seven out of 9 studies reported haemodynamic data. There were no formal meta-analyses performed due to the type of results reported in the studies, rather the evidence was synthesised into a narrative review (Nicholson, Christopher, 2004).

The systematic review found that oxygen administration resulted in; an unchanged heart rate but a fall in stroke volume and cardiac volume, a rise in systemic vascular resistance, and either a slight rise or no change in arterial blood pressure (Nicholson, Christopher, 2004).

Five of the 9 studies reported metabolic data. Lactate levels were measured in 2 studies; one found oxygen reduced lactate levels in the patients tested, while the second study found no change with oxygen. Two studies examined lactate extraction ratios; 1 showing oxygen had no effect and the other indicating that ratios were worse with oxygen administration. Another study found oxygen administration resulted in an increase in the cardiac enzyme aspartate aminotransferase (Nicholson, Christopher, 2004).

ECG data were reported in 3 of the 9 studies. Two studies examined ST-segment depression and T wave changes; 1 study found that oxygen did not prevent the onset of ischaemic changes, and the other found oxygen administration was not associated with any changes to the ST-segment. The third study used a 49-lead precordial ECG mapping technique and noted occurrences of ST-segment elevation and the sum of all ST-segment elevation. ST-segment elevation is usually ascribed to myocardial injury-infarction and this study may not have measured the same effect as the other studies using electrocardiogram data. This third study found oxygen administration reduced both the number of occurrences of ST-segment elevation and the sum of all the ST-segment elevations (Nicholson, Christopher, 2004).

None of the studies reported any respiratory side effects, and only 1 study reported any other side effects, namely, nausea resulting in withdrawal from oxygen administration (Nicholson, Christopher, 2004).

The systematic review found that there was a lack of strong evidence for using oxygen as a treatment in patients with suspected acute MI, although it was recognised that all patients with systemic hypoxaemia should have this corrected by oxygen administration (Nicholson, Christopher, 2004).

The first randomised controlled trial examined oxygen administration in patients who had had a suspected acute MI within the previous 24 hours and who were under 65 years (Rawles, J. M. and Kenmure, A. C., 1976). Patients were excluded if they had the following; clinical evidence of right or left heart failure, chronic bronchitis or emphysema or breathlessness from any other cause, transferred from other wards for treatment of arrhythmias, undergone cardiac arrest before admission, suffered from cardiogenic shock. One hundred and five consecutive patients were randomised to receive oxygen and 95 patients to receive air. MI was not confirmed in 25 patients in the oxygen group and 18 patients in the air group, and these patients were excluded from subsequent analysis. Oxygen or compressed air was given through an MC mask at a flow rate of 6 l/min for 24 hours. The mean PaO_2 was higher in the oxygen group compared with the air group (18.2 (SE 1.56) IU/ml versus 8.7 (SE 2.9) IU/ml, $P < 0.001$) (Rawles, J. M. and Kenmure, A. C., 1976).

During the study there was one death in the oxygen group and two deaths in the air group. Overall there were nine deaths in the oxygen group compared with three in the air group (9/80 patients (11%) in the oxygen patients versus 3/77 patients (4%) in the air group), although this difference was not significant it should be noted that the trial was not powered to detect significance for this outcome. There was a significantly greater rise in the serum myocardial enzyme aspartate aminotransferase (which is a measure of infarct size); 99.9 (SE 7.1) IU/ml for the oxygen group versus 80.7 (SE 6.6) IU/ml in the control group ($P < 0.05$). Oxygen administration increased sinus tachycardia compared with air ($P < 0.05$) (Rawles, J. M. and Kenmure, A. C., 1976).

The randomised controlled trial found that oxygen administration did not reduce the incidences of the following arrhythmias: atrial ectopics, atrial tachycardia, atrial flutter, atrial fibrillation, sinus bradycardia, junctional rhythm, accelerated idoventricular rhythm, ventricular ectopics, ventricular tachycardia, ventricular fibrillation, heart block. Systolic ejection times did not differ between the two groups on the first or second day. The study indicated

that oxygen treatment had no benefit for patients with acute MI; rather the evidence suggests that there may be potential harm with oxygen treatment in patients with normal oxygen saturation levels (Rawles, J. M. and Kenmure, A. C., 1976).

The second randomised controlled trial examined the use of supplementary oxygen therapy and the role of pulse oximetry in 50 consecutive patients with acute MI admitted to the coronary care unit within six hours of the onset of thrombolytic therapy (Wilson, A. T. and Channer, K. S., 1997). Patients with central cyanosis, pulmonary disease requiring oxygen independent of the cardiac status or those in whom blood gas estimation showed a PCO_2 > 5.5 kPa and patients with left ventricular failure requiring inotropic support were excluded. Forty two subjects completed the study. Twenty two received continuous oxygen at 4 l/min by face mask; 20 received no supplemental oxygen except for central cyanosis or respiratory distress. Patients were studied for the first 24 hours following admission to the coronary care unit (Wilson, A. T. and Channer, K. S., 1997).

Twenty (48%) of the total 42 patients in the study had periods of at least moderate hypoxaemia (SpO_2 < 90%) and 8 (19%) patients had severe hypoxaemia (SpO_2 < 80%). Seven of the 8 severely hypoxaemic patients (88%) were in the group which received no supplemental oxygen (P < 0.05 compared with oxygen group) and this was clinically undetected in all but one case. The mean lowest SpO_2 level was significantly lower in the no oxygen compared with the oxygen group (P < 0.05). There were no differences in the prescription of opiates between the two groups. There were no significant differences between the groups in the incidence or type of arrhythmias (11 patients in each group) or ST-segment changes (oxygen group versus no supplemental oxygen group: 4 and 3 patients, respectively). No surrogate use of measurement infarct size was performed nor was mortality reported. This small study indicates that the measurement of oxygen saturation is justified to guide oxygen treatment, although it does not provide evidence of the benefit of oxygen treatment for all patients with acute MI (Wilson, A. T. and Channer, K. S., 1997).

The British Thoracic Society has recently published a guideline for emergency oxygen use in adult patients based on expert opinion and a review of the literature that identified the same studies reviewed in this section (O'Driscoll, B. R., Howard, L. S., and Davison, A. G., 2008). It states that most patients with acute coronary artery syndromes are not hypoxaemic and the benefits / harms of oxygen therapy are unknown in such cases. The recommendations are as follows;

1) In myocardial infarction and ACS, aim at an oxygen saturation of 94 to 98% or 88 to 92% if the patient is at risk of hypercapnic respiratory failure.

2) Patients with serious emergency conditions such as myocardial infarction and ACS should be monitored closely but oxygen therapy is not required unless the patient is hypoxaemic:

   - If hypoxaemic, the initial oxygen therapy is nasal cannulae at 2 to 6 l/min or simple face mask at 5 to 10 l/min unless oxygen saturation is < 85% (use reservoir mask) or if at risk from hypercapnia

   - The recommended initial target saturation range, unless stated otherwise, is 94% to 98%

   - If oximetry is not available, give oxygen as above until oximetry or blood gas results are available

   - If patients have COPD or other risk factors for hypercapnic respiratory failure, aim at a saturation of 88% to 92% pending blood gas results but adjust to 94% to 98% if the $PaCO_2$ is normal (unless there is a history of respiratory failure requiring NIV or IPPV) and recheck blood gases after 30 to 60 minutes.

4.3.2.3 Health economic evidence

No health economic evidence reporting the incremental value of oxygen use in the early management of the relevant patient group was found in the

literature. Oxygen is in routine use and not expensive, (BP composite cylinder with integral headset to specification, 1360 litres costs £9.48).

4.3.2.4 Evidence to recommendations

No evidence was found which examined the efficacy of supplementary oxygen in unselected patients with chest pain of suspected cardiac origin, and the GDG appraised the evidence in patients with acute MI. The British Thoracic Society had also recently reviewed the evidence on this topic. Rather unexpectedly, given current clinical practice to administer oxygen routinely to patients with acute chest pain of suspected cardiac origin, the conclusion drawn from the available evidence from one well conducted systematic review and one well conducted randomised controlled trial, and further confirmed by the recommendations in the The British Thoracic Society guideline, was that supplementary oxygen has not been shown to be beneficial in patients with an acute MI and may be harmful. The GDG considered it important to emphasise that supplementary oxygen should not be routinely administered to patients with acute chest pain of suspected cardiac origin, but that oxygen saturation levels should be monitored and used to guide its administration. The recommendations in the The British Thoracic Society guideline were used to inform the thresholds at which oxygen should be administered, and the target oxygen saturation to be achieved.

4.3.3 Pain Management

4.3.3.1 Evidence statements for pain management

1 One small randomised controlled trial in patients with chest pain and suspected acute MI found that intravenous buprenorphine (0.3 mg) gave greater pain relief at 5 minutes compared with intravenous diamorphine (5 mg), although subsequent pain relief up to 6 hours was similar in both treatments. No major side effects were reported in either group. (Hayes, M. J., Fraser, A. R., and Hampton, J. R., 1979)

2 One small randomised controlled trial in patients with suspected acute MI or unstable angina with chest pain that had been unresponsive to nitroglycerine found that morphine (10 mg) and nalbuphine (20 mg) reduced pain within 5 minutes after intravenous administration. Pain relief increased during the observed 120 minutes. There was no difference in the pain relief between the morphine and nalbuphine groups. There was no difference in respiration rate, systolic or diastolic blood pressure between the two groups or in the side effects of nausea, dizziness or drowsiness. (Hew, E., Haq, A., and Strauss, H., 1987)

3 One small randomised controlled trial in patients with chest pain and suspected acute MI found that there was no difference in degree pain relief between nalbuphine (≤ 20 mg) and intravenous diamorphine (≤ 5 mg) plus metoclopramide (10 mg). Pain relief occurred within 10 minutes of administration and up to the observed 120 minutes. No differences were reported in the side effects of nausea, vomiting or dizziness, or in systolic diastolic blood pressure, heart rate between the two groups. (Jamidar, H. A., Crooks, S. W., and Adgey, A. A., 1987)

4 One small randomised controlled trial in patients with chest pain and suspected acute MI found that intravenous diamorphine (5 mg) was associated with greater complete pain relief compared with morphine (10 mg) and pentazocine (30 mg) 10 minutes after initial injection, pain relief with diamorphine (5 mg) and methadone were similar. Complete pain relief at 30, 60 and 120 minutes was similar in all four pain management groups. (Scott, M. E. and Orr, R., 1969).

5 One cohort study in patients with chest pain and suspected acute MI found that intravenous morphine administration (5 mg) reduced pain within 20 minutes and pain reduction remained for the observed 8 hours. Higher morphine requirement (5 mg repeated if

necessary) was associated with the following; male gender, history of angina pectoris, previous CHF, initial degree of suspicion of acute MI, presence of ST-segment elevation on entry ECG, presence of ST-segment depression on entry ECG, and Q wave on entry ECG. In addition, morphine requirement was highest in patients with the greatest suspicion of MI, rather than patients with possible myocardial ischaemia. (Everts, B., Karlson, B. W., Herlitz, J. et al, 1998)

6 One cohort study in patients with acute chest pain of suspected cardiac origin found that pain intensity was higher in the home prior to presentation in the coronary care unit. Pain intensity and morphine requirement was greatest in patients with a confirmed MI diagnosis compared with those who did not have an MI. (Herlitz, J., Richter, A., Hjalmarson, A. et al, 1986).

4.3.3.2 Clinical evidence

In adults presenting with acute chest pain, what is the clinical and cost-effectiveness of pain (for example, sublingual and buccal nitrates, diamorphine, morphine with anti-emetic) management?

Six studies were reviewed, 4 studies were randomised controlled trials (Hayes, M. J., Fraser, A. R., and Hampton, J. R., 1979) (Hew, E., Haq, A., and Strauss, H., 1987) (Jamidar, H. A., Crooks, S. W., and Adgey, A. A., 1987) (Scott, M. E. and Orr, R., 1969) and 2 studies were cohort studies (Everts, B., Karlson, B. W., Herlitz, J. et al, 1998) (Herlitz, J., Richter, A., Hjalmarson, A. et al, 1986). Only one study examined co-administration of pain relief with an anti-emetic (Jamidar, H. A., Crooks, S. W., and Adgey, A. A., 1987).

The first randomised controlled trial examined buprenorphine and diamorphine for pain relief in patients with suspected or ECG proven acute MI (Hayes, M. J., Fraser, A. R., and Hampton, J. R., 1979). There were three separate studies in 3 separate patient groups. Ten patients in study group 1 received buprenorphine (0.3 mg) and were monitored for haemodynamic

changes. Seventy patients in study group 2 were randomised to receive either intravenous buprenorphine (0.3 mg) (50 patients) or sublingual buprenorphine (0.4 mg) (20 patients). One hundred and thirteen patients in study group 3 were randomised to receive either intravenous buprenorphine (0.3 mg) (59 patients, mean age 55(SD 10) years, 49 men) or intravenous diamorphine (5 mg) (59 patients, 56(SD 10) years, 42 men). The mean duration of chest pain was 5.5(SD 7.3) hours. The time, degree and duration of pain relief were measured using an unmarked visual analogue scale which was scored by the patient, and scoring was expressed as a percentage of the initial score (Hayes, M. J., Fraser, A. R., and Hampton, J. R., 1979)

In the study group 1 all 10 patients had ECG-proven acute MI, and had had prior diamorphine treatment but required further analgesia for recurrent pain. The patients were all given intravenous buprenorphine (0.3 mg), and the systemic blood pressure, heart rate, and pulmonary artery pressure were monitored. Intravenous buprenorphine led to no significant change in heart rate, systemic diastolic blood pressure or systemic arterial systolic pressure. There was a sustained fall in systemic arterial systolic pressure of about 10 mmHg, however this did not reach statistical significance (at 1 hour, t = 1.14191, $P < 0.1$). For study group 2 in patients with suspected acute MI, pain relief was measured for 45 minutes. The intravenous buprenorphine (0.3 mg) group achieved considerably faster pain relief compared with the sublingual buprenorphine (0.4 mg) group (Hayes, M. J., Fraser, A. R., and Hampton, J. R., 1979).

Pain relief in patients in study group 3 was monitored for 6 hours. Measurements from the visual analogue scale found that the mean starting pain score was similar in the two groups. Of the 59 patients in the intravenous buprenorphine (0.3 mg) group, 49% of patients did not require further analgesia after an initial dose compared with 42% in the diamorphine group (5 mg). At 5 minutes the percentage pain relief in the buprenorphine group was lower compared with diamorphine group ($P < 0.01$), however at 15 minutes the pain relief was similar in the two groups. There was no significant difference in the subsequent analgesia requirement for pain relief between the

two groups during the 6 hour study period. No major side effects were reported in either group. Twelve patients in the buprenorphine group and 7 patients in the diamorphine group vomited in the 6 hour study period, but this difference between the two groups was not statistically significant. Twelve patients in the buprenorphine group and 15 patients in the diamorphine group were subsequently found to have inconclusive evidence of acute MI (Hayes, M. J., Fraser, A. R., and Hampton, J. R., 1979).

The second randomised controlled trial in patients with moderately severe or severe chest pain due to a suspected MI or unstable angina compared intravenous nalbuphine (20 mg) with intravenous morphine (10 mg) for pain relief (Hew, E., Haq, A., and Strauss, H., 1987). Patients were included if their pain was unresponsive to sublingual nitroglycerin. The exclusion criteria were; heart rate was less than 50 beats per minute, systolic blood pressure < 90 mmHg cardiac shock, acute or chronic renal failure, valvular heart disease, signs of right or left ventricular failure, pulmonary oedema, or if the patient was or suspected of being a drug user. Fifty three patients received either nalbuphine (20 mg) (24 patients, mean age 60 years (SD not given), 21 men) or morphine (10 mg) (29 patients, mean age 62 years, 21 men) (Hew, E., Haq, A., and Strauss, H., 1987).

The study reported the pain scores, side effects, change in blood pressure, and change in heat rate in each group. Study observers recorded the patient's vital signs and pain at 0, 5 15, 30, 60 and 120 minutes after drug administration. Pain was evaluated using an eleven point scale (0 = none, 10 = severe). Pain relief was evaluated using a five point scale (0 = none; 4 = complete). At the end of the study the observer rated the overall therapeutic response (both for pain and pain relief) on a five point scale (0 = poor; 4 = excellent) (Hew, E., Haq, A., and Strauss, H., 1987).

The mean pain scores for the nalbuphine group were consistently lower compared with morphine group, with the difference greatest at 5 minutes, (nalbuphine = 1.88, morphine = 3.48, P = 0.08). However the overall therapeutic response was not significant (P = 0.10). Pain relief in the

nalbuphine group was consistently lower compared with morphine group (greatest at 5 minutes) however the overall therapeutic response was not significant (*P* = 0.10). Neither group had significant changes in systolic or diastolic blood pressure or heart rate. Respiration rate was similar in both groups and there was no clinically significant depression in respiration rate for either group. There was no significant difference in nausea, dizziness or drowsiness reported in the two groups. Neither group had a significant change in either systolic or diastolic blood pressure over the 120 minute observation period. Mean heart rate did not change significantly in either group during the observation period (Hew, E., Haq, A., and Strauss, H., 1987).

The third randomised controlled trial compared nalbuphine with diamorphine plus metoclopramide for pain relief in patients with suspected acute MI (Jamidar, H. A., Crooks, S. W., and Adgey, A. A., 1987). One hundred and seventy six patients met the inclusion criteria of moderate or severe chest pain due to suspected acute MI and no previous administration of analgesia. Of the 176 patients, 87 patients received nalbuphine (≤ 20 mg) (mean age 61 years, 51 men), and 89 patients received intravenous diamorphine (≤ 5 mg) with metoclopramide (10 mg) (mean age 62 years, 30 men). Patients were withdrawn from the trial if they required further pain relief after 15 to 20 minutes (12.6% of patients in the nalbuphine group and 6.7% of patients in the diamorphine group) (Jamidar, H. A., Crooks, S. W., and Adgey, A. A., 1987).

The study reported pain relief at 10, 30, 60 and 120 minutes, any side effects, blood pressure and heart rate. The pain score rated by observers was; no pain (grade = 0), moderate pain defined as chest discomfort not associated with sweating or distress (grade = 2) and severe pain defined as severe pain accompanied by obvious distress (grade = 3). Seventy seven percent of patients in the morphine group and 69% of patients in the nalbuphine group had satisfactory pain relief at 10 minutes (grade = 0 or 1). Forty four percent of patients in the nalbuphine group and 39% of patients in the morphine group had total pain relief at 10 minutes (grade = 0), and the mean pain score was similar for both the nalbuphine and diamorphine group at each time

assessment. There was no difference in the 2 groups in the number of drug doses or the overall summation of pain score at all time points. Pain relief reoccurred in 5 patients in the nalbuphine group and 2 patients in the diamorphine group but this difference was not significant (Jamidar, H. A., Crooks, S. W., and Adgey, A. A., 1987).

There was no difference in the systolic or diastolic blood pressure, heart rate or the mean peaks of CK, AST and LDH in the two groups. Nausea or vomiting was reported in 14 patients in the nalbuphine group compared with 15 patients in the morphine group. Dizziness was reported in 14 patients in the nalbuphine group compared with 15 patients in the morphine group (Jamidar, H. A., Crooks, S. W., and Adgey, A. A., 1987).

The fourth randomised controlled trial examined the pain relief effects of diamorphine, methadone, morphine and pentazocine all administered intravenously in 118 patients with suspected acute MI and severe or moderate chest pain (Scott, M. E. and Orr, R., 1969). The age range in the total study population was 30 to 79 years (79% of patients were aged between 50 to 69 years) and 89 patients were male. Patients received one dose of diamorphine (5 mg) (30 patients), methadone (10 mg) (31 patients), morphine (10 mg) (29 patients) or pentazocine (30 mg) (25 patients). Patients were excluded if they had cardiac shock, cardiac failure, severe nausea, pronounced bradycardia, had received potent analgesic or anti-emetic in previous 4 hours. The study reported pain relief at 10, 30, 60 and 120 minutes after drug administration. Pain was assessed as severe, moderate, mild, or absent following drug administration (Scott, M. E. and Orr, R., 1969).

The study reported that all four drugs gave pain relief to some extent in approximately 90% of the total study population at 10 and 30 minutes after administration. At the 10 minute time point, patients who received diamorphine had greater complete pain relief compared with both the morphine group ($P < 0.05$) and the pentazocine group ($P < 0.05$), while pain relief with methadone and diamorphine were similar. At 30 minutes complete pain relief was not significantly different in any of the groups and

approximately 40% of patients in each group reported complete pain relief. Severe nausea requiring subsequent administration of an anti-emetic was needed in 8, 11, 4 and 7 patients in the diamorphine, methadone, morphine and pentazocine groups, respectively (no significant differences). Only patients in the pentazocine group had an increase in blood pressure from baseline compared with the other groups ($P < 0.05$), the other groups had no or little appreciable change in blood pressure compared with initial blood pressure (Scott, M. E. and Orr, R., 1969).

The first cohort study examined pain relief effects of morphine in 10 patients with suspected acute MI (Everts, B., Karlson, B. W., Herlitz, J. et al, 1998). The mean age was 69.3(SE 0.23) years and 7 patients were male. Patients were given intravenous morphine (5 mg) over 1 minute. Patients were included in the study if they had chest pain or symptoms suggestive of an acute MI, had a confirmed or suspected acute MI or myocardial ischaemia and were hospitalised for more than 1 day. The study reported pain intensity on the Numerical Rating Scale (NRS) where patients were asked to rate pain from 0 (no pain) to 10 (most severe pain patient could imagine). Readings were made at 10, 20, 45 and 90 minutes and 2, 3, 4, 5, 6, and 8 hours post administration (Everts, B., Karlson, B. W., Herlitz, J. et al, 1998).

Pain administration was 6.6(SE 0.6) on the NRS before morphine administration. Twenty minutes after morphine administration, 7 of the 10 patients reported complete pain relief at 1 or more measurement points during the 3 hours of the study period. Three patients required further analgesia. It should be noted that the patient sample size was very small (10 patients) for this part of the study evaluation, and pain relief was not compared with a control group, hence pain relief may have resulted from recovery in symptoms, rather than pain relief due to morphine administration (Everts, B., Karlson, B. W., Herlitz, J. et al, 1998).

The study also examined patient characteristics that were associated with higher morphine requirement in 2988 patients over 3 days of hospitalisation. The following were independent predictors of higher morphine requirement ;

male gender, history of angina, history of CHF, initial degree of suspicion of acute MI, presence of ST-segment elevation on entry ECG, presence of segment ST-segment depression on entry ECG, Q wave on entry ECG. Fifty two percent of patients did not require morphine while 9% required more than 20 mg of morphine. The mean morphine requirement over 3 days was 6.7(SE 0.2) mg. The study reported that after intravenous morphine administration there was a reduction in the diastolic blood pressure and a similar trend in systolic blood pressure but this was not significant. After intravenous morphine the heart rate was reduced, but respiratory frequency remained the same before and after intravenous morphine in all patients (Everts, B., Karlson, B. W., Herlitz, J. et al, 1998).

The second cohort study examined chest pain intensity according to clinical history, intensity of pain at home, initial ECG findings, initial heart rate and systolic blood pressure, final extent of infarction, and morphine requirement (Herlitz, J., Richter, A., Hjalmarson, A. et al, 1986). Six hundred and fifty three patients with suspected acute MI admitted to a coronary care unit were asked to score chest pain from 0 to 10 (0 = no pain, 10 = most severe pain patient could imagine) until a pain interval of 12 hours appeared. If the patient was asleep a score of 0 was reported. Pain was scored at the following times; maximum score at home and thereafter every second hour after admission to the coronary care unit. Patients were given morphine intravenously for severe pain while sublingual nitroglycerine was given if symptoms were indicative of angina. The age range was 33 to 92 years with a median of 70 years. Six hundred and fifteen patients were male (Herlitz, J., Richter, A., Hjalmarson, A. et al, 1986).

Of ninety eight percent of patients who had chest pain at home, only 51% had pain on arrival at the coronary care unit which may have occurred because symptoms and / or pain subsided. Elderly patients had a similar pain pattern according to pain intensity, pain duration and morphine requirement compared with younger patients during the study period. A prior history of MI, angina or CHF did not alter the pattern of pain. Patients with higher pain intensity at home had more pain in the first 24 hours, and a longer duration of

pain compared with patients with a lower home pain intensity score, despite receiving more morphine. Pain course was not affected by initial heart rate, however higher initial systolic blood pressure was associated a more severe pain course, a longer pain duration, and a greater morphine requirement (Herlitz, J., Richter, A., Hjalmarson, A. et al, 1986).

Analysis of pain scores in the home was divided into 3 patient groups; namely definite acute MI, possible acute MI and non diagnosed acute MI. Acute MI was confirmed in 45% of patients and possible acute MI in 11.9%. Patients with initial ECG recordings consistent with an acute MI did not have a higher home pain intensity score compared with patients without ECG findings indicative of an acute MI. During the first 48 hours, patients with ECG-confirmed acute MI had a higher accumulative morphine requirement compared with patients without ECG findings (8.8(SE 0.8) mg versus 4.1(SE 0.4) mg, respectively, $P < 0.001$), and a higher mean duration of pain compared with patients without ECG findings (19 (SE 1.3) hours versus 12.9 (SE 0.8) hours, respectively, $P < 0.001$) (Herlitz, J., Richter, A., Hjalmarson, A. et al, 1986).

The 4 randomised controlled studies recruited small numbers of patients and were of low quality with a high risk of bias. Generally, studies did not report adequate recruitment methods, concealment methods, baseline characteristics, exclusion / inclusion criteria and the pain scores were not validated within the studies or against other known pain scores. The cohort studies were of low quality with a high risk of bias. One study only recruited ten patients. The second study did not report adequate baseline characteristics, inclusion / exclusion criteria, statistical analysis of results, and the pain score was not validated within the study or against other known pain scores.

4.3.3.3 Health economic evidence

This clinical question was designated as low priority for economic evaluation, and so no specific search of the economic literature was undertaken. No

relevant health economic evaluations were found, relating to this question, in either the scoping, or the update searches, undertaken for this Guideline.

4.3.3.4 Evidence to recommendations

The GDG considered that prompt and effective management of chest pain was an important priority in the management of patients with acute chest pain of suspected cardiac origin and that patients should be treated to be completely pain free. The GDG's appraisal of the evidence in section 4.2.4 found that, whilst the response to nitroglycerin is not helpful as a diagnostic tool in differentiating cardiac chest pain from non cardiac chest pain, it is effective as a therapeutic agent for pain relief in some patients. However, in many patients additional pain relief will be required. Limited evidence, which was generally of poor quality and with a high risk of bias, was found to inform how this should be achieved, and from that available the GDG concluded that opioids should be used if nitroglycerin is not effective in achieving complete pain relief.

4.3.4 Anti-platelet therapy

4.3.4.1 Evidence statements for anti-platelet therapy

1 One cohort study in patients with acute MI found that pre hospital administration of aspirin reduced mortality at 7 and 30 days compared with patients receiving aspirin at hospital admission or during hospital admission. (Barbash, Israel M., Freimark, Dov, Gottlieb, Shmuel et al, 2002)

2 Extrapolated evidence from patients diagnosed with ACS, suggests that there are benefits to giving aspirin immediately.

5 No studies evaluating the cost-effectiveness of anti-platelet therapy in unselected patients with acute chest pain were identified.

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4.3.4.2 Clinical evidence

In adults presenting with chest pain of suspected cardiac origin, what is the clinical and cost-effectiveness of anti-platelet therapy (aspirin, clopidogrel alone or in combination) compared with a placebo?

No systematic reviews or randomised controlled trials were identified in patients with acute chest pain; only one cohort study was considered to be helpful to inform the GDG and this was reviewed (Barbash, Israel M., Freimark, Dov, Gottlieb, Shmuel et al, 2002).

The cohort study examined the use of aspirin administered pre hospital compared with post hospital admission to assess the association between timing of aspirin administration and clinical outcomes in patients with acute MI (Barbash, Israel M., Freimark, Dov, Gottlieb, Shmuel et al, 2002). Inclusion criteria were patients with ST-segment elevation and Killip Class I-III who had received aspirin treatment either before or after admission. Patients were excluded if they had cardiogenic shock or were unconscious. A total of 922 patients were included in the study, of these 338 received aspirin before admission to hospital (after symptom onset) and 584 received aspirin at / or after admission to hospital. The dose of aspirin was > 200 mg. The mean age was 63(SD 13) years and 11% were male. Patients who received aspirin before admission to hospital were more likely to be treated with heparin, ticlopidine / clopidogrel, glycoprotein IIb/IIIa receptor antagonists (Barbash, Israel M., Freimark, Dov, Gottlieb, Shmuel et al, 2002).

Cumulative mortality rates at 7 and 30 days were assessed from medical charts. There was a lower mortality rate in patients who received aspirin before admission to hospital compared with those post admission at 7 days (2.4% versus 7.3%, $P < 0.002$) and 30 days (4.9% versus 11.1%, $P < 0.001$). After adjustments for baseline and prognosis-modifying factors (age, gender, history of MI, diabetes mellitus, hypertension, Killip Class on admission and primary reperfusion) the result remained significant at 7 days (OR 0.43 95%CI 0.18 to 0.92), and was reported as significant at 30 day follow up (OR 0.60 95%CI 0.32 to 1.08). Compared with post hospital aspirin therapy, pre

hospital administration of aspirin was associated with a reduction in the following in-hospital complications; asystole ($P < 0.001$), resuscitation ($P < 0.001$) and ventilation ($P < 0.002$) (Barbash, Israel M., Freimark, Dov, Gottlieb, Shmuel et al, 2002).

A subgroup analysis was conducted of both patients selected for primary reperfusion (thrombolysis or primary PCI) (518 patients) and patients who did not have reperfusion therapy (404 patients). In the reperfusion patients, pre hospital aspirin treatment reduced cardiovascular rehospitalisation compared with post hospital admission aspirin treatment (19% versus 26%, $P < 0.07$, respectively), and reduced mortality at 7 days (1.4% versus 5.8%, respectively) and at 30 days (3.3% versus 6.8%, respectively). For patients who did not have reperfusion therapy mortality was lower for pre hospital aspirin administration compared with post hospital admission aspirin administration patients at 7 days (4.4% versus 8.9%, respectively, $P = 0.13$) and at 30 days (8.0% versus 15.7%, respectively, $P < 0.04$). The results indicate that pre-hospital aspirin administration improves mortality outcome in patients with acute ST-segment elevation MI (Barbash, Israel M., Freimark, Dov, Gottlieb, Shmuel et al, 2002).

4.3.4.3 Health Economic Evidence

No health economic evidence evaluating the incremental cost-effectiveness of anti-platelet therapy in the relevant patient group was found in the literature. The Drug Tariff (Jan 2008) indicates that Aspirin only costs 28p per month, (£3.36 per year), with Clopidogrel costing £37.83 per month (£453.96 per year).

4.3.4.4 Evidence to recommendations

No evidence was found for the effectiveness of anti-platelet agents compared with placebo in unselected patients with suspected acute MI or ACS. However, there is good evidence for the benefit of aspirin in patients with acute MI and ACS (Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients, 2002) and in one cohort study in patients with acute MI

found that pre hospital administration was associated with a lower mortality compared with administration at or during admission hospital admission. The GDG concluded that a single loading dose of aspirin, in a dose consistent with that recommended in guidelines for acute MI or ACS, should be given as soon as possible to patients with acute chest pain of suspected cardiac origin, pending further assessment. The GDG further discussed if this loading dose should only be for those not already taking aspirin and concluded that identifying early which patients are taking aspirin and ensuring recent concordance, and only treating those not taking chronic aspirin therapy might lead to inappropriate delays and or inadequate treatment. However, the GDG were of the opinion that other anti-platelet agents, such as clopidogrel, should only be given following an initial assessment which had refined the diagnosis, and that management of those with acute MI or ACS be informed by other relevant guidelines.

4.4 Investigations and Diagnosis

4.4.1 Introduction

Cardiac biomarkers are proteins that are released into the cardiac interstitium due to the compromised integrity of myocyte cell membranes as a result of myocardial ischaemia. Up to the1980s, there were only a few assays available for the retrospective detection of cardiac tissue necrosis, such as the enzymatic methods for creatine kinase and lactate dehydrogenase catalytic activities. However, in the last 20 years highly sensitive and specific assays for the detection of myocardial necrosis have been developed including troponin I, troponin T and myoglobin. Assays for markers of myocardial function, including cardiac natriuretic peptides, have also become available. The measurement of some of these newer biomarkers has been incorporated into internationally recognised diagnostic criteria for acute MI because of their greater diagnostic accuracy compared with older markers. The WHO traditionally defined acute MI as requiring the presence of at least 2 of 3 diagnostic criteria; an appropriate clinical presentation, typical ECG changes, and raised cardiac enzymes essentially total CK or its MB isoenzyme (CK-MB) activities (Gillum, R. F., Fortmann, S. P., Prineas, R. J. et al, 1984). The Joint European Society of Cardiology (ESC) and the American College of Cardiology (ACC) committee published a consensus document in 2000 for a new definition of MI (Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction, 2000). The ESC / ACC definition of acute MI required the rise and fall of a biomarker of myocardial necrosis (unlike the WHO definition which did not stipulate a fall) together with other criteria; ischaemic symptoms, development of pathological Q waves. The ECC / ACC definition was updated in 2007 owing to considerable advances in the diagnosis and management of MI since the its original publication, and it has been adopted as a universal definition of myocardial infarction (Thygesen, K., Alpert, J. S., and White, H. D., 2007). The full definition is given on page 194. Specifically for biomarkers it states;

"detection of rise and / or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit"

Troponin I and T

Troponin is a complex of three polypeptides found in muscle fibres. One polypeptide (troponin I) binds to actin, another (troponin T) binds to tropomyosin, and the third (troponin C) binds to calcium ions. Calcium ions bind to troponin, the troponin changes shape, forcing tropomyosin away from the actin filaments. Myosin cross-bridges then attach onto the actin resulting in muscle contraction. Skeletal and cardiac forms are structurally distinct, and antibodies have been developed that react only with the cardiac forms of troponin I and troponin T. Troponin I and T levels peak 6 to 12 hours after onset of an acute MI, and duration of detection of troponin I may be 7 to 10 days, duration of detection of troponin T may be up to 7 to 14 days.

Creatinine kinase (CK)

Creatinine kinase is an enzyme responsible for transferring a phosphate group from ATP to creatinine. CK enzyme consists of two subunits, which can be either B (brain type) or M (muscle type). There are, therefore, three different isoenzymes: CK-MM, CK-BB and CK-MB. Total CK (the activity of the MM, MB, and BB isoenzymes) is not myocardial-specific. However, the MB isoenzyme (also called CK-2) comprises about 40% of the CK activity in cardiac muscle, and 2% or less of the activity in most muscle groups and other tissues. MB usually becomes abnormal 3 to 4 hours after an MI, peaks in 10 to 24 hours, and returns to normal within 72 hours.

Myoglobin

Myoglobin is a protein found in both skeletal and myocardial muscle. It is released rapidly after tissue injury and may be elevated as early as 1 hour after myocardial injury, though it may also be elevated due to skeletal muscle trauma. A diagnosis of acute MI is unlikely if myoglobin values do not rise within 3 to 4 hours from onset of symptoms.

4.4.2 Use of biomarkers

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4.4.2.1 Evidence statements for biomarkers

1 The two systematic reviews and twelve cohort studies indicate that troponin I and T have the highest sensitivities and specificities for the diagnosis of acute MI compared to CK-MB, CK and myoglobin. CK-MB had the second highest sensitivities and specificities for diagnosis of acute MI. (Balk, E. M., Ioannidis, J. P., Salem, D. et al, 2001) (Ebell, M. H., Flewelling, D., and Flynn, C. A., 2000), (Guo, Xiaobi, Feng, Jianzhang, and Guo, Hengshan, 2006) (Kost, G. J., Kirk, J. D., and Omand, K., 1998) (Chiu, A., Chan, W. K., Cheng, S. H. et al, 1999) (Falahati, Alireza., Sharkey, Scott W., Christensen, Dane. et al, 1999) (Eggers, Kai Marten, Oldgren, Jonas, Nordenskjöld, Anna et al, 2004) (Fesmire, Francis M., Christenson, Robert H., Fody, Edward P. et al, 2004) (Gust, R., Gust, A., Böttiger, B. W. et al, 1998) (al Harbi, Khalid., Suresh, C. G., Zubaid, Mohammad. et al, 2002) (Vatansever, S., Akkaya, V., Erk, O. et al, 2003) (Planer, David, Leibowitz, David, Paltiel, Ora et al, 2006) (Zarich, Stuart W., Qamar, Asad U., Werdmann, Michael J. et al, 2002) (Zimmerman, J., Fromm, R., Meyer, D. et al, 1999)

2 No evidence was found in unselected patients with acute chest pain of suspected cardiac origin to support testing biomarkers outside of hospital.

3 The evidence did not support the lone use of myoglobin to diagnose acute MI.

4 One systematic review showed serial testing of all biomarkers improved the sensitivity. (Balk, E. M., Ioannidis, J. P., Salem, D. et al, 2001)

5 The sensitivity of troponins achieves a maximum 10 to 12 hours after onset of symptoms or 6-9 hours after presentation. (Ebell, M. H., Flewelling, D., and Flynn, C. A., 2000)

7 Two published health economic models indicate that biomarker testing, at the time of presentation to A&E, for patients presenting with chest pain and no diagnostic ECG changes, is both effective and either cost-effective (£17,432/QALY in 2000). (Goodacre, S. and Calvert, N., 2003) or cost-saving (Mant, J., McManus, R. J., Oakes, R.-A. L. et al, 2004)

8 There is health economic evidence to show that biomarker measurement at presentation, and at 6 hours after onset of pain, is also cost-effective (£18,567/QALY in 2000) compared with a strategy of testing at presentation only, but admitting patients for a 24 hour period of observation followed by biomarker testing is not cost-effective (£36,000/QALY in 2000). (Goodacre, S. and Calvert, N., 2003)

9 There is evidence from 2 non-UK costing studies that serial troponin T testing either in addition to or instead of CK-MB serial testing is likely to be cost-saving compared to use of serial CK-MB alone. (Choi, Y. F., Wong, T. W., and Lau, C. C., 2004; Zarich, S., Bradley, K., Seymour, J. et al, 2001)

10 No health economics evidence specifically addressing the cost-effectiveness of myoglobin was found. It was excluded from economic analysis in one published study due to its poor sensitivity and specificity relative to CK-MB and troponin T. (Choi, Y. F., Wong, T. W., and Lau, C. C., 2004)

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4.4.2.2 Clinical evidence

What is the utility and cost-effectiveness of cardiac biomarkers in evaluation of individuals with chest pain of suspected cardiac origin?

The following biomarkers were assessed troponin I, troponin T, creatine kinase (CK), creatine kinase-MB (CKMB), creatine kinase-MB isoforms (CKMB isoforms) and myoglobin.

Two systematic reviews (Balk, E. M., Ioannidis, J. P., Salem, D. et al, 2001) (Ebell, M. H., Flewelling, D., and Flynn, C. A., 2000), 1 opened labeled randomised controlled trial (Alp, N. J., Bell, J. A., and Shahi, M., 2001), and 12 cohort studies were reviewed (Guo, Xiaobi, Feng, Jianzhang, and Guo, Hengshan, 2006) (Kost, G. J., Kirk, J. D., and Omand, K., 1998) (Chiu, A., Chan, W. K., Cheng, S. H. et al, 1999) (Falahati, Alireza., Sharkey, Scott W., Christensen, Dane. et al, 1999) (Eggers, Kai Marten, Oldgren, Jonas, Nordenskjöld, Anna et al, 2004) (Fesmire, Francis M., Christenson, Robert H., Fody, Edward P. et al, 2004) (Gust, R., Gust, A., Böttiger, B. W. et al, 1998) (al Harbi, Khalid., Suresh, C. G., Zubaid, Mohammad. et al, 2002) (Vatansever, S., Akkaya, V., Erk, O. et al, 2003) (Planer, David, Leibowitz, David, Paltiel, Ora et al, 2006) (Zarich, Stuart W., Qamar, Asad U., Werdmann, Michael J. et al, 2002) (Zimmerman, J., Fromm, R., Meyer, D. et al, 1999).

The first systematic review (search date 1998) examined the diagnostic performance of the measurement of biomarkers on presentation and of serial biomarker measurements for the diagnosis of acute MI and ACS (Balk, E. M., Ioannidis, J. P., Salem, D. et al, 2001). Meta-analyses were performed using the results from diagnostic studies conducted in patients with acute chest pain (or symptoms suggestive of acute MI or coronary artery syndromes) for the following biomarkers; troponin I, troponin T, CK, CK-MB, myoglobin, and the combination of CK-MB and myoglobin (Balk, E. M., Ioannidis, J. P., Salem, D. et al, 2001).

The systematic review identified 7 studies that evaluated the performance of a single troponin I test in the diagnosis of acute MI. However, 3 studies did not

report specificity data and were excluded from analyses. Two of the 4 included studies were of all eligible emergency department patients, while the other 2 studies were in patients admitted to the hospital from the emergency department. Reported troponin I testing for all studies was at time of presentation with acute chest pain. From meta-analyses, the sensitivity of troponin I was 39% (95%CI 10% to 78%) and the specificity was 93% (95%CI 88% to 97%). The prevalence of acute MI in the 4 studies ranged from 6% to 39% with a total number of 1149 patients. Detail of the timing of the troponin I test from onset of symptoms was not given for the individual studies, except that it was reported that in one study where patients had a mean duration of symptoms of 2 hours the sensitivity was 23%, while in a second study where patients had a average of 7 hours of symptoms the sensitivity was 100%. This marked variation in test sensitivity was attributed to the heterogeneity in study participants. No studies were identified that examined the use of single troponin I for the identification of partients with ACS (Balk, E. M., Ioannidis, J. P., Salem, D. et al, 2001).

Two studies were identified that examined the use of serial troponin I testing. One study recruited all eligible patients in the emergency department (773 patents, 6% acute MI prevalence, 41% unstable angina prevalence, stated timing of tests; presentation and ≥ 4 hours after presentation). Serial troponin I testing had a sensitivity and specificity for the diagnosis of ACS of 44% and 98%, respectively, while for the diagnosis of acute MI the sensitivity and specificity were 100% and 83%, respectively. The second study was in patients admitted to the coronary care unit considered to be at moderate risk of acute MI due to indeterminate ECG findings (620 patients, 9% acute MI prevalence, stated timing of tests; serial testing over 8 hours, specific time points not given). The sensitivity and specificity of serial troponin I testing for the diagnosis of acute MI in this study was 90% and 96%, respectively. Sensitivity and specificity for ACS was not reported in this study (Balk, E. M., Ioannidis, J. P., Salem, D. et al, 2001).

The systematic review identified 9 studies that evaluated the diagnostic performance of a single troponin T test; however 3 studies were excluded due

to insufficient data reporting. Of the remaining 6 studies, 4 studies recruited all eligible patients in the emergency department, 1 study drew blood prior to arrival to the emergency department, and 1 study only included patients admitted to the hospital. The prevalence of acute MI ranged from 6% to 39% in the 6 studies. The study that only included patients admitted to the hospital had an acute MI prevalence of 15%. Reported troponin T testing for all studies was at time of presentation with acute chest pain, however, information on the timing of the single troponin T test from onset of symptoms was not given. The sensitivity range for troponin T in the 6 studies was 15% to 53% (1348 patients), and the specificity range was 89% to 98%. The sensitivity and specificity for the study that only included patients admitted to the hospital were 15% and 97%, respectively. Meta-analyses for all six studies gave a troponin T sensitivity of 39% (95%CI 26% to 53%) and a specificity of 93% (95%CI 90% to 96%). Meta-analyses for the 5 studies that recruited all eligible patients in the emergency department (1171 patients) gave a troponin T sensitivity of 44% (95%CI 32% to 56%) and a specificity of 92% (95%CI 88% to 95%). No studies were identified that examined the use of single troponin T for the identification of partients with ACS (Balk, E. M., Ioannidis, J. P., Salem, D. et al, 2001).

For serial troponin T testing, 3 studies were identified that had sufficient data for meta-analyses. One study included all eligible patients in the emergency department (773 patients, acute MI prevalence 6%, sensitivity 94%, specificity 89%), 1 study was in a highly selected emergency department population (32 patients, acute MI prevalence 78%, sensitivity 100%, specificity 86%), and 1 study included only patients admitted to hospital (98 patients, acute MI prevalence 21%, sensitivity 90%, specificity 87%). Meta-analyses for the use of troponin T for diagnosis of acute MI gave a sensitivity of 93% (95%CI 85% to 97%) and a specificity of 85% (95%CI 76% to 91%) (total patient number; 904). The systematic review did not give details of the timing of the serial troponin T tests. The study that recruited all emergency department patients and the study that recruited highly selected emergency department patients reported sensitivities of 31% and 45% for the diagnosis of ACS, respectively,

and specificities of 98% and 97%, respectively (Balk, E. M., Ioannidis, J. P., Salem, D. et al, 2001).

The systematic review identified 12 eligible studies that examined the performance of a single CK test in the diagnosis of acute MI. Ten studies were in all patients admitted to the emergency department, and 2 studies were in patients admitted to hospital. The acute MI prevalence ranged from 7% to 41% with a total of 3195 patients. Acute MI prevalence in the 2 studies in hospitalized patients was 29% and 15%. Reported CK testing was at time of presentation with acute chest pain. Information on the timing of the single CK test from onset of symptoms was not given. Meta-analyses of the results from all 12 studies for the use of CK for diagnosis of acute MI gave a sensitivity of 37% (95%CI 21% to 44%) and a specificity of 87% (95%CI 80% to 91%). Meta-analyses of the results from the 10 studies in patients in the emergency department were not done. No studies were identified that examined the use of single troponin T for the identification of partients with ACS (Balk, E. M., Ioannidis, J. P., Salem, D. et al, 2001).

For serial CK testing, 2 studies were identified in patients presenting to the emergency department that had a 26% and a 43% prevalence of acute MI. The review did not report the timing of the serial CK tests. One study reported a sensitivity of 69% and specificity of 84%, respectively, for the use of serial CK in the diagnosis of acute MI, and the second study reported a sensitivity of 99% and specificity of 68%, respectively. No studies were identified that examined the serial CK testing for the identification of patients with ACS (Balk, E. M., Ioannidis, J. P., Salem, D. et al, 2001).

The analysis identified 19 studies that evaluated the diagnostic performance of a single CK-MB test; 10 studies in patients presenting to the emergency department, and 9 studies in hospitalized patients. The prevalence of acute MI ranged from 6% to 42% with a total of 6425 patients. Reported CK-MB testing was at time of presentation with acute chest pain. Information on the timing of the single CK-MB test from onset of symptoms was not given. Meta-analyses of the results from all 19 studies for the use of CK-MB for diagnosis

of acute MI gave a sensitivity of 42% (95%CI 36% to 48%) and a specificity of 97% (95%CI 96% to 98%). Meta-analyses of the results from 7 emergency department studies gave a sensitivity of 44% (95%CI 35% to 53%) and a specificity of 96% (95%CI 94% to 97%) (2404 patients in total). Information on the timing of the single CK-MB test from onset of symptoms was not given. No studies were identified that examined the use of single CK-MB for the identification of partients with ACS (Balk, E. M., Ioannidis, J. P., Salem, D. et al, 2001).

For the use of serial CK-MB testing in diagnosis of acute MI, 14 studies were identified, 7 studies in patients presenting to the emergency department, and 7 studies in hospitalized patients The prevalence of acute MI was 1% to 43%, with a total of 11 625 patients. Meta-analyses of the results from all 14 studies gave a sensitivity of 79% (95%CI 71% to 86%) and a specificity of 96% (95%CI 95% to 97%). Meta-analyses of the results from 7 emergency department studies in a total of 3229 patients gave a sensitivity of 80% (95%CI 61% to 91%) and a specificity of 96% (95%CI 94% to 98%). The systematic review did not report the timing of the serial CK-MB tests. One study was identified that examined the use of serial CK-MB testing in the diagnosis of ACS. The study recruited 1042 patients and the prevalence of ACS was 14%. The sensitivity and specificity were 31% and 95%. No information was given on the timing of the tests (Balk, E. M., Ioannidis, J. P., Salem, D. et al, 2001).

The systematic review identified 18 studies that examined the diagnostic performance of a single myoglobin test in the identification of acute MI; 10 studies were in patients in the emergency department and 8 studies in hospitalized patients. The prevalence of acute MI ranged from 6% to 62% in the studies with a total of 4172 patients. Reported myoglobin testing was at time of presentation with acute chest pain. Information on the timing of the single myoglobin test from onset of symptoms was not given. Meta-analyses of the results from all 18 studies gave a sensitivity of 49% (95%CI 43% to 55%) and a specificity of 91% (95%CI 87% to 94%). Meta-analyses of the results from 10 emergency department studies in a total of 1395 patients gave

a sensitivity of 49% (95%CI 41% to 57%) and a specificity of 93% (95%CI 88% to 96%). No information on the timing of the test from onset of symptoms was given. One study was identified that examined the single myoglobin test for the diagnosis of ACS. Eighty six patients were enrolled, and the prevalence of ACS, sensitivity and specificity were 52%, 16% and 100%, respectively (Balk, E. M., Ioannidis, J. P., Salem, D. et al, 2001).

The systematic review identified 10 studies that examined serial testing with myoglobin for the diagnosis of acute MI; 5 studies in emergency department patients and 5 studies in hospitalized patients. The prevalence of acute MI ranged from 11% to 41% in the studies with a total of 1277 patients. Meta-analyses of the results from all 10 studies gave a sensitivity of 89% (95%CI 80% to 94%) and a specificity of 87% (95%CI 80% to 92%). Meta-analyses of the results from 5 emergency department studies gave a sensitivity of 90% (95%CI 76% to 96%) and a specificity of 92% (95%CI 82% to 97%) (831 patients in total). No studies were identified that examined the use of single CK-MB for the identification of partients with ACS (Balk, E. M., Ioannidis, J. P., Salem, D. et al, 2001).

The second systematic review (search date 1999) evaluated the use of troponin I and troponin T in the diagnosis of acute MI in patients presenting to the emergency department with acute chest pain (Ebell, M. H., Flewelling, D., and Flynn, C. A., 2000). Six studies were identified that evaluated the diagnostic performance of troponin I Prevalence of acute MI in the identified studies was not reported. Meta-analyses for the sensitivity and specificity of troponin I at 1, 2, 3, 4, 5 and 6 hours from onset of pain are detailed in Table 16. The most accurate test performance was at 6 hours from onset of pain with a sensitivity of 90% and a specificity of 95% (Ebell, M. H., Flewelling, D., and Flynn, C. A., 2000).

Fourteen studies were identified that evaluated the diagnostic performance of troponin T in the identification of patients with acute MI. Prevalence of acute MI in the identified studies was not reported. Sensitivity and specificity values are detailed in Table 16 for troponin T at 2 assay cutoff off values of; > 0.1

ng/ml and > 0.2 ng/ml at the following time points; 1, 2, 3, 4, 6, 8 and 10 hours from onset of pain. Sensitivity was greatest for troponin T > 0.1 ng/ml at 10 hours from onset of pain (93%), while the specificity at this time point was 80%). Specificity was greatest for troponin T > 0.1 ng/ml at 1 and 2 hours from onset of pain, (87% for both timepoints) while the sensitivity was 47% and 53% respectively. Sensitivity was greatest for troponin T > 0.2 ng/ml at 8 and 10 hours from onset of pain (96% for both timepoints), while the specificities were 81% and 80% respectively. Specificity was greatest for troponin T > 0.2 ng/ml at 1 and 2 hours from onset of pain, (87% for both timepoints), while the sensitivities were 14% and 33%, respectively (Ebell, M. H., Flewelling, D., and Flynn, C. A., 2000).

Table 16

Summary of data for troponin T and I tests for diagnosing acute MI

	Hours from onset of chest pain	Sensitivity	Specificity	PLR	NLR
Troponin T>0.1*					
	1	0.47	0.87	3.7	0.6
	2	0.53	0.87	3.9	0.5
	3	0.58	0.86	4.1	0.5
	4	0.64	0.85	4.2	0.4
	6	0.74	0.83	4.4	0.3
	8	0.84	0.81	4.5	0.2
	10	0.93	0.80	4.6	0.1
Troponin T>0.2†					
	1	0.14	0.87	1.1	1.0
	2	0.33	0.87	2.5	0.8
	3	0.50	0.86	3.5	0.6
	4	0.65	0.85	4.3	0.4
	6	0.86	0.83	5.1	0.2
	8	0.96	0.81	5.2	0.05
	10	0.96	0.80	4.7	0.05
Troponin 1>0.1‡					
	1	0.13	0.95	2.7	0.9
	2	0.34	0.95	6.8	0.7
	3	0.52	0.95	10	0.5
	4	0.67	0.95	13	0.34
	5	0.80	0.95	16	0.2
	6	0.90	0.95	18	0.1

NOTE: Values are calculated from the best-fit curve for sensitivity and specificity. While troponin 1 appears to be more accurate, these data are based on the results of a single relatively small study and should be interpreted with caution.
PLR = postitive likelihood ratio; NLR = negative likelihood ratio.
Permissions granted from original source respectively (Ebell, M. H., Flewelling, D., and Flynn, C. A., 2000).

The randomised open labeled trial evaluated a rapid troponin I based protocol in patients with acute chest pain compared with standard management for the diagnosis of non ST-segment elevation acute MI (Alp, N. J., Bell, J. A., and Shahi, M., 2001). The rapid troponin I based protocol for diagnosis was based on the admission ECG (ST depression or abnormal T wave inversion) and 6 h troponin I (assay cut off value for diagnosis of 0.1 ng/ml). The standard management arm for diagnosis was based on ECG and serial cardiac enzyme testing with CK and AST. Patients were included if they were referred to a coronary care unit with acute chest pain of suspected cardiac origin within 24 hours of presentation and were > 18 years. Patients were excluded if there was evidence of ST-segment elevation on admission ECG or evidence of MI within the previous 2 weeks. Three hundred and ninety seven patients were recruited, of which 62% percent were men, and the mean age in the troponin I arm was 62.2 years, and in the standard protocol arm was 63.5 years. The outcome measures were major cardiac adverse event at 30 days (cardiac death, or non fatal MI defined as a creatine kinase level of 2 times the upper limit of reference range), and urgent revascularization during admission or up to 30 days post admission, and length of stay in the coronary care unit (Alp, N. J., Bell, J. A., and Shahi, M., 2001).

Table 17 details the outcome results for the standard management and troponin I protocol groups based upon ECG findings and troponin I findings. As shown Table 17 the troponin I protocol allowed earlier discharge of the low risk group (normal ECG) compared with the standard management group (mean 10 hours versus mean 30 hours, respectively) without an increased incidence of adverse events. The troponin I protocol had a greater accuracy compared with the standard management protocol for identification of the moderate risk of cardiac events group (troponin negative / ECG indicative of ischaemia; 15% major adverse event rate during admission and 30 day follow up), and the high risk group (troponin I positive; 75% major adverse event rate). It should be noted that this subgroup analysis has compared the troponin I negative group with the negative standard management group. The benefit of randomization is lost as the two negative groups are differently

defined in the two arms of the study, and the results should be interpreted in light of this (Alp, N. J., Bell, J. A., and Shahi, M., 2001).

Table 17

Combined pre-discharge and 30-day follow-up outcomes

Endpoint	Standard management (n=180)		Troponin I (TnI) Management protocol (n=217)		
	iECG (n=61)	nECG (n=119)	TnI + ve (n – 51)	TnI – ve iECG (n=57)	TnI – ve nECG (n=109)
Admission time (h) (mean, median, IQR)	57, 56, 31	30, 22, 34	86, 82, 32	21, 14, 36	10, 7, 14
MI (95%CI)	35% (23 – 48%)	3% (1 – 7%)	63% (48 – 75%)	9% (3 – 19%)	1% (0 – 5%)
Revascularization (95%CI)	2% (0 – 9%)	2% (0 – 6%)	8% (2 – 19%)	4% (1 – 12%)	1% (0-5%)
Death (95%CI)	0% (0 – 6%)	0% (0 – 3%)	4% (1 – 13%)	2% (0 – 9%)	1% (0 – 5%)
Combined major adverse cardiac event (95%CI)	37% (24 – 49%)	5% (1 - 9%)	75% (60 – 85%)	15% (7 – 28%)	3% (1 – 8%)

MI, non-fatal myocardial infarction; IQR, interquartile range, iECG, ischaemic ECG; nECG, normal ECG; TnI, troponin I.
Permission granted from original source (Alp, N. J., Bell, J. A., and Shahi, M., 2001).

The first diagnostic cohort study evaluated the diagnostic performance of troponin T test for the identification of patients with acute MI (Guo, Xiaobi, Feng, Jianzhang, and Guo, Hengshan, 2006). Five hundred and two consecutive patients with symptoms and ECG findings suggestive of myocardial ischaemia were enrolled (median age 72 years, 237 men). Patients' onset of chest pain ranged from 0.5 hours to 24 hours. Troponin T testing was performed at admission, and 6 and 12 hours after admission. The troponin T assay cut off value for diagnosing acute MI for was 0.1 ng/ml. The median time of the first test was 4 hours after onset of chest pain (Guo, Xiaobi, Feng, Jianzhang, and Guo, Hengshan, 2006).

Of the 502 patients, ECG findings identified 111 patients with ST-segment elevation acute MI and 35 patients with non ST-segment elevation acute MI. One hundred and thirty nine troponin T positive patients and 7 troponin T negative patients were diagnosed as having either an ST-segment elevation or non ST-segment elevation acute MI (the 7 troponin negative patients were

diagnosed based on ECG changes and ischaemic symptoms alone). Sensitivity, specificity, PPV and negative predictive value (NPV) for the use of elevated troponin T in the diagnosis of acute MI were; 95% , 94%, 87% and 98%, respectively (Guo, Xiaobi, Feng, Jianzhang, and Guo, Hengshan, 2006).

The second diagnostic study evaluated the use of troponin I, troponin T, CK-MB and myoglobin in the diagnosis of acute MI in 54 patients with acute chest pain and other symptoms suggestive of myocardial ischaemia (Kost, G. J., Kirk, J. D., and Omand, K., 1998). Biomarker testing was performed at presentation and 3, 6 and 12±1.5 hours after presentation hours. The assay cut off values for diagnosing acute MI for troponin I, troponin T, CK-MB, CK-MB isoforms (MB1 and MB2), and myoglobin were; 1.5 ng/ml, 0.1 ng/ml, 5.9 U/l and 1.8 U/l , 7.5 ng/ml, and 100 ng/ml, respectively. Diagnosis of acute MI was according to World Health Organization criteria (Gillum, R. F., Fortmann, S. P., Prineas, R. J. et al, 1984). Of 54 patients, 10 (19%) were diagnosed with acute MI. Single overall sensitivity and specificity values were reported for each biomarker. Serial troponin T testing gave the best overall diagnostic performance compared with the other biomarkers with a sensitivity of 90% and a specificity of 100%. The sensitivity and specificity of serial troponin T were 90% and 91%, respectively. The sensitivity and specificity of serial CK-MB were 90% and 90%, respectively. The serial CK-MB isoforms test had the lowest sensitivity compared with the other biomarkers at 70% with a specificity of 99%. The serial myoglobin test had the lowest specificity compared with other biomarkers at 75%, with a sensitivity of 80%. Additional statistical diagnostic performance results are given in the paper (Kost, G. J., Kirk, J. D., and Omand, K., 1998).

The third study determined sensitivities of troponin I, CK-MB, myoglobin and a combined triple test of troponin I, myoglobin and CK-MB, at 0 up to > 72 hours from the onset of chest pain (Chiu, A., Chan, W. K., Cheng, S. H. et al, 1999). The diagnostic thresholds for troponin I, CK-MB, myoglobin were; < 2.0 ng/ml, < 0.5 ng/ml and < 90 ng/ml, respectively. Patients were included in the study if an initial diagnosis of acute MI was made based on two of the three criteria; (1) development of Q wave, (2) ST-segment depression or elevation (3) serial

changes in CPK. Eighty seven patients were recuruited from the emergency department with a mean age of 67 years, and 59 were men (Chiu, A., Chan, W. K., Cheng, S. H. et al, 1999).

The sensitivities of the biomarkers for the diagnosis of acute MI at the different time points are detailed in Table 18. Specificity values were not determined. None of the biomarkers had good sensitivity within the first 4 hours after an acute MI. Both myoglobin and CK-MB had greatest sensitivity between 4 to 8 hours, while troponin I and CKMB were had greatest sensitivity between 8 hours to 24 hours. The combined triple test of troponin I, myoglobin and CK-MB had excellent sensitivity from 4 to 72 hours (Chiu, A., Chan, W. K., Cheng, S. H. et al, 1999).

Table 18

Sensitivity of myoglobin, CKMB (mass), troponin-I and the combined approach in specific time frames

Hours since infarct	0-4	4-8	8-12	12-24	24-48	48-72	>72
Patients (n)	34	26	41	76	76	69	67
Myoglobin (%) 95%CI	55.8 38.1-72.4	92.3 73.4-98.7	85.4 70.1-93.9	75.0 63.5-83.9	43.4 32.3-55.2	20.3 11.0-32.0	14.0 6.7-25.0
CKMB mass (%) 95%CI	44.1 27.6-61.9	96.2 78.4-99.8	97.6 85.6-99.99	97.4 90.0-99.5	93.4 84.7-97.6	71.0 58.7-81.0	22.8 13.2-34.8
Troponin-I (%) 95%CI	35.3 20.3-53.4	80.7 60.0-92.7	92.7 79.0-98.1	97.4 90.0-99.5	96.1 88.1-99.0	97.1 89.0-99.5	93.0 82.2-97.4
Combined (%) 95%CI	61.8 43.6-77.3	96.2 78.4-99.8	97.6 85.6-99.5	97.4 90.0-99.5	98.7 91.9-99.9	98.6 91.1-99.9	94.7 84.4-99.4

Permission granted from original source (Chiu, A., Chan, W. K., Cheng, S. H. et al, 1999).

The fourth study examined the diagnostic performance of the serial measurement of biomarkers in patients with acute chest pain of suspected cardiac origin admitted to a coronary care unit (Eggers, Kai Marten, Oldgren, Jonas, Nordenskjöld, Anna et al, 2004). Patients were included if chest pain was > 15 minutes duration in the previous 12 hours. Patients with evidence of pathological ST-segment elevation on admission ECG requiring immediate perfusion therapy were excluded. The study recruited 197 patients with a median age of 66 years (range 55 to 75 years) and 130 were male. Troponin I, CK-MB and myoglobin were measured at presentation and 6 and 12 hours after presentation; the assay cut off value for diagnosis for troponin I was 0.1

μg/l, for CK-MB was 3.5 μg/l and for myoglobin in men was 98 μg/l and for women was 56 μg/l. The index event was classified by an independent end point evaluator. Acute MI was diagnosed if one on the following was fulfilled in addition to the acute chest pain; development of Q wave with 24 hours, or elevated troponin I levels within 24 hours. ACS was diagnosed if new ST-segment depression or T wave inversion occurred within 24 hours (Eggers, Kai Marten, Oldgren, Jonas, Nordenskjöld, Anna et al, 2004).

The median time from onset of chest pain to the first blood sample in the study participants was 5.5 hours (interquartile range 3.4 to 9.6 hours). The cause of admission was as follows in the 197 patients; acute MI 43 patients (22%), ACS 30 patients (15%), other heart disease 43 patients (10%), and unspecified chest pain 19 patients (32%). Sensitivities of the biomarkers for the diagnosis of acute MI at a given specificity of 95% are detailed in the paper (Eggers, Kai Marten, Oldgren, Jonas, Nordenskjöld, Anna et al, 2004). Troponin I gave the highest sensitivity at all time points, although an acceptable high sensitivity of ≥ 95% was not found before 12 hours post admission. CK-MB and myoglobin had poorer diagnostic performance compared with troponin I. The cumulative sensitivities at 2 hours for troponin I, CK-MB and myoglobin were 93%, 79% and 67%, respectively. The cumulative specificities at 2 hours for troponin I, CK-MB and myoglobin were 81%, 88% and 86%, respectively. At 6 hours the cumulative sensitivities for troponin I and CK-MB were 98% and 81%, and the corresponding specificities were 76% and 88% respectively (Eggers, Kai Marten, Oldgren, Jonas, Nordenskjöld, Anna et al, 2004).

The fifth study examined the diagnostic performance of troponin I and CK-MB in the identification of acute MI (Falahati, Alireza., Sharkey, Scott W., Christensen, Dane. et al, 1999). Three hundred and twenty seven consecutive patients were recruited; inclusion and exclusion criteria were not reported. The diagnosis of acute MI was according to WHO criteria (Gillum, R. F., Fortmann, S. P., Prineas, R. J. et al, 1984). The assay cut off point for diagnosis of acute MI was 0.8 μg/l for troponin I, and 5.0 μg/l for CK-MB. The study reported one result for both sensitivity and specificity based on the

"peak concentration" results for each biomarker; for troponin I this was between 12 to 18 hours, and for CK-MB this was between 6 to 12 hours (Falahati, Alireza., Sharkey, Scott W., Christensen, Dane. et al, 1999).

The study evaluated CK, CK-MB and troponin I to diagnose AMI every 6 to 8 hours from admission for 24 to 48 hours. Sixty two patients were diagnosed with acute MI (19%). The study found that the diagnostic sensitivity and specificity at peak concentration for troponin I (100% and 96%, respectively) were superior to those of CK-MB (88% and 93%, respectively) (Falahati, Alireza., Sharkey, Scott W., Christensen, Dane. et al, 1999).

The sixth study compared the diagnostic performance of CK-MB and myoglobin in patients with acute chest pain of suspected cardiac origin and baseline troponin measurement of ≤1.0 ng/ml (Fesmire, Francis M., Christenson, Robert H., Fody, Edward P. et al, 2004). Nine hundred and seventy five consecutive patients were enrolled, with a mean age of 60(SD 15) years and 488 were male. CK-MB and myoglobin measurement was at presentation and at 2 hours; the assay cut off point for diagnosis of acute MI for CK-MB was 10.4 ng/ml and for myoglobin was 116.3 ng/ml. Acute MI was diagnosed if chest pain was ≤ 20 minutes, and any one of the following criteria was found within 24 hours; new Q wave formation, an increase in troponin > 1.0 ng/ml, or patient death by cardiac or unknown cause (Fesmire, Francis M., Christenson, Robert H., Fody, Edward P. et al, 2004).

Acute MI was diagnosed in 44 of the 975 study participants (4.5%). The sensitivity and specificity of myoglobin at admission were 22% and 88%, respectively. The sensitivity and specificity of myoglobin at 2 hours were 48% and 77%, respectively. The sensitivity and specificity of CK-MB at admission were 0 and 98%, respectively. The sensitivity and specificity of CK-MB at 2 hours were 91% and 78%, respectively (Fesmire, Francis M., Christenson, Robert H., Fody, Edward P. et al, 2004).

The seventh diagnostic study evaluated a rapid qualitative beside immunoassay for troponin T in the pre hospital setting for the diagnosis of acute MI (Gust, R., Gust, A., Böttiger, B. W. et al, 1998). Sixty eight patients

with acute, central, crushing chest pain strongly suspected to be acute MI were included. The chest pain had to be radiating to the neck or one or both shoulders and not be relieved by rest or sublingual glyceryl trinitrate. The mean age of study participants was 69(SD 12) years, and 47 were male. The assay troponin T cut of value for diagnosis of acute MI was 0.2 μg/l (Gust, R., Gust, A., Böttiger, B. W. et al, 1998).

Sixteen patients were diagnosed with acute MI according to WHO criteria (Gillum, R. F., Fortmann, S. P., Prineas, R. J. et al, 1984). Thirteen patients (19%) were diagnosed with ACS; the criterion for diagnosis was not given. The sensitivity of the rapid troponin assay was 25% and the specificity was 98% (Gust, R., Gust, A., Böttiger, B. W. et al, 1998).

The eighth study examined the diagnostic performance of troponin T testing in the community setting (Planer, David, Leibowitz, David, Paltiel, Ora et al, 2006). Patients were included if their chest pain was of at least 20 consecutive minutes beginning at least 8 hours before presentation, and they were aged over 30 years. Patients were excluded from the study if they had renal failure, ST-segment elevation on ECG, a diagnosis of ACS or had undergone revascularization within 2 weeks prior to presentation. Three hundred and forty nine patients were included in the study, the mean age was 58.6(SD 14.2) years, and 406 were male. Following assessment by a primary care physician, troponin T testing was performed. The assay cut off value for referral to hospital was 0.08 μg/l. Patients with a negative troponin T and negative clinical assessment were sent home. A final diagnosis of acute MI was based on the Joint European Society of Cardiology / American College of Cardiology Committee criteria and recorded at hospital discharge (Planer, David, Leibowitz, David, Paltiel, Ora et al, 2006).

A total of 238 patients (68%) were sent home by the primary care physician, and 111 patients (38%) were referred to the emergency department. Of these 111 patients, 4 had positive troponin tests. A diagnosis of acute MI was confirmed in-hospital in all 4 patients. Of the remaining 107 troponin negative patients who had been referred to the emergency department, only 42 were

hospitalised (39%), one of which was diagnosed with acute MI after a troponin T elevation 48 hours after hospital admission. A further 17 patients were diagnosed with ACS. Follow up at 2 months of the 238 patients who were sent home by the primary care physician found that 1 patient had an acute MI and 1 patient had unstable angina. The PPV of the primary care physician to predict hospitalization was 41%, and the NPV was 94%. The overall prevalence of acute MI was 1.7%. The sensitivity and specificity of community troponin T testing for the diagnosis of acute MI within 72 hours were 83% and 100%, respectively (Planer, David, Leibowitz, David, Paltiel, Ora et al, 2006).

The ninth study examined the diagnostic performance of a single troponin T or single CK-MB test at presentation to the emergency department compared with serial CK-MB testing for the identification of patients with acute MI (Zarich, Stuart W., Qamar, Asad U., Werdmann, Michael J. et al, 2002). Two hundred and sixty seven patients with acute MI were included; the mean age was 61.8(SD 14) years and 130 were male. Exclusion criteria were history of chest trauma or renal failure. The troponin T assay cut off value for diagnosis of acute MI was 0.1 μg/l, the CK-MB value was a total CK of > 150 U/l with an MB fraction of > 17 U/l and > 5% but < 25% of total CK. Serial CK-MB testing was performed at presentation and 4, 8 and 16 hours after presentation (Zarich, Stuart W., Qamar, Asad U., Werdmann, Michael J. et al, 2002).

Of the 267 patients, 60 patients had a final diagnosis of acute MI based on WHO criteria, and 26 patients had acute coronary artery syndrome based on class III criteria in the Braunwald classification (Braunwald, E., 1989). The sensitivity and specificity for troponin T were 87% and 94%, respectively. The sensitivity and specificity for CK-MB were 47% and 83%, respectively. The sensitivity and specificity for serial CK-MB were 95% and 87%, respectively (Zarich, Stuart W., Qamar, Asad U., Werdmann, Michael J. et al, 2002).

The tenth study evaluated establishing a gradient of risk in patients with ACS using serial troponin I measurements (al Harbi, Khalid., Suresh, C. G., Zubaid, Mohammad. et al, 2002). The study included 124 patients, 86 patients in group 1 who had suspected acute MI or ACS, and 38 control subjects who

were healthy and age-matched with no history of cardiovascular disease or any other chronic disease. Group 1 patients were admitted to a coronary care unit for further evaluation. Only Group 1 patients had serial troponin testing at presentation and 8 and 16 hours after presentation. Group 2 subjects had a single troponin I test. The assay cut off value was 0.05 ng/ml (al Harbi, Khalid., Suresh, C. G., Zubaid, Mohammad. et al, 2002).

Of the 86 patients in group 1, 51 patients were diagnosed with acute MI based on classical clinical symptoms and development of Q wave and 35 patients were diagnosed with ACS based on Braunwald classification (Braunwald, E., 1989) and absence of ST-segment abnormalities on ECG. Only 1 healthy control of 38 had a troponin I value > 0.1 ng/ml, which was 0.121 ng/ml. Thirty two healthy control subjects (84%) had troponin I values < 0.05 ng/ml. The 99^{th} percentile value in the healthy study population was estimated to be 0.05 ng/ml (al Harbi, Khalid., Suresh, C. G., Zubaid, Mohammad. et al, 2002).

For a diagnosis of acute MI, sensitivity and specificity for troponin I (> 0.05 ng/ml) were as follows; at admission (60% and 82%, respectively), at 8 hours (88% and 72%, respectively), and at 16 hours (93% and 79%, respectively). Sensitivity and specificity for troponin I (> 0.3 ng/ml) were as follows; at admission (38% and 93%, respectively), at 8 hours (80% and 86%, respectively), and at 16 hours (87% and 88%, respectively) (al Harbi, Khalid., Suresh, C. G., Zubaid, Mohammad. et al, 2002).

For a diagnosis of ACS, sensitivity and specificity for troponin I (> 0.5 ng/ml) were as follows; at admission (38% and 55%, respectively), at 8 hours (62% and 13%, respectively), and at 16 hours (61% and 6%, respectively). Sensitivity and specificity for troponin I (> 0.3 ng/ml) were as follows; at admission (85% and 21%, respectively), at 8 hours (74% and 45%, respectively), and at 16 hours (76% and 67%, respectively) (al Harbi, Khalid., Suresh, C. G., Zubaid, Mohammad. et al, 2002).

The eleventh study compared the diagnostic performance of troponin T, CK and myoglobin in patients with acute chest pain presenting to the emergency

department (Vatansever, S., Akkaya, V., Erk, O. et al, 2003). Thirty three patients diagnosed with acute MI based on ST-segment elevation and 27 healthy control subjects were included in the study. The mean age in the acute MI group was 51(±11 (not defined as either SD or SE)) years, and 28 patients were male, and the mean age in the control group was 51(±12 (not defined as either SD or SE)) years, and 25 subjects were male. The assay threshold values for diagnosis for the biomarkers were not given (Vatansever, S., Akkaya, V., Erk, O. et al, 2003).

Troponin T, myoglobin and CK testing was performed presentation and 2 hours after presentation in the acute MI patients and one single test was performed on the controls. Sensitivity and specificity values for CK were 64% and 90% at admission, respectively, and 79% and 90% at 2 hours after admission, respectively. Sensitivity and specificity values for troponin T were 76% and 90% at admission, respectively, and 97% and 90% at 2 hours after admission, respectively. Sensitivity and specificity values for myoglobin were 85% and 90% at admission, respectively, and 97% and 90% at 2 hours after admission, respectively. The biomarker levels in the control subjects were not reported numerically, but shown graphically to be less than those of the acute MI patient group at the 2 time points for all 3 biomarkers (Vatansever, S., Akkaya, V., Erk, O. et al, 2003).

The twelfth study examined the diagnostic performance of myoglobin, troponin T, troponin I and CK-MB subforms, total CK-MB activity and total CK-MB mass for the identification of patients with acute MI (Zimmerman, J., Fromm, R., Meyer, D. et al, 1999). Testing was performed at presentation to the emergency department and at 1, 2, 4, 6, 10, 18 and 22 hours after presentation. The assay cut off point values for acute MI diagnosis, for troponin I was 1.5 ng/ml, for troponin T was 0.1 ng/ml, for CK-MB subforms was MB2 to MB1 ratio of 1.6, for total CK-MB activity was 9 IU/l, for total CK-MB mass was ≥7 ng/ml, and for myoglobin was 85 ng/ml. Nine hundred and fifty five were included. The inclusion criteria were; chest pain lasting for 15 minutes or longer, and occurring within the previous 24 hours, and age > 21 years. The mean age was 55(SD 13) years and 571 were male. The

diagnostic criteria for acute MI was a CK-MB mass ≥7 ng/ml and a CK-MB index (CK-MB mass / CK) ≥ 2.5% determined by the results of the core laboratory in ≥ 2 samples obtained in the first 24 hours after hospital arrival or in 1 sample if only one was available for analysis (Zimmerman, J., Fromm, R., Meyer, D. et al, 1999).

Acute MI was confirmed in 119 of 955 patients (13%) based on CK-MB mass criteria. ST-segment elevation on ECG was only found in 45% of these patients. Thirty six patients had Q wave infarcts and 83 patients had non Q wave infarcts. CK-MB subforms was most sensitive and specific (91% and 89%, respectively) within 6 hours of chest pain onset, followed by myoglobin (sensitivity; 78.7%, specificity; 89.4%). For late diagnosis, total CK-MB activity was the most sensitive and specific (96% and 98%, respectively) at 10 hours from onset, followed by troponin I (sensitivity; 92.3%, specificity; 93.2%. Troponin T had a sensitivity of 86.5% and a specificity of 96.4%). Further details of the diagnostic performance of the cardiac biomarkers at at 1, 2, 4, 6, 10, 18 and 22 hours after presentation are given in the paper (Zimmerman, J., Fromm, R., Meyer, D. et al, 1999).

4.4.2.3 Universal definition of acute MI

The universal definition of an MI is;

“detection of rise and / or fall of cardiac biomarkers (preferably troponin) with at least one value (Diercks, D. B., Kontos, M. C., Chen, A. Y. et al, 2009)above the 99th percentile of the upper reference limit together with evidence of myocardial ischaemia with at least one of the following:

- Symptoms of ischaemia
- ECG changes indicative of new ischaemia (new ST-T changes or new left branch bundle block (LBBB))
- Development of pathological Q wave in the ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.”

(Thygesen, K., Alpert, J. S., and White, H. D., 2007)

The expert consensus document that a MI is diagnosed when “blood levels of sensitive and specific biomarkers such as cardiac troponin or CKMB are increased in the clinical setting of acute myocardial ischaemia” (Thygesen et al, 2007). The document continues to state that the preferred biomarker for diagnosing acute MI is troponin I or T and should be taken at 6 to 9 hours from onset of symptoms. If the troponin I or T test is negative but an acute MI is strongly suspected further tests should be carried out between 12 and 24 hours after. If troponin I or T are not available CK-MB should be used again at 6 to 9 hours from onset of symptoms. Troponin I or T are the preferred biomarkers due to their near 100% sensitivity for diagnosing acute MI. The universal definition of MI also recognizes the importance of distinguishing a spontaneous acute MI related to ischaemia due to a primary coronary event such as plaque erosion and / or rupture, fissuring or dissection, a ‘Type 1 MI’, from a MI secondary to ischaemia due to either increased oxygen demand or decreased supply, such as coronary spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension, a ‘Type 2 MI’ (Thygesen, K., Alpert, J. S., and White, H. D., 2007).

4.4.2.4 Health economic evidence

Four papers have been included in the review of the health economics literature. The first study (Mant, J., McManus, R. J., Oakes, R.-A. L. et al, 2004) was an HTA that included a Monte Carlo decision analytic simulation model to evaluate the cost-effectiveness of four diagnostic strategies for suspected ACS. The model was used to assess the incremental cost-effectiveness of adding hospital point of care troponin T testing to determine whether to administer thrombolytic therapy to patients with negative A&E resting ECGs. The model structure facilitates two sub-analyses which consider the incremental benefit of troponin T testing for patients with and without pre-hospital telemetry ECG.

The model took a UK NHS costing perspective and included costs incurred during the 28-day time horizon. Effectiveness was measured as the proportion of patients who survived to 28 days after surviving the first 24 hours.

Base case results showed that the two diagnostic strategies which included point of care troponin T testing dominated the two strategies which did not. In other words, the results of the analysis showed that irrespective of whether the ECG and the administration of thrombolysis are in A&E or pre-hospital, the inclusion of troponin T testing improves effectiveness and reduces total costs within the 28-day time horizon. The least costly strategy based the decision to give thrombolytic therapy on the A&E ECG and a single troponin T measurement if the ECG was negative. The incremental cost per additional one percent surviving to 28-days was £65,825 for the second troponin T based testing strategy, (pre-hospital thrombolysis given, based on positive telemetry ECG and in hospital based on A&E ECG and troponin T measurement, if telemetry ECG is negative) compared with the first and least cost strategy. These results were robust to first and second order probabilistic sensitivity analyses, which varied the pain to needle time and cost of telemetry ECG.

The authors concluded that the use of A&E point of care testing for troponin T in patients presenting with acute chest pain in primary care and with negative ECG changes is likely to be cost-effective compared with equivalent strategies excluding such testing.

A second economic evaluation (Goodacre, S. and Calvert, N., 2003) was undertaken to estimate the relative cost-effectiveness of different diagnostic strategies for a hypothetical group of patients presenting with acute, undifferentiated chest pain. The 3 strategies compared included one of cardiac enzyme testing at presentation, one of testing at presentation and again 6 hours after the onset of pain and one of admitting patients for 24 hours and then testing. The authors did not state the specific cardiac enzymes used in the analysis, but the modelled test sensitivities and specificities are included in Table 19.

Table 19

Sensitivities and specificities of testing strategies (range used for sensitivity analysis)

Strategy	Sensitivity for AMI	Sensitivity for UA	Specificity
No cardiac enzyme testing	0	0	100
Cardiac enzyme testing at presentation	0.45 (0.3-0.6)	0.10 (0.05-0.15)	0.95 (0.85-0.98)
Cardiac enzyme testing at presentation and again at 6 hours after onset of pain	0.85 (0.6-0.95)	0.20 (0.1-0.4)	0.95 (0.85-0.98)
Cardiac enzyme testing after 24 hour admission to hospital	0.98 (0.9-1.0)	0.50 (0.3-0.7)	0.95 (0.85-0.98)

Cost-effectiveness was measured as the incremental cost per QALY gained by the different strategies compared with the next most effective strategy, including the baseline strategy of discharging all patients home with no further testing. Their decision analytic model took an NHS costing perspective and used 2000/01 prices in sterling. A lifetime time horizon was used, and both costs and effects were discounted at a rate of 6% per annum.

Results of the base case incremental analysis indicated that a strategy of cardiac enzyme testing upon presentation, yielded a cost per QALY of £17,400 compared to a strategy of sending all patients home with no testing. A strategy of serial testing at presentation, and again 6 hours after the onset of pain, was more effective and more costly, with an ICER of £18,500 per QALY. A strategy of admitting patients for a 24-hour period of observation followed by enzyme testing generated an incremental cost of £36,000 per QALY gained.

Base case results were insensitive to variation of prevalence of acute myocardial infarction or unstable angina; acute MI or unstable angina health utility values; mortality estimates; treatment effect estimates; costs of treating acute MI and unstable angina; cost of terminal care; and cost of long term treatment of survivors. Results were sensitive to variation in the cost of each strategy, the cost of ruling out false positives, and the effect of false positive diagnosis on quality of life.

The authors conclude that strategies based on short periods of observation are likely to represent a more efficient use of resources than those requiring overnight admission. Although costs of biomarkers have reduced since the time of the original study, costs of overnight admissions have risen, thereby giving further weight to the conclusions of the original analysis.

The third study was a randomised controlled trial (Zarich, S., Bradley, K., Seymour, J. et al, 2001) that included an analysis of the resource impact of using troponin T as an additional test compared with a control group in 891 patients presenting to an American emergency department. Patients presented with chest pain or symptoms suspicious for myocardial ischaemia of more than 30 minutes duration that warranted an evaluation for myocardial infarction. Although 23% of the cohort did not present with chest pain, a sub-group analysis of those that did is presented.

Patients randomised to the intervention group (n = 447) received a standard clinical evaluation of serial ECG and CK-MB determinations with the addition of serial troponin T determinations measured at presentation and 3 and 12 hours post presentation. The control group (n = 409) received standard clinical evaluation without serial troponin T measurements. Primary study endpoints were emergency department and hospital length of stay and total charges. Secondary endpoints included death and nonfatal MI at 30 days post-discharge.

Within the group of patients presenting with chest pain, the authors reported a stronger trend toward a reduced length of stay and significant reduction in total charges in the intervention group compared with the control group. In patients with ACS, both length of stay and total charges were significantly lower in the intervention group. Amongst patients without ACS, fewer intervention group patients were admitted to hospital compared with the controls and there was a significant reduction in length of stay. The authors indicate that troponin T determinations appear to be particularly useful in patients who have a falsely elevated CKMB values. Cardiac events at 30 days

occurred in 3.1% of patients and did not differ between intervention and control groups for the whole cohort and subgroups.

The authors conclude by saying that the utilisation of troponin T led to a 20-25% reduction in length of stay and total charges in high and low risk patients with and without ACS and a 7% to 11% reduction in unnecessary admissions. On average, total charges for patients in the intervention group were $1,540 less than for those in the control group. This represents a potential cost savings of $920 per patient. The authors assert that the annual savings to the hospital based on this analysis were estimated at $4 million in total charges ($2.4 million in costs). Savings are predominantly due to reduced length of stay in patients with and without ACS and to reduced admissions for patients without ACS in the troponin T group.

Finally, a prospective study (Choi, Y. F., Wong, T. W., and Lau, C. C., 2004) was undertaken to assess the value and cost saving potential of serial measurements, at presentation and again at 6 to 8 hours after admission if the initial blood results were normal, of three cardiac biomarkers namely, CKMB, myoglobin and troponin T, in the diagnosis of patients with chest pain presenting to a Hong Kong emergency department. The final diagnosis was defined as either acute MI, ischaemic heart disease with no proven infarction or atypical chest pain without ischaemic heart disease. The study presents a simple cost-benefit analysis, with effectiveness measured as the cost of resources not used when unnecessary admission was avoided and when future acute MIs were prevented through diagnosis with cardiac biomarkers. The perspective was unclear, but only direct medical costs measured in current (assumed 2003/04) Hong Kong dollars were included.

In terms of diagnostic value, the performance of troponin T was superior to CK-MB and myoglobin. The sensitivity and specificity of troponin T was 100% and 99% respectively. For CK-MB, sensitivity was 57% and specificity was 94%. Myoglobin had a very low sensitivity of 29% and specificity of 89%.

Results of the economic analysis showed that testing for troponin T would yield a cost savings of an estimated of HK$171,000 compared with testing for

CK-MB. This was attributed to the superior sensitivity and specificity of troponin T over CK-MB. Although the troponin T test was about HK$20 more expensive per unit, the savings generated by avoiding unnecessary hospital admissions (HK$142,000) and from correctly diagnosing significant CAD and thus avoiding future AMI (HK$53,200) made it a cost saving option. The study deemed myoglobin to be of no value due to its lack of specificity. No sensitivity analysis was undertaken.

The authors admit that theirs was an over-simplified analysis for the reason that many costs and/or savings were not included. They suspect their estimation of savings to be conservative given their crude approximation of the cost of a future acute MI. During interpretation of this study, the high sensitivity and specificity of troponin T testing is this study was noted by the GDG.

Although the cost-benefit studies are non-UK NHS based studies, the net saving results demonstrated by Choi et al (2001) and by Zarich et al (2003) would very likely be repeated if replicated using NHS costings.

4.4.2.5 Evidence to recommendations

The evidence for the use of biochemical markers of myocardial necrosis such as troponins and CK-MB to aid diagnosis in patients with acute chest pain is well established. This is not so for markers of ischaemia and for other markers such as BNP.

The majority of patients presenting to the emergency department with acute chest pain do not have MI or ACS and expert opinion in GDG was that about 5% of unselected patients would do so. Patients with an MI or ACS must be identified effectively and in a timely manner to ensure they receive appropriate treatment as early as possible. Others, who do not have MI or ACS, may be discharged, providing other conditions do not require admission.

Troponin is a more sensitive and specific marker for myocardial necrosis than other biochemical markers, including CK-MB and myoglobin, although the

GDG acknowledged that the biomarkers being evaluated in the studies were often part of the definition to make a diagnosis of acute MI. In addition to being clinically effective troponin was also found to be to be cost-effective. During the appraisal of the evidence the GDG noted that one study examining the cost-effectiveness of troponin testing was linked to the decision to administer thrombolytic therapy, and queried the authors assumption that the decision to administer thrombolytic therapy could be based on a positive troponin T test when the resting ECG was negative, given that it does not reflect current clinical practice. However, the conclusion of the GDG was that whilst this is not current practice, the overall conclusions from the study that troponin testing is cost effective were still likely to be valid, and had been confirmed by other studies. It was further noted that troponin was the preferred marker recommended in the 'Universal Definition of MI', and that troponin levels also provide prognostic information, although many studies analysing their prognostic value were studies evaluating a particular therapeutic intervention in patients with ACS and unstable angina, rather than in unselected patients with acute chest pain.

Myocardial necrosis and troponin release may occur due to reasons other than ACS and the GDG emphasised the importance of interpreting the results in an individual patient, taking into consideration the overall clinical and ECG findings, to identify those with non-ACS causes for myocardial necrosis. However, this distinction is not always straightforward as some conditions other than ACS, which result in troponin release, may also present with chest pain. In some patients further specialist assessment and diagnostic testing will be required, before a conclusion can be reached.

The GDG discussed the timing of troponin testing. The diagnostic criteria for an acute MI, includes "detection of rise and /or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit" and thus a baseline troponin measurement is recommended. The timing of the second sample was discussed as earlier testing could potentially lead to the earlier discharge of many patients. However, having appraised the evidence the GDG agreed that the second

sample be taken 10 to 12 hours after the onset of symptoms, for optimal sensitivity. The GDG noted that earlier rule out protocols, including one with testing 6 hours after admission, had been evaluated, but felt that the adverse consequences of a false negative test were substantial, and recommended a more cautious approach routinely. However, the GDG recognized that troponin assays were evolving and the highly sensitive assays currently being developed and evaluated, are likely to lead to opportunities for earlier testing.

4.4.3 Multislice CT coronary angiography for emergency department triage of patients with acute chest pain

In the past few years a number of pilot studies have examined the utility of multislice CT in the emergency department in the differential diagnosis of acute chest pain. To date these studies consist of small numbers of patients (around 100 patients), they have been conducted primarily in the USA, and they are limited in scope because each represents the experience of one centre. There are differences in study protocols, patient recruitment, scanners used, angiography protocols and angiographic analyses. This makes direct comparison of these studies difficult with respect to reviewing and interpretation. The authors of these studies while stating the potential promise of multislice CT, do emphasise that further evaluation needs to be done. There are other considerations as given below.

- Currently the use of multislice CT coronary angiography in the emergency department would reduce diagnostic time, however this becomes less important with the evolving technology of reduce waiting time for biomarker assay results.

- Multislice CT coronary angiography will identify a group of patients with sub clinical CAD i.e. disease that is not the cause of the current chest pain episode. The significance of this will need to be evaluated in large studies in the recruitment of unselected consecutive chest pain patients.

- It has not been established if the patient in the emergency department should receive a dedicated CT coronary angiogram, or have an entire thoracic scan. A dedicated coronary CT coronary angiogram would give the best possible images of the coronary arteries, but allows limited visualisations of other structures that may be responsible for chest pain. The benefit of an entire scan is that it would rule out pulmonary embolism and aortic dissection, however, this would involve increased radiation dose, increased scanning time, and possible less than optimal visualisation of coronary arteries.

- The best use of the multislice CT scanner in the emergency department has not been established. Images could be obtained as soon as possible after initial assessment (history, risk factors, examination) and the first set of cardiac enzymes. In which case the multislice CT coronary angiography results would be used as a component of the decision to discharge or admit the patient. Alternatively multislice CT coronary angiography could be used to aid in determining what further monitoring and treatment is indicated after a decision has been made to admit the patient. Hence it is unclear at which point multislice CT coronary angiography would fit into an algorithm used in the emergency department, and what would be the most cost-effective use of multislice CT coronary angiography in the emergency department. This may have implications on cost-effectiveness.

- Current preliminary findings indicate that multislice CT coronary angiography in the emergency department has potential for the ruling out of CAD. When stenosis of > 50% is detected the patient would undergo further non invasive or invasive testing, but the precise course of further evaluation is uncertain at this stage due to the limited literature. Resolving this could potentially be a large piece of work, and would impact on the current care pathway.

- Owing to the limited number of studies, health economic evaluation of multislice CT coronary angiography in the emergency department may be difficult, particularly as there is no information regarding the subsequent testing of patients when stenosis is > 50%.

To illustrate the current literature four studies were reviewed (Hoffmann, U., Nagurney, J. T., Moselewski, F. et al, 2006). (Coles, D. R., Wilde, P., Oberhoff, M. et al, 2007), (Johnson, T. R., Nikolaou, K., Wintersperger, B. J. et al, 2007) (Rubinshtein, R., Halon, D. A., Gaspar, T. et al, 2007).

The first study recruited consecutive patients presenting to the emergency department with acute chest pain that had an inconclusive clinical evaluation (Hoffmann, U., Nagurney, J. T., Moselewski, F. et al, 2006). Patients were included if they had no or non-diagnostic ECG changes, normal initial cardiac biomarkers, sinus rhythm, the ability to perform a breath hold of 10 to15 seconds and were > 18 years. Patients were excluded if they had elevated troponin-I or creatine kinase-MB levels, new diagnostic ECG changes (ST-segment elevation or depression > 1 mm or T-wave inversion > 4 mm in > 2 anatomically contiguous leads), a serum creatinine > 1.3 mg/dl, haemodynamic or clinical instability (systolic blood pressure < 80 mm Hg, clinically significant atrial or ventricular arrhythmias, persistent chest pain despite therapy). The study recruited 103 patients who underwent 64-slice CT coronary angiography; 83 Caucasians, 20 African American, 66% were men and the mean age was 53.8(SD 12.2) years. A panel of experts blinded to the results of the 64-slice CT coronary angiogram determined the absence or presence of ACS based upon the evidence accumulated during the index hospitalization and at 5 month follow up. Diagnosis was according to the American College of Cardiology / American Heart Association guidelines) (Hoffmann, U., Nagurney, J. T., Moselewski, F. et al, 2006).

A final diagnosis of ACS was made in 14 patients (14%), 5 had an acute MI and 9 had unstable angina pectoris. ACS was ruled out in the remaining 89 patients (86%). Telephone follow-up was completed in 81 of the 89 patients (91%) who did not have an ACS during the index hospitalization. None of

these patients reported suffering a major cardiovascular adverse event. For the detection of significant stenosis of > 50, 64-slice CT coronary angiography was found to have a sensitivity of 100% and a specificity of 46% (Hoffmann, U., Nagurney, J. T., Moselewski, F. et al, 2006).

The second study included patients with acute chest pain within 24 hours of admission, in sinus rhythm and with symptoms suggestive of ACS but with a clinical evaluation (Coles, D. R., Wilde, P., Oberhoff, M. et al, 2007). Patients were excluded if they had ST-segment elevation, were haemodynamically unstable or needed immediate coronary angiography. One hundred and twenty patients were included in the study with a mean age of 61.9(SD 10.7) years and 65% were men. One hundred and three patients underwent 16-slice CT coronary angiography. Invasive coronary angiography was the reference standard (Coles, D. R., Wilde, P., Oberhoff, M. et al, 2007).

In the patient based analysis of all native vessels, 16-slice CT coronary angiography correctly identified 77 out of 84 patients with at least ≥ 50% stenosis. 16-slice CT coronary angiography correctly excluded CAD in 16 patients. The sensitivity was 92% (95%CI 83% to 87%), specificity 55% (95%CI 35% to 74%), PPV of 86% (95%CI 76% to 93%), and NPV of 70% (95%CI 47% to 87%). The accuracy of 16-slice CT coronary angiography to diagnose significant disease depending on calcium score is given in the paper (Coles, D. R., Wilde, P., Oberhoff, M. et al, 2007).

The third study recruited 55 consecutively patients with acute chest pain (35 men, aged 67(SD 10) years) that were referred from the emergency department by cardiologists or emergency physicians (Johnson, T. R., Nikolaou, K., Wintersperger, B. J. et al, 2007). Patients were referred if ECG findings were absent or inconclusive and cause of their chest pain was unclear. Twenty four patients had signs of atherosclerosis of the coronary arteries. The diagnostic accuracy of 16-slice CT coronary angiography was compared with coronary angiography as the reference standard for the detection of significant (> 50%) stenosis in 20 patients. There were 16 true-positive results, including eight cases of occlusion, three false-positive results,

and one false-negative. Thus sensitivity and specificity were 94% and 77%, respectively. The PPV was 84%, and the NPV was 91% (Johnson, T. R., Nikolaou, K., Wintersperger, B. J. et al, 2007).

The fourth study included 58 patients with a mean age 56(SD 10) years, and 64% were men) (Rubinshtein, R., Halon, D. A., Gaspar, T. et al, 2007). One third of the group (22 patients, 38%) had previously diagnosed CAD. Patients were included if they were considered to be at intermediate-risk; normal baseline ECG, normal initial biomarkers, no exclusion criteria such as clinical suspicion of pulmonary embolism, aortic dissection, or pericarditis), clinical symptoms of definite ischemic origin but without high-risk features (not included in the study because of clear diagnosis) or symptoms of uncertain origin but compatible with possible ACS (Rubinshtein, R., Halon, D. A., Gaspar, T. et al, 2007).

64-slice CT coronary angiography findings were positive in 23 of the 58 patients (40%) (≥ 50% stenosis), 11 of whom (48%) had a prior history of myocardial revascularisation (7 PCI, 4 CABG). In the 35 64-slice CT coronary angiography-negative patients, 2 patients had a non coronary cause of chest pain (1 chronic aortic dissection, 1 pancreatic tumor). One other patient had subclavian artery stenosis proximal to a functional left internal mammary artery bypass graft (Rubinshtein, R., Halon, D. A., Gaspar, T. et al, 2007).

ACS was diagnosed in 20 out 23 of the multislice CT coronary angiography positive patients. Coronary angiography was performed in 17 patients (74%) and confirmed obstructive CAD in 16, with 1 false-positive with multislice CT coronary angiography. The 64-slice CT coronary angiography sensitivity for diagnosis of ACS was 100% (20/20 patients) (95% confidence interval 100 to 100%), specificity 92% (35/38 patients) (95%CI, 83 to 100%), PPV 87% (20/23 patients) (95%CI, 72 to 100%), and NPV 100% (35/35 patients) (95%CI, 100% to 100%). There were no deaths or MIs in the follow-up period in the 35 patients who were discharged from the emergency department (Rubinshtein, R., Halon, D. A., Gaspar, T. et al, 2007).

4.4.3.1 Cost-effectiveness of multi sliced CT for acute chest pain in the emergency department

The health economics update search identified two decision analytic model cost-effectiveness analyses from the United States (Ladapo, J. A., Hoffmann, U., Bamberg, F. et al, 2009) (Khare, R. K., Courtney, D. M., Powell, E. S. et al, 2008). Both assess the cost-effectiveness of 64-slice CT coronary angiography in low risk patients presenting with chest pain in the emergency department. Ladapo and colleagues (Ladapo, J. A., Hoffmann, U., Bamberg, F. et al, 2009) define their low risk acute chest pain patients as having presented to an emergency department and having no history of heart disease, negative initial troponins, and normal or non-diagnostic ECGs. Ladapo models a hypothetical cohort of 55 year old men and women separately, whilst Khare (Khare, R. K., Courtney, D. M., Powell, E. S. et al, 2008) models a hypothetical cohort of 55 year old men and an assumed CAD prevalence of 2%, 6%, and 10%.

In Ladapo et al (Ladapo, J. A., Hoffmann, U., Bamberg, F. et al, 2009) the comparator is a Standard of Care (SoC) option involving biomarkers and stress testing (either MPS with SPECT, stress echocardiography or exercise ECG). In Khare et al (Khare, R. K., Courtney, D. M., Powell, E. S. et al, 2008) the comparators are stress echocardiography or stress ECG. The models are similar in structure, and they both appear to take a US healthcare payer perspective, despite Ladapo's indication of having taken a societal perspective. Both models assess QALY outcomes using published estimates of quality adjusted survival. Both studies based their estimates of test characteristic on the outcomes of a clinical trial by Goldstein et al(Goldstein, J. A., Gallagher, M. J., O'Neill, W. W. et al, 2007).

Both models produce favourable results for 64-slice CT coronary angiography, with base case and sensitivity analyses results which are either cost-effective or more often cost-saving. 64-slice CT coronary angiography was cost-saving in women and cost-effective in men in Ladapo's model, whilst it was cost saving for a wide range of modelled scenarios in the Khare model.

4.4.3.2 Evidence to recommendations

The GDG appraised the evidence for the use of multislice CT coronary angiography in unselected patients with chest pain of suspected cardiac origin and was of the opinion that there was insufficient evidence currently on which make a recommendation for its use in the emergency department in such patients. They acknowledged that this was an evolving area, which was the subject of on-going research, but the published evidence found to date was in small cohorts of patients and further research is required.

The GDG noted the results of two recently published decision analytic model analyses from the United States examining the cost-effectiveness of 64-slice CT coronary angiography in low risk patients with acute chest pain (Ladapo, J. A., Hoffmann, U., Bamberg, F. et al, 2009) (Khare, R. K., Courtney, D. M., Powell, E. S. et al, 2008). However, before CT coronary angiography can be incorporated into an acute chest pain pathway, the GDG considered that de novo, NHS based, economic evaluation should be undertaken, in unselected acute chest pain patients, when better evidence from comparative clinical trials becomes available. In particular, this should be when there is greater clarity on the relative costs, and test accuracies, of the emerging highly sensitive biomarkers. The cost-effectiveness of multislice CT angiography for rule out of obstructive CAD in patients with troponin negative ACS has been included as a recommendation for future research. The GDG recognised that CT imaging has an established role in current clinical practice to investigate selected patients with chest pain, for example those with suspected pulmonary embolism or aortic dissection, but it was beyond the scope of this guideline to appraise the evidence or make recommendations for this group of patients.

Return to Recommendations

5 People presenting with Stable Chest Pain

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 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 who 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 who 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.

Return 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 likelihood ratio (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 20. 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; nitroglycerin 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%, 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 20). 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 20) (Chun, Andrea Akita and McGee, Steven R., 2004).

Table 20

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 30-49 † 50-70 >70	 14,569 15,681 15,481 15,266	 0-1 16-38 62-73 2-52	 97-98 47-57 44-56 67-99	 0.1 (0-1.1) 0.6 (0.5-0.7) 1.3 (1.3-1.4) 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) <200 201-250 251-300 >300	 1585 1585 1585 1585	 10-11 27-31 34-35 24-29	 58-71 60-65 76-83 93-94	 0.3 (0.2-0.4) 0.8 (0.7-0.9) 1.7 (1.2-2.3) 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 Any 1 Any 2 3 or more	 6434 6434 6434 6434	 7 35 39 18	 78 57 73 92	 0.3 (0.3-0.4) 0.8 (0.8-0.9) 1.4 (1.3-1.6) 2.2 (1.9-2.6)	 - - - -

Table 20					
Diagnosing CAD in patients with stable, intermittent chest pain					
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 granted 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 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 21 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 21

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

Table 22 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 22

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 granted 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 22, and a second estimate of disease likelihood was determined using data on the presence or absence of symptoms detailed in Table 23. 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 23. 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 23

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 granted 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(SD 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 who 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 24 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 24

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 granted 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 25 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 907 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 25

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 granted 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 who 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. Pre-infarction 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 who 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 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).

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 3 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 the 168 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 revascularisation), 30 had died of cardiovascular causes, 19 had died of non cardiac causes, 18 had undergone angioplasty, and 62 had had CABG (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 (109 patients); age, gender, chest pain (type), diabetes, smoking, hyperlipidaemia, prior MI, and significant Q waves and ST-T wave changes. For severe disease (45 patients) 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 (12 patients), 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. While the model had previously been validated in another stable chest pain population (Pryor, D. B., Harrell, F. E., Jr., Lee, K. L. et al, 1983), it should be noted that the additional identification of predictors of CAD in this study was based on very small patient numbers, and as such the results should be interpreted with caution (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 greater 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 0.72 (95%CI 0.59 to 0.87). 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, PCI, or CABG. 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(SD 9.5) years and 66% were male. Sixty percent of patients had significant CAD and 40% had normal coronary anatomy. As detailed in Table 26 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 26

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

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. 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).

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

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

Return to Recommendations

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 from 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)

5.1.2.2 Introduction

Historically, the descriptions of chest pain symptoms associated with ACS have been based on the presentation characteristics of men.

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 ECG, cardiologist and typical symptom scores both remained independently 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 than among men (*P* < 0.001 for the difference between the hazard ratio for women versus men). This finding was also true for symptom scores (*P* < 0.001 for the difference between the hazard ratio for women versus men). Analyses conducted in the study that appeared to have examined the statistical interaction between the subgroups of cardiologist summaries versus symptom scores (although alternatively, this may have been a series of interaction tests), found that for both the cardiologist summaries and the 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, revascularisation 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). It should be noted that *P* values for the hazard ratios were not reported. 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(SD 11.7) years and 64.1(SD 11.8) years, respectively. Men had been diagnosed with CAD for longer than women with a mean of 12.9(SD 9.6) years versus 8.8(SD 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 = 0.001), 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 CABG 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(SD 7.95) for men and 4.23(SD 3.34) for women). Men reported a mean of 1.7(SD1.8) days since their last pain episode and women reported a mean of 1.9(SD 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(SD 2.7) versus men 5.03(SD 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 21, 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 22. 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 from 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 from 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 from 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)

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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 ECG, cardiologist and typical symptom scores both remained predictive of a diagnosis of angina. Analyses conducted in the study that appeared to have examined the statistical interaction between the subgroups of cardiologist summaries versus symptom scores (although alternatively, this may have been a series of interaction tests), found that for the cardiologist summaries subgroup, South Asians with typical symptoms were as likely as Caucasians with typical symptoms to have a coronary outcome (South Asians versus Caucasians hazard ratio; 1.27, 95%CI 0.89 to 1.81) (adjusted for age, sex, ethnic background, diabetes, hypertension, smoking, secondary prevention treatment, revascularisation and exercise ECG result)). For the symptom score subgroup South Asians with typical symptoms were more likely than Caucasians with typical symptoms to have a coronary outcome (South Asians versus Caucasians adjusted hazard ratio 1.41, 95%CI 1.04 to 1.91). *P* values for the interactions between hazard ratios were not reported. 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. Had there been clinically significant differences based on ethnicity, these would have been incorporated into the economic models developed for this guideline. Diagnostic treatment pathway for all patients should be a function of pre-test likelihood of disease, based on symptoms, history, and clinical examination.

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

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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.

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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?

Two systematic reviews (Chun, Andrea Akita and McGee, Steven R., 2004) (Mant, J., McManus, R. J., Oakes, R.-A. L. et al, 2004), and two studies utilizing logistic regression modeling 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 two systematic reviews (Chun, Andrea Akita and McGee, Steven R., 2004) (Mant, J., McManus, R. J., Oakes, R.-A. L. et al, 2004) also examined the used of ECG in patients presenting with acute chest pain and they have been discussed in section 4.2.5 of the guideline.

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 27 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 27			
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 granted 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 (Chun, Andrea Akita and McGee, Steven R., 2004). 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. 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.

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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). 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(SD 16) %, range 23% to 100%) and specificities (weighted mean 77(SD 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). Studies that had > 20% of patients with prior CAD were excluded from the analyses. The majority of studies selected in the systematic review had excluded patients with significant resting ECG abnormalities. (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 from 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 (Tl201 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 who 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 multislice 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 three Agatston calcium score groups (0 to 100, 101 to 400, > 400). (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)

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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 from a single 64-slice CT coronary angiography scan compared with an 80 year old man. A 20 year old woman had a 23 fold relative risk of cancer single 64-slice CT coronary angiography scan 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 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)

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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 results of the diagnostic test in a given population can be summarised in a contingency table, which allows the evaluation of test.

Contingency table for the evaluation of a diagnostic test in a population (N)				
		Disease	No disease	Total
Result of test	Positive	a	b	a+b
	Negative	c	d	c+d
		a+c	b+d	N

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 by the total number of subjects without the disease. In the contingency table the value of sensitivity is; a / (a + c) and the value of specificity is; d / (b + d).

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 less likely is a negative (normal) test to be found in a subject with the disease than in a subject without the condition. In the contingency table PLR is the division between sensitivity and proportion of false positives; [a/(a+c)]/[b/(b+d)]. As the proportion of false positives or [b/(b+d)] is equal to 1-[d/(b+d)] or alternatively 1 - specificity, subsequently the PLR = sensitivity/1 – specificity. In the contingency table NLR is the division between the proportion of false negatives and specificity; [c/(a+c)]/[d/(b+d)]. As the proportion of false negatives or [c/(a+c)] is equal to 1-[a/(a+c)] or alternatively 1 - sensitivity, subsequently the NLR = 1 - sensitivity/specificity.

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.

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 for example a PPV of 80% means that 80% of subjects with a positive test result have the disease). 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). In the contingency table the value of the PPV is; a / (a + b) and the NPV is; d / (c + d). However, predictive values change with prevalence and as such are not stable parameters. Prevalence is defined as existing cases / population at risk. In the contingency table its value is; (a + c) / N.

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 pooled 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 who 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 measured relative to the isoelectric line 60 to 80 ms after the J point (the point of inflection at the junction of the S wave and the ST segment) 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 140 kg deteriorates with increasing body weight, although this is less of a problem with more recent advances in technology. The disadvantages of nuclear perfusion imaging compared with the other functional imaging techniques are that it involves a significant radiation dose (6 to 8mSv although this can potentially be reduced with newer technologies) and although one day protocols are possible may require 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 ischaemia 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(SD 16) % (range 23% to 100%) and for specificity was 77(SD 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. Bi-variate 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 bi-variate 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 bi-variate 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 bi-variate 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. It should be noted that the regression analysis did not take account of differing sample sizes of the studies included in the analysis. 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 (regression coefficient; -0.077, *P* = 0.0001), comparison with a 'better' test such as thallium scintigraphy (regression coefficient; -0.047, *P* = 0.0003), exclusion of patients on digitalis (regression coefficient; 0.033, *P* = 0.008), and publication year (regression coefficient; 0.0061, *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 (regression coefficient; -0.044, *P* = 0.05), exclusion of patients with prior MI (regression coefficient; -0.037, *P* = 0.005), exclusion of patients with LBBB (regression coefficient; 0.032, *P* = 0.002), and use of hyperventilation before exercise (regression coefficient; -0.064, *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 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 28, 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 28

Exercise ECG for chronic chest pain

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

Table 29 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%CIs for the 9 studies where patients were not taking drugs quoted in the systematic review appear to be incorrect as they do not tally with the meta-analysis estimate. The values have been calculated and the NLR is 0.38 (95%CI 0.09 to 1.56) (Mant, J., McManus, R. J., Oakes, R.-A. L. et al, 2004).

Table 29

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 granted 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 of 2.25 (95%CI 1.84 to 2.66), and negative likelihood ratio 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 (SD or SE not reported) 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 from 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%) (Heijenbrok-Kal, M. H., Fleischmann, K. E., and Hunink, M. G., 2007).

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%) (Heijenbrok-Kal, M. H., Fleischmann, K. E., and Hunink, M. G., 2007).

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 (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. CABG 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. A difference in mean exercise time from coronary angiography of 1 minute was defined as the minimum clinically significant difference. Therefore if the confidence limits for the difference were both between -1 and +1, the difference was considered not clinically significant. 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 (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(SD 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 $\geq$ 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(SD 842) (range 0 to 7224, median 115) and 310(SD 714) (range 0 to 5490, median 114), respectively. 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(SD 1124) versus 76(SD 217) for Agatston score, respectively ($P < 0.01$), and 486(SD 940) versus 53(SD 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 were 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).

The details of age and gender-based calcium score percentiles for the Volume and Agatston scores in the entire study population are detailed in the paper (Knez, A., Becker, A., Leber, A. et al, 2004). 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).

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 detailed in the paper (Knez, A., Becker, A., Leber, A. et al, 2004), they, and indicated 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).

Overall the results of the study indicated 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(SD 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).

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, $P < 0.001$). The study demonstrated that calcium scoring considerably altered the post test probability across a wide range of patients. Those patients who exhibited the greatest change from pre- to post-test probability were those patients with pre-test probabilities ranging from 20% to 70% (see Table in paper for further detail) (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 $\geq$ 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%). Details of the mean calcium scores for men and women are detailed given in the paper (Haberl, R., Becker, A., Leber, A. et al, 2001). 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).

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%. Thus, exclusion of coronary calcification was associated with an extremely low probability of coronary stenoses ≥ 50% in men and women (Haberl, R., Becker, A., Leber, A. et al, 2001).

Details of the sensitivities and specificities of coronary calcium scores at various score ranges are given in the paper (Haberl, R., Becker, A., Leber, A. et al, 2001). 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).

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 30.

Table 30

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

	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)

PPV = positive predictive value. *NPV*= negative predictive value. Results are presentment as number of patients with diagnostic test statistic in parenthesis.

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

There was a highly significant correlation between calcium score and the degree of CAD by the Kruskal-Wallis test (see Table 31). 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 31) (Herzog, C., Britten, M., Balzer, J. O. et al, 2004).

Table 31

Correlation between degree of coronary heart disease (CHD) and calcium score

Kruskal-Wallis test results

	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

RCA = right coronary artery, LCA = left coronary artery, LCX = left circumflex branch.

Permissions granted 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 30). The PPV 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 PCI or CABG (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 PCI or,CABG as well as 55 vessels that were difficult to evaluate due to motion artifacts. 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 ≥ 50% and a severe stenosis was defined as a reduction of ≥ 70% (Kitamura, A., Kobayashi, T., Ueda, K. et al, 2005).

The sensitivities, specificities, positive and negative predictive values for coronary calcification (calcium score ≥ 1) in moderate stenosis were 84%, 47%, 37% and 89%, respectively. The sensitivities, specificities, positive and negative predictive values for coronary calcification (calcium score ≥ 1) in severe stenosis were 89%, 43%, 20% and 96%, respectively. Thus, the sensitivity and negative predictive value in patients with moderate stenosis were lower compared with patients with severe stenosis, while, specificity and PPV were higher in patients with moderate stenosis compared with severe stenosis patients. ROC curve analysis for the prediction of severe and moderate stenosis using calcium scoring were 0.80(SD 0.04) ($P < 0.001$) and 0.75(SD 0.04) ($P < 0.001$). Sensitivity, specificity, and predictive value for the detection of severe stenosis by calcium score level from 0.1 to 1000 is given in detail in the paper (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(SD 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 $\geq$ 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 $\geq$ 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 $\geq$ 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. At a calcium threshold of $\geq$ 1, the sensitivity and specificity at the segment level were 84% and 53%, respectively. At the vessel level the sensitivity and specificity were 97% and 25%, respectively (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(SD 139) versus 32(SD 63) for segments, 272(SD 254) versus 62(SD 107) for vessels and 700(SD 541) versus 99(SD 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 (not defined as either SD or SE)) 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. Thirty five patients 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 the paper (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 very small patient numbers made the result inconclusive (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 (not defined as either SD or SE)) years (range 34 to 81 years). The exclusion criteria were; previous percutaneous angioplasty or surgical

revascularisation, valve replacement, pacemaker implantation, cardiac arrhythmia. The 340 patients constituted 95% of all patients referred for testing. In 19 patients, artifacts 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(SD 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 32) (Knez, A., Becker, A., Leber, A. et al, 2004).

Table 32

Total calcium score value distribution depending on CAD severity in angiography*

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

*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)

Permissions granted 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 33 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 were 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 PPV, 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 33

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

Table 34 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 34

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 granted 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(SD 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(SD 382) (range 0 to 6941) and 348(SD 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(SD 987) versus 97(SD 112) (*P* = 0.01), respectively, Volume score 483(SD 527) versus 89(SD 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 predictive value 98%) (Becker, A., Leber, A., White, C. W. et al, 2007).

The diagnostic accuracy of both calcium scores are detailed in the paper (Becker, A., Leber, A., White, C. W. et al, 2007). 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).

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(SD 13) years) and 64-slice CT coronary angiography (60 patients, 47 men, mean age 60(SD 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(SD 530) (range 0 to 2546). In the 0 to 100 group, the mean score was 18(SD 21) (range 0 to 81), in the 101 to 400 group the mean score was 281(SD 100) (range 102 to 397), and in the > 400 group the mean was 1077(SD 731) (range 428 to 2546). The overall mean Agatston score in the 64-slice CT coronary angiography population was 446(SD 877) (range 0 to 6264). In the 0 to 100 group, the mean score was 14(SD 21) (range 0 to 70), in the 101 to 400 group the mean score was 213(SD 74) (range 111 to 336), and in the > 400 group the mean was 1088(SD 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 (SD 530) (range 0 to 2546) and 446 (SD 877) (range 0 to 6264), respectively (Pundziute, G., Schuijf, J. D., Jukema, J. W. et al, 2007).

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 that were given for non interpretation of segments included; small vessel size, motion artifacts, insufficient contrast enhancement and missing slice or trigger artifact. 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 (Pundziute, G., Schuijf, J. D., Jukema, J. W. et al, 2007)

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).

At the patient level, 16-slice CT coronary angiography detected obstructive coronary lesions in 18 (44%) patients, and the overall sensitivity and specificity were 89% and 87%, respectively. For 64-slice CT coronary angiography, obstructive coronary lesions were detected in 32 (53%) patients, and the overall sensitivity and specificity were 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, see paper for further details) (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 iodine-containing contrast and has been regarded as a moderate to high radiation diagnostic technique (12 to 15 mSv), although recent technical advances are improving radiation efficiency considerably.

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 was

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%) (Einstein, A. J., Henzlova, M. J., and Rajagopalan, S., 2007).

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 35 (Einstein, A. J., Henzlova, M. J., and Rajagopalan, S., 2007).

Table 35

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 granted 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), although as noted earlier recent technical advances are improving radiation efficiency

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 artifacts 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 too 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 who 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 re-stenosis 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 re-stenosis 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 re-stenosis. 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 re-stenosis 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 were 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 were 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 were 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. 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 decision tree model was used to display the proper temporal and logical sequence of the clinical decision problem of diagnosis. Although in reality, it may take a patient weeks or even months to move from the first decision node to a final diagnosis, the model assumes this period is fixed. 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 revascularisation). 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 in terms total cost, accurate diagnoses and QALYs 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 36 summarises these results as well as those from the other prevalence rates modelled.

Table 36

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.

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 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 prevalence's 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 stress echocardiography.

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 who had known or suspected CAD and who had been referred to receive non-urgent invasive coronary to one of four groups; 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-6D 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 versus 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 seen by interventionists had higher mean costs and all four groups seen by non-interventionsists had lower mean costs. There were no significant QALY differences between interventionist and non-interventionist patient sub-groups.

Discussion and 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.

When considering the results of this trial, it should be born in mind that the patients selected for the trial are representative of only a sub-group of stable chest pain patients being considered by this Guideline. That is, the CeCAT trial patients already had known or suspected CAD, and had had an exercise test which had resulted in a non-urgent referral for invasive angiography. Some 25-30% of patients had had a previous MI, and the majority of patients

were already on cardiovascular medication. This group of patients is therefore likely to have a relatively high pre-test likelihood of CAD compared to the more general non-differentiated group under consideration in the Guideline.

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 37.

Table 37

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. These costs were based on local non-Medicare fees. 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 38.

Table 38

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

Table 38

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
	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 (£69,149)[8] 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 (£14,869) per additional correct diagnosis. EBCT >0 is more expensive and more effective with an ICER of $89,350 (£64,494) compared with EBCT >37. The most expensive and effective strategy is direct to invasive coronary angiography with an ICER of $92,800 (£66,984) 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 (£4,331). EBCT >37 is slightly more effective than EBCT >80 with an ICER of $7,000 (£5,053) 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 (£14,508). The most expensive and effective strategy remains direct to invasive coronary angiography with an ICER of $25,100 (£18,711) 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 (£3,826). 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 (£5,269) 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.

[8] Converted to UK sterling based on 1999 GDP per capita purchasing power parities (US$1:£0.7218) source http://www.gapminder.org/gapminder-world/documentation/#gd001 accessed 22/08/09 21:07

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 39 for summary of incremental analysis of strategies excluding EBCT >37, >80 and >168.

Table 39

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 prevalence's. 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 (£40,205) 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 (£12,993). EBCT >0 is a more effective strategy than stress echocardiography with an ICER of $22,500 (£16,241) per additional correct diagnosis. Invasive coronary angiography is the most costly and most effective strategy, with an ICER of $92,800 (£66,984) 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 a calcium score threshold of >37, >80 or >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. EBCT using a threshold of >0 is cost saving compared with stress thallium testing at 20% CAD prevalence and above.

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.

The results of Rumberger et al's analysis should be interpreted and applied with caution for a number of reasons. First, EBCT, using any calcium score threshold, is not the exact technology under investigation in this guideline. While the results do demonstrate the potential impact of different calcium score thresholds, their applicability needs to be interpreted in light of even newer technologies like multislice CT coronary angiography. Second, the study took place in the United States and the authors state that costs were derived from local non-Medicare fees. Given the substantial differences between the US and the UK in terms of the health care reimbursement

system, total costs reported by Rumberger et al are unlikely to be directly translatable to a UK setting.

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 summarised in Table 40.

Table 40

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 41. 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 41

Total costs and consequences of different diagnostic strategies

	Strategy 1	Strategy 2	Strategy 3	Strategy 4	Strategy 5	Strategy 6	Strategy 7	Strategy 8
	ECG-SPECT-CA	ECG-CT-CA	ECG-CA	SPECT-CA	CT-CA	CA	ECG-CT	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)

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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 42 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 42

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

	Strategy 2	Strategy 3	Strategy 7
	ECG-CT-CA	ECG-CA	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 (Khare, R. K., Courtney, D. M., Powell, E. S. et al, 2008; Ladapo, J. A., Hoffmann, U., Bamberg, F. et al, 2009).

The authors stop short of presenting incremental cost-utility analysis. Doing so would indicate that for the CAD prevalence's 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 coronary angiography 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 43) 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 43

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 insensitive to the parameters varied (Tables 4 and 5 of Appendix F). 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 evaluation 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 be equivocal (indeterminate) in respect of evaluation of the functional significance of anginal chest pain. 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 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 disease in the range 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 (figure 2.2.1). There are two alternative treatment arms/pathways in the model: first line functional 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 (indeterminate) functional test result. Patients with an equivocal first line functional test result, are assumed to 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 2008 Mowatt model are appropriate (Mowatt, G., Cummins, E., Waugh, N. et al, 2008) . 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, are assumed to then have a second line functional test (MPS with SPECT). The base case assumes that no second line test results are equivocal. 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) (Sculpher, M., Smith, D., Clayton, T. et al, 2002; Sharples, L., Hughes, V., Crean, A. et al, 2007), (Department of Health, 2008)). All base case input parameter values are presented below Table 44.

Table 44

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 the patient population modelled 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 (WTP) 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 discussion section of Appendix F). 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 estimated by the model

(Pt), then the model indicates that first line functional testing is likely to be considered cost-effective compared to first line anatomical testing and vice versa using our WTP threshold assumption.

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 with no equivocal results, 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 is unlikely to be considered cost-effective compared to 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. Again, this analysis assumes that invasive coronary angiography is 100% accurate with no equivocal test results.

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 45).

Table 45

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 WTP threshold), the model estimates that more than 74% of the 64-slice CT coronary angiography results would have to give an equivocal/indeterminate 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 lends 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 relatively stable in 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 the conclusions regarding the relative cost-effectiveness of first line functional testing compared to first line invasive coronary angiography. We believe that we would have seen similar results had we used Stress Echocardiography or stress MR perfusion imaging in place of MPS with SPECT (see discussion section Appendix F).

Mainly 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 and a fuller discussion of the limitations of our analysis are presented 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. The GDG were of the opinion that this included patients with typical angina and a pretest likelihood of CAD of > 90%. Similarly those with non cardiac chest pain may be diagnosed following clinical assessment, and in these patients and those with a very low likelihood of CAD alternative explanations other than angina should generally be explored first. In those with typical angina and a very low likelihood of CAD, the GDG emphasized causes such as hypertrophic cardiomyopathy should be considered.

In some 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 it is these patients who 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-analysed, 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 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.

The Guideline Development Group also carefully considered the risk of radiation exposure from diagnostic tests. It discussed that the risk needs to be considered in the context of radiation exposure from everyday life, the substantial intrinsic risk that a person will develop cancer during their lifetime and the potential risk of failing to make an important diagnosis if a particular test is not performed. The commonly accepted estimate of the additional lifetime risk of dying from cancer with 10 millisieverts of radiation is 1 in 2000[9]. The Guideline Development Group emphasised that the recommendations in this guideline are to make a diagnosis of chest pain, not to screen for CAD. Most people diagnosed with non-anginal chest pain after clinical assessment need no further diagnostic testing. However in a very small number of people, there are remaining concerns that the pain could be ischaemic, in which case the risk of undiagnosed angina outweighs the risk of any potential radiation exposure.

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 (61% to 90%) 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

[9] Gerber TC et al.(2009) Ionizing radiation in cardiac imaging: a science advisory from the American Heart Association Committee on Cardiac Imaging of the Council on Clinical Cardiology and Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention. Circulation 19:1056–1065.

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 who the GDG were discussing are most likely to have CAD and high coronary calcium scores, and 64-slice CT coronary angiography will be less accurate in assessing the severity of any coronary stenosis, and thus the functional significance of disease may be uncertain. Therefore a functional imaging test was preferred.

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.

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 angiography was the preferred first line testing strategy was less than 30%. 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-slice 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.

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 help 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 or 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 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 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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