National Guideline Centre

Final version

Recent-onset chest pain of suspected cardiac origin: assessment and diagnosis

NICE guideline CG95

Methods, evidence and recommendations

November 2016

Final version

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Update information

Minor changes since publication

January 2020: the title of the guideline was updated to clarify that it covers chest pain of suspected cardiac origin. A footnote to recommendation 1.2.6.1 was changed to update a link to the universal definition of myocardial infarction, and a cross-reference to related NICE medical technologies guidance was added to section 1.3.

These changes can be seen in the short version of the guideline at:

http://www.nice.org.uk/guidance/CG95

Disclaimer

Funding

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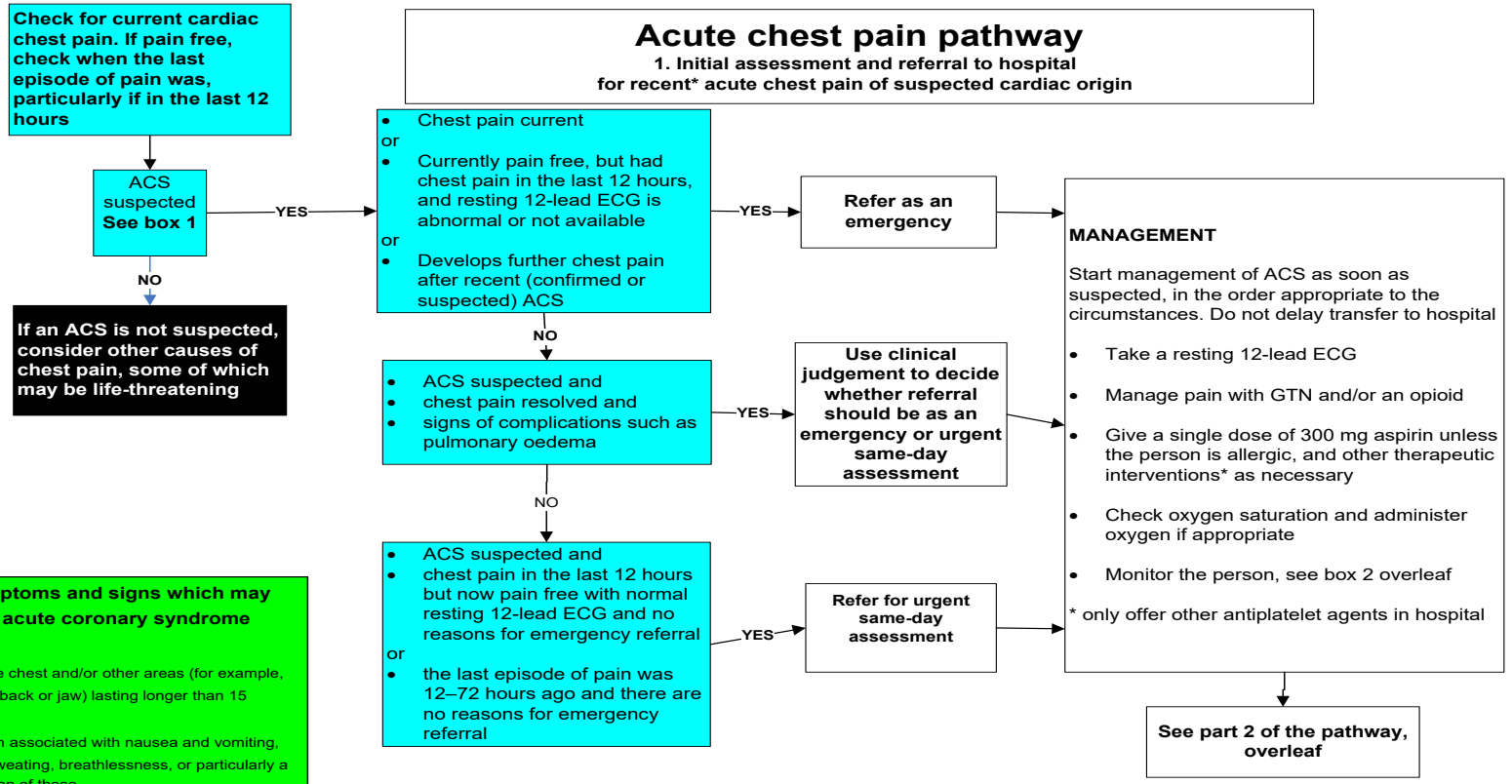
Contents

2 Guideline summary

2.1 Algorithms

2.1.1 Acute chest pain algorithm

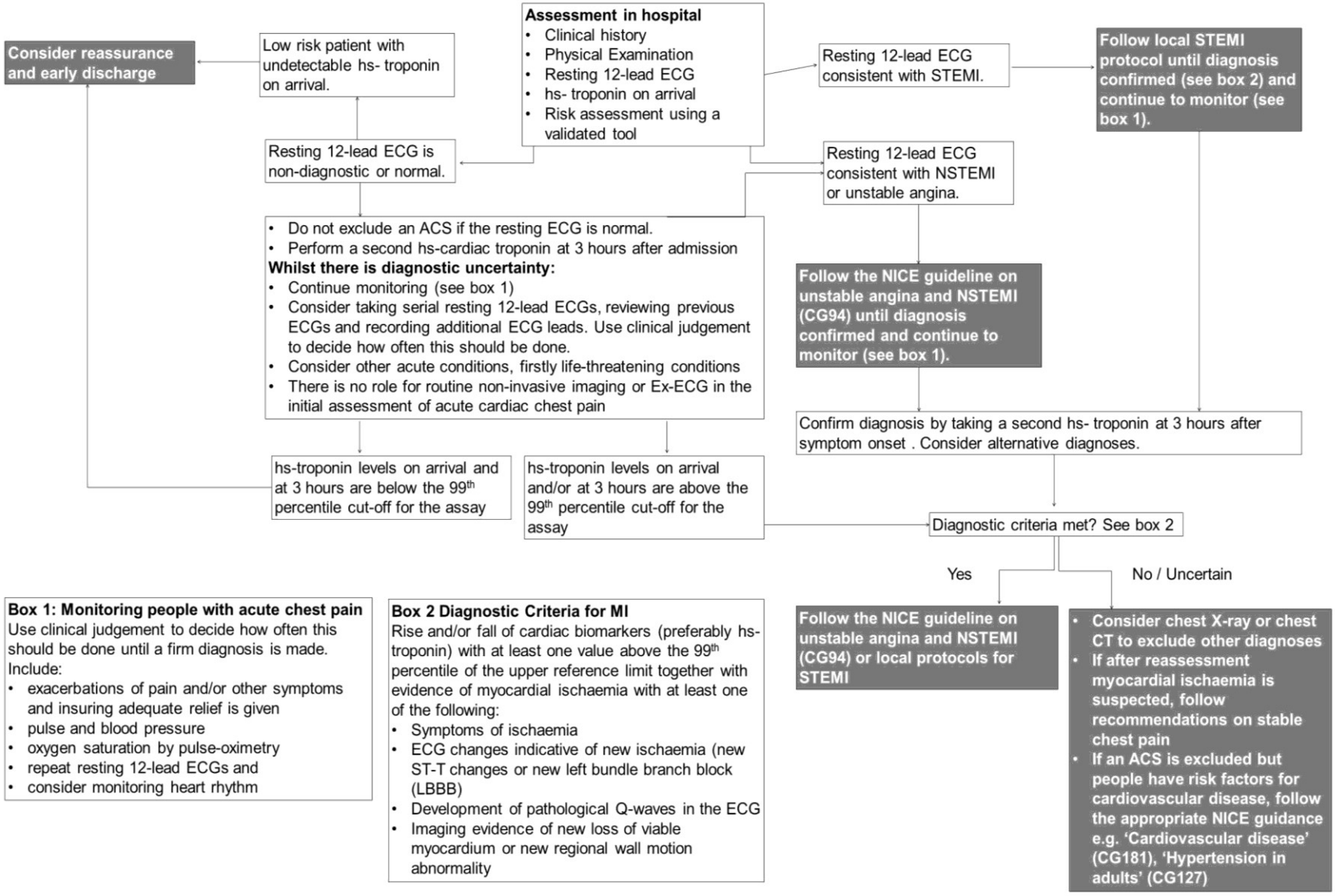
The algorithms should be read with the recommendations in this document. The updated algorithm includes the new 2016 recommendations.



* 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, 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

Acute Cardiac Chest Pain Pathway

2. Investigation and diagnosis in hospital

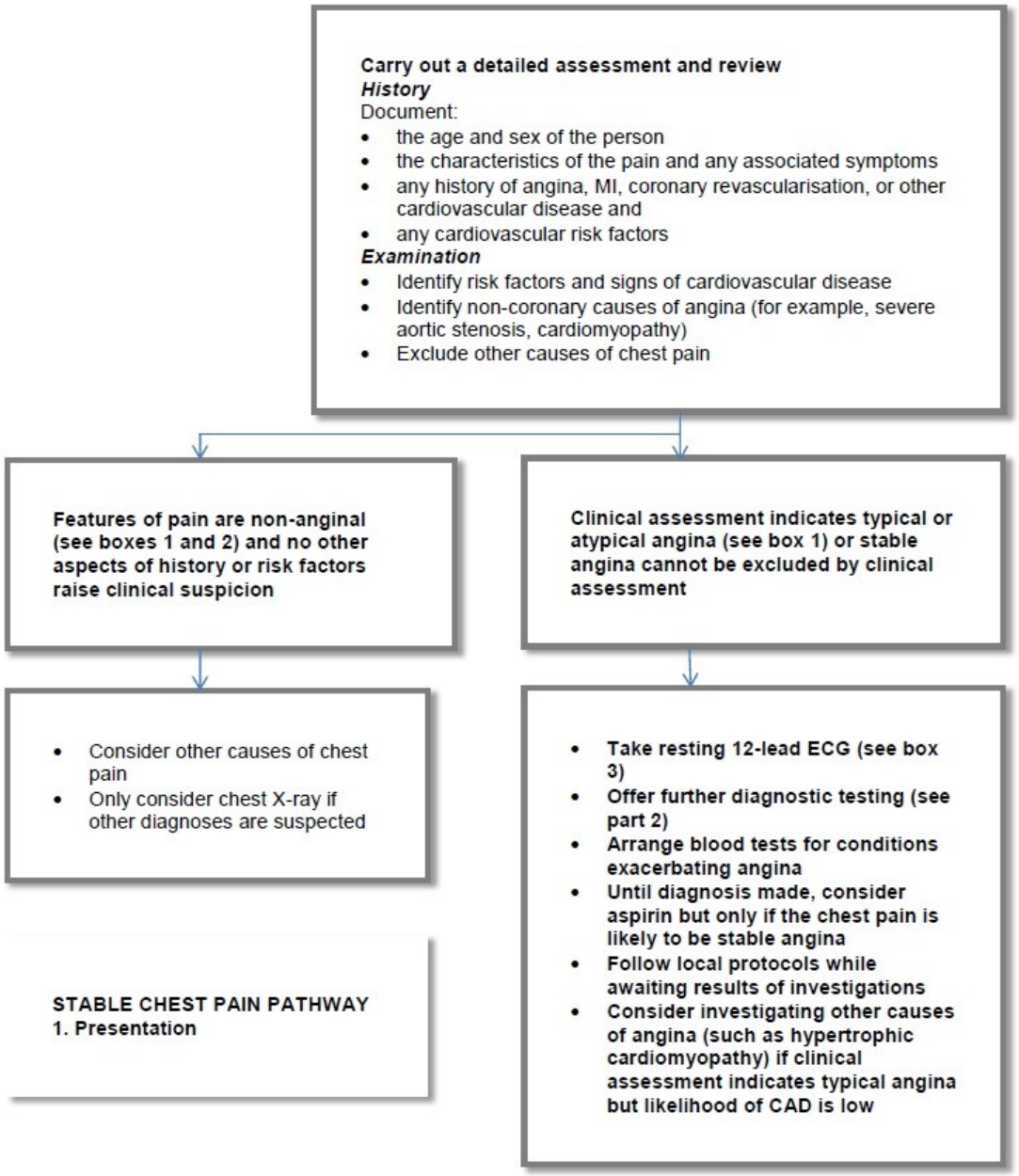


Box 1: Monitoring people with acute chest pain
Use clinical judgement to decide how often this should be done until a firm diagnosis is made. Include:
- exacerbations of pain and/or other symptoms and insuring adequate relief is given
- pulse and blood pressure
- oxygen saturation by pulse-oximetry
- repeat resting 12-lead ECGs and
- consider monitoring heart rhythm

Box 2 Diagnostic Criteria for MI
Rise and/or fall of cardiac biomarkers (preferably hs-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 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

2.1.2 Stable chest pain algorithm

The algorithms should be read with the recommendations in this document. The updated algorithm includes the new 2016 recommendations.



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 a diagnosis of stable angina more likely

Box 2 Stable angina is unlikely if chest pain is:

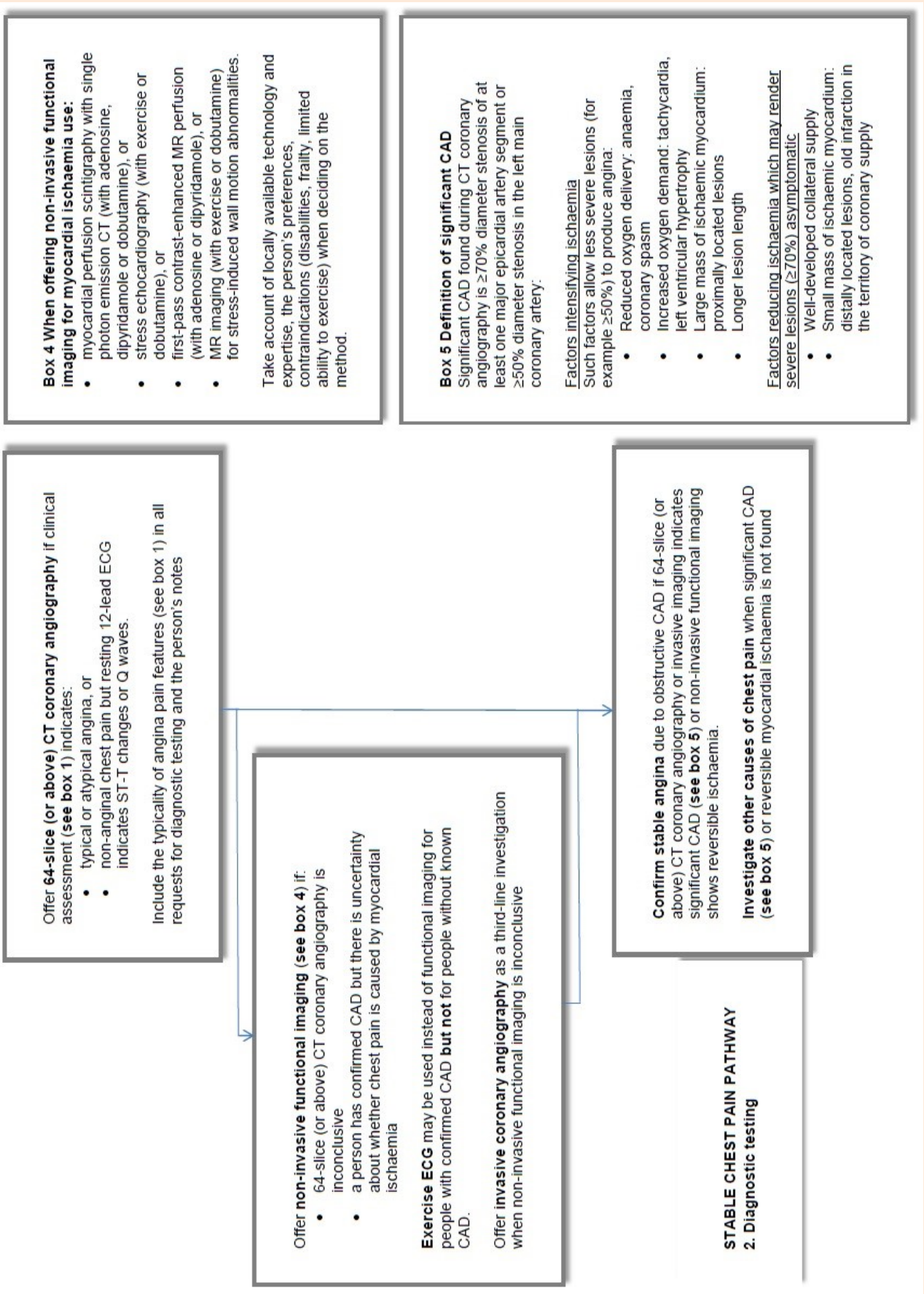
- continuous or very prolonged and/or
- unrelated to activity and/or
- brought on by breathing in and/or
- associated with symptoms such as dizziness, palpitations, tingling or difficulty swallowing

Box 3 Changes on a resting12-lead ECG consistent with CAD which may indicate ischaemia or previous infarction

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

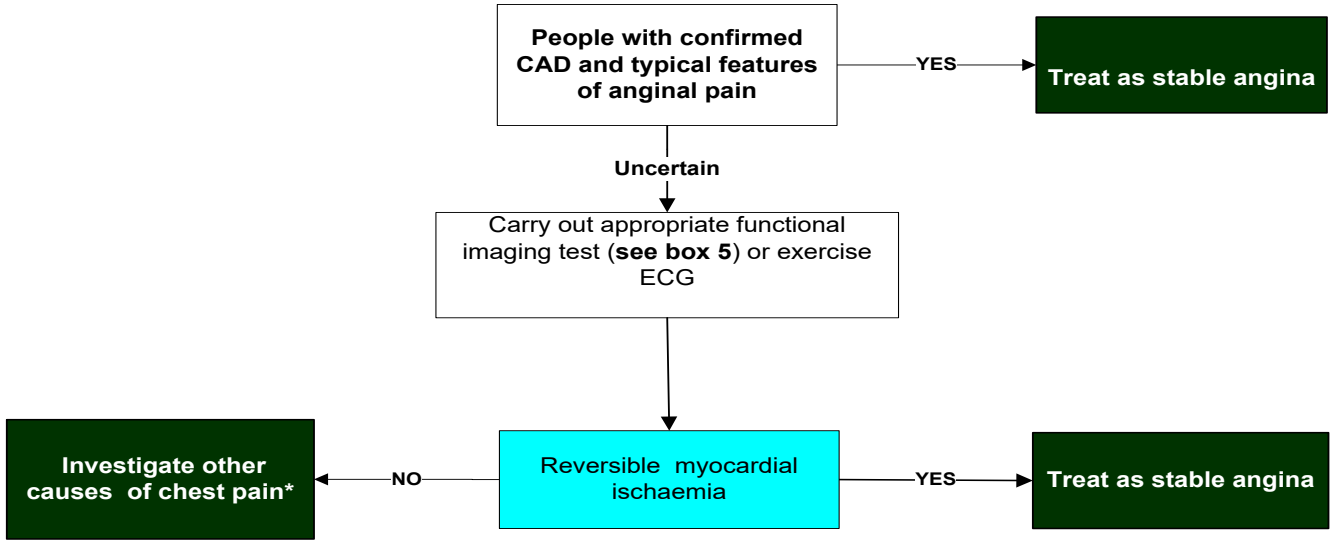
Results may not be conclusive. Consider resting 12-lead ECG changes together with people's clinical history and risk factors. Note that a normal resting 12-lead ECG does not rule out stable angina.

Update 2016


Box 4 When offering non-invasive functional imaging for myocardial ischaemia use:
• myocardial perfusion scintigraphy with single photon emission CT (with adenosine, dipyridamole or dobutamine), or
• stress echocardiography (with exercise or dobutamine), or
• first-pass contrast-enhanced MR perfusion (with adenosine or dipyridamole), or
• MR imaging (with exercise or dobutamine) for stress-induced wall motion abnormalities.
Take account of locally available technology and expertise, the person's preferences, contraindications (disabilities, frailty, limited ability to exercise) when deciding on the method.
Box 5 Definition of significant CAD
Significant CAD found during CT 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 which 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
Offer 64-slice (or above) CT coronary angiography if clinical assessment (see box 1) indicates:
• typical or atypical angina, or
• non-anginal chest pain but resting 12-lead ECG indicates ST-T changes or Q waves.
Include the typicality of angina pain features (see box 1) in all requests for diagnostic testing and the person's notes
Offer non-invasive functional imaging (see box 4) if:
• 64-slice (or above) CT coronary angiography is inconclusive
• a person has confirmed CAD but there is uncertainty about whether chest pain is caused by myocardial ischaemia
Exercise ECG may be used instead of functional imaging for people with confirmed CAD but not for people without known CAD.
Offer invasive coronary angiography as a third-line investigation when non-invasive functional imaging is inconclusive
Confirm stable angina due to obstructive CAD if 64-slice (or above) CT coronary angiography or invasive imaging indicates significant CAD (see box 5) or non-invasive functional imaging shows reversible ischaemia.
Investigate other causes of chest pain when significant CAD (see box 5) or reversible myocardial ischaemia is not found
STABLE CHEST PAIN PATHWAY
2. Diagnostic testing

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.

Note: This recommendation updates and replaces recommendation 1.1 of NICE technology appraisal guidance 73.

* 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.

2.2 Full list of recommendations

1.1 Providing information for people with chest pain

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. **[2010]**

1.1.1.2 Offer people a clear explanation of the possible causes of their symptoms and the uncertainties. **[2010]**

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. **[2010]**

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. **[2010]**

1.1.1.5 Offer information about the risks of diagnostic testing, including any radiation exposure. **[2010]**

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. **[2010]**

1.1.1.7 Offer information after diagnosis as recommended in the relevant disease management guidelines.[a] **[2010]**

1.1.1.8 Explain if the chest pain is non-cardiac and refer people for further investigation if appropriate. **[2010]**

1.1.1.9 Provide individual advice to people about seeking medical help if they have further chest pain. **[2010]**

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 the NICE guideline on unstable angina and

[a] For example, the NICE guidelines on unstable angina and NSTEMI (CG94), generalised anxiety disorder and panic disorder in adults (CG113) and gastro-oesophageal reflux disease and dyspepsia in adults (CG184).

NSTEMI (CG94) 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

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. **[2010]**

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

- 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. **[2010]**

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. **[2010]**

1.2.1.4 Do not use people's response to glyceryl trinitrate (GTN) to make a diagnosis. **[2010]**

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. **[2010]**

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. **[2010]**

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. **[2010]**

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. **[2010]**

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. **[2010]**

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. **[2010]**

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. **[2010]**

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. **[2010]**

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, 1.2.6.7 and 1.2.6.8). **[2010]**

1.2.2 Resting 12-lead 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. **[2010]**

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). **[2010]**

1.2.2.3 Follow the NICE guideline on unstable angina and NSTEMI (CG94) 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). **[2010]**

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 the NICE guideline on unstable angina and NSTEMI (CG94) if these conditions are likely. Continue to monitor (see recommendation 1.2.3.4). **[2010]**

1.2.2.5 Do not exclude an ACS when people have a normal resting 12-lead ECG. **[2010]**

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. **[2010]**

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. **[2010]**

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). **[2010]**

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.

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. **[2010]**

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 (the NICE guideline on unstable angina and NSTEMI or local protocols for STEMI). **[2010]**

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 (SpO2) of less than 94% who are not at risk of hypercapnic respiratory failure, aiming for SpO2 of 94–98%
- people with chronic obstructive pulmonary disease who are at risk of hypercapnic respiratory failure, to achieve a target SpO2 of 88–92% until blood gas analysis is available. **[2010]**

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. **[2010]**

1.2.3.5 Manage other therapeutic interventions using appropriate guidance (the NICE guideline on unstable angina and NSTEMI or local protocols for STEMI). **[2010]**

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

1.2.4.1 Take a resting 12-lead ECG and a blood sample for high-sensitivity troponin I or T measurement (see section 1.2.5) on arrival in hospital. **[2010, amended 2016]**

Update 2016

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. **[2010]**

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. **[2010]**

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

1.2.5.1 Do not use high-sensitivity troponin tests for people in whom ACS is not suspected. **[new 2016]**

1.2.5.2 For people at high or moderate risk of MI (as indicated by a validated tool), perform high-sensitivity troponin tests as recommended in the NICE diagnostics guidance on myocardial infarction (DG15). **[new 2016]**

1.2.5.3 For people at low risk of MI (as indicated by a validated tool):

- perform a second high-sensitivity troponin test as recommended in the NICE diagnostics guidance on myocardial infarction (DG15) if the first troponin test at presentation is positive
- consider performing a single high-sensitivity troponin test only at presentation to rule out NSTEMI if the first troponin test is below the lower limit of detection (negative). **[new 2016]**

1.2.5.4 Ensure that patients understand that a detectable troponin on the first high-sensitivity test does not necessarily indicate that they have had an MI. **[new 2016]**

Update 2016

1.2.5.5 Do not use biochemical markers such as natriuretic peptides and high-sensitivity C-reactive protein to diagnose an ACS. **[2010]**

1.2.5.6 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. **[2010]**

1.2.5.7 When interpreting high-sensitivity troponin measurements, take into account:

- the clinical presentation
- the time from onset of symptoms
- the resting 12-lead ECG findings
- the pre-test probability of NSTEMI
- the length of time since the suspected ACS
- the probability of chronically elevated troponin levels in some people
- that 99th percentile thresholds for troponin I and T may differ between sexes. **[2010, amended 2016]**

Update 2016

1.2.6 Making a diagnosis

1.2.6.1 When diagnosing MI, use the universal definition of myocardial infarction.[208] This is the detection of rise and/or fall of cardiac biomarkers values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile of the upper reference limit and at least one of the following:

- symptoms of ischaemia
- new or presumed new significant ST-segment-T wave(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].

[b] 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.

Update 2016

- identification of an intracoronary thrombus by angiography. **[2010, amended 2016]**

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. **[2010]**

1.2.6.3 When a raised troponin level is detected in people with a suspected ACS, follow the appropriate guidance (the NICE guideline on unstable angina and NSTEMI or local protocols for STEMI) until a firm diagnosis is made. Continue to monitor (see recommendation 1.2.3.4). **[2010]**

1.2.6.4 When a diagnosis of ACS is confirmed, follow the appropriate guidance (the NICE guideline on unstable angina and NSTEMI or local protocols for STEMI). **[2010]**

Update 2016

1.2.6.5 Reassess people with chest pain without raised troponin levels 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. **[2010, amended 2016]**

1.2.6.6 Do not routinely offer non-invasive imaging or exercise ECG in the initial assessment of acute cardiac chest pain. **[new 2016]**

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. **[2010]**

1.2.6.8 Consider a chest X-ray to help exclude complications of ACS such as pulmonary oedema, or other diagnoses such as pneumothorax or pneumonia. **[2010]**

1.2.6.9 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 the NICE guidelines on cardiovascular disease and hypertension in adults. **[2010]**

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.

Update 2016

1.3.1.1 Exclude a diagnosis of stable angina if clinical assessment indicates non-anginal chest pain (see recommendation 1.3.3.1) and there are no other aspects of the history or risk factors raising clinical suspicion. **[new 2016]**

1.3.1.2 If clinical assessment indicates typical or atypical angina (see recommendation 1.3.3.1), offer diagnostic testing (see sections 1.3.4, 1.3.5 and 1.3.6). **[new 2016]**

1.3.2 Clinical assessment

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. **[2010]**

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. **[2010]**

1.3.3 Making a diagnosis based on clinical assessment

1.3.3.1 Assess the typicality of chest pain as follows:

- Presence of three of the features below is defined as typical angina.
- Presence of two of the three features below is defined as atypical angina.
- Presence of one or none of the features below is defined as non-anginal chest pain.

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. **[2010, amended 2016]**

Update 2016

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. **[2010]**

1.3.3.3 Do not define typical and atypical features of anginal chest pain and non-anginal chest pain differently in ethnic groups. **[2010]**

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:

- age
- whether the person is male
- cardiovascular risk factors including:
  - a history of smoking
  - diabetes
  - hypertension
  - dyslipidaemia
  - family history of premature CAD
  - other cardiovascular disease
- history of established CAD, for example previous MI, coronary revascularisation. **[2010]**

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). **[2010]**

1.3.3.6 Consider investigating other causes of angina, such as hypertrophic cardiomyopathy, in people with typical angina-like chest pain and a low likelihood of CAD. **[2010, amended 2016]**

Update 2016

1.3.3.7 Arrange blood tests to identify conditions which exacerbate angina, such as anaemia, for all people being investigated for stable angina. **[2010]**

1.3.3.8 Only consider chest X-ray if other diagnoses, such as a lung tumour, are suspected. **[2010]**

1.3.3.9 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 the NICE guideline on cardiovascular disease and the NICE guideline on hypertension in adults. **[2010]**

1.3.3.10 For people in whom stable angina cannot be excluded on the basis of the clinical assessment alone, take a resting 12-lead ECG as soon as possible after presentation. **[2010, amended 2016]** Updat e 2016

1.3.3.11 Do not rule out a diagnosis of stable angina on the basis of a normal resting 12-lead ECG. **[2010]**

1.3.3.12 Do not offer diagnostic testing to people with non-anginal chest pain on clinical assessment (see recommendation 1.3.3.1) unless there are resting ECG ST-T changes or Q waves. **[new 2016]** Updat e 2016

1.3.3.13 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. **[2010]**

1.3.3.14 For people with confirmed CAD (for example, previous MI, revascularisation, previous angiography) in whom stable angina cannot be excluded based on clinical assessment alone, see recommendation 1.3.4.4 about functional testing. **[2010, amended 2016]** Update 2016

1.3.3.15 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. **[2010]**

1.3.3.16 Follow local protocols for stable angina[c] while waiting for the results of investigations if symptoms are typical of stable angina. **[2010]**

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

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.

1.3.4.1 Include the typicality of anginal pain features (see recommendation 1.3.3.1) in all requests for diagnostic investigations and in the person's notes. **[2010, amended 2016]** Update 2016

1.3.4.2 Use clinical judgement and take into account people's preferences and comorbidities when considering diagnostic testing. **[2010]**

1.3.4.3 Offer 64-slice (or above) CT coronary angiography if:

[c] Stable angina. NICE guideline CG126 (2011).

- clinical assessment (see recommendation 1.3.3.1) indicates typical or atypical angina, or
- clinical assessment indicates non-anginal chest pain but 12-lead resting ECG has been done and indicates ST-T changes or Q waves. **[new 2016]**

Update 2016

1.3.4.4 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. **[2010]**

1.3.5 Additional diagnostic investigations

1.3.5.1 Offer non-invasive functional imaging (see section 1.3.6) for myocardial ischaemia if 64-slice (or above) CT coronary angiography has shown CAD of uncertain functional significance or is non-diagnostic. **[2016]**

1.3.5.2 Offer invasive coronary angiography as a third-line investigation when the results of non-invasive functional imaging are inconclusive. **[2016]**

Update 2016

1.3.6 Use of non-invasive functional testing for myocardial ischaemia

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 (for example, disabilities, frailty, limited ability to exercise) when deciding on the imaging method. [This recommendation updates and replaces recommendation 1.1 of 'Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction' (NICE technology appraisal guidance 73)]. **[2016]**

Update 2016

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. **[2010]**

1.3.6.3 Use exercise or dobutamine for stress echocardiography or MR imaging for stress-induced wall motion abnormalities. **[2010]**

1.3.6.4 Do not use MR coronary angiography for diagnosing stable angina. **[2010]**

1.3.6.5 Do not use exercise ECG to diagnose or exclude stable angina for people without known CAD. **[2010]**

1.3.7 Making a diagnosis following investigations

Box 1 Definition of significant coronary artery disease

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

Update 2016

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 which 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. **[new 2016]**

Update 2016

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

- significant CAD (see box 1) is found during invasive or 64-slice (or above) CT coronary angiography, **or**
- reversible myocardial ischaemia is found during non-invasive functional imaging. **[2016]**

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 **or**
- reversible myocardial ischaemia is not found during non-invasive functional imaging **[2016]**

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. **[2010]**

2.3 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.

2.3.1 Acute chest pain

2.3.1.1 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.

[d] Stable angina. NICE guideline CG126 (2011).

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.

2.3.1.2 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.

2.3.2 Stable chest pain

2.3.2.1 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.

2.3.2.2 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.

2.3.3 Research recommendations 2016

No research recommendations were made for this update.

Update 2016

3 Introduction

While there has been a decline in mortality from Coronary heart disease (CHD) it is still the most common cause of death in the UK, with 15% of men and 7% of women dying from the disease. In 2014 over 69,000 deaths were attributed to CHD. CHD is also the most common cause of premature death in the UK. 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.

Chest pain is a very common symptom: 20% to 40% of the general population will experience unspecified chest pain in their lives[185]. In the UK, up to 1% of visits to a general practitioner are due to chest pain[158]. 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[17,83,151].

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 acute coronary syndrome (ACS) is suspected, and the second is for people with intermittent stable chest pain in whom stable angina is suspected. Acute and intermittent stable chest pain are different in their presentation, investigative pathways and diagnostic criteria. The guideline is set out accordingly; chapter 5 provides guidance on providing information for people with acute or stable chest pain, chapter 6 provides guidance on patients presenting with acute chest pain and chapter 7 on people presenting with chest pain suspected of being angina (which will be referred to as stable chest pain). 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.

Update 2016

The diagnosis and management of chest pain that is clearly unrelated to the heart (for example traumatic chest wall injury, herpes zoster infection) is not considered once myocardial ischaemia is not included in this guideline.

4 Development of the guideline

4.1 What is a NICE guideline?

NICE guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. These may also include elements of social care or public health measures. We base our guidelines on the best available research evidence, with the aim of improving the quality of healthcare. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

New guidelines are produced using the following steps:

- A guideline topic is referred to NICE from NHS England.
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Guideline Centre (NGC).
- The NGC establishes a Guideline Committee.
- A draft guideline is produced after the group assesses the available evidence and makes recommendations.
- There is a consultation on the draft guideline.
- The final guideline is produced.

This is a partial update of Chest pain of recent onset (NICE clinical guideline 95). See section 3.2 on how this guideline was updated.

The NGC and NICE produce a number of versions of this guideline:

- The 'full guideline' contains all the recommendations, plus details of the methods used and the underpinning evidence.
- The 'NICE guideline' lists the recommendations.
- NICE Pathways brings together all connected NICE guidance.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk.

Update 2016

4.2 How this guideline was updated

The NICE guideline on chest pain (NICE clinical guideline CG95) was reviewed in December 2014 as part of NICE's routine surveillance programme to decide whether it required updating. The surveillance report identified new evidence relating to: the use of non-invasive tests for the diagnosis

of coronary artery disease (CAD) in people with stable chest pain of suspected cardiac origin, clinical prediction models which may impact on the assessment of the pre-test likelihood of CAD in this population, and the use of computed tomography is the assessment of people with acute chest pain (see Appendix A for the full surveillance report).

This guidance is a partial update of NICE clinical guideline 95 (published March 2010). New and updated recommendations have been included on the diagnosis of people with acute chest pain and the assessment and diagnosis in people with stable chest pain.

Recommendations are marked to indicate the year of the last evidence review [2010] if the evidence has not been updated since the original guideline, [2010, amended 2016] if the evidence has not been updated since the original guideline, but changes have been made that alter the meaning of the recommendation, [2016] if the evidence has been reviewed but no change has been made to the recommendation and [new 2016] if the evidence review has been added or updated.

There has been consultation on the updated and new recommendations. The sections updated are marked 'Update 2016'. The original NICE guidance and supporting documents are available from https://www.nice.org.uk/guidance/cg95.

Appendix V contains all the evidence and discussion that underpinned the original CG95 recommendations that have been updated in this guideline. The updated evidence is contained within this document.

4.3 Who developed this guideline?

Update 2016

4.3.1 The Chest pain of recent onset 2010 guideline

A multidisciplinary Guideline Development Committee (GDG) comprising health professionals and researchers as well as lay members developed this guideline (see the list of committee members and the acknowledgements in Appendix B).

The National Institute for Health and Care Excellence (NICE) funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Professor Adam Timmis in accordance with guidance from NICE.

The group met approximately every 5-6 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix V.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers (research fellows), health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

4.3.2 The acute chest pain update (2016)

A multidisciplinary Guideline Committee (GC) comprising healthcare professionals and researchers as well as lay members developed this guideline (see the list of Guideline Committee members and the acknowledgements in Appendix B).

The National Institute for Health and Care Excellence (NICE) funds the National Guideline Centre (NGC) and thus supported the development of this guideline. The GC was convened by the NGC and chaired by Professor Jonathan Mant in accordance with guidance from NICE.

The group met approximately every 5-8 weeks during the development of the guideline. At the start of the guideline development process all GC members declared interests including consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry. At all subsequent GC meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix C.

Staff from the NGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers (research fellows), health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the GC.

Update 2016

4.3.3 The stable chest pain update (2016)

The NICE clinical guidelines update team update discrete parts of published clinical guidelines as requested by NICE's Guidance Executive.

This part of the update has been updated using a standing committee of healthcare professionals, research methodologists and lay members from a range of disciplines and localities. For the duration of the update the core members of the committee are joined by up to 6 additional members who have specific expertise in the topic being updated, hereafter referred to as 'topic expert members'.

In chapter 7 where 'the committee' is referred to, this means the entire committee, both the core standing members and topic expert members.

Where 'standing committee members' is referred to, this means the core standing members of the committee only.

Where 'topic expert members' is referred to this means the recruited group of members with topic expertise.

All of the core members and the topic expert members are fully voting members of the committee.

Details of the committee membership and the NICE team can be found in Appendices B and T respectively. The committee members' declarations of interest can be found on the NICE website.

4.3.4 What this guideline covers

Adults (18 years and older) who have recent onset chest pain/discomfort of suspected cardiac origin, with or without a prior history and/or diagnosis of cardiovascular disease.

Recommendations will be made, as appropriate and based on the evidence, for specific groups. In this guideline, for example, they may be particular issues for women and black and minority ethnic groups.

For further details please refer to the original scope in Appendix V. The 2010 review questions are in Appendix V. The update review questions are in section 4.1.

4.3.5 What this guideline does not cover

People who have traumatic chest injury without cardiac symptoms.

People in whom the cause of their chest pain/discomfort is known to be related to another condition, and without cardiac symptoms.

4.3.6 Relationships between the guideline and other NICE guidance

To find out what NICE has said on topics related to this guideline, see our web page on cardiovascular conditions.

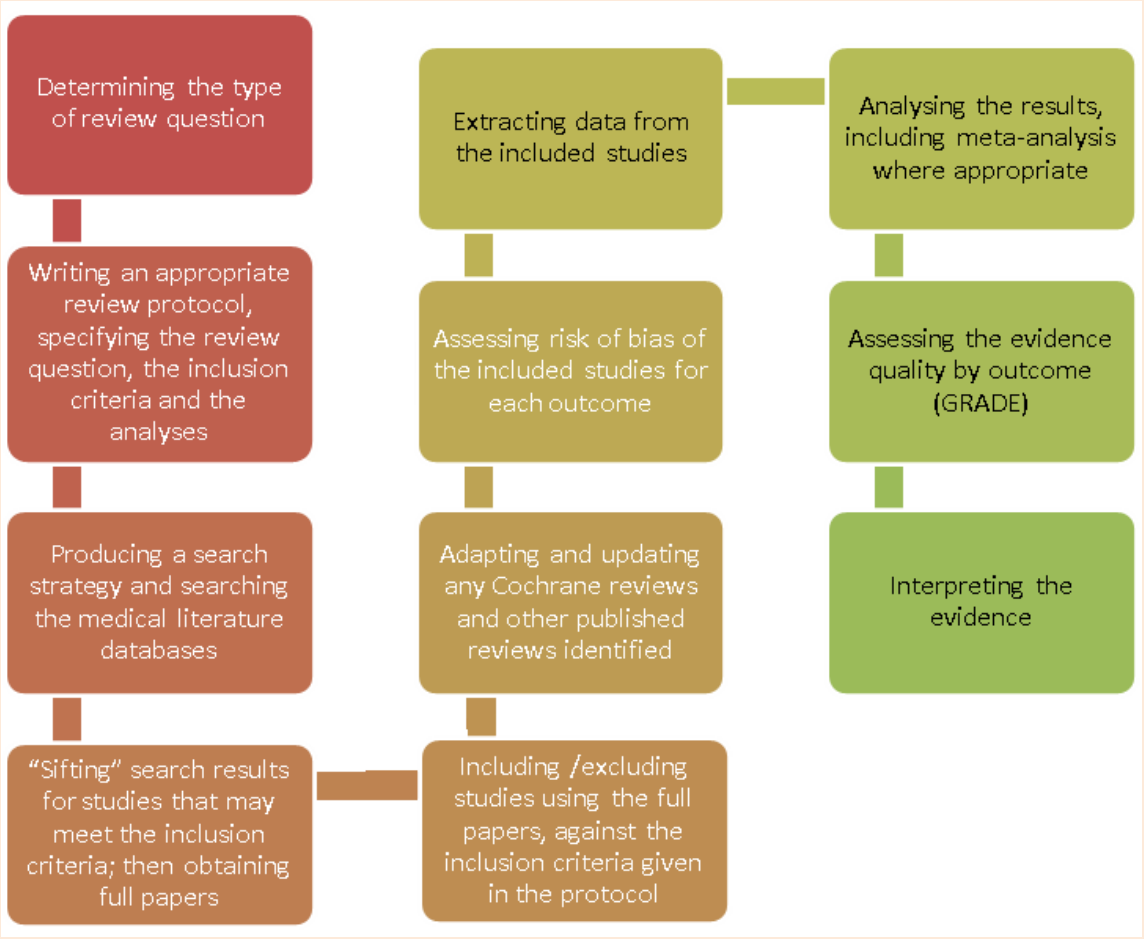
Update 2016

5 Methods 2016

This chapter sets out in detail the methods used to review the evidence in the updates and to develop the recommendations that are presented in subsequent chapters of this guideline. This guidance was developed in accordance with the methods outlined in the NICE guidelines manual, 2014.[155] Details specific to the evidence reviews are outlined in the chapters 6 and 7 .See Appendix V for the description of the methods used to develop the 2010 guidance.

Sections 4.1 to 4.3 describe the process used to identify and review clinical evidence (summarised in Figure 1), Sections 4.2 and 4.3 describe the process used to identify and review the health economic evidence, and Section 4.4 describes the process used to develop recommendations.

Figure 1: Step-by-step process of review of evidence in the guideline



Update 2016

5.1 Developing the review questions and outcomes

Review questions were developed using a PICO framework (patient, intervention, comparison and outcome) for intervention reviews; using a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy.

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the GC. The review questions were drafted by the technical team and refined and validated by the committee. The questions were based on the key clinical areas identified in the scope (Appendix V) and in the surveillance review (Appendix A).

A total of 20 review questions were identified in the original guideline (see Appendix V), 4 were identified for the updates.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

Table 1: Review questions

Chapter	Type of review	Review questions	Outcomes
6	Diagnostic	In low, medium and high risk people under investigation for acute chest pain of suspected cardiac origin, what is the accuracy of high-sensitivity troponin assay to identify NSTEMI/unstable angina?	Sensitivity/specificity and other test accuracy measures
6	Intervention and diagnostic	A) In people under investigation for acute chest pain of suspected cardiac origin, what is the clinical and cost-effectiveness of non-invasive imaging compared to standard practice, when each is followed by the appropriate treatment for NSTEMI/unstable angina, in order to improve patient outcomes? b) In people under investigation for acute chest pain of suspected cardiac origin are non-invasive imaging tests more accurate compared to standard practice to identify whether NSTEMI/unstable angina is present, as indicated by the reference standard?	a) Efficacy outcomes: All-cause mortality at 30-day and 1-year follow-up (or closest time point) Cardiovascular mortality at 30 days and 1 year follow-up (or closest time point) Myocardial infarction at 30-day follow-up Percutaneous coronary intervention (PCI) at 30-day follow-up Coronary artery bypass graft (CABG) at 30-day follow-up Hospitalisation 30-day follow-up for cardiac causes (or closest time point) Hospitalisation at 30-day follow-up for non-cardiac causes (or closest time point) Quality of life Adverse events related to index non-invasive test Adverse events related to treatment: major bleeding Process outcomes: Number of people receiving treatment Length of hospital stay b) Secondary accuracy outcomes: Sensitivity/specificity and other test accuracy measures
7	Diagnostic	In people with stable chest pain of suspected cardiac origin, what is the accuracy, clinical utility and cost effectiveness of:	Sensitivity/specificity and other test accuracy measures

Update 2016

Chapter	Type of review	Review questions	Outcomes
		• non-invasive diagnostic tests • invasive diagnostic tests • calcium scoring	
7	Risk prediction	What is the accuracy, clinical utility and cost effectiveness of clinical prediction models/tools (clinical history, cardiovascular risk factors, physical examination) in evaluating people with stable chest pain of suspected cardiac origin?	ROC curve - AUC (c-statistic, c-index) Sensitivity and specificity

5.2 Searching for evidence

5.2.1 Clinical literature search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE guidelines manual 2014.[155] Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Where possible, searches were restricted to papers published in English. Studies published in languages other than English were not reviewed. All searches were conducted in Medline, Embase, and The Cochrane Library.

Update 2016

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking GC members to highlight any additional studies. Searches were quality assured by a second information scientist before being run. The questions, the study types applied, the databases searched and the years covered can be found in Appendix H.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially relevant publications obtained in full text. These were assessed against the inclusion criteria.

All references sent by stakeholders were considered. Searching for unpublished literature was not undertaken. The NGC and NICE do not have access to drug manufacturers' unpublished clinical trial results, so the clinical evidence considered by the GC for pharmaceutical interventions may be different from that considered by the Medicines and Healthcare products Regulatory Agency (MHRA) and European Medicines Agency for the purposes of licensing and safety regulation.

5.2.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to acute chest pain in Medline, Embase, the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment database (HTA) from March 2009 onwards (NHS EED ceased to be updated after March 2015). Where possible, searches were restricted to papers published in English. Studies published in languages other than English were not reviewed.

The health economic search strategies are included in Appendix H. Identifying and analysing evidence of effectiveness

Research fellows/technical analysts conducted the tasks listed below, which are described in further detail in the rest of this section:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population, and reported on outcomes of interest (review protocols are included in Appendix D).
- Critically appraised relevant studies using the appropriate study design checklist as specified in the NICE guidelines manual.[155]
- Extracted key information about interventional study methods and results using 'Evibase', NGC's purpose-built software. Evibase produces summary evidence tables, including critical appraisal ratings. Key information about non-interventional study methods and results was manually extracted onto standard evidence tables and critically appraised separately (evidence tables are included in Appendix I).
- Generated summaries of the evidence by outcome. Outcome data were combined, analysed and reported according to study design:
  - Randomised data were meta-analysed where appropriate and reported in GRADE profile tables.
  - Diagnostic data studies were meta-analysed where appropriate or presented as a range of values in adapted GRADE profile tables
- A sample of a minimum of 20% of the abstract lists were double-sifted by a senior research fellow and any discrepancies were rectified. All of the evidence reviews were quality assured by a senior research fellow. This included checking:
  - papers were included or excluded appropriately
  - a sample of the data extractions
  - correct methods were used to synthesise data
  - a sample of the risk of bias assessments.

Update 2016

5.2.3 Inclusion and exclusion criteria

The inclusion and exclusion of studies was based on the criteria defined in the review protocols, which can be found in Appendix D. Excluded studies by review question (with the reasons for their exclusion) are listed in Appendix N. The GC was consulted about any uncertainty regarding inclusion or exclusion.

The key population inclusion criterion was:

- People with acute chest pain
- People with stable chest pain

The key population exclusion criterion was:

- People with acute chest pain due not thought to be cardiac in origin

Conference abstracts were not automatically excluded from any review. The abstracts were initially assessed against the inclusion criteria for the review question and further processed when a full publication was not available for that review question. If the abstracts were included the authors were contacted for further information. No relevant conference abstracts were identified for this

guideline. Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

5.2.4 Type of studies

Randomised trials, non-randomised trials, and observational studies (including diagnostic or prognostic studies) were included in the evidence reviews as appropriate.

For the intervention review in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that can produce an unbiased estimate of the intervention effects. Crossover RCTs were not appropriate for the question on the clinical and cost effectiveness of non-invasive imaging. If non-randomised studies were appropriate for inclusion (for example, non-drug trials with no randomised evidence) the GC stated a priori in the protocol that either certain identified variables must be equivalent at baseline or else the analysis had to adjust for any baseline differences. If the study did not fulfil either criterion it was excluded. Please refer to the review protocols in Appendix D for full details on the study design of studies selected for each review question.

For diagnostic review questions, diagnostic RCTs, cross-sectional studies and retrospective studies were included.

5.2.5 Methods of combining clinical studies

5.2.5.1 Data synthesis for intervention reviews

Update 2016

Where possible, meta-analyses were conducted using Cochrane Review Manager (RevMan5)[180] software to combine the data given in all studies for each of the outcomes of interest for the review question.

All analyses were stratified for risk, which meant that studies with people with different risk were not combined and analysed together. If a study did not specify risk, then prevalence was used. For some questions additional stratification was used, and this is documented in the individual review question protocols (see Appendix D). When additional strata were used this led to substrata (for example, 2 stratification criteria leads to 4 substrata, 3 stratification criteria leads to 9 substrata) which were analysed separately.

5.2.5.1.1 Analysis of different types of data

Dichotomous outcomes

Fixed-effects (Mantel-Haenszel) techniques (using an inverse variance method for pooling) were used to calculate risk ratios (relative risk, RR) for the binary outcomes, which included:

- All-cause mortality
- Cardiovascular mortality
- Myocardial infarction at 30-day follow-up
- Percutaneous coronary intervention (PCI)
- Coronary artery bypass graft (CABG)
- Adverse events.

The absolute risk difference was also calculated using GRADEpro[84] software, using the median event rate in the control arm of the pooled results.

For binary variables where there were zero events in either arm or a less than 1% event rate, Peto odds ratios, rather than risk ratios, were calculated. Peto odds ratios are more appropriate for data with a low number of events.

Continuous outcomes

Continuous outcomes were analysed using an inverse variance method for pooling weighted mean differences. These outcomes included:

- heath-related quality of life (HRQoL)
- length of stay in hospital

The means and standard deviations of continuous outcomes are required for meta-analysis.

5.2.5.1.2 Heterogeneity

Statistical heterogeneity was assessed for each meta-analysis estimate by considering the chi-squared test for significance at $p<0.1$ or an I-squared (I^2) inconsistency statistic (with an I-squared value of more than 50% indicating significant heterogeneity) as well as the distribution of effects. Where significant heterogeneity was present, predefined subgrouping of studies was carried out for either:

- age, for example <70 years versus ≥70 years, ≤40 years versus >40 years
- diabetes
- ethnicity
- gender
- impaired renal function
- obesity
- people with disabilities
- pre-existing CAD compared with no prior history of CAD

Update 2016

If the subgroup analysis resolved heterogeneity within all of the derived subgroups, then each of the derived subgroups were adopted as separate outcomes (providing at least 1 study remained in each subgroup). For example, instead of the single outcome of 'all-cause mortality', this was separated into 2 outcomes 'all-cause mortality in people aged under 70' and 'all-cause mortality in people aged over 70'. Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. Any subgroup differences were interpreted with caution as separating the groups breaks the study randomisation and as such is subject to uncontrolled confounding.

For some questions additional predefined subgrouping was applied, and this is documented in the individual review question protocols (see Appendix D). These additional subgrouping strategies were applied independently, so subunits of subgroups were not created, unlike the situation with strata. Other subgrouping strategies were only used if the age category subgroup was unable to explain heterogeneity; these further subgrouping strategies were then applied in order of priority. Again, once a subgrouping strategy was found to explain heterogeneity from all derived subgroups, further subgrouping strategies were not used.

If all predefined strategies of subgrouping were unable to explain statistical heterogeneity within each derived subgroup, then a random effects (DerSimonian and Laird) model was employed to the entire group of studies in the meta-analysis. A random-effects model assumes a distribution of populations, rather than a single population. This leads to a widening of the confidence interval

around the overall estimate, thus providing a more realistic interpretation of the true distribution of effects across more than 1 population. If, however, the GC considered the heterogeneity was so large that meta-analysis was inappropriate, then the results were described narratively.

5.2.5.2 Data synthesis for diagnostic test accuracy reviews

Two separate review protocols were produced to reflect the 2 different diagnostic study designs.

5.2.5.2.1 Diagnostic RCTs

Diagnostic RCTs (sometimes referred to as test-and-treat trials) are a randomised comparison of 2 diagnostic tests, with study outcomes being clinically important consequences of the diagnosis (patient-related outcome measures similar to those in intervention trials, such as mortality). Patients are randomised to receive test A or test B, followed by identical therapeutic interventions based on the results of the test (so someone with a positive result would receive the same treatment regardless of whether they were diagnosed by test A or test B). Downstream patient outcomes are then compared between the 2 groups. As treatment is the same in both arms of the trial, any differences in patient outcomes will reflect the accuracy of the tests in correctly establishing who does and does not have the condition. Data were synthesised using the same methods for intervention reviews (see Section 4.2.5.1.1 above).

5.2.5.2.2 Diagnostic accuracy studies

For diagnostic test accuracy studies, a positive result on the index test was found if the patient had values of the measured quantity above or below a threshold value, and different thresholds could be used. The thresholds were pre specified by the GC including whether or not data could be pooled across a range of thresholds. Diagnostic test accuracy measures used in the analysis were: area under the receiver operating characteristics (ROC) curve (AUC), and, for different thresholds (if appropriate), sensitivity and specificity. The threshold of a diagnostic test is defined as the value at which the test can best differentiate between those with and without the target condition. In practice this varies amongst studies. If a test has a high sensitivity then very few people with the condition will be missed (few false negatives). For example, a test with a sensitivity of 97% will only miss 3% of people with the condition. Conversely, if a test has a high specificity then few people without the condition would be incorrectly diagnosed (few false positives). For example, a test with a specificity of 97% will only incorrectly diagnose 3% of people who do not have the condition as positive. For this guideline, sensitivity was considered more important than specificity due to the consequences of a missed diagnosis (false negative result). People who are missed may experience a cardiac event. Coupled forest plots of sensitivity and specificity with their 95% CIs across studies (at various thresholds) were produced for each test, using RevMan5.[180] In order to do this, 2×2 tables (the number of true positives, false positives, true negatives and false negatives) were directly taken from the study if given, or else were derived from raw data or calculated from the set of test accuracy statistics.

Update 2016

Diagnostic meta-analysis was conducted where appropriate: that is, when 3 or more studies were available per threshold. Test accuracy for the studies was pooled using the bivariate method for the direct estimation of summary sensitivity and specificity using a random-effects approach in WinBUGS software.[225] The advantage of this approach is that it produces summary estimates of sensitivity and specificity that account for the correlation between the 2 statistics. Other advantages of this method have been described elsewhere.[179,214,215] The bivariate method uses logistic regression on the true positives, true negatives, false positives and false negatives reported in the studies. Overall sensitivity and specificity and confidence regions were plotted (using methods outlined by Novielli 2010.[160]) Pooled sensitivity and specificity and their 95% CIs were reported in the clinical evidence summary tables. For scores with fewer than 3 studies, median sensitivity and the paired specificity were reported where possible. If an even number of studies were reported the results of the study with

the lower sensitivity value of the 2 middle studies was reported. If there are two scores both will be reported.

If appropriate, to allow comparison between tests, summary ROC curves were generated for each diagnostic test from the pairs of sensitivity and specificity calculated from the 2×2 tables, selecting 1 threshold per study. A ROC plot shows true positive rate (sensitivity) as a function of false positive rate (1 minus specificity). Data were entered into RevMan5[180] and ROC curves were fitted using the Moses-Littenberg approach. In order to compare diagnostic tests, 2 or more tests were plotted on the same graph. The performance of the different diagnostic tests was then assessed by examining the summary ROC curves visually: the test that had a curve lying closest to the upper left corner (100% sensitivity and 100% specificity) was interpreted as the best test.

Heterogeneity or inconsistency amongst studies was visually inspected in the forest plots and pooled diagnostic meta-analysis plots. If heterogeneity was detected the results of the studies were presented separately.

5.2.6 Appraising the quality of evidence by outcomes

5.2.6.1 Intervention reviews

The evidence for outcomes from the included RCTs and, where appropriate, observational studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro[84]) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results.

Each outcome was first examined for each of the quality elements listed and defined in Table 2.

Update 2016

Table 2: Description of quality elements in GRADE for intervention studies

Quality element	Description
Risk of bias	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect. Examples of such limitations are selection bias (often due to poor allocation concealment), performance and detection bias (often due to a lack of blinding of the patient, healthcare professional or assessor) and attrition bias (due to missing data causing systematic bias in the analysis).
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of effect estimates between studies in the same meta-analysis.
Imprecision	Results are imprecise when studies include relatively few patients and few events (or highly variable measures) and thus have wide confidence intervals around the estimate of the effect relative to clinically important thresholds. 95% confidence intervals denote the possible range of locations of the true population effect at a 95% probability, and so wide confidence intervals may denote a result that is consistent with conflicting interpretations (for example a result may be consistent with both clinical benefit AND clinical harm) and thus be imprecise.
Publication bias	Publication bias is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies. A closely related phenomenon is where some papers fail to report an outcome that is inconclusive, thus leading to an overestimate of the effectiveness of the intervention for that outcome.
Other issues	Sometimes randomisation may not adequately lead to group equivalence of confounders, and if so this may lead to bias, which should be taken into account.

Quality element	Description
	Potential conflicts of interest, often caused by excessive pharmaceutical company involvement in the publication of a study, should also be noted.

Details of how the 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) were appraised for each outcome are given below. Publication or other bias was only taken into consideration in the quality assessment if it was apparent.

5.2.6.1.1 Risk of bias

The main domains of bias for RCTs are listed in Table 3. Each outcome had its risk of bias assessed within each study first. For each study, if there were no risks of bias in any domain, the risk of bias was given a rating of 0. If there was risk of bias in just 1 domain, the risk of bias was given a 'serious' rating of −1, but if there was risk of bias in 2 or more domains the risk of bias was given a 'very serious' rating of −2. A weighted average score was then calculated across all studies contributing to the outcome, by taking into account the weighting of studies according to study precision. For example if the most precise studies tended to each have a score of −1 for that outcome, the overall score for that outcome would tend towards −1.

Table 3: Principle domains of bias in randomised controlled trials

Limitation	Explanation
Selection bias (sequence generation and allocation concealment)	If those enrolling patients are aware of the group to which the next enrolled patient will be allocated, either because of a non-random sequence that is predictable, or because a truly random sequence was not concealed from the researcher, this may translate into systematic selection bias. This may occur if the researcher chooses not to recruit a participant into that specific group because of: • knowledge of that participant's likely prognostic characteristics, and • a desire for one group to do better than the other.
Performance and detection bias (lack of blinding of patients and healthcare professionals)	Patients, caregivers, those adjudicating or recording outcomes, and data analysts should not be aware of the arm to which patients are allocated. Knowledge of the group can influence: • the experience of the placebo effect • performance in outcome measures • the level of care and attention received, and • the methods of measurement or analysis all of which can contribute to systematic bias.
Attrition bias	Attrition bias results from an unaccounted for loss of data beyond a certain level (a differential of 10% between groups). Loss of data can occur when participants are compulsorily withdrawn from a group by the researchers (for example, when a per-protocol approach is used) or when participants do not attend assessment sessions. If the missing data are likely to be different from the data of those remaining in the groups, and there is a differential rate of such missing data from groups, systematic attrition bias may result.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results can also lead to bias, as this may distort the overall impression of efficacy.
Other limitations	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules. • Use of unvalidated patient-reported outcome measures. • Lack of washout periods to avoid carry-over effects in crossover trials. • Recruitment bias in cluster-randomised trials.

Update 2016

5.2.6.1.2 *Indirectness*

Indirectness refers to the extent to which the populations, interventions, comparisons and outcome measures are dissimilar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention. As for the risk of bias, each outcome had its indirectness assessed within each study first. For each study, if there were no sources of indirectness, indirectness was given a rating of 0. If there was indirectness in just 1 source (for example in terms of population), indirectness was given a 'serious' rating of −1, but if there was indirectness in 2 or more sources (for example, in terms of population and treatment) the indirectness was given a 'very serious' rating of −2. A weighted average score was then calculated across all studies contributing to the outcome by taking into account study precision. For example, if the most precise studies tended to have an indirectness score of −1 each for that outcome, the overall score for that outcome would tend towards −1.

5.2.6.1.3 *Inconsistency*

Inconsistency refers to an unexplained heterogeneity of results for an outcome across different studies. When estimates of the treatment effect across studies differ widely, this suggests true differences in the underlying treatment effect, which may be due to differences in populations, settings or doses. When heterogeneity existed within an outcome (chi-squared $p<0.1$, or $I^2>50\%$), but no plausible explanation could be found, the quality of evidence for that outcome was downgraded. Inconsistency for that outcome was given a 'serious' score of −1 if the I^2 was 50–74%, and a 'very serious' score of −2 if the I^2 was 75% or more.

If inconsistency could be explained based on pre-specified subgroup analysis (that is, each subgroup had an $I^2<50\%$), the GC took this into account and considered whether to make separate recommendations on the outcomes based on the subgroups defined by the assumed explanatory factors. In such a situation the quality of evidence was not downgraded for those emergent outcomes.

Update 2016

Since the inconsistency score was based on the meta-analysis results, the score represented the whole outcome and so weighted averaging across studies was not necessary.

5.2.6.1.4 *Imprecision*

The criteria applied for imprecision were based on the 95% CIs for the pooled estimate of effect, and the minimal important differences (MID) for the outcome. The MIDs are the threshold for appreciable benefits and harms, separated by a zone either side of the line of no effect where there is assumed to be no clinically important effect. If either end of the 95% CI of the overall estimate of effect crossed 1 of the MID lines, imprecision was regarded as serious and a 'serious' score of −1 was given. This was because the overall result, as represented by the span of the confidence interval, was consistent with 2 interpretations as defined by the MID (for example, both no clinically important effect and clinical benefit were possible interpretations). If both MID lines were crossed by either or both ends of the 95% CI then imprecision was regarded as very serious and a 'very serious' score of −2 was given. This was because the overall result was consistent with all 3 interpretations defined by the MID (no clinically important effect, clinical benefit and clinical harm). This is illustrated in Figure 3. As for inconsistency, since the imprecision score was based on the meta-analysis results, the score represented the whole outcome and so weighted averaging across studies was not necessary.

The position of the MID lines is ideally determined by values reported in the literature. 'Anchor-based' methods aim to establish clinically meaningful changes in a continuous outcome variable by relating or 'anchoring' them to patient-centred measures of clinical effectiveness that could be regarded as gold standards with a high level of face validity. For example, a MID for an outcome could be defined by the minimum amount of change in that outcome necessary to make patients feel

their quality of life had 'significantly improved'. MIDs in the literature may also be based on expert clinician or consensus opinion concerning the minimum amount of change in a variable deemed to affect quality of life or health. For binary variables, any MIDs reported in the literature will inevitably be based on expert consensus: as such, MIDs relate to all-or-nothing population effects rather than measurable effects on an individual, and so are not amenable to patient-centred 'anchor' methods.

In the absence of values identified in the literature, the alternative approach to deciding on MID levels is the 'default' method, as follows:

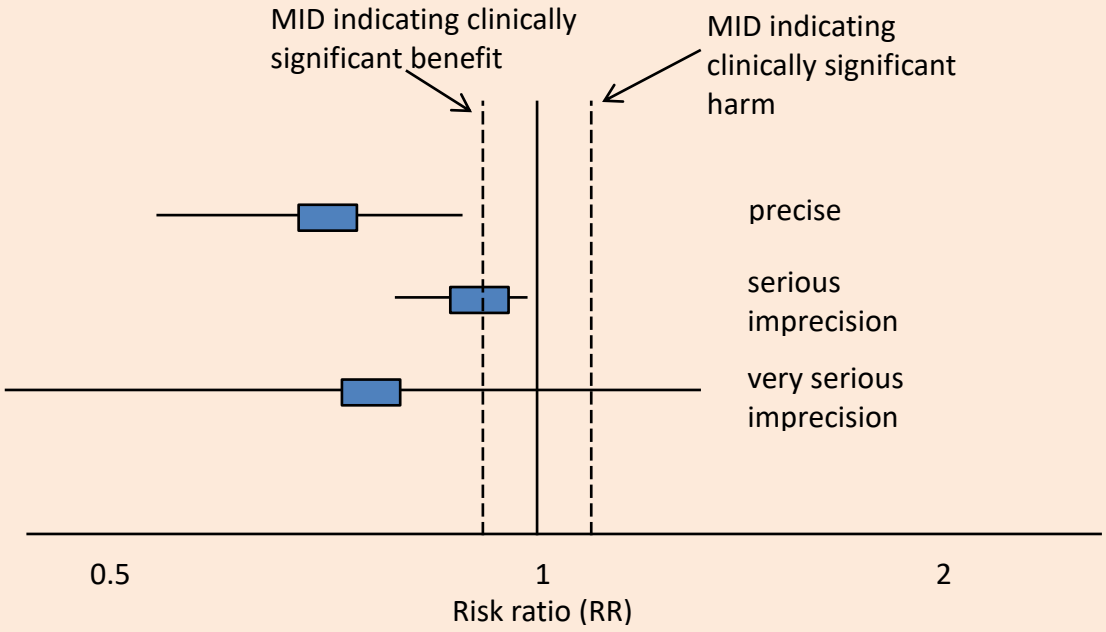
- For categorical outcomes the MIDs were taken to be RRs of 0.75 and 1.25. For 'positive' outcomes such as 'patient satisfaction', the RR of 0.75 was taken as the line denoting the boundary between no clinically important effect and a clinically significant harm, whilst the RR of 1.25 was taken as the line denoting the boundary between no clinically important effect and a clinically significant benefit. For 'negative' outcomes such as 'bleeding', the opposite occurs, so the RR of 0.75 was taken as the line denoting the boundary between no clinically important effect and a clinically significant benefit, whilst the RR of 1.25 was taken as the line denoting the boundary between no clinically important effect and a clinically significant harm.
- For mortality any change was considered to be clinically important and the imprecision was assessed on the basis of the whether the confidence intervals crossed the line of no effect, that is whether the result was consistent with both benefit and harm.
- For continuous outcome variables the MID was taken as half the median baseline standard deviation of that variable, across all studies in the meta-analysis. Hence the MID denoting the minimum clinically significant benefit was positive for a 'positive' outcome (for example, a quality of life measure where a higher score denotes better health), and negative for a 'negative' outcome (for example, a visual analogue scale [VAS] pain score). Clinically significant harms were the converse of these. If baseline values were unavailable, then half the median comparator group standard deviation of that variable was taken as the MID.
- If standardised mean differences were used, then the MID was set at the absolute value of +0.5. This follows because standardised mean differences are mean differences normalised to the pooled standard deviation of the 2 groups, and are thus effectively expressed in units of 'numbers of standard deviations'. The 0.5 MID value in this context therefore indicates half a standard deviation, the same definition of MID as used for non-standardised mean differences.

The default MID value was subject to amendment after discussion with the GC. If the GC decided that the MID level should be altered, after consideration of absolute as well as relative effects, this was allowed, provided that any such decision was not influenced by any bias towards making stronger or weaker recommendations for specific outcomes.

For this guideline, no appropriate MIDs for continuous or dichotomous outcomes were found in the literature, and so the default method was adopted.

Update 2016

Figure 2: Illustration of precise and imprecise outcomes based on the 95% CI of dichotomous outcomes in a forest plot (Note that all 3 results would be pooled estimates, and would not, in practice, be placed on the same forest plot)



Update 2016

5.2.6.1.5 Overall grading of the quality of clinical evidence

Once an outcome had been appraised for the main quality elements, as above, an overall quality grade was calculated for that outcome. The scores (0, −1 or −2) from each of the main quality elements were summed to give a score that could be anything from 0 (the best possible) to −8 (the worst possible). However scores were capped at −3. This final score was then applied to the starting grade that had originally been applied to the outcome by default, based on study design. All RCTs started as High quality and the overall quality became Moderate, Low or Very Low quality if the overall score was −1, −2 or −3 points respectively. The significance of these overall ratings is explained in Table 4. The reasons for downgrading in each case were specified in the footnotes of the GRADE tables.

Observational interventional studies started at Low quality, and so a score of −1 would be enough to take the grade to the lowest level of Very Low quality. Observational studies could, however, be upgraded if there were all of: a large magnitude of effect, a dose-response gradient, and if all plausible confounding would reduce the demonstrated effect.

Table 4: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

5.2.6.2 Diagnostic studies

Risk of bias and indirectness of evidence for diagnostic data were evaluated by study using the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) checklists (see Appendix H in the NICE guidelines manual 2014[155]). Risk of bias and applicability in primary diagnostic accuracy studies in QUADAS-2 consists of 4 domains (see Figure 3):

- patient selection
- index test
- reference standard
- flow and timing.

Figure 3: Summary of QUADAS-2 with list of signalling, risk of bias and applicability questions

Domain	Patient selection	Index test	Reference standard	Flow and timing
Description	Describe methods of patient selection. Describe included patients (prior testing, presentation, intended use of index test and setting)	Describe the index test and how it was conducted and interpreted	Describe the reference standard and how it was conducted and interpreted	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2×2 table (refer to flow diagram). Describe the time interval and any interventions between index test(s) and reference standard
Signalling questions (yes/no/ unclear)	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?
	Was a case–control design avoided?	If a threshold was used, was it pre-specified?	Were the reference standard results interpreted without knowledge of the results of the index test?	Did all patients receive a reference standard?
	Did the study avoid inappropriate exclusions?			Did all patients receive the same reference standard?
				Were all patients included in the analysis?
Risk of bias; (high/low/ unclear)	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns regarding applicability (high/low/ unclear)	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

Update 2016

5.2.6.2.1 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results for an outcome across different studies. Inconsistency was assessed by inspection of the sensitivity OR (based on the primary measure) using the point estimates and 95% CIs of the individual studies on the forest plots. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold set by the GC (the threshold above which it would be acceptable to recommend a test). For example, the GC might have set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by 1 increment if the individual studies varied across 2 areas [(0-20%, 20-50%)] and by 2 increments if the individual studies varied across 3 areas [(for example, 0–20%, 20-50% and 90–100%)]. Reasons for heterogeneity between studies included age of population and the prevalence of risk factors, for example hypertension.

5.2.6.2.2 Imprecision

The judgement of precision was based on visual inspection of the confidence region around the summary sensitivity and specificity point from the diagnostic meta-analysis, if a diagnostic meta-analysis was conducted. Where a diagnostic meta-analysis was not conducted, imprecision was assessed according to the range of point estimates or, if only 1 study contributed to the evidence, the 95% CI around the single study. As a general rule (after discussion with the GC) the evidence was downgraded by 1 increment if the individual studies varied across 2 areas [(0-20%, 20-50%)] and by 2 increments if the individual studies varied across 3 areas [(for example, 0–20%, 20-50% and 90–100%)]. Imprecision was assessed on the primary outcome measure for decision-making.

5.2.6.2.3 Overall grading

Quality rating started at High for prospective and retrospective cross sectional studies, and each major limitation (risk of bias, indirectness, inconsistency and imprecision) brought the rating down by 1 increment to a minimum grade of Very Low, as explained for intervention reviews.

Update 2016

5.2.7 Assessing clinical importance

The GC assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro[84] software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio.

The assessment of clinical benefit, harm, or no benefit or harm was based on the point estimate of absolute effect for intervention studies, which was standardised across the reviews. The GC considered for most of the outcomes in the intervention reviews that if at least 100 more participants per 1000 (10%) achieved the outcome of interest in the intervention group compared to the comparison group for a positive outcome then this intervention was considered beneficial. The same point estimate but in the opposite direction applied for a negative outcome. For the critical outcome of mortality any reduction represented a clinical benefit. For adverse events 50 events or more per 1000 (5%) represented clinical harm. For continuous outcomes if the mean difference was greater than the minimally important difference (MID) then this represented a clinical benefit or harm. For outcomes such as mortality any reduction or increase was considered to be clinically important.

This assessment was carried out by the GC for each critical outcome, and an evidence summary table was produced to compile the GC's assessments of clinical importance per outcome, alongside the evidence quality and the uncertainty in the effect estimate (imprecision).

5.2.8 Clinical evidence statements

Clinical evidence statements are summary statements that are included in each review chapter, and which summarise the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements are presented by outcome and encompass the following key features of the evidence:

- The number of studies and the number of participants for a particular outcome.
- An indication of the direction of clinical importance (if one treatment is beneficial or harmful compared to the other, or whether there is no difference between the 2 tested treatments).
- A description of the overall quality of the evidence (GRADE overall quality).
- For diagnostic accuracy reviews the median and range were presented. Where there are 2 studies the lowest values and the range were reported.

5.3 Identifying and analysing evidence of cost-effectiveness

The GC is required to make decisions based on the best available evidence of both clinical effectiveness and cost-effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost-effectiveness') rather than the total implementation cost.[155] Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Health economic evidence was sought relating to the key clinical issues being addressed in the guideline. Health economists:

- Undertook a systematic review of the published economic literature.
- Undertook new cost-effectiveness analysis in priority areas.

Update 2016

5.3.1 Literature review

The health economists:

- Identified potentially relevant studies for each review question from the health economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using economic evaluations checklists as specified in the NICE guidelines manual. [155]

5.3.1.1 Inclusion and exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequences analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as health economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost-effectiveness without disaggregated costs and effects were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded. Studies published before 2001 and studies from non-OECD countries or the USA were also excluded, on the basis that the applicability of such studies to the present UK NHS context is likely to be too low for them to be helpful for decision-making.

Remaining health economic studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. However, in this guideline, no economic studies were excluded on the basis that more applicable evidence was available.

For more details about the assessment of applicability and methodological quality see Table 5 below and the economic evaluation checklist (Appendix G of the 2012 NICE guidelines manual[155]) and the health economics review protocol in Appendix E.

When no relevant health economic studies were found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GC to inform the possible economic implications of the recommendations.

5.3.1.2 NICE health economic evidence profiles

Table 5: Content of NICE health economic evidence profile

Item	Description
Study	Surname of first author, date of study publication and country perspective with a reference to full information on the study.
Applicability	An assessment of applicability of the study to this guideline, the current NHS situation and NICE decision-making:[(a)] • Directly applicable – the study meets all applicability criteria, or fails to meet 1 or more applicability criteria but this is unlikely to change the conclusions about cost-effectiveness. • Partially applicable – the study fails to meet 1 or more applicability criteria, and this could change the conclusions about cost-effectiveness. • Not applicable – the study fails to meet 1 or more of the applicability criteria, and this is likely to change the conclusions about cost-effectiveness. Such studies would usually be excluded from the review.
Limitations	An assessment of methodological quality of the study:[(a)] • Minor limitations – the study meets all quality criteria, or fails to meet 1 or more quality criteria, but this is unlikely to change the conclusions about cost-effectiveness. • Potentially serious limitations – the study fails to meet 1 or more quality criteria, and this could change the conclusions about cost-effectiveness. • Very serious limitations – the study fails to meet 1 or more quality criteria, and this is highly likely to change the conclusions about cost-effectiveness. Such studies would usually be excluded from the review.
Other comments	Information about the design of the study and particular issues that should be considered when interpreting it.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
Cost-effectiveness	Incremental cost-effectiveness ratio (ICER): the incremental cost divided by the incremental effects (usually in £ per QALY gained).
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

(a) Applicability and limitations were assessed using the economic evaluation checklist in Appendix G of the 2012 NICE guidelines manual[155]

Update 2016

5.3.2 Undertaking new health economic analysis

As well as reviewing the published health economic literature for each review question, as described above, new health economic costing analysis was undertaken by the health economist in selected areas. Priority areas for new analysis were agreed by the GC after formation of the review questions and consideration of the existing health economic evidence.

The GC identified the question on non-invasive imaging as the highest priority area for original health economic analysis. This was due to the potential significant economic impact of recommending routine non-invasive imaging in all emergency departments to diagnose acute coronary syndrome. The GC also considered that the potential recommendations from the high-sensitivity troponin question would lead to either the same or fewer tests being done, not more tests. This meant the high-sensitivity troponin question had no significant resource impact, but instead only a potential cost saving to the NHS. A cost analysis was undertaken for the non-invasive imaging question to inform relevant recommendations in the acute chest pain reviews.

The following general principles were adhered to in developing the cost analysis:

- Methods were consistent with the NICE reference case for interventions with health outcomes in NHS settings.[39,155]
- The GC was involved in the design, selection of inputs and interpretation of the results.
- Inputs were based on the clinical literature supplemented with other published data sources where possible.
- Inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The analysis was peer-reviewed by another health economist at the NGC.

Full methods for the cost analysis are described in Appendix P.

Update 2016

5.3.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GCs should consider when judging whether an intervention offers good value for money.[42] In general, an intervention was considered to be cost-effective (given that the estimate was considered plausible) if either of the following criteria applied:

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the GC recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.[42]

When QALYs or life years gained are not used in the analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

5.3.4 In the absence of health economic evidence

When no relevant published health economic studies were found, and a new analysis was not prioritised, the GDG made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the review of clinical effectiveness evidence.

The UK NHS costs reported in the guideline are those that were presented to the GC and were correct at the time recommendations were drafted. They may have changed subsequently before the time of publication. However, we have no reason to believe they have changed substantially.

5.4 Developing recommendations

Over the course of the guideline development process, the GC was presented with:

- Evidence tables of the clinical and health economic evidence reviewed from the literature. All evidence tables are in Appendix I.
- Summaries of clinical and health economic evidence and quality (as presented in Chapters 6 and 7).
- Forest plots and summary ROC curves (Appendix M).

Recommendations were drafted on the basis of the GC's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally in an economic model, or informally. Firstly, the net clinical benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the GC took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net clinical benefit was moderated by the importance placed on the outcomes (the GC's values and preferences), and the confidence the GC had in the evidence (evidence quality). Secondly, the GC assessed whether the net clinical benefit justified any differences in costs between the alternative interventions.

Update 2016

When clinical and health economic evidence was of poor quality, conflicting or absent, the GC drafted recommendations based on its expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared to the economic benefits, current practices, recommendations made in other relevant guidelines, the preferences of lay members and equality issues. The consensus recommendations were agreed through discussions in the GC. The GC also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see Section 5.4.1 below).

The GC considered the appropriate 'strength' of each recommendation. This takes into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' in that the GC believed that the vast majority of healthcare and other professionals and patients would choose a particular intervention if they considered the evidence in the same way that the GC had. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost-effective. However, there is often a closer balance between benefits and harms, and some patients would not choose an intervention whereas others would. This may happen, for example, if some patients are particularly averse to some side effect and others are not. In these circumstances the recommendation is generally weaker, although it may be possible to make stronger recommendations about specific groups of patients.

The GC focused on the following factors in agreeing the wording of the recommendations:

- The actions health professionals need to take.
- The information readers need to know.
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weaker recommendations).
- The involvement of patients (and their carers if needed) in decisions on treatment and care.
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions (see Section 9.2 in the 2014 NICE guidelines manual[155]).

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter.

5.4.1 Research recommendations

When areas were identified where good evidence was lacking, the GC considered making recommendations for future research. Decisions about the inclusion of a research recommendation were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

5.4.2 Validation process

This guidance was subject to a 4-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders were responded to in turn and posted on the NICE website.

Update 2016

5.4.3 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will undertake a review of whether the evidence base has progressed significantly, or if there has been a change in practice or new evidence to alter the guideline recommendations and warrant an update.

5.4.4 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of this guideline and the literature used in support of this guideline.

5.4.5 Funding

The National Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on the acute chest pain section of the guideline.

6 Information for patients

6.1 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: that is, 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.

6.2 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[5].

6.3 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)[5]. 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[5].

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)[5].

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[5].

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[5].

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[5].

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 questionnaire 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[5].

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[5].

6.4 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.

7 People presenting with acute chest pain

7.1 Introduction

This section 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 GC 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 high sensitivity troponin negative results), and these patients have been identified for further assessment according to the stable chest pain recommendations in Chapter 7.

Other life threatening conditions may also present with acute chest pain. The GC 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.

7.2 Assessment

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

7.2.1.1 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.[20,136,205]

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.[205]

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.[20]

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.[136]

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.[192]

7.2.1.2 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[20,136,205], and one cohort study[192] 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)[205]. 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[205].

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 6 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[205].

Table 6

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[205].

The second systematic review on the accuracy of 10 elements of the clinical history identified 28 prospective and retrospective cohort studies (search date 2006)[20]. 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[20].

Table 7 and Table 8 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[205], 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[205]. 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[20].

Table 7

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[20].

Table 8

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	I2a (%)		#		95%CI	I2a (%)
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					

Table 8										
	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		1	79	66.9 to 91.2	Only one
	Specificity		67	61.8 to 71.1	study			39	25.1 to 52.4	study
	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	Sensitivity	6	26	20.7 to 32.2	91		0		No studies	
nausea	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					
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	

Table 8										
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
I2a = test for heterogeneity
Permissions granted from original source[20].

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[136]. 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[136].

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 9). 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)[136].

Table 9

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	

Table 9					
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[136].

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[136].

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[192]. 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[192].

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, hyperlipidaemia, and family history all typical, atypical was defined as absence or only one risk factor[192].

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[192].

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[192].

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[192].

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[192].

7.2.1.3 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.

7.2.1.4 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 lifesaving. 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 6.2.6.1).

7.2.2 Gender differences in symptoms

7.2.2.1 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.[29,168]

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.[168]

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.[29]

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.[168]

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.[113]

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.[126]

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.[126]

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.[44]

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.[45],

7.2.2.2 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[213] despite the repeated documented lower angiographic disease burden and more often preserved left ventricular function compared with men[153]. 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[29,168], three cohort studies[45,113,126], and one case controlled study were reviewed[44].

The first systematic review (search date 2002) examined the gender differences in the presentation of acute MI and ACS[168]. 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[168].

As shown in Table 10 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)[168].

As detailed in Table 10, 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)[168].

Table 10

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[168].

The second systematic review (search date 2005) examined the gender differences in the presenting symptoms of ACS[29]. 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[168]. 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 labelled 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[29].

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[29].

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)[30] 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[29].

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[29].

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[29].

The first cohort study compared symptoms of acute MI in women versus men[113]. 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[113].

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[113].

The second cohort study examined sex-related differences in the clinical history and risk factors associated with ST-segment elevation acute MI[126]. 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[126].

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)[126].

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[44]. 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[44].

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)[44].

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)[44].

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 11[44].

Table 11
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/m2)	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[44].

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[45]. 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)[45].

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 coronary 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)[45].

7.2.2.3 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.

7.2.2.4 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.

7.2.3 Ethnic differences between symptoms

7.2.3.1 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.[117,125]

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.[139]

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.[139]

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.[139]

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.[139]

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.[139]

7 One cohort study in patients presenting with ACS found that Asian patients were younger and more likely to be diabetic compared with Caucasians.[206]

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.[206]

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.[9].

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.[9].

11 No health economic evidence was identified.

7.2.3.2 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[9,132] although other reports conflict with these findings[19,223]. 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[13]. 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[38,49,201]. 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[117,125,139] and two studies compared Asian patients with Caucasian patients[9,206].

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[117]. 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[117].

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[117].

Sub group analysis of patients with a final diagnosis of acute Ml 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 ≥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)[117].

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)[117].

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[139]. 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 12[139].

Table 12
Medical history and clinical characteristics of patients on admission

	Men			Women		
Variable	% Caucasian*	% African American†	P	% Caucasian‡	% African American§	P
Medical history						

Table 12 **Medical history and clinical characteristics of patients on admission**						
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[139]						

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[139].

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[139].

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)[139].

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[125]. 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[125].

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[125].

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)[125].

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[125].

The fourth cohort study compared the symptom presentation in Asian and Caucasian patients with ACS[206]. 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[206].

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 13. 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[206].

Table 13

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

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The distribution of reported discomfort for Asians and Caucasians is detailed in Table 14 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)[206].

Table 14

Comparison of pain characteristics between Asian and Caucasian groups

	Asian patients, n=604	Caucasian patients, n=2301	P Value

Table 14			
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[206].			

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%)[206].

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[206].

The fifth cohort study assessed the differences in presentation of acute MI between Bangladeshi patients and Caucasian patients[9]. 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[9].

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 patient's age, sex, risk factors and proficiency in English[9].

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[9].

7.2.3.3 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.

7.2.3.4 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[9] 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.

7.2.4 Use of nitrates in the diagnosis of acute chest pain

7.2.4.1 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.[60,91,200,202]

7.2.4.2 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[60,91,202] and one retrospective cohort study[200] 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[202]. 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 (for example 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)[202].

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)[202].

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[202].

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[202].

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[202].

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[202].

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[60]. 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 ≤ 5, (2) moderate reduction, 34% to 84% relief if initial pain score > 5, or 25% to 28% reduction if initial pain score was ≤ 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[60].

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[60].

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 (for example pressure, stabbing, dullness) or associated symptoms (for example 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%)[60].

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%)[60].

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)[60].

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[91]. 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[91].

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[91].

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 one 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[91].

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[91].

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[91].

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[91].

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[91].

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[200]. 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[200].

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 (≥50% stenosis of the left main artery or ≥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[200].

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[200].

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)[200].

7.2.4.3 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.

7.2.4.4 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.

7.2.5 Resting 12 lead ECG

7.2.5.1 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.[136]

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.[46]

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.[149]

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.[111]

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).[188]

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.[52]

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.[67]

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.[162]

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.[8]

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.[61]

7.2.5.2 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[46,111,136,149], and six cohort studies[8,52,61,67,162,188] were identified in patients with acute chest pain. Two of the systematic reviews examined studies in both acute and stable patients with chest pain[46,136]. One systematic reviewed out of hospital ECG[111], 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[61]. Two cohort studies assessed the use of ECG and chest pain scores[188],[52], one cohort examined the use of serial ECG[67] and two cohorts examined computer assessment of ECG[8,162].

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[136]. 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[136].

As detailed in Table 15, 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[136].

Table 15

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

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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 16[136].

Table 16					
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)

Table 16					
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)
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 (that is, a decision by a front-line physician, not an outside expert) and adequate follow up.
AMI, acute MI.
Permissions granted from original source[136].

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[46]. Seven out of 9 studies were identified in this systematic review were identified in[136]. 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)[46].

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))[46].

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[149]. 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%, $P = 0.22$)[149].

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)[111]. 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)[111].

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[111].

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[188]. A total of 609 patients were consecutively recruited; the mean age was 64(SD 12) years and 67% were men[188].

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 17). 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 ($P = 0.7$)[188].

Table 17

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
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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[52]. 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[52].

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[52].

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[52].

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%[52].

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[52].

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[67]. 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[67].

Patients were diagnosed with acute MI if they met WHO diagnostic criteria[80]. 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%[67].

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)[67].

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%, $P < 0.001$)[67].

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[67].

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[162]. 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[162].

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[162].

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[162].

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[8]. 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[8].

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[8].

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[8].

The sixth cohort study examined the use and impact of pre-hospital ECG for patients with acute ST-segment elevation MI[61]. 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)[61].

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[61].

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[61].

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)[61].

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)[61].

7.2.5.3 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.

7.2.5.4 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.

7.2.6 Early assessment in hospital

7.2.6.1 Other causes of chest pain

The differential diagnosis of patients presenting with chest pain is extensive, ranging from relatively benign musculoskeletal aetiologies 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 18 details the symptoms of some of the causes of non-ischaemic cardiac chest pain as published by The European Society of Cardiology Task Force Report[152]. Note that for some diseases, the differentiating symptoms and signs include diagnostic interventions.

Table 18

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 PaO2 and PaCO2 decreased
Hyperventilation	The main symptom is dyspnoea, as in pulmonary embolism

Table 18	
	Often a young patient Tingling and numbness of the limbs, dizziness PaCO2 decreased, PaO2 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[152].	

Use of chest X ray

7.2.6.2 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.

7.2.6.3 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.

7.2.6.4 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.

7.2.6.5 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.

7.3 Early management

7.3.1 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.

7.3.2 Oxygen

7.3.2.1 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.[156]

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.[177]

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.[224]

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

7.3.2.2 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[156]. A second more recent systematic review[222] identified 2 randomised controlled trials in addition to the studies identified by the first systematic review[156]. Rather than appraise the second systematic review it was decided to appraise the 2 randomised controlled trials individually[177,224].

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[156]. 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[156].

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[156].

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[156].

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[156].

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[156].

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[156].

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[177]. 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/minute for 24 hours. The mean PaO2 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, $P < 0.001$)[177].

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 ($P < 0.05$)[177].

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[177].

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[224]. Patients with central cyanosis, pulmonary disease requiring oxygen independent of the cardiac status or those in whom blood gas estimation showed a $PCO2 > 5.5$ 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/minute 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[224].

Twenty (48%) of the total 42 patients in the study had periods of at least moderate hypoxaemia ($SpO2 < 90\%$) and 8 (19%) patients had severe hypoxaemia ($SpO2 < 80\%$). 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 SpO2 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[224].

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[161]. 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/minute or simple face mask at 5 to 10 l/minute 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 PaCO2 is normal (unless there is a history of respiratory failure requiring NIV or IPPV) and recheck blood gases after 30 to 60 minutes.

7.3.2.3 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).

7.3.2.4 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 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 British Thoracic Society guideline were used to inform the thresholds at which oxygen should be administered, and the target oxygen saturation to be achieved.

7.3.3 Pain management

7.3.3.1 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.[88]

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.[97]

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.[114]

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.[193].

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.[66]

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.[92].

7.3.3.2 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[88,97,114,193] and 2 studies were cohort studies[66,92]. Only one study examined co-administration of pain relief with an anti-emetic[114].

The first randomised controlled trial examined buprenorphine and diamorphine for pain relief in patients with suspected or ECG proven acute MI[88]. 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[88]

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[88].

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[88].

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[97]. 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)[97].

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)[97].

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[97].

The third randomised controlled trial compared nalbuphine with diamorphine plus metoclopramide for pain relief in patients with suspected acute MI[114]. 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)[114].

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[114].

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[114].

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[193]. 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[193].

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[193].

The first cohort study examined pain relief effects of morphine in 10 patients with suspected acute MI[66]. 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[66].

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[66].

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[66].

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[92]. 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[92].

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[92].

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, $P < 0.001$)[92].

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.

7.3.3.3 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.

7.3.3.4 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 6.2.4 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.

7.3.4 Anti-platelet therapy

7.3.4.1 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.[10]

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

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

7.3.4.2 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[10].

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[10]. 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[10].

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 ($P < 0.002$)[10].

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[10].

7.3.4.3 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).

7.3.4.4 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[47] 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.

7.4 Investigations and diagnosis

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 or non-ischaemic injury. 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 Joint ESC/ACCF/AHA/WHF Task Force for the Third Universal Definition of Myocardial Infarction .[208] is given on page 274. Specifically for biomarkers it states;

Update 2016

“detection of rise and / or fall of cardiac biomarkers values [preferably cardiac troponin (cTn)] 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

7.4.1 High sensitivity cardiac troponins

Introduction

The use of standard troponin assays is routine and in 2015 NICE diagnostics guidance on myocardial infarction (DG15) recommended that high sensitivity troponin tests are an option for the early rule out of NSTEMI in people presenting with acute chest pain. High sensitivity troponin assays can detect lower levels of troponin in the blood within 4 hours compared to the standard assays at 10–12 hours, improving the early detection and management of MI. NICE DG15 recommends that everyone presenting with acute chest pain has 2 troponin tests regardless of ACS risk. This review question examines whether high-sensitivity troponin assays could be used differently in people presenting with acute chest pain according to their ACS risk.

Update 2016

7.4.1.1 Review question: In low, medium and high risk people under investigation for acute chest pain of suspected cardiac origin, what is the clinical and cost effectiveness of high-sensitivity troponin assay methods compared to standard cardiac troponins to identify/rapidly rule-out NSTEMI/unstable angina and to improve patient outcomes?

For full details see review protocol in Appendix D.

Table 19: Characteristics of review question

Population	Target condition and presentation: • adults (age ≥18 years) presenting with acute chest pain/discomfort of suspected cardiac origin. Strata (as defined by study): • high risk • medium risk • low risk.
Intervention	High-sensitivity cardiac troponin (hs-cTn) assays: The recommended definition of a hs-cTn assay uses 2 criteria: • The total imprecision, coefficient of variation (CV), of the assay should be ≤10% at the

	99th percentile value of a healthy reference population. • The limit of detection (LoD) of the assay should be such as to allow measurable concentrations to be attainable for at least 50% (ideally >95%) of healthy individuals.
Comparison	• Tn T or I measurement on presentation and 10–12 hours after the onset of symptoms • any other hs-cTn test, as specified above, or no comparators • no test.
Outcomes	**Efficacy outcomes:** • all-cause mortality during 30 days and 1 year follow-up period (or closest time point) • cardiovascular mortality during 30 days and 1 year follow-up period (or closest time point) • myocardial infarction during 30 day follow-up period **Process outcomes:** • time to discharge • early discharge (≤4 hours after initial presentation) without MACE during follow-up **Secondary accuracy outcomes:** • sensitivity/specificity and other test accuracy measures.
Study design	RCT Systematic review

7.4.1.2 Review question: In low, medium and high risk people with suspected (or under investigation for) acute chest pain, is high sensitivity troponin more accurate compared to troponin or eventual clinical diagnosis to identify whether NSTEMI or unstable angina is present, as indicated by the reference standard?

Update 2016

For full details see review protocol in Appendix D.

Table 20: Characteristics of review question

Population	Adults (age ≥18 years) presenting with acute chest pain/discomfort of suspected cardiac origin. Acute chest pain is defined as 'pain, discomfort or pressure in the chest, epigastrium, neck, jaw, or upper limb without an apparent non-cardiac source attributed to a suspected, but not confirmed AMI.' Include studies that compare different risks and studies that report accuracy for different risk stratifications. • High risk • Medium risk • Low risk For papers which do not report TIMI, GRACE or other validated risk tool scores we will map prevalence to the risks reported in TIMI.
Target condition	NSTEMI/unstable angina (UA)
Index test	High-sensitivity cardiac troponin (hs-cTn) assays: The recommended definition of a hs-cTn assay uses 2 criteria: • The total imprecision, coefficient of variation (CV), of the assay should be ≤10% at the 99th percentile value of a healthy reference population. • The limit of detection (LoD) of the assay should be such as to allow measurable concentrations to be attainable for at least 50% (ideally >95%) of healthy individuals.

Reference standards	• Composite reference standard on the contemporary universal definition of myocardial infarction[e] • Reference assays used to diagnose myocardial necrosis, for example: ○ serial high sensitivity troponin assays ○ standard troponin T or I assays or a combination of them
Statistical measures [or] Outcomes	Test accuracy 2×2 tables Specificity Sensitivity
Study design	• Cross-sectional studies and cohort studies (including both retrospective and prospective analyses) Case-control studies to be included only if no other evidence is identified

7.4.1.2.1 Clinical evidence

Clinical effectiveness

No systematic reviews or RCTs were identified on the clinical effectiveness of high-sensitivity troponin assay methods compared to standard cardiac troponins to identify/rapidly rule-out NSTEMI/unstable angina.

Diagnostic accuracy review

Update 2016

A search was conducted for cross-sectional and cohort studies (including both retrospective and prospective analyses) assessing the diagnostic test accuracy of test high sensitivity cardiac troponins to identify whether the condition is present (as indicated by the reference standard) in people under investigation for acute chest pain. See also the study selection flow chart in Appendix F, sensitivity and specificity forest plots and receiver operating characteristics (ROC) curves in Appendix M, study evidence tables in Appendix I and exclusion list in Appendix N.

Thirteen diagnostic accuracy studies were included in the review;[2,3,18,48,64,70,98,112,130,143,178,189,194] these are summarised in Table 21 below. Evidence from these is summarised in the clinical evidence profile below (see Table 23 and Table 24). The predictive values are presented in Table 25.

A variety of index tests at different thresholds were used and blood taken at different time points (see Table 22). The aim of all studies was to assess the diagnostic test accuracy of identifying acute chest pain due to NSTEMI. No studies included patients with unstable angina (UA). Studies were excluded if they included patients with a diagnosis of STEMI and the results were not reported separately for the STEMI and NSTEMI/UA populations. One study only included people aged 75 years and over.[18] Two studies[130,143] included patients who presented to coronary care units. The maximum time from symptom onset to presentation for these studies was 12 hours.

Two studies[70,130] reported the median TIMI score and 1 study[18] the GRACE score in the patient population. For the remaining studies, prevalence of NSTEMI and unstable angina was calculated for each study. This was mapped to the rate at 14 days of death, or new or recurrent myocardial infarction, or severe recurrent anginal chest pain requiring urgent revascularization reported in TIMI.

- Score of 0–1 = 4.7% risk
- Score of 2 = 8.3% risk
- Score of 3 = 13.2% risk

[e] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD et al. Third universal definition of myocardial infarction. Circulation. 2012; 126(16):2020-2035

- Score of 4 = 19.9% risk
- Score of 5 = 26.2% risk
- Score of 6–7 = at least 40.9% risk

The corresponding score was then used to classify the population as low, moderate or high risk:

- 0-8% Low risk (score 0 to 2)
- 9%-20% Moderate risk (score 3 to 4)
- 21% or more High risk (score 5 or more)

One study in the moderate risk group reported diagnostic accuracy data at presentation and at two hours for the same threshold.[130] Three studies in the high risk group reported diagnostic accuracy data at presentation and at two hours for the same threshold.[2,3,143] One study reported serial samples at 0, 2, 4 and 8 hours after the onset of symptoms.[189] One study in older adults reported data at presentation and 3–4 hours after presentation.[18]

Update 2016

Table 21: Summary of studies included in the review

Study	Index test	Reference test	Population	Demographics	Prevalence and risk strata	Comments
Studies reporting TIMI or GRACE score						
Borna 2016[18] Prospective cohort	The HScTnT analyses were performed with the use of the Elecsys 2010 system (Roche) with a limit of detection of 2 ng/l, a 99thpercentile cut-off of 14 ng/l, and a coefficient of variation of less than 10 at 13 ng/l	AMI was diagnosed according to the joint European Society of Cardiology/American College of Cardiology/ American Heart Association/World Heart Federation Task Force. In addition, all diagnoses and ECGs were reviewed by 2 cardiologists. In patients with a HScTnT >14 ng/l, a 20% rise or fall was considered sufficient for an AMI diagnoses together with a clinical course suggestive of ACS.	N=477 February 2010 to March 2012 Inclusion criteria: All patients ≥75 years with chest pain suspicious of ACS if they were admitted to the ED or the medical observation unit. Exclusion criteria: Patients identified as low risk and discharged home from the ED. STEMI patients	Median (IQR) age: 82 (77–85) Male (%): 53 White (%): NR Previous CAD (%): 59 Previous family history (%): NR Previous revascularisation (%): 47 Diabetes (%): 24 Smoking (%): NR Hypertension (%): 59 Dyslipidaemia (%): 48 Mean (SD) BMI: NR Time to presentation: NR	Median (IQR) GRACE score 142 (125–164) NSTEMI 127/477 (27%) Moderate	Reports absolute and change of 5% or more at different thresholds
Freund 2011[70] Prospective cohort	Samples collected 3 to 9 hours later were analysed. Plasmatic highly sensitive	AMI was diagnosed according to the joint European Society of Cardiology/American College of	N=317 August 2005 to January 2007	– N=258 Mean (SD) age: 56 (17)	TIMI – 1 (0–2) Low NSTEMI	

Study	Index test	Reference test	Population	Demographics	Prevalence and risk strata	Comments
	cardiac TnT (HScTnT) concentrations were measured using the HScTnT onestep electrochemiluminescence immunoassay on an Elecsys 2010 analyzer (Roche Diagnostics, Meylan, France). The measuring range extended from 0.003 to 10 µg/L. The threshold for this method is 0.014 µg/L and corresponds to the 99th percentile. The CV was found to be < 10% at	Cardiology/ American Heart Association/World Heart Federation Task Force redefinition of MI guidelines. Diagnosis of AMI required a cTnI increase above the 10% coefficient of variation (CV) value associated with at least one of the following: symptoms of ischaemia, new ST-T changes or a new Q wave on an electrocardiogram, imaging of new loss of viable myocardium or normal cTnI on admission. Unstable angina was diagnosed in patients with constant normal cTnI levels and a history or clinical symptoms consistent with ACS.	Inclusion criteria: Consecutive hospital outpatients (>18 years of age) who presented to the ED with chest pain suggestive of ACS with the onset or peak occurring within the previous 6 hours. No STEMI included in the sub-group extracted. Exclusion: Chronic kidney disease requiring dialysis.	Male (%): 64 White (%): NR Previous CAD (%): 22 Previous family history (%): 30 Previous revascularisation (%): NR Diabetes (%): 12 Smoking (%): 38 Hypertension (%): 34 Dyslipidaemia (%): 33 Mean (SD) BMI: NR Time to presentation: NR	22/258 (8.53%)	

Study	Index test	Reference test	Population	Demographics	Prevalence and risk strata	Comments
	0.014 µg/L					
Kurz 2010[130] Prospective cohort	All laboratory measurements on the new high sensitive cardiac troponin T assay (TnThs) were performed in the research laboratory of Roche Diagnostics in Penzberg, Germany. Lower detection limit of TnThs was 3 pg/ml (=0.003 lg/L). The inter-assay coefficient of variation was 8% at 10 pg/ml and 2.5% at 100 pg/ml. The intra-assay coefficient of variation was	Unstable angina and non-ST-segment elevation myocardial infarction (non-STEMI) were diagnosed using the joint European Society of Cardiology/American College of Cardiology/American Heart Association/World Heart Federation Task Force redefinition of myocardial infarction guidelines. Patients with cTnT concentrations at presentation below the 10% CV diagnostic cut-off (0.03 lg/L) received a final diagnosis of unstable angina or evolving non-STEMI depending on the presence of an	N=94 May 2008– December 2008 Inclusion criteria: consecutively, patients with symptoms suggestive of ACS admitted to the chest pain unit. Exclusion criteria: Patients with ST-segment elevation at presentation were excluded as were patients with severe kidney dysfunction (glomerular filtration rate \60 ml/min/1.73 m^2) and patients undergoing percutaneous coronary intervention during follow-up sampling.	Mean (SD) age: 65.6 (10.8) Male (%): 71.3 White (%): NR Previous CAD (%): 50 Previous family history (%): 31.9 Previous Revascularisation (%): CABG -17 Diabetes (%): 30.9 Smoking (%): 22.3 Hypertension (%): 77.7 Dyslipidaemia (%): 64.9 Mean (SD) BMI: 28.1 (4.1) Time to presentation: early (less than 4 hours) - 42.6% late (greater than 4 hours - 56.4% Median time from onset: 358 minutes (152–929.3 minutes)	NSTEMI: 28/94 (38%) Median (IQR) TIMI – 3 (2/4) High	Patients admitted to chest pain unit

Study	Index test	Reference test	Population	Demographics	Prevalence and risk strata	Comments
	5% at 10 pg/ml and 1% at 100 pg/ml. Preliminary data demonstrated detectable concentrations in 2 normal reference populations with an overall 99th percentile value of 13.5 pg/ml.	elevated cTnT concentration in at least 1 of the consecutive samples collected within 24 hours after index event.				
Studies reporting prevalence (and mapped to the TIMI score)						
Aldous 2011[2] Aldous 2012[3] Prospective cohort	Roche Elecsys hs-cTnT LOD: 5 99th centile: 14 Coefficient of variation: <10% at 13	AMI was diagnosed if there was a rise and/or fall of the cTnI (≥20)% with ≥1 value at the 99th percentile. Conventional troponins were measured using Abbott Diagnostics TnI (LoD 10 ng/l, 99th centile 28 ng/l, CV <10% at 32 ng/l,	N=939 November 2007–December 2010 New Zealand Inclusion criteria: Adults (≥18 years) with symptoms suggestive of cardiac ischemia (acute chest, epigastric, neck, jaw or arm pain or discomfort or	Median age (IQR): 65(56, 76) Male (%): 60 White (%): 89 Previous CAD (%): 52 Previous family history (%): 60 Previous revascularisation (%): 30 Diabetes (%): 17 Smoking (%): 61 Hypertension (%): 61 Dyslipidaemia (%): 58	NSTEMI 110/939 (21.8%) High	Reports peak 14 0–2 hours (see Table 24 for further explanation)

Study	Index test	Reference test	Population	Demographics	Prevalence and risk strata	Comments
		decision threshold 30 ng/l). Timing: On presentation, and at 2 hours and 6–12 hours. Where there was no change in cTnI, AMI was diagnosed if there was objective evidence of myocardial ischemia, including new ischemic electrocardiogram changes, positive stress testing or significant coronary artery disease detect by coronary angiography (1 or more coronary stenosis of ≥70% or revascularisation procedure) and no clear alternative cause for cardiac troponin elevation. Diagnosis made by an independent cardiologist blind to	pressure without an apparent non-cardiac source). Exclusion criteria: ST-segment elevation on ECG; unable to provide informed consent; would not be available to follow-up. Conventional troponins were measured using Abbott Diagnostics TnI (LoD 10 ng/l, 99th centile 28 ng/l, CV <10% at 32 ng/l, decision threshold 30 ng/l) Timing: On presentation, and at 2 hours and 6–12 hours	Median BMI (IQR): 28(25, 31) Median (IQR) time to presentation (hours): 6.3 (3.3, 13.3)		

Study	Index test	Reference test	Population	Demographics	Prevalence and risk strata	Comments
		the assay results but with knowledge of the serial laboratory cTnI.				
Collinson 2013[48] Prospective cohort	Roche Elecsys hs-cTnT LOD: 3 99th centile: 14 Coefficient of variation: <10% at 30 ng/l	The universal definition of myocardial infarction was used to categorise patients into those with or without an AMI utilising clinical, ECG, trial and local laboratory-derived cardiac troponin values and troponin measurements subsequently performed in the trial central laboratory on the admission and 90 minute samples using the Siemens Ultra assay as the predicate troponin method. Patients were classified as having an AMI on the	N=850 UK Patients presenting to the emergency department with chest pain due to suspected, but not proven, AMI. Exclusion criteria: ECG changes diagnostic for AMI or high risk ACS (>1 mm ST deviation, or >3 mm inverted T waves); known CAD with prolonged (>1 hour) or recurrent typical cardiac-type pain; proven or suspected serious non-cardiac pathology (for example PE); co-morbidity or social problems requiring hospital admission even if AMI ruled out; obvious non-cardiac cause of chest pain (for example pneumothorax or muscular pain); presentation >12 hours	Median age (IQR): 54(44, 64) Male (%): 60 Previous AMI (%): 40 Previous family history (%): Previous revascularisation (%): 1 Diabetes (%): 8 Smoking (%): 28 Hypertension (%): 35 Dyslipidaemia (%): 24 Median (IQR) time to presentation (hours): 8.25 (5.17 to 12.30)	NSTEMI 67/850 (7.9%) Low	Reports peak 14 0–2 hours (see Table 24 for further explanation)

Study	Index test	Reference test	Population	Demographics	Prevalence and risk strata	Comments
		basis of appropriate clinical features, electrocardiographic changes and the presence of a rise in troponin level above the diagnostic discriminant of the relevant assay in use locally and no alternative clinical cause of a troponin rise. Patients with a troponin rise consistent with an AMI and a final diagnosis of ACS or an AMI were classified as having an AMI. Patients with no troponin rise consistent with an AMI and a final diagnosis that was neither ACS nor an AMI were classified as not having an AMI. Patients with a final diagnosis of ACS or an AMI but no troponin rise were	after most significant episode of pain.			

Study	Index test	Reference test	Population	Demographics	Prevalence and risk strata	Comments
		assessed by a single reviewer blind to treatment group who reviewed the initial and next-day ECG and categorised these patients as having an AMI only if an ECG showed ST-segment elevation and coronary reperfusion was performed. Patients with a troponin rise and a final diagnosis other than ACS or an AMI were assessed by 2 reviewers blinded to treatment group who reviewed case details and decided whether or not an AMI was the most likely diagnosis. Disagreements were resolved by discussion and patients classified as having an AMI or not. All patients with a				

Study	Index test	Reference test	Population	Demographics	Prevalence and risk strata	Comments
		cTnI (measured on the Siemens Ultra assay) exceeding the 99th percentile or a troponin measurement from the local laboratory exceeding the 99th percentile were reviewed and the final diagnosis confirmed.				
Eggers 2012[64] Prospective cohort	Roche Elecsys hs-cTnT LOD: 3 99th centile: 14 Coefficient of variation: <10% at 13	Diagnosis was made based on the ESC/ACC consensus document. cTnI (Stratus CS, Siemens Healthcare Diagnostics, Deerfield, IL, USA). Non-STEMI defined as: cTnI above the 99th percentile of 0.07 µg/l at least at 1 measurement together with a ≥20% rise and/or fall and an absolute change ≥0.05 µg/l within 24 hours. To allow for the calculation of	N=360 May 2000 (FAST II), October 2002 (FASTER I) – March 2001 (FAST II), August 2003 (FASTER I) Sweden Inclusion criteria: Chest pain with ≥15 minutes duration within the last 24 hours (FAST II-study), or the last 8 hours (FASTER I-study). Analysis restricted to patients with symptom onset <8 hours. Exclusion criteria: ST-segment elevation on the admission 12-lead ECG leading to immediate	Male (%): 66 Previous AMI (%): 38 Previous revascularisation (%): 18 Diabetes (%): 18 Smoking (%): 18 Hypertension (%): 43 Dyslipidaemia (%): 38 Delay <4 hours (%): 40	NSTEMI 128/360 (35.6%) High	

Study	Index test	Reference test	Population	Demographics	Prevalence and risk strata	Comments
		relative changes, cTnI was set to 0.02 µg/l (that is, a concentration below the lowest level of detection) when reported as 0.00 or 0.01 µg/l. Timing: 8 time points during the first 24 hours following enrolment. Patients with typical angina pain at rest in combination with ST-segment depression but not fulfilling biochemical criteria for non-STEMI were considered to suffer from unstable angina.	reperfusion therapy or its consideration was used as exclusion criterion.			
Hochholzer (2011)[98] Prospective cohort	Roche Elecsys hs-cTnT LOD: 2 ng/l 99th centile: 14 ng/l Coefficient of variation: <10% at 13 ng/l	Joint ESC, ACC, AHA and WHF[(a)] Conventional troponins were measured using Roche cTnT 4th generation assay (CV <10% at 35 ng/l), Beckman Coulter Accu cTnI (CV <10%	N=724 Date recruited: April 2006 – April 2008 Country: Switzerland, Spain, USA and Germany Inclusion criteria: Consecutive adults presenting to the ED with symptoms suggestive of AMI at rest or minor	Median age (IQR): 63 (50-75) Male (%): 66 Previous AMI (%): 25 Previous CAD (%): 35 Previous revascularisation (%): 28 Impaired rental function (GFR <60 ml/minute): 12	NSTEMI 93/724 (13%) Moderate	Demographic characteristics include STEMI patients (30% of total), but results presented are for NSTEMI only. Reference Test assumed to be

Study	Index test	Reference test	Population	Demographics	Prevalence and risk strata	Comments
		at 60 ng/l), or Abbott Axsym cTnI ADV (CV <10% at 160 ng/l). A positive test was defined as change ≥30% of 99th centile or 10% CV level, within 6–9 hours. Timing: On presentation and at 6–9 hours. Final diagnoses were adjudicated by 2independent cardiologists blind to hsTnT results. Where there was disagreement a third cardiologist was consulted.	exertion within the last 12 hours. Exclusion criteria: Positive troponin test prior to presentation, cardiogenic shock, terminal kidney failure requiring dialysis, or anaemia requiring transfusion	Diabetes (%): 16 Smoker (current) (%): 25 Hypertension (%): 61 Dyslipidaemia (%): 43 Median BMI (IQR): 26 (24–29)		the same as Irfan as not completely reported in paper.
Irfan (2013)[112] Prospective cohort	Roche Elecsys hs-cTnT LOD: 3 ng/l 99th Centile: 14 ng/l Coefficient of variation: <10% at 13 ng/l Beckman Coulter hs-cTnI LOD: 2 ng/l	Joint ESC, ACC, AHA and WHF[(a)] Conventional troponins were measured using Roche cTnT 4th generation assay (CV <10% at 35 ng/l), Beckman Coulter Accu cTnI (CV <10% at 60 ng/l), or Abbott Axsym cTnI ADV (CV <10% at 160 ng/l). A positive test was	N=830 Date recruited: April 2006 – June 2009 Country: Switzerland, Spain, USA and Germany Inclusion criteria: Consecutive adults presenting to the ED with symptoms suggestive of AMI (for example acute chest pain, angina pectoris) within an onset or peak within the last 12 hours.	Median age (IQR): 64 (51-75) Male (%): 67 Previous AMI (%): 25 Previous CAD (%): 36 Renal insufficiency (%): 11 Diabetes (%): 20 Hypertension (%): 64 Hypercholesterolaemia (%): 47 Median BMI (IQR): 26 (24-30)	NSTEMI 108/830 (13%) Moderate	NG15 reported this as NSTEMI only; however reporting in paper is not clear. Final diagnoses list NSTEMI at 13% and do not list STEMI as a diagnosis for any participants so we are assuming population was

Study	Index test	Reference test	Population	Demographics	Prevalence and risk strata	Comments
	99th centile: 9 ng/l Coefficient of variation: lower than 99th centile	defined as change ≥30% of 99th centile or 10% CV level, within 6– 9 hours. Timing: On presentation and at 6–9 hours. Final diagnoses were adjudicated by 2 independent cardiologists blind to hsTnT results. Where there was disagreement a third cardiologist was consulted.	Exclusion criteria: Acute trauma and terminal kidney failure requiring dialysis.			NSTEMI only.
Melki 2011[143] Prospective cohort	Roche Elecsys hs-cTnT LOD: 2 99th Centile: 14 Coefficient of variation: <10% at 13	An acute MI was defined using the universal definition. Conventional troponin Roche 4th generation TnT (LoD 10 ng/l, 10% CV at 35 ng/l), or Beckman Coulter Access AccuTnI (LoD 10 ng/l, 99th centile 40 ng/l, CV <10% at 60 ng/l Timing: On presentation and 9 to 12 hours later	N=233 August 2006 - January 2008 Sweden Inclusion criteria: Patients admitted to a coronary care unit with chest pain or other symptoms suggestive of ACS within 12 hours of admission. Exclusion criteria: Patients with persistent ST-	Median age (IQR): 65(55, 76) Male (%): 67 Previous AMI (%): 30 Previous revascularisation (%): 21 Diabetes (%): 23 Smoking (%): 17 Hypertension (%): 50 Mean symptom onset (95% CI/range/IQR, hours): 5 (3, 8)	NSTEMI 114/233 (48.9%) High	Patients admitted to a coronary care unit

Study	Index test	Reference test	Population	Demographics	Prevalence and risk strata	Comments
		Final diagnosis determined by the individual cardiologist, then adjudicated by 2 independent evaluators; all 3 were blinded to hs-TnT results.	segment elevation.			
Reichlin (2011)[178] Prospective cohort	Roche Elecsys hs-cTnT LOD: 3 99th centile: 14 Coefficient of variation: <10% at 13	Joint ESC, ACC, AHA and WHF[(a)] Conventional troponins were measured using Roche cTnT 4th generation assay (CV <10% at 35 ng/l), Beckman Coulter Accu cTnI (CV <10% at 60 ng/l), or Abbott Axsym cTnI ADV (CV <10% at 160 ng/l). A positive test was defined as change ≥30% of 99th centile or 10% CV level, within 6–9 hours. Timing: On presentation and at 6–9 hours. Final diagnoses were adjudicated by 2 independent cardiologists blind to	N= 590 Date recruited: April 2006–June 2009 Country: Switzerland, Spain, USA and Germany. Inclusion criteria: Consecutive adults presenting to the ED with symptoms suggestive of AMI (for example acute chest pain, angina pectoris) within an onset or peak within the last 12 hours. Exclusion criteria: Terminal kidney failure requiring dialysis.	Median age (IQR): 64 (51–67) Male (%): 67 Previous AMI (%): 25 Previous CAD (%): 37 Diabetes (%): 22 Smoker (current and past) (%): 60 Hypertension (%): 64 Hypercholesterolaemia (%): 47 Median BMI (IQR): 27 (24–30)	NSTEMI 67/590 (11%) Moderate	

Study	Index test	Reference test	Population	Demographics	Prevalence and risk strata	Comments
		hsTnT results. Where there was disagreement a third cardiologist was consulted.				
Santalo 2013[189] Prospective cohort	Roche Elecsys hs-cTnT LOD: NR 99th centile: 14 Coefficient of variation: <10% at 9.3	National Academy of Clinical Biochemistry and International Federation of Clinical Chemistry Committee[(b)] Roche cTnT; NSTEMI was defined as cTnT >10 ng/l and ΔcTnT >20% Timing: 30 minutes after arrival and at 2, 4 and 6–8 hours or until discharge. Final diagnosis was made by an adjudication committee.	N=358 Date recruited: NR Country: Spain Inclusion criteria: Adult (>18 years) described as presenting with acute coronary syndromes and symptom duration ≥5 minutes; population included 174 people with a final diagnosis of non-acute coronary syndromes. Exclusion criteria: ST-segment elevation; new left bundle branch block; pre-admission thrombolytic therapy; defibrillation or cardioversion before sampling; pregnancy; renal failure requiring dialysis; unstable angina within 2 months; CABG within 3 months.	Mean age (range): 69 (27, 93) Male (%): 68 Previous CAD (%): 35 Diabetes (%): 26 Hypertension (%): 62 Presentation within 3 hours: 46.2%	NSTEMI 79/358 (22%) High	Unstable angina patients included but no diagnostic accuracy data presented. Data presented for 0, 2, 4 and 6–8 hours after presentation.
Sebbane 2013[194] Prospective cohort	Roche Elecsys hs-cTnT LOD: 5 99th centile: 14	Diagnosis if acute MI was made using the universal definition.	N=248 December 2009–November 2011	Median age (IQR): 61(48, 75) Male (%): 63	NSTEMI 25/248 (13%) Moderate	

Study	Index test	Reference test	Population	Demographics	Prevalence and risk strata	Comments
	Coefficient of variation: <10% at 13	Patients with clinical signs and symptoms consistent with acute ischaemia associated with ECG changes and/or at least 1 positive cTnI result together with a rise or fall within the last 6 hours of admission were categorised as having an AMI. cTnI measured using the Access2 analyser (Access Immunosystem, Beckman Instruments, France). The LoD was <10 ng/l and the decision threshold was 40 ng/l Timing: Conventional cardiac troponin (cTnI) on presentation, 6 hours later and beyond as needed. Two independent emergency department	France Inclusion criteria: Adults presenting to the ED with chest pain of recent (within 12 hours of presentation) Exclusion criteria: Traumatic causes of chest pain. STEMI was defined by the persistent elevation of the ST segment of at least 1 mm in 2 contiguous ECG leads or by the presence of a new left bundle-branch block with positive cardiac enzyme results. Patients with STEMI were excluded from the analysis for our review.			

Study	Index test	Reference test	Population	Demographics	Prevalence and risk strata	Comments
		physicians, blinded to hs-cTnT results				

(a) Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. J Am Coll Cardiol 2007;50(22):2173-95.
(b) Apple FS, Jesse RL, Newby LK, Wu AHB, Christenson RH, Cannon CP, et al. National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: analytical Issues for biochemical markers of acute coronary syndromes. Clin Chem 2007;53(4):547-551.

Table 22: Summary of the different high sensitivity troponin assays, time from presentation and standard troponins

Study	Assay	Limit of detection	99th Centile	Coefficient of variation	Threshold[a]	Time from presentation	Standard troponin details
Low risk							
Collinson 2013[38]	Roche Elecsys hs-cTnT assay	3	14	<10% and 13	14 Peak 14 - a test strategy defining a positive result as a peak value above the 99th percentile diagnostic t	Admission Change (90 minutes minus admission value)	Conventional troponins were measured using one of the following methods: Siemens cTnI Ultra (LoD 6 ng/l, 99th centile 40 ng/l, CV 10% at 30 ng/l; Abbott cTnI (LoD 10 ng/l, 99th centile 12 ng/l, CV 10% at 32 ng/l; Beckman AccuTnI (LoD 10 ng/l, 99th centile 40 ng/l, CV 10% at 60 ng/l; Roche cTnT (LoD 10 ng/l, 99th centile 10 ng/l, CV 10% at 30 ng/l Timing: On presentation and at 10 to 12 hours
Freund 2011[61]	Roche Elecsys hs-cTnT assay	3	14	<10% at 13	14	Admission	cTnI (Siemens Healthcare Diagnostica Inc., NewaRK, USA or Access analyser Beckman

Update 2016

Study	Assay	Limit of detection	99th Centile	Coefficient of variation	Threshold[a]	Time from presentation	Standard troponin details
							Coulter Inc., Brea, USA). Threshold for Siemens assay 140 ng/l, CV ≤10% Threshold for Beckman assay 60 ng/l, CV 10% Timing: On presentation and at 3–9 hours if needed
Moderate risk							
Borna 2016[19]	Roche Elecsys hs-cTnT assay	5	14	<10% at 13	14, 20 and 30 Change with threshold 14, 20 and 30 at presentation and/or at > 5 ng/l at 3–4 hours	On presentation and 3–4 hours	Not reported
Hochholzer (2011)[85]	Roche Elecsys hs-cTnT assay	5	14	<10% at 13	11	Admission	Conventional troponins were measured using Roche cTnT 4th generation assay (CV <10% at 35 ng/l), Beckman Coulter Accu cTnI (CV <10% at 60 ng/l), or Abbott Axsym cTnI ADV (CV <10% at 160 ng/l). A positive test was defined as change ≥30% of 99th centile or 10% CV level, within 6–9 hours. Timing: On presentation and 6–9 hours
Irfan (2013)[94]	Roche	5	14	<10% at 13	Change 17%	On presentation and	Conventional troponins

Study	Assay	Limit of detection	99th Centile	Coefficient of variation	Threshold[a]	Time from presentation	Standard troponin details
	Elecsys hs-cTnT assay					at 1 hour	were measured using Roche cTnT 4th generation assay (CV <10% at 35 ng/l), Beckman Coulter Accu cTnI (CV <10% at 60 ng/l), or Abbott Axsym cTnI ADV (CV <10% at 160 ng/l). A positive test was defined as change ≥30% of 99th centile or 10% CV level, within 6–9 hours. Timing: On presentation and 6–9 hours
Irfan (2013)[112]	Beckman Coulter Access hs-cTnI	2	9	<10% at 9	Change 27%	On presentation and at one hour	Conventional troponins were measured using Roche cTnT 4th generation assay (CV <10% at 35 ng/l), Beckman Coulter Accu cTnI (CV <10% at 60 ng/l), or Abbott Axsym cTnI ADV (CV <10% at 160 ng/l). A positive test was defined as change ≥30% of 99th centile or 10% CV level, within 6–9 hours. Timing: On presentation and 6–9 hours
Reichlin (2011)[144]	Roche Elecsys hs-	5	14	<10% at 13	change 30%	On presentation and at 2 hours	Conventional troponins were measured using

Update 2016

Study	Assay	Limit of detection	99th Centile	Coefficient of variation	Threshold[a]	Time from presentation	Standard troponin details
	cTnT assay						Roche cTnT 4th generation assay (CV <10% at 35 ng/l), Beckman Coulter Accu cTnI (CV <10% at 60 ng/l), or Abbott Axsym cTnI ADV (CV <10% at 160 ng/l). A positive test was defined as change ≥30% of 99th centile or 10% CV level, within 6–9 hours. Timing: On presentation and 6–9 hours
Sebbane 2013[157]	Roche Elecsys hs-cTnT assay	5	14	<10% at 13	14 18	On presentation or sample taken during pre-hospital management	cTnI measured using the Access2 analyser (Access Immunosystem, Beckman Instruments, France). The LoD was <10 ng/l and the decision threshold was 40 ng/l Timing: Convention cardiac troponin (cTnI) on presentation, 6 hours later and beyond as needed
High risk							
Aldous 2011[4] Aldous 2012[5]	Roche Elecsys hs-cTnT assay	5	14	<10% at 13	14 5 3 14 5	On presentation 2 hours after presentation	Conventional troponins were measured using Abbott Diagnostics TnI (LoD 10 ng/l, 99th centile 28 ng/l, CV <10% at 32

Update 2016

Study	Assay	Limit of detection	99th Centile	Coefficient of variation	Threshold[a]	Time from presentation	Standard troponin details
					3 Peak 14 14 and 20% 14 or 20%	0 to 2 hours from presentation	ng/l, decision threshold 30 ng/l) Timing: On presentation, and at 2 hours and 6–12 hours
Eggers 2012[54]	Roche Elecsys hs-cTnT assay	3	14	<10% at 13	14 45.7	On presentation	cTnI (Stratus CS, Siemens Healthcare Diagnostics, Deerfield, IL, USA). Non-STEMI defined as: cTnI above the 99th percentile of 0.07 µg/l at least at one measurement together with a ≥20% rise and/or fall and an absolute change ≥0.05 µg/l within 24 hours. To allow for the calculation of relative changes, cTnI was set to 0.02 µg/l (that is, a concentration below the lowest level of detection) when reported as 0.00 or 0.01 µg/l. Timing: eight time points during the first 24 hours following enrolment
Kurz 2010[109]	Roche Elecsys hs-cTnT assay	3	13.5	8% at 10	9.5 14 14 14 and change 20%	On presentation Within 3 hours of presentation On presentation and	4th generation cTnT (Roche Elecsys, Mannheim, Germany) LoD 10 ng/l, diagnostic threshold 30 ng/l Diagnosis of NSTEMI

Update 2016

Study	Assay	Limit of detection	99th Centile	Coefficient of variation	Threshold[a]	Time from presentation	Standard troponin details
						within 3 hours	required elevated cTnT concentration in at least one of the consecutive samples collected within 24 hours of the index event Timing: On presentation, at 6 hours and at least one sample between presentation and 6 hours
Melki 2011[121]	Roche Elecsys hs-cTnT assay	2	14	<10% at 13	14 14	On presentation 2 hours after presentation	Conventional troponin Roche 4th generation TnT (LoD 10 ng/l, 10% CV at 35 ng/l), or Beckman Coulter Access AccuTnI (LoD 10 ng/l, 99th centile 40 ng/l, CV <10% at 60 ng/l Timing: On presentation and 9–12 hours later
Santalo 2013[152]	Roche Elecsys hs-cTnT assay	NR	14	10% at 9.3	14 Change 20%	On presentation On presentation at 2,4,6, and 8 hours or until discharge	Roche cTnT; NSTEMI was defined as cTnT >10 ng/l and ΔcTnT >20% Timing: 30 minutes after arrival and at 2,4 and 6–8 hours or until discharge

(a) The threshold used to define when a high sensitivity troponin result is positive. The threshold is based on testing of reference populations, which vary widely from assay to assay. It is measured in ng/l

(b) The limit of blank is the highest apparent analyte concentration (analytical noise) expected to be found when replicates of a blank sample containing no analyte are tested. The limit of detection is the lowest analyte concentration likely to be reliably distinguished from the limit of blank and at which detection is feasible. The limit of detection (LoD) of the assay should be such as to allow measurable concentrations to be attainable for at least 50% (ideally >95%) of healthy individuals.

Update 2016

(c) The coefficient of variation is a standardized measure of dispersion of a probability distribution or frequency distribution. The total imprecision, co-efficient of variation (CV), of the assay should be ≤10% at the 99th percentile value for the healthy reference population.

Table 23: Clinical evidence profile: High-sensitivity troponins

Index test (high sensitivity troponin ng/l) (Threshold)	Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity/ (95% CI)	Quality
Low risk 0 hours (at admission)									
Index test at 14	2	1093	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	No serious imprecision[d]	0.79 (0.67-0.88) 0.91 (0.71-0.99)	0.96 (0.94-0.97) 0.85 (0.80-0.89)	LOW
Index test at peak 14	1	847	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	Serious imprecision[d]	0.87 (0.73-0.92)	0.94 (0.93-0.96)	VERY LOW
Moderate risk 0 hours (at admission)									
Index test at 11	1	724	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	No serious imprecision[d]	0.97 (0.91-0.99)	0.72 (0.68-0.75)	LOW
Index test at 14	1	249	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	Serious imprecision[d]	0.76 (0.55-0.91)	0.85 (0.79-0.90)	VERY LOW
Index test at 18	1	192	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	Serious imprecision[d]	0.76 (0.55-0.91)	0.90 (0.84-0.94)	VERY LOW
Moderate risk older adults 0 hours (at admission)									
Index test at 14	1	477	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	Serious imprecision[d]	0.91 (0.84-0.95)	0.43 (0.38-0.48)	VERY LOW
Moderate risk older adults 3–4 hours									

Index test (high sensitivity troponin ng/l) (Threshold)	Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity 95% CI)	Specificity/ 95% CI)	Quality
Index test at 14	1	477	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	No serious imprecision[d]	1.00 (0.97-1.00)	0.93 (0.87-0.92)	LOW
Index test at 20	1	477	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	Serious imprecision[d]	0.93 (0.87-0.92)	0.39 (0.34-0.44)	VERY LOW
Index test at 30	1	477	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	Serious imprecision[d]	0.90 (0.83-0.95)	0.75 (0.70-0.79)	VERY LOW
High risk 0 hours (at admission)									
Index test at 3	1	939	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	No serious imprecision[d]	0.96 (0.92-0.98)	0.48 (0.44-0.52)	LOW
Index test at 5	1	939	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	Serious imprecision[d]	0.94 (0.89 to 0.97)	0.58 (0.55 to 0.62)	VERY LOW
Index test at 9.5	1	94	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	Serious imprecision[d]	0.83 (0.69-0.92)	0.77 (0.63-0.88)	VERY LOW
Index test at 14	5	1984	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	Serious imprecision[d]	0.86 (0.66-0.96)	0.77 (0.64-0.87)	VERY LOW
Index test at 45.7	1	360	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	Serious imprecision[d]	0.51 (0.42 to 0.60)	0.95 (0.92-0.98)	VERY LOW
High risk 2 hours									

Update 2016

Index test (high sensitivity troponin ng/l) (Threshold)	Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity 95% CI)	Specificity/ 95% CI)	Quality
Index test at 3	1	939	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	No serious imprecision[d]	0.98 (0.95-0.99)	0.42 (0.39-0.46)	LOW
Index test at 5	1	939	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	No serious imprecision[d]	0.96 (0.92-0.98)	0.54 (0.50-0.57)	LOW
Index test at 14	2	1172	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	Serious imprecision[d]	1.00 (0.71-0.86) 0.92 (0.88-0.95)	0.79 (0.71-0.86) 0.80 (0.77-0.83)	VERY LOW
High risk – 3 hours									
Index test at 14	1	94	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	Serious imprecision[d]	1.00 (0.87-1.00)	0.77 (0.58-0.90)	VERY LOW

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making

(a) Risk of bias was assessed using the QUADAS-2 checklist

(b) Inconsistency was assessed by inspection of the sensitivity and specificity forest plots (based on the primary measure), or summary area under the curve (sROC) plots across studies, using the point estimates and confidence intervals

(c) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability

(d) The judgement of precision was based on visual inspection of the confidence region in the diagnostic meta-analysis if a diagnostic meta-analysis was conducted. Where a diagnostic meta-analysis was not conducted imprecision was assessed according to the range of point estimates. If sensitivity varied across 2 areas <50%, 50% to 90% and 90% to 100% a rating of serious imprecision was given or for three areas very serious imprecision

Table 24: Clinical evidence profile: High sensitivity troponins (studies reporting change scores) all at a threshold of 14

Index test (high sensitivity troponin ng/l) (Threshold)(time sample taken, 0 is at admission)	Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity 95% CI)	Specificity/ 95% CI)	Quality

Index test (high sensitivity troponin ng/l) (Threshold)(time sample taken, 0 is at admission)	Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity 95% CI)	Specificity/ 95% CI)	Quality
Moderate risk – change from 0 to 1 and 3 hours									
17%	1	791	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	No serious imprecision[d]	0.60 (0.50-0.69)	0.72 (0.69-0.75)	LOW
27% (AccuTnI+3 troponin I assay)	1	590	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	No serious imprecision[d]	0.64 (0.52-0.76)	0.84 (0.81-0.87)	LOW
30%	1	830	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	No serious imprecision[d]	0.63 (0.53-0.72)	0.66 (0.62 to 0.70)	LOW
High risk – 20% change									
Between 0 and 3 hours (threshold 14 and 20% change)	1	939	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	Serious imprecision[d]	0.49 (0.42-0.57)	0.94 (0.92-0.96)	VERY LOW
Between 0 and 3 hours (threshold 14 or 20% change)	1	939	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	No serious imprecision[d]	0.97 (0.94-0.99)	0.65 (0.61-0.68)	LOW
Between 0 and 8 hours	1	358	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	No serious imprecision[d]	1.00 (0.95-1.00)	0.66 (0.60-0.72)	LOW
Between 0 and 3 hours	1	94	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	Serious imprecision[d]	0.42 (0.23-0.63)	0.10 (0.02 to 0.27)	VERY LOW
High risk – 20% change at different time point (same study)									
0 hours	1	358	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	No serious imprecision[d]	0.80 (0.69-0.88)	0.91 (0.87-0.94)	LOW

Index test (high sensitivity troponin ng/l) (Threshold)(time sample taken, 0 is at admission)	Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity 95% CI)	Specificity/ 95% CI)	Quality
2 hours	1	358	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	Serious imprecision[d]	0.91 (0.83-0.96)	0.90 (0.86-0.94)	VERY LOW
4 hours	1	358	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	No serious imprecision[d]	0.99 (0.93-1.00)	0.89 (0.85-0.93)	LOW
8 hours	1	358	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness [c]	No serious imprecision[d]	1.00 (0.95-1.00)	0.86 (0.82-0.90)	LOW

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making

(e) Risk of bias was assessed using the QUADAS-2 checklist

(f) Inconsistency was assessed by inspection of the sensitivity and specificity forest plots (based on the primary measure), or summary area under the curve (sROC) plots across studies, using the point estimates and confidence intervals

(g) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability

(h) The judgement of precision was based on visual inspection of the confidence region in the diagnostic meta-analysis if a diagnostic meta-analysis was conducted. Where a diagnostic meta-analysis was not conducted imprecision was assessed according to the range of point estimates. If sensitivity varied across 2 areas <50%, 50% to 90% and 90% to 100% a rating of serious imprecision was given or for three areas very serious imprecision

Table 25: Summary of negative and positive predictive values

Index test (high sensitivity troponin ng/l) (Threshold) (time sample taken, 0 is at admission)	Number of studies	n	Median negative predictive value (range)	Median positive predictive value (range)
Low risk				
Index test at 14 threshold 0 hours	2	1093	0.98 0.99	0.36 0.62
Index test at peak threshold of 14 minus admission	1	847	0.99	0.57
Moderate risk 0 hours				

Moderate risk – older adults 3–4 hours				

Index test (high sensitivity troponin ng/l) (Threshold) (time sample taken, 0 is at admission)	Number of studies	n	Median negative predictive value (range)	Median positive predictive value (range)
Index test at 11 threshold 0 hours	1	724	0.99	0.34
Index test at 14 threshold 0 hours	1	249	0.96	0.43
Index test at 18 threshold 0 hours	1	192	0.96	0.53
Moderate risk – older adults				
Index test at 14 threshold 0 hours	1	477	0.99	0.40
Index test at threshold 14	1	477	0.99	0.40
Index test at threshold 20	1	477	0.96	0.46
Index test at threshold 30	1	477	0.95	0.75
Moderate risk change				
Index test at 14 threshold 17% change 0–3 hours	1	791	0.92	0.24
Index test at 14 threshold 27% change 0–3 hours	1	590	0.95	0.35
Index test at 14 threshold 30% change 0–3 hours	1	830	0.92	0.22
High risk 0 hours				
Index test at 3 threshold 0 hours	1	939	0.98	0.34
Index test at 5 threshold 0 hours	1	939	0.97	0.39
Index test at 9.5 threshold 0 hours	1	94	0.82	0.78
Index test at 14 threshold 0 hours	5	1984	0.96 (0.71-0.98)	0.63 (0.47-0.84)
Index test at 45.7 threshold 0	1	360	0.78	0.86
High risk 2 hours				
Index test at 3 threshold 2 hours	1	939	0.99	0.32
Index test at 5 threshold 2 hours	1	939	0.98	0.37
Index test at 14 threshold 2 hours	2	1172	0.97	0.56-0.82
High risk 3 hours				
Index test at 14 threshold 3 hours	1	94		0.79
High risk change				

Update 2016

Index test at 14 threshold and 20% change 0–3 hours	1	939	0.87	0.70
Index test at 14 threshold or 20% change 0–3 hours	1	939	0.99	0.43
Index test at 14 threshold 20% change 0–3 hours	1	358	0.17	0.29
Index test at 14 threshold 20% change 0–8 hours	1	94	1.00	0.66
High risk serial measurements change				
Index test at 14 threshold 20% change 0 hours	1	358	0.94	0.72
Index test at 14 threshold 20% change 2 hours	1	358	0.97	0.72
Index test at 14 threshold 20% change 4 hours	1	358	1.00	0.72
Index test at 14 threshold 20% change 8 hours	1	358	-	0.68

7.4.1.2.2 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in Appendix E.

7.4.1.2.3 Evidence statements

Clinical

Thirteen cohort studies that evaluated high-sensitivity troponins at thresholds that range from 3 to 45.7 ng/l were included in the review. All studies used the Elecsys Troponin T assay with the exception of one study that used this and the AccuTnI+3 troponin I assay. The results from this study are indicated in the evidence statement.

For the low prevalence group, two studies demonstrated poor sensitivity and specificity, high negative predictive values but poor positive predictive values for high-sensitivity troponins identifying NSTEMI/unstable angina:

- Low quality evidence from two studies of 1093 adults showed a sensitivity of 79 and 91% and a specificity of 96 and 85% on admission at a threshold of 14
- Very low quality evidence from one study of 847 showed a sensitivity of 87% and a specificity of 94% for change score.

For the moderate prevalence group, two studies demonstrated poor sensitivity and specificity, high negative predictive values but poor positive predictive values for high-sensitivity troponins identifying NSTEMI/unstable angina when the test is performed at admission. The findings were similar for older adults.

- Low quality evidence from one study of 724 adults showed a sensitivity of 97% and specificity of 82% on admission at a threshold of 11
- Very low quality evidence from one study of 249 adults showed a sensitivity of 76% and specificity of 85% on admission at a threshold of 14
- Very low quality evidence from one study of 192 adults showed a sensitivity of 76% and specificity of 90% on admission at a threshold of 18.
- Low and Very low quality evidence from one study in older adults of 477 adults showed a sensitivity of 91% and specificity of 43% on admission at a threshold of 14. When performed at three to four hours the sensitivity at the same threshold was 100% and specificity 93%. At a threshold of 20 and 30 sensitivity was 90 and 93% and specificity 39 and 75%.
- Low quality evidence from two studies of 791 and 830 adults showed a sensitivity of 60 and 63% and a specificity of 66 to 72% for a change score of 17 and 30% for a threshold of 14.
- Low quality evidence from one study of 590 adults showed a sensitivity of 64% and a specificity of 84% for a change score of 27% for a threshold of 14 (AccuTnI+3 troponin I assay)

For the high prevalence group, five studies demonstrated poor sensitivity and specificity, high negative predictive values but poor positive predictive values for high-sensitivity troponins when performed on admission for identifying NSTEMI/unstable angina. Sensitivity improves when the test is performed after admission.

Update 2016

- Low to Very low quality evidence from five studies of between 94 and 1984 adults showed a sensitivity of between 51% and 94% and a specificity of 48% to 95% on admission at a threshold of between 3 and 45.7.
- Low to Very low quality evidence from two studies of between 939 and 1172 adults showed a sensitivity of 92% and 100% and a specificity of 42% and 88% at two hours at a threshold of between 3 and 14.
- Very low quality evidence from one study of 94 adults showed a sensitivity of 100% and a specificity of 77% at three hours at a threshold of 14.
- Low to Very low quality evidence from three studies of between 94 and 939 adults showed a sensitivity of 42% and 100% and a specificity of 10% and 94% for a change of 20% at a threshold of 14.
- Low to Very low quality evidence from one study of 358 adults showed a sensitivity of 91% and 100% and a specificity of 86% and 91% for a change of 20% at a threshold of 14 at 0, 2, 4 and 8 hours.

Economic

- No relevant economic evaluations were identified.

7.4.1.2.4 Recommendations and link to evidence

Recommendations	**1.2.5.1 Do not use high- sensitivity troponin tests for people in whom ACS is not suspected.** **1.2.5.2 For people at high or moderate risk of MI (as indicated by a validated tool), perform high-sensitivity troponin tests as recommended in the NICE diagnostics guidance on myocardial infarction (DG15).** **1.2.5.3 For people at low risk of MI (as indicated by a validated tool):** • **perform a second high-sensitivity troponin test as recommended in the NICE diagnostics guidance on myocardial infarction (DG15) if the first troponin test at presentation is positive** • **consider performing a high-sensitivity troponin test only at presentation to rule out NSTEMI if the first troponin test is below the lower limit of detection (negative).** **1.2.5.4 Ensure that patients understand that a detectable troponin on the first high-sensitivity test does not necessarily indicate that they have had an MI.**
Definition of risk	The GC discussed who is a 'low risk' patient. Risk was defined in terms of TIMI scores and categorised as below. TIMI Score of 0–1 = 4.7% risk Score of 2 = 8.3% risk Score of 3 = 13.2% risk Score of 4 = 19.9% risk

Update 2016

	Score of 5 = 26.2% risk Score of 6–7 = at least 40.9% risk The corresponding score was then used to clarify the population as low, moderate or high risk: 0-8% Low risk (score 0 to 2) 9%-20% Moderate risk (score 3 to 4) 21% or more High risk (score 5 or more)
Relative values of different diagnostic measures and outcomes	Clinical effectiveness review The GC considered the critical outcomes were: all-cause mortality, cardiovascular mortality and myocardial infarction. The committee also considered process outcomes such as time to discharge and early discharge without a late major adverse cardiac event (MACE) as important. No RCT evidence was identified reporting patient outcomes for different diagnostic strategies. Trials with a mixed population including STEMI were not considered suitable to derive guidance for the NSTEMI/UA population and were excluded from discussion. Diagnostic test accuracy review The GC considered sensitivity to be critical for decision making. High sensitivity indicates that the test correctly identifies people with the condition. If a condition is treatable and the consequences of missing a case are serious, high sensitivity is required. Missing a case of non-ST elevation (NSTEMI) or unstable angina (UA) may have serious consequences including death and future major adverse cardiac events. The GC also considered specificity to be important. The higher the specificity the greater the confidence that an individual without NSTEMI will have a negative finding. Low specificity means that more people without the condition might stay in hospital longer than necessary, have more diagnostic tests, receive unnecessary procedures and treatments with increased anxiety for both the individual and family members. Negative and positive predictive values were considered useful by the GC. These values indicate the probability that a person does not have the condition given that the test result is negative or that a person does have the condition if the test result is positive. Unlike sensitivity and specificity, negative and positive predictive values vary according to prevalence and should only be considered in this context.
Quality of the clinical evidence	The majority of studies had a high risk of bias based on the QUADAS-2 instrument. All of the evidence was graded at very low to low quality. This assessment arose from lack of blinding of those applying the reference standard to the result of the high-sensitivity troponins and a large number of patients not having the reference standard investigation (typically coronary angiography). Such verification bias occurs when a study selectively includes patients for disease verification (or exclusion) by gold standard testing, based on positive or negative results of preliminary testing. The consequences of this on the apparent test accuracy was difficult to ascertain. The GC considered that the diagnostic criteria used in these studies were an accurate reflection of current clinical practice and that this source of bias did not

Update 2016

	reduce confidence in the results. Imprecision was evaluated according to the width of confidence intervals across the following three categories: <50%, ≥50% and >90%. For all risk groups, approximately half of the results had serious imprecision. The results crossed the ≥50% and >90% boundary. All studies were comprised of NSTEMI populations and were therefore directly applicable.
Trade-off between clinical benefits and harms	While diagnostic cohort studies indicated a high sensitivity of high sensitivity troponin for the studies with a high prevalence of NSTEMI, they do not tell us whether adopting a particular diagnostic strategy improves patient outcomes. Evidence on patient outcomes comparing 2 diagnostic interventions is ideally provided by the RCTs, but no such evidence was available for high-sensitivity troponins. Sensitivity and specificity: Low prevalence Only two studies reported data on populations with a low prevalence of NSTEMI. On presentation and at threshold of 14 ng/l sensitivity ranged from 75 to 91% and specificity 85 to 96%. Moderate prevalence Only a small number of studies in populations with a moderate prevalence of NSTEMI were available. Across three different diagnostic thresholds sensitivity on presentation ranged from 76 to 97% and specificity 72 to 90%. In adults over 75 years, sensitivity increased from 91% to 100% on presentation and at 3 to 4 hours respectively. High prevalence Pooled results for five studies at a threshold of 14 ng/l resulted in a sensitivity of 86% and sensitivity of 77% on presentation. At 2 and 3 hours sensitivity improved to between 92 and 100% and specificity between 79 and 88%. At three hours sensitivity was 100% and specificity 72%. Negative and positive predictive values: Across all of the prevalence groups, the negative predictive values were high with majority 95% or higher, with the highest values for the lower prevalence group as expected, but the positive predictive values were low with the majority less than 50%. The GC were most interested in the performance of the test in the low prevalence group. On the basis of a negative predictive value of 99%, a negative result on presentation would indicate that a patient did not have ACS, so might be safely discharged home without being kept in hospital for a second test. The GC noted that the consequences of wrongly discharging a low risk patient who actually does have the condition may not be as serious as in the high risk groups. The risk of a serious adverse outcome in this group, even if experiencing an ACS, is lower than in the other groups.

Update 2016

	The low prevalence group represents a high proportion of people presenting to accident and emergency, and discharging people home after a single blood test would considerably decrease demand on services. The GC therefore considered that in some low risk patients a single blood test could be used as a basis for discharge. The GC noted that the sensitivity of the test improves if the threshold Is lowered but these data were available in the high prevalence group only. Nevertheless, the committee agreed that this was likely to apply to low risk patients as well. Therefore, in order to minimise the risk of incorrectly discharging a patient with ACS, the committee felt that the cut off for a positive test should be set at the conservative lower limit of detection for the assay. For patients at moderate to high risk, the GC considered that sensitivity of a single test on presentation was insufficient to make a decision to discharge. The evidence shows that sensitivity improves when a second test is performed at approximately 3 hours. The GC therefore supported NICE DG15 recommending the use of high-sensitivity troponins to rule out NSTEMI in the emergency department in this group of patients. A test performed at a single point in time, in particular the low positive predictive value in low risk groups, has poor accuracy. The GC made a strong recommendation not to test for high-sensitivity troponins if ACS is not suspected. The committee recommended that the test should not be used in patients presenting to accident and emergency with chest pain with a clear non-cardiac diagnosis. All of the evidence was on people with NSTEMI and the committee were therefore unable to make a recommendation on people with unstable angina.
Trade-off between net clinical effects and costs	The cost-effectiveness analysis conducted for NICE DG15 found that performing two high-sensitivity troponin tests (one at presentation and one at 3 hours), is cost effective compared to two standard troponin tests (one at presentation and one at 10–12 hours). No further evidence was found that contradicts this result, therefore two high-sensitivity tests were considered to be cost-effective. The cost of high-sensitivity troponin tests (£20) used in the economic analysis conducted in DG15 was presented to the GC. They considered that in some low risk patients, a single high-sensitivity troponin test could be used as a basis for discharge. This would lower costs as these patients would need fewer tests and also spend less time in the ED. The majority of the committee agreed that in this low risk population there would be minimal risk of a serious adverse outcome if someone had a false negative troponin test.
Other considerations	The purpose of this review was not to replace the recommendations in DG15 but to see if additional recommendations could be made for people with different risks of ACS. The GC noted that the algorithm in DG15 has been validated[167]

Update 2016

	The committee recommended that anyone with suspected ACS should have a high-sensitivity troponin test at presentation. The GC noted that people may present with a number of symptoms for example dyspnoea, syncope, epigastric pain, arm pain and delirium. The threshold for people presenting with atypical symptoms may need to be modified. In addition people may present with chest pain that is psychological in origin. This may that require a referral to mental health services. The GC discussed the risk assessment of people and defined this in terms of TIMI scores. The scores and associated categorisation of risk are listed above in the definition of risk box. The committee recognised that GRACE is commonly used in clinical practice and were reassured that the TIMI and GRACE scoring system would result in a similar risk categorisation. In the evidence review, risk has been defined in terms of TIMI and GRACE scores. However, the committee noted that these scoring systems included the result of a troponin test and this would need to be taken into account in the initial assessment of risk at presentation. The committee discussed the possibility that people at low risk of ACS could be discharged if the high-sensitivity troponin test was below the lower limit of detection. The GC noted that the use of high-sensitivity troponin over standard troponin comes at the expense of specificity. Information for patients and carers needs to reflect the fact there are more false positives. The GC noted that it was important that patients who are discharged from accident and emergency are advised to return if their chest pain recurs. The committee agreed that this is particularly important to mitigate the potential low risk adverse consequences of discharging some low risk patients on the basis of a single test. For further information on information and support please refer to chapter 5.

Update 2016

7.4.2 Non-invasive imaging for the identification of people with NSTEMI/unstable angina

Introduction

A number of different non-invasive 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. Currently none of these tests are used routinely in ruling out a myocardial infarction (MI) in people with acute chest pain of suspected cardiac origin. Newer non-invasive cardiac imaging techniques, including stress myocardial perfusion imaging, stress cardiac magnetic resonance imaging and multi-detector computed tomography angiography, may help the early identification of people with NSTEMI in people presenting with acute chest pain and uncertain diagnosis following ECG and troponin testing. This review examines the usefulness of the tests in this population.

7.4.2.1 Review question: In people under investigation for acute chest pain of suspected cardiac origin, what is the clinical and cost-effectiveness of non-invasive imaging compared to standard practice, when each is followed by the appropriate treatment for NSTEMI/unstable angina, in order to improve patient outcomes?

For full details see review protocol in Appendix D.

Table 26: PICO characteristics of review question

Population and target condition	All adults (age ≥18 years) with acute chest pain/discomfort of suspected cardiac origin under investigation for NSTEMI/unstable angina, and who have had initial triage including: • clinical history • signs and symptoms assessment • physical examination • ECG • high sensitivity troponin I or T, or standard sensitivity troponin I or T.

Index diagnostic tests + treatment	Index diagnostic tests:
	• coronary computed tomography angiography (coronary CT angiography)
	  ○ multi-detector CT (MDCT) (≥64-slice CT scanner)
	  ○ dual X-ray source MDCT
	• myocardial perfusion scintigraphy (MPS):
	  ○ single photon emission CT (SPECT)
	  ○ positron emission tomography (PET)
	• cardiac magnetic resonance imaging (cardiac MRI)
	• stress perfusion cardiac MRI
	• echocardiography
	  ○ resting
	  ○ stress
	• Plus standard practice (treatment)
	To include:
	• aspirin
	• ticagrelor/clopidogrel
	• beta blocker
	• ACE inhibitor
	• statin
	• anticoagulant for example fondaparinux, low molecular weight heparin, prasugrel
	• revascularisation where warranted.

Comparator + treatment or treatment alone (no test)	Comparator: • Standard practice To include: • aspirin • ticagrelor/clopidogrel • beta blocker • ACE inhibitor • statin • anticoagulant for example fondaparinux, low molecular weight heparin, prasugrel • revascularisation where warranted. • one index test versus a second index test
Outcomes	Efficacy outcomes: • all-cause mortality at 30-day and 1-year follow-up (or closest time point) • cardiovascular mortality at 30-day and 1-year follow-up (or closest time point) • myocardial infarction at 30-day follow-up • percutaneous coronary intervention (PCI) at 30-day follow-up • coronary artery bypass graft (CABG) at 30-day follow-up • hospitalisation at 30-day follow-up for cardiac causes (or closest time point) • hospitalisation at 30-day follow-up for non-cardiac causes (or closest time point)

Update 2016

	• quality of life at 1 year (or closest time point) • adverse events related to index non-invasive test at 30 days (or closest time point) • adverse events related to treatment: major bleeding at 30 days (or a closest time point) Process outcomes: • number of people receiving treatment • length of hospital stay Secondary accuracy outcomes: • sensitivity/specificity and other test accuracy measures.
Study design	RCTs

7.4.2.2 Review question: In people under investigation for acute chest pain of suspected cardiac origin are non-invasive imaging tests more accurate compared to standard practice to identify whether NSTEMI/unstable angina is present, as indicated by the reference standard?

For full details see review protocol in Appendix D.

Table 27: Characteristics of review question

Population	All adults (age ≥18 years) with acute chest pain/discomfort of suspected cardiac origin under investigation for NSTEMI/unstable angina, and have had initial triage including: • clinical history • signs and symptoms assessment • physical examination • ECG • high sensitivity troponin I or T, or standard sensitivity troponin I or T
Target condition	NSTEMI/unstable angina
Settings	Emergency department and other hospital settings (for example coronary care unit)
Index tests	• coronary computed tomography angiography (coronary CT angiography) ○ multidetector CT (MDCT) (≥64-slice CT scanner) ○ dual X-ray source MDCT • myocardial perfusion scintigraphy (MPS): ○ single photon emission CT (SPECT) ○ positron emission tomography (PET) • cardiac magnetic resonance imaging (cardiac MRI) • stress perfusion cardiac MRI • echocardiography ○ resting ○ stress • Plus standard practice (treatment) To include: • aspirin • ticagrelor/clopidogrel • beta blocker • ACE inhibitor • statin • anticoagulant for example fondaparinux, low molecular weight heparin, prasugrel revascularisation where warranted.

Update 2016

Comparator test	• standard practice To include: • aspirin • ticagrelor/clopidogrel • beta blocker • ACE inhibitor • statin • anticoagulant for example fondaparinux, low molecular weight heparin, prasugrel • revascularisation where warranted. • one index test versus a second index test
Reference standards	• coronary angiography • ACS (NSTEMI/unstable angina) as defined by the American College of Cardiology/American Heart Association Guidelines • ACS (NSTEMI/unstable angina) as defined by European Society of Cardiology Guidelines
Statistical measures	2×2 tables Specificity Sensitivity Positive predictive value Negative predictive value
Study design	• cross-sectional studies and cohort studies (including both retrospective and prospective analyses) • case-control studies to be included only if no other evidence is identified

Update 2016

7.4.2.2.1 Clinical evidence

Clinical effectiveness

Eleven studies were included in the review;[55,81,82,85,101,102,133-135,146,211] these are summarised in Table 28 below. Evidence from these studies is summarised in the clinical evidence summaries below (Table 29, Table 30, Table 31, Table 32, Table 33, Table 34, Table 35, Table 36). See also the study selection flow chart in Appendix F, forest plots in Appendix M, study evidence tables in Appendix I, GRADE tables in Appendix K and excluded studies list in Appendix N.

Five studies compared 64-slice or higher multi-detector computed tomography (MDCT) angiography versus standard practice.[55,82,101,102,134,135] One study compared MDCT angiography with exercise ECG.[85] Two studies were identified comparing SPECT with standard practice, one investigating the utility of resting SPECT[211] and the other investigating the utility of stress SPECT.[133] Two studies compared stress magnetic resonance imaging (MRI) with standard practice.[146,147] Only three studies reported medication use as part of standard practice during study follow-up.[55,101,102,135]

Table 28: Summary of studies included in the review

	Intervention (criteria used to make a positive diagnosis) **Comparison**	**Population, n**	**Follow-up** **Outcomes**	**Comments**
ACRIN PA 2012[135] USA	64-slice MDCT (≥50% stenosis of the left medial	n=1370 MDCT: n=908	30 days • CV mortality • Non-fatal MI	ED admission/discharge criteria: • NR

	Intervention (criteria used to make a positive diagnosis) Comparison	Population, n	Follow-up Outcomes	Comments
Multicentre 5 sites (3 sites had OU)	(LM), left anterior descending artery (LAD), Left or right coronary artery, or first order branch) Standard practice	Standard practice: n=462 Low risk (TIMI risk score ≤2)	• PCI • CABG	
BEACON 2016[55] The Netherlands Multicentre 2 university and 5 community hospitals	64-slice or higher MDCT (≥50% stenosis) Standard practice	n=500 MDCT: n=250 Standard practice: n=250	30 days • All-cause mortality • PCI • CABG	ED admission/discharge criteria: • Physician decision according to European 2011 and American Heart Association (AHA)/American College of Cardiology (ACC) 2014 guidelines
CATCH 2013[134] Denmark Single centre University hospital	320-slice MDCT (>50% stenosis in LM artery or ≥70% other large coronary artery) Standard practice	n=600 MDCT: n=299 Standard practice: n=301	120 days • Cardiac death • Non-fatal MI • Hospitalisation for cardiac causes	ED admission/discharge criteria: • Not applicable as participants recruited within 7 days of discharge
CT-COMPARE 2014[85] Australia Single centre Academic hospital	64- or 128-slice MDCT Exercise ECG	n=562 MDCT: n=322 Exercise ECG: n=240	30 days and 1 year • All-cause mortality	ED admission/discharge criteria: MDCT group • Stenosis <50% discharged Exercise ECG group • Subjects without evidence of myocardial ischemia were discharged, subjects with positive or equivocal exercise ECG results were managed at discretion of the treating cardiologist
CT-STAT 2011[81] USA Multicentre 11 university and community hospital sites	64- to 320-slice MDCT • SPECT: resting SPECT, or stress if results were normal (standard exercise treadmill or pharmacologic [adenosine or dipyridamole])	n=699 MDCT: n=361 SPECT: n=338	In-hospital • All-cause mortality • Non-fatal MI • PCI • CABG	ED admission/discharge criteria: MDCT group • Stenosis >70% referred for ICA • Stenosis 26% to 70% or calcium score >100 Agaston U recommended to cross over for a rest-stress myocardial perfusion (MP)Discharged if no coronary artery narrowing >25% and/ or calcium score <100 Agaston U SPECT • Development of ischaemic ECG

Update 2016

	Intervention (criteria used to make a positive diagnosis) Comparison	Population, n	Follow-up Outcomes	Comments
				abnormalities, elevated biomarkers, and equivocal or abnormal MPI were to be referred for admission and/or ICA • Discharged if normal or probably normal scan
Goldstein 2007[82] USA Single centre Hospital	64-slice MDCT (>70% stenosis) Standard practice	n=197 MDCT: n=99 Standard practice: n=98	In-hospital • All-cause mortality • Non-fatal MI • PCI • CABG	ED admission/discharge criteria: MDCT group • Stenosis >70% referred for ICA • Stenosis 26% to 70%, calcium score Agaston U, non-diagnostic scan referred for nuclear stress testing • Discharged if no coronary artery narrowing >25% and/or calcium score under 100 Agaston U Standard practice group • Development of ECG abnormalities, elevated biomarkers or abnormal stress test referred for ICA
Lim 2008[133] Singapore Single centre General hospital	Stress SPECT (≥5% of the left ventricle or LVEF <50% with regional wall motion abnormalities) Standard practice	n=1689 Stress SPECT: n=1125 Standard practice: n=564	30 day and 1 year • Cardiac death	ED admission/discharge criteria: Stress SPECT group • positive scan admitted • normal scan discharged from ED with cardiology outpatient appointment within 2 weeks • equivocal scan retested 4–72 hours later Standard practice group • Decision based on treating physicians risk assessment of ACS
Miller 2010[147] USA Single centre	Stress MRI in an observation unit Standard practice (inpatient-based strategy)	n=110 Stress MRI: n=52 Standard practice: n=57	30 day • Cardiac death • Non-fatal MI • PCI • CABG	ED admission/discharge criteria • NR
Miller 2013[146] USA Single centre	Stress MRI in an observation unit Standard practice (inpatient-based strategy)	n=105 Stress MRI: n=52 Standard practice: n=53	90 day • Cardiac death	ED admission/discharge criteria • NR

Update 2016

	Intervention (criteria used to make a positive diagnosis) Comparison	Population, n	Follow-up Outcomes	Comments
ROMICAT-II[101,102] Multicentre USA	64-slice MDCT (NR) Standard practice	n=1000 MDCT: n=501 Standard practice: n=499	28 days • All-cause mortality • Non-fatal MI • PCI • CABG • Hospitalisation for chest pain	ED admission/discharge criteria: • NR
Udelson 2002[211] 7 academic medical centres and community hospitals	Resting SPECT (definite perfusion abnormality and/or regional or global function) Standard practice	n=2475 Resting SPECT: n=1215 Standard practice: n=1260	30 days • All-cause mortality • PCI • CABG	ED admission/discharge criteria: • NR

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CV, cardiovascular; LVEF, left ventricular ejection fraction; ECG, electrocardiogram; ICA, invasive coronary angiography; LAD, left anterior descending; LM, left medial descending; LC, left circumflex; LVEF, left ventricular ejection fraction; MDCT, multi-detector computed tomography; MI, myocardial infarction; MPI, myocardial perfusion, NR, not reported; OU, observation unit; PCI, percutaneous intervention; SPECT, single photon emission computed tomography; TIMI, Thrombolysis in Myocardial Infarction

Update 2016

Table 29: Clinical evidence summary: MDCT versus standard practice at 30 days follow-up

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with MDCT versus standard management 30-day (95% CI)
All-cause mortality	1687 (3 studies)	MODERATE[a] due to risk of bias	Not estimable	-	No events in control or intervention arm
Cardiovascular mortality	2046 (2 studies)	VERY LOW[ab] due to risk of bias, imprecision	Peto OR 0.18 (0.00 to 9.39	1 per 1000	0 fewer per 1000 (from 0 fewer to 0 more)
Non-fatal MI	2946 (3 studies)	VERY LOW[ab] due to risk of bias, imprecision	RR 0.58 (0.25 to 1.38)	10 per 1000	4 fewer per 1000 (from 7 fewer to 4 more)
PCI	1687 (3 studies)	LOW[ab] due to risk of bias, imprecision	RR 1.67 (1.08 to 2.58)	37 per 1000	25 more per 1000 (from 3 more to 58 more)
CABG	1687 (3 studies)	VERY LOW[ab] due to risk of bias, imprecision	RR 0.89 (0.34 to 2.29)	10 per 1000	1 fewer per 1000 (from 6 fewer to 12 more)
Readmission due to cardiac causes	576 (1 study)	VERY LOW[ab] due to risk of bias, imprecision	RR 0.65 (0.25 to 1.64)	38 per 1000	13 fewer per 1000 (from 28 fewer to 24 more)

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b]Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 30: Clinical evidence summary: MDCT versus SPECT at 30 days follow-up

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with MDCT versus SPECT 30-day (95% CI)

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with MDCT versus SPECT 30-day (95% CI)
All-cause mortality	699 (1 study)	LOW[a] due to risk of bias	Not estimable	-	No events in control or intervention arm
Non-fatal MI	699 (1 study)	VERY LOW[ab] due to risk of bias, imprecision	Peto OR 0.24 (0.05 to 1.22)	15 per 1000	10 fewer per 1000 (from 30 fewer to 0 more)
PCI	699 (1 study)	VERY LOW[ab] due to risk of bias, imprecision	RR 1.05 (0.41 to 2.66)	24 per 1000	1 more per 1000 (from 14 fewer to 39 more)
CABG	699 (1 study)	VERY LOW[ab] due to risk of bias, imprecision	Peto OR 6.99 (0.98 to 49.89)	0 per 1000	10 more (0 to 20 more)

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b]Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 31: Clinical evidence summary: MDCT versus exercise ECG at 30 days follow-up

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with MDCT versus Exercise ECG 30-day (95% CI)
All-cause mortality	562 (1 study)	LOW[a] due to risk of bias	Not estimable	-	No events in control or intervention arm

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 32: Clinical evidence summary: MDCT versus exercise ECG at 1 year follow-up

Outcomes	Number of	Quality of the evidence	Relative	Anticipated absolute effects

	participants (studies) Follow up	(GRADE)	effect (95% CI)	Risk with control	Risk difference with MDCT versus Exercise ECG 1 year (95% CI)
All-cause mortality	562 (1 study)	VERY LOW[ab] due to risk of bias, imprecision	RR 1.49 (0.13 to 15.55)	4 per 1000	2 more per 1000 (from 4 fewer to 61 more)

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[b]Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 33: Clinical evidence summary: Resting SPECT versus standard practice at 30 days follow-up

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with SPECT versus standard management 30-day (95% CI)
All-cause mortality	2475 (1 study)	VERY LOW[ab] due to risk of bias, imprecision	Peto OR 2.08 (0.38 to 11.36)	2 per 1000	2 more per 1000 (from 1 fewer to 16 more)
PCI	2475 (1 study)	VERY LOW[ab] due to risk of bias, imprecision	RR 0.95 (0.64 to 1.41)	40 per 1000	2 fewer per 1000 (from 14 fewer to 16 more)
CABG	2475 (1 study)	VERY LOW[ab] due to risk of bias, imprecision	RR 0.63 (0.35 to 1.11)	24 per 1000	9 fewer per 1000 (from 15 fewer to 3 more)

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[b]Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 34: Clinical evidence summary: Stress SPECT versus standard practice at 30 days follow-up

Outcomes	Number of	Quality of the	Relative	Anticipated absolute effects

	participants (studies) Follow up	evidence (GRADE)	effect (95% CI)	Risk with control	Risk difference with stress SPECT versus standard management 30-day (95% CI)
Cardiac mortality	1508 (1 study)	LOW[a] due to risk of bias	Not estimable	-	No events in control or intervention arm

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 35: Clinical evidence summary: Stress SPECT versus standard practice at 1 year follow-up

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with stress SPECT versus standard management 1 year (95% CI)
Cardiac mortality	1508 (1 study)	VERY LOW[ab] due to risk of bias, imprecision	Peto OR 4.50 (0.41 to 49.62)	0 per 1000	0 fewer (fewer to 10 more)

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b]Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 36: Clinical evidence summary: Stress MRI versus standard practice at 30 days follow-up

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with stress MRI versus standard management 30-day (95% CI)
All-cause mortality	105 (1 study)	LOW[a] due to risk of bias	Not estimable	-	No events in control or intervention arm
Cardiac mortality	110 (1 study)	LOW[a] due to risk of bias	Not estimable	-	No events in control or intervention arm
Non-fatal MI	110 (1 study)	VERY LOW[ab] due to risk of bias, imprecision	Peto OR 1.08 (0.07 to 17.46)	18 per 1000	0 more per 1000 (from 5 fewer to 5 more)

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with stress MRI versus standard management 30-day (95% CI)
PCI	110 (1 study)	VERY LOW[ab] due to risk of bias, imprecision	RR 0.22 (0.03 to 1.78)	88 per 1000	68 fewer per 1000 (from 85 fewer to 68 more)
CABG	110 (1 study)	VERY LOW[ab] due to risk of bias, imprecision	Peto OR 7.97 (0.16 to 402.62)	0 per 1000	20 more per 1000 (from 30 fewer to 70 more)
Stress testing adverse events	110 (1 study)	LOW[a] due to risk of bias	Not estimable	-	No events in control or intervention arm

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b]Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

7.4.2.2.2 Diagnostic test accuracy review

Forty studies were included in the review.

All diagnostic test accuracy (DTA) data were derived from populations that had acute chest pain and initial negative or non-diagnostic electrocardiogram (ECG) and no elevation in cardiac biomarkers.

DTA was analysed according to 4 risk stratification categories based on the study prevalence of non-ST-elevation myocardial infarction (NSTEMI) and/or unstable angina (UA). Namely, ≤10%, >10% to 20%, >20% to 50% and greater than 50%. The majority of studies identified were conducted in populations with a prevalence of ≤10% or 20% to >50%.

The studies included in the review for the most part discharged participants if imaging test results ruled out NSTEMI or UA without referring the participants to invasive coronary angiography (ICA). In clinical practice it would have been unethical to perform an invasive test such as ICA in patients testing negative on non-invasive imaging. Almost all of these studies used a combined reference standard of ICA and major adverse cardiac events (MACE) at a specified follow-up. Accordingly there may have been reference standard verification bias which could have serious implications in test accuracy.

Multi-detector computed tomography angiography:

- One study compared the accuracy of MDCT in a population with three different prevalences of NSTEMI and/or UA, namely >10% to 20%, 20% to 50% and >50%.[36]
- Nine studies were in populations with NSTEMI and/or UA prevalence of <10%.[12,75,82,87,100-104,135] Three studies were in populations with a prevalence between >10% to 20%.[36,43,85]
- Four studies were conducted in populations with a prevalence of between >20% to 50%[36,119,184,212]
- Four studies had populations of >50% prevalence.[36,142,216,220]

Details of these studies are summarised in Table 37. The clinical evidence profile is given in Table 44.

Dual source computed tomography angiography:

- One study had a prevalence of NSTEMI or UA of 3%[86] and the second a prevalence of 14%.[118]

Details of these studies are summarised in Table 38. The clinical evidence profile is given in Table 45.

Single photon emission tomography:

- Seven studies examined the diagnostic test accuracy of single photon emission computed tomography (SPECT)[1,12,51,53,69,75,218]
- Two studies were in resting SPECT and five examined stress SPECT.
- All the studies either had prevalences of NSTEMI and/or UA of ≤10% or >10% to 20%.

Details of these studies are summarised in Table 39. The clinical evidence profile is given in Table 46.

Stress echocardiography:

- Three studies had populations with prevalences of ≤10%[11,16,21]
- Two studies had prevalences between >10% to 20%[50,53]
- Two studies had prevalences of between >20% to 50%[109,210]
- Three studies had prevalences of >50%.[7,73,108]

Details of these studies are summarised in Table 40. The clinical evidence profile is given in Table 47.

Update 2016

Cardiac magnetic resonance imaging:

- One study investigated resting MRI in a population with a prevalence of NSTEMI and/or UA between >20% to 50%.[131]
- One study used stress MRI with a population prevalence of ≤10%[147] and a second study using stress MRI was in a population with a prevalence between >10% to 20%.[218]

Details of these studies are summarised in Table 41. The clinical evidence profile is given in Table 48.

Exercise echocardiography:

- Two studies were in population prevalences of ≤10%[4,85]
- Two studies were in prevalences between >10% to 20%[14,51]
- One study was in a population prevalence of >50%[73]

Details of these studies are summarised in Table 42. The clinical evidence profile is given in Table 49.

The negative and positive values for all of imaging techniques are summarised in Table 52.

Meta-analysis of sensitivity and specificity data was performed when there were 3 or greater study results for a given test and population. The results are summarised in Table 43.

See also the study selection flow chart in Appendix F, sensitivity and specificity forest plots and receiver operating characteristics (ROC) in Appendix M.

Update 2016

Table 37: Summary of 64-slice or higher multi-detector computed tomography studies included in the review

Study Country Study type	Index test (positive criterion)	Reference standard(s): population percentage (positive criterion)	Population, n Prevalence NSTEMI and/or UA Prior tests TIMI risk score (where reported)
ACRIN PA 2012[135] USA RCT Single centre	64-slice MDCT (≥50% stenosis of the LM, LAD, LF, or artery, or first order branch)	• ICA: 5% (≥70% stenosis) • MACE at 30-days: 95% (cardiac death, acute MI, ACS)	• n=667 • ≤10% • No evidence of ischaemia on ECG, TIMI risk score 0–2
Beigel 2009[12] Israel Prospective cohort Single centre	64-slice MDCT (>50% stenosis)	• ICA: 7% (NR) • MACE at 5 months (repeat cardiac chest pain, ICA, PCI, ACS, death)	n=308 ≤10% Negative ECG and troponin I or T
Chang 2008[36] Korea Prospective cohort Single centre	64-slice MDCT (≥50%)	• ACC/AHA guideline for ACS: 14% • MACE: 86%	n=123 >10% to 20% Non-diagnostic ECG (short duration symptoms)
Chang 2008[36]	64-slice MDCT (≥50%)	• ACC/AHA guideline for ACS: 51% • MACE: 49%	n=123

Study Country Study type	Index test (positive criterion)	Reference standard(s): population percentage (positive criterion)	Population, n Prevalence NSTEMI and/or UA Prior tests TIMI risk score (where reported)
Korea Prospective cohort Single centre			>20% to 50% Non-diagnostic ECG
Chang 2008 [36] Korea Prospective cohort Single centre	64-slice MDCT (≥50%)	• ACC/AHA guideline for ACS: 71% • MACE: 29%	n=123 >50% ECG suggesting ischaemia (ST depression, T wave inversion) or typical chest pain with known CAD
Christiaens 2012[43] France Prospective cohort Two centres	64-slice MDCT (≥50% stenosis)	• ICA: 19% (≥50%) • MACE at 6 months: 81% (CVD events)	• n=175 • Negative ECG and troponin • >10% to 20% • TIMI risk score ○ 0 to 2: 86% ○ >2 to 3: 14%
CT-COMPARE 2014[85] USA RCT	64- or 128-slice MDCT (>50% stenosis)	• ACS using case report forms based on Cardiac Society of Australia and New Zealand guidelines	n=322 >10% to 20% No evidence of ischaemia on ECG, and negative troponin

Study Country Study type	Index test (positive criterion)	Reference standard(s): population percentage (positive criterion)	Population, n Prevalence NSTEMI and/or UA Prior tests TIMI risk score (where reported)
Gallagher 2007[75] USA Prospective cohort Single centre	64-slice MDCT (>50% stenosis and CAC>400)	• ICA: 12% (>70% stenosis) • MACE at 30 days: 88% (cardiac death, non-fatal MI or unstable angina)	n=85 ≤10% Negative serial ECG and cardiac biomarkers, low risk by Reilly/Goldman criteria
Goldstein 2007[82] USA RCT Single centre	64-slice MDCT (>70% stenosis)	• ICA: 14% (NR) • MACE at 30 days: 86% (cardiac death, non-fatal MI or unstable angina)	n=99 ≤10% Negative ECG and cardiac biomarkers
Hascoët 2012[87] France Prospective cohort Single centre	64-slice MDCT(≥50%)	• ICA: 24% (≥50%) • MACE at median (IQR) 15 (7–19) months (CV death, MI, revascularisation): 76%	n=123 ≤10% Negative ECG and troponin
Hollander 2007[104] USA Prospective cohort Single centre	64-slice MDCT (≥50% stenosis)	• ICA: 15% (≥50% stenosis) • MACE: 85% (cardiac death or non-fatal MI) at 30 days	n=54 ≤10% Normal or non-specific ECG, negative cardiac biomarkers

Study Country Study type	Index test (positive criterion)	Reference standard(s): population percentage (positive criterion)	Population, n Prevalence NSTEMI and/or UA Prior tests TIMI risk score (where reported)
Hollander 2009[103] USA Prospective cohort Single centre	64-slice MDCT (≥50% stenosis)	ICA: 3% (≥50% stenosis) MACE at 30 days: 97% (cardiac death or non-fatal MI)	n=519 ≤10% Normal or non-specific ECG, negative cardiac biomarkers, TIMI risk score 0–2
Johnson 2007[119] Germany Prospective cohort Single centre	64-slice MDCT (>50% stenosis)	ICA:100% (>50% stenosis)	n=55 >20% to 50% No ECG evidence of MI or ischaemia
Meijboom 2008[142] The Netherlands Prospective cohort Three centres	64-slice MDCT (≥50% stenosis)	ICA:100% (≥50% stenosis)	n=127 >50% Unstable angina, negative ECG and troponin; NSTEMI, negative ECG raised troponin

Update 2016

Study Country Study type	Index test (positive criterion)	Reference standard(s): population percentage (positive criterion)	Population, n Prevalence NSTEMI and/or UA Prior tests TIMI risk score (where reported)
ROMICAT 2009[100] USA RCT Single centre	64-slice MDCT (>50% stenosis)	ACS • Acute MI developed positive troponin during serial testing at 6 hours or 9 hours after presentation • UA according to the ACC/ AHA and ESC guidelines	n=368 ≤10% Negative ECG and troponins on presentation
ROMICAT-II 2008[101,102] USA RCT	64-slice MDCT (NR)	• ICA: 6% (>50% stenosis) • MACE at 28 days: 4% (CVD events)	n=501 ≤10% No ischaemic changes on ECG, initial troponin negative
Rubinshtein 2007[184] Israel Prospective cohort Single centre	64-slice MDCT (≥50% stenosis)	• ICA: 74% (≥50% stenosis) • SPECT: 26% (perfusion defects indicative of myocardial ischaemia)	• n=58 • Negative ECG and biomarkers, but symptoms compatible with ACS, or, clinical symptoms of definite ischaemic origin without high risk factors • >20% to 50%
Ueno 2009[212] Japan Prospective cohort Single centre	64-slice MDCT (>50% stenosis)	ACC/AHA guideline for ACS: 100%	n=36 Negative ECG and cardiac biomarkers >20% to 50%

Study Country Study type	Index test (positive criterion)	Reference standard(s): population percentage (positive criterion)	Population, n Prevalence NSTEMI and/or UA Prior tests TIMI risk score (where reported)
van Velzen 2012[216] The Netherlands Retrospective cohort Single centre	320-slice MDCT (≥50% stenosis)	ICA:100% (≥50% stenosis)	n=106 >50% Negative for STEMI
von Ziegler 2014[220] Germany Prospective cohort Single centre	64-slice MDCT (>50% stenosis)	ICA:100% (≥50% stenosis)	n=134 >50% Negative for STEMI and elevated troponin

Table 38: Summary of dual source computed tomography (DSCT) studies included in the review

Study Country Study type	Index test (positive criterion)	Reference standard(s): population percentage (positive criterion)	Population, n Prevalence NSTEMI and/or UA Prior tests TIMI risk score (where reported)
Johnson 2008[118]	DSCT (>50% stenosis)	• ICA: 100% (>50% stenosis)	n=109

Study Country Study type	Index test (positive criterion)	Reference standard(s): population percentage (positive criterion)	Population, n Prevalence NSTEMI and/or UA Prior tests TIMI risk score (where reported)
Germany Prospective cohort Single centre			>10% to 20% Negative ECG and troponin
Hansen 2010[86] Australia Prospective cohort Single centre	DSCT (>50% stenosis)	ICA:100% (>70% stenosis)	n=91 ≤10% Negative ECG and cardiac biomarkers

Table 39: Summary of rest and stress single photon emission computed tomography (SPECT) studies included in the review

Study Country Study type	Diagnostic test (positive criterion)	Reference standard(s): population percentage (positive criterion)	Population, n Prevalence NSTEMI and/or UA Prior tests TIMI risk score (where reported)
Beigel 2009[12] Israel Prospective cohort Single centre	Stress SPECT (ischaemia and angina pain and/or decrease in SBP >10 mmHg)	• ICA: 7% (NR) • MACE at 5 months (repeat cardiac chest pain, ICA, PCI, ACS, death)	n=322 ≤10% Negative ECG and troponin I or T

Study Country Study type	Diagnostic test (positive criterion)	Reference standard(s): population percentage (positive criterion)	Population, n Prevalence NSTEMI and/or UA Prior tests TIMI risk score (where reported)
Conti 2001[51] Italy Prospective cohort Single centre	Rest SPECT (perfusion defects)	• ICA (≥50% stenosis) and/or acute MI during hospital stay acute MI: 31% • MACE at 6 months: 69% (sudden death or ischaemic cardiac events)	n=80 >20% to 50% Negative ECG, cardiac biomarkers, ECHO, subjects presenting <3 h from pain onset
Conti 2001[51] Italy Prospective cohort Single centre	Stress SPECT (perfusion defects)	• ICA (≥50% stenosis) and/or acute MI during hospital stay acute MI: 31% • MACE at 6 months: 69% (sudden death or ischaemic cardiac events)	n=151 >10% to 20% Negative ECG, cardiac biomarkers, ECHO, subjects presenting ≥3 h from pain onset
Conti 2005[53] Italy Prospective cohort Single centre	Stress SPECT (perfusion defects and abnormal wall motion)	• ICA: 30% (≥50% stenosis) • MACE at 30 days 6 months: 70% (sudden death, non-fatal MI, PCI, CABG readmission for chest pain, significant stenosis (>50%))	n=503 >10% to 20% Negative ECG, cardiac biomarkers, ECHO, subjects presenting ≥3 h from pain onset
Conti 2011[1]	Stress SPECT (perfusion	• ICA (≥50% stenosis)	n=1089

Update 2016

Study Country Study type	Diagnostic test (positive criterion)	Reference standard(s): population percentage (positive criterion)	Population, n Prevalence NSTEMI and/or UA Prior tests TIMI risk score (where reported)
Italy Prospective cohort Single centre	defects)	• MACE at 6 months: 69% (sudden death or ischaemic cardiac events)	>10% to 20% Negative results after 6 h work-up of serial ECG and serial troponin
Forberg 2009[69] Sweden Prospective cohort Single centre	Rest SPECT (perfusion defects)	• ACS defined from ACC/AHA and ESC guidelines	n=40 ≤10% Negative ECG and Troponin T
Gallagher 2007[75] USA Prospective cohort Single centre	Stress SPECT (perfusion defect)	• ICA: 12% (>70% stenosis) • MACE at 30 days: 88% (cardiac death, non-fatal MI or unstable angina)	n=85 ≤10% Negative serial ECG and cardiac biomarkers, low risk by Reilly/Goldman criteria
Vogel- Claussen 2009[218] USA Prospective cohort Single centre (Stress SPECT and stress MRI)	Stress SPECT (perfusion defects)	• ICA: 12% (≥70% stenosis): 4/31 • 256-slice MDCT: 1/31(≥70% stenosis) • MACE at mean (SD) 14 (4.7) months: 69% (all-cause mortality, MI, stroke)	n=31 >10% to 20% Negative results after 6 hour work-up of serial ECG and serial troponin

Update 2016

Study Country Study type	Diagnostic test (positive criterion)	Reference standard(s): population percentage (positive criterion)	Population, n Prevalence NSTEMI and/or UA Prior tests TIMI risk score (where reported)

Table 40: Summary of echocardiography studies included in the review

Study Country Study type	Diagnostic test (positive criterion)	Reference standard(s): population percentage (positive criterion)	Population, n Prevalence NSTEMI and/or UA Prior tests TIMI risk score (where reported)
Atar 2000[7] USA Prospective cohort Single centre	Pacing stress ECHO (New or worsened wall motion abnormality (WMA))	• ICA: 100% (≥75%)	n=53 >50% Negative ECG and cardiac biomarkers
Bedetti 2005[11] Italy Prospective cohort Multicentre 6 sites	Stress ECHO (New or worsened WMA)	• ICA: 8% (≥50% stenosis) • MACE at 13 months: 92% (cardiac death, non-fatal MI)	n=546 ≤10% Negative ECG and cardiac biomarkers

Study Country Study type	Diagnostic test (positive criterion)	Reference standard(s): population percentage (positive criterion)	Population, n Prevalence NSTEMI and/or UA Prior tests TIMI risk score (where reported)
Bholasingh 2003[16] USA Prospective cohort Single centre	Stress ECHO (New WMA)	• ICA: 7% (≥50% stenosis) • MACE at 30 days: 93% (cardiac death, non-fatal MI, unstable angina, PCI, CABG)	n=377 ≤10% Negative ECG
Buchsbaum 2001[21] USA Prospective cohort Single centre	Stress ECHO (New WMA)	• ICA: 5% • (≥50% stenosis) • MACE at 6 months: 95%	n=145 ≤10% Normal ECG, negative creatine kinase
Conti 2005[53] Italy Prospective cohort Single centre (stress SPECT and stress ECHO)	Stress SPECT Stress ECHO (New WMA)	• ICA: 30% (≥50% stenosis) • MACE at 30 days, 6 months: 70% (sudden death, non-fatal MI, PCI, CABG readmission for chest pain, significant stenosis [>50%])	n=503 >10% to 20% Negative results after 6 hour work-up of serial ECG and serial troponin
Conti 2015[50] Italy Prospective cohort	Stress ECHO (New WMA)	• ICA (≥50% stenosis) • MACE at 3 months (ACS, CV death, revascularisation)	n=188 >10% to 20% Negative ECG and high sensitivity troponin I

Study Country Study type	Diagnostic test (positive criterion)	Reference standard(s): population percentage (positive criterion)	Population, n Prevalence NSTEMI and/or UA Prior tests TIMI risk score (where reported)
Single centre			
Gaibazzi 2011[72] Italy Prospective cohort Single centre	Stress ECHO (New WMA)	• ICA: 71% (≥50% stenosis) • MACE at 6 months (Cardiac death, non-fatal MI, revascularisation)	n=92 >50% Negative ECG
Iglesias-Garriz 2005[108] Spain Prospective cohort Single centre	Stress ECHO (≥2 adjacent segments of WMA)	• ICA: 100% (>% stenosis)	n=78 >50% Negative ECG and troponin I
Innocenti 2013 [109] Italy Prospective cohort Single centre	Stress ECHO (New WMA)	• ICA: 23% (≥50% stenosis) • MACE: at 6 months: 77% (cardiac death, non-fatal ACS, revascularisation)	n=434 >20% to 50% Negative ECG and cardiac biomarkers
Tsutsui 2005[210]	Stress	• ICA: 39% (>50% stenosis)	n=158

Study Country Study type	Diagnostic test (positive criterion)	Reference standard(s): population percentage (positive criterion)	Population, n Prevalence NSTEMI and/or UA Prior tests TIMI risk score (where reported)
USA Prospective cohort Single centre	ECHO (≥2 adjacent segments of WMA)	• MACE at 6 months: 46% (cardiac death, non-fatal MI, UA, revascularisation)	>20% to 50% Negative ECG and creatine kinase

Table 41: Summary of magnetic resonance imaging (MRI) included in the review

Study Country Study type	Diagnostic test (positive criterion)	Reference standard(s): population percentage (positive criterion)	Population, n Prevalence NSTEMI and/or UA Prior tests TIMI risk score (where reported)
Kwong 2003[131] USA Prospective cohort Single centre	MRI (regional wall abnormality or delayed hyper-enhancement)	• ACC/AHA guideline for ACS: 14%	n=667 >10% to 20% No evidence of ischaemia on ECG, TIMI risk score 0-2
Miller 2010[147] USA RCT	Stress MRI (wall motion- perfusion-abnormalities, delayed enhancement)	• ACS defined as one of the following: acute MI, ischaemia leading to revascularisation, death likely related to ischaemia, discharge diagnosis of definite/probable UA or inducible ischaemia on stress test	n=52 ≤10% Negative ECG and troponin I

Study Country Study type	Diagnostic test (positive criterion)	Reference standard(s): population percentage (positive criterion)	Population, n Prevalence NSTEMI and/or UA Prior tests TIMI risk score (where reported)
Vogel- Claussen 2009[218] USA Single centre (Stress SPECT and stress MRI)	Stress MRI (reversible regional perfusion deficit in a coronary artery territory lasting for >6 heart beats)	• ICA: 12% (≥70% stenosis): 4/31 • 256-slice MDCT: 1/31(≥70% stenosis) • MACE at mean (SD) 14 (4.7) months: 69% (all-cause mortality, MI, stroke)	n=31 >10% to 20% Negative results after 6 hour work-up of serial ECG and serial troponin

Table 42: Summary of exercise ECG studies included in the review

Study Country Study type	Diagnostic test (positive criterion)	Reference standard(s): population percentage (positive criterion)	Population, n Prevalence NSTEMI and/or UA Prior tests TIMI risk score (where reported)
Amsterdam 2002[4] USA Prospective cohort Single centre	Exercise ECG (exercise-induced ST-segment alterations)	• ICA: 7% (NR) • Stress MPS: 9% (NR) • Stress ECHO: 3% (NR) • MACE at 30 days: 84% (cardiac death, non-fatal MI, non-invasive imaging test showing CAD)	n=765 ≤10% Negative ECG or minor ST-T changes (<0.5 mm ST depression and/or flat but not inverted T wave, some participants cardiac biomarker [some not tested])
Bennett 2013[14]	Exercise ECG	• ICA: 18% (NR)	n=196

Study Country Study type	Diagnostic test (positive criterion)	Reference standard(s): population percentage (positive criterion)	Population, n Prevalence NSTEMI and/or UA Prior tests TIMI risk score (where reported)
UK Retrospective cohort Single centre		• Readmission for chest pain at 12 months: 82%	>10% to 20% Negative ECG and troponin T
CT-COMPARE 2014[85] USA RCT	Exercise ECG	• ACS using case report forms based on Cardiac Society of Australia and New Zealand guidelines	n=240 ≤10% No evidence of ischaemia on ECG, and negative troponin
Conti 2001[51] Italy Prospective cohort Single centre	Exercise ECG	• ICA (≥50% stenosis) • MACE at 6 months: 69% (sudden death or ischaemic cardiac events)	n=151 >10% to 20% Negative ECG, cardiac biomarkers, ECHO, subjects presenting ≥3 hours from pain onset
Gaibazzi 2011[72] Italy Prospective cohort Single centre	Exercise ECG	• ICA (≥50% stenosis) and/or acute MI during hospital stay acute MI: 31% • MACE at 6 months: 69% (sudden death or ischaemic cardiac events)	n=151 >10% to 20% Negative ECG, cardiac biomarkers, ECHO, subjects presenting ≥3 hours from pain onset

Table 43: Summary of meta-analyses of sensitivity and specificity results

Test	Number of studies	Prevalence of NSTEMI or UA (%)	Sensitivity, median (95%CI)	Specificity, median (95%CI)
MDCT	9	≤10%	median (95%CI): 0.95 (0.86 to 0.99)	median (95%CI) 0.95 (0.89 to 0.98)
MDCT	3	>10% to 20%	median (95%CI): 0.95 (0.71 to 0.99)	median (95%CI): 0.97 (0.87 to 0.99)
MDCT	4	>20% to 50%	median (95%CI): 0.98 (0.89 to 1.00)	median (95%CI): 0.92 (0.78 to 0.97)
MDCT	4	>50%	median (95%CI): 0.99 (0.93 to 1.00)	median (95%CI): 0.82 (0.52 to 0.95)
DSCT	1	≤10%	1.00 (0.29 to 1.00)	0.99 (0.94 to 1.00)
DSCT	1	>10% to 20%	1.00 (0.78 to 1.00)	0.96 (0.89 to 0.99)
Rest SPECT	1	≤10%	1.00 (0.16 to 1.00)	0.71 (0.54 to 0.85)
Rest SPECT	1	>20% to 50%	0.94 (0.71 to 1.00)	0.75 (0.62 to 0.85)
Stress SPECT	2	≤10%	(i) 0.60 (0.41 to 0.77) (ii) 0.71 (0.29 to 0.96)	(i) 0.95 (0.92 to 0.97) (ii) 0.90 (0.81 to 0.95)
Stress SPECT	4	>10% to 20%	median (95%CI): 0.86 (0.62 to 0.95)	median (95%CI): 0.86 (0.72 to 0.94)
Stress ECHO	3	≤10%	median (95%CI): 0.75 (18 to 96)	median (95%CI): 97 (88 to 99)
Stress ECHO	2	>10% to 20%	(i) 0.85 (0.76 to 0.92) (ii) 0.60 (0.36 to 0.81)	(i) 0.95 (0.93 to 0.97) (ii) 0.96 (0.92 to 0.99)
Stress ECHO	2	>20 to 50%	(i) 0.90 (0.82 to 0.95) (ii) 0.63 (0.47 to 0.76)	(i) 0.92 (0.89 to 0.95) (ii) 0.82 (0.73 to 0.89)
Stress ECHO	3	>50%	median (95%CI): 0.75 (26 to 95)	median (95%CI): 70 (32 to 91)
Rest MRI	1	≤10%	0.89 (0.72, 0.98)	0.86 (0.79, 0.91)
Stress MRI	1	≤10%	1.00 (0.03, 1.00)	0.90 (0.77, 0.97)
Stress MRI	1	>10% to 20%	1.00 (0.48, 1.00)	0.96 (0.80, 1.00)
Exercise ECG	2	≤10%	(i) 0.94 (0.81 to 0.99) (ii) 0.80 (0.28 to 0.99)	(i) 0.87 (0.85 to 0.90) (ii) 00.91 [0.86, 0.94)
Exercise ECG	2	>10% to 20%	-	-
Exercise ECG	1	>50%	0.65 (0.43 to 0.84)	0.75 (0.53 to 0.90)

Update 2016

Test	Number of studies	Prevalence of NSTEMI or UA (%)	Sensitivity, median (95%CI)	Specificity, median (95%CI)

ECHO, echocardiography; ECG, electrocardiogram; MDCT, multidetector computed tomography; MRI, magnetic resonance imaging; NSTEMI, non-ST elevation myocardial infarction; SPECT, single photon emission computed tomography; UA, unstable angina

Table 44: Clinical evidence profile: 64-slice or higher multi-detector computed tomography (MDCT)

Index test (Threshold)	Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (median/ range/ 95% CI)	Specificity % (median/ range/ 95% CI)	Quality
Index test									
MDCT: prevalence of NSTEMI/UA ≤10%	9	2616	Serious risk of bias[a]	No serious inconsistency[b]	Serious indirectness[c]	Serious imprecision[d]	Pooled 0.95 (0.86 to 0.99)	Pooled 0.95 (0.89 to 0.98)	VERY LOW
MDCT: prevalence of NSTEMI/UA 10% to 20%	3	473	Serious risk of bias[a]	No serious inconsistency[b]	Serious indirectness[c]	Serious imprecision[d]	Pooled 0.95 (0.71 to 0.99)	Pooled 0.97 (0.87 to 0.99)	VERY LOW
MDCT: prevalence of NSTEMI/UA >20% to 50%	4	208	Serious risk of bias[a]	No serious inconsistency[b]	Serious indirectness[c]	Serious imprecision[d]	Pooled 0.98 (0.89 to 1.00)	Pooled 0.92 (0.78 to 0.97)	VERY LOW
MDCT: prevalence of NSTEMI/UA >50%	4	374	Serious risk of bias[a]	No serious inconsistency[b]	Serious indirectness[c]	No serious imprecision[d]	Pooled 0.99 (0.93 to 1.00)	Pooled 0.82 (0.52 to 0.95)	LOW
MDCT, multi-detector computed tomography; NSTEMI, non-ST elevation myocardial infarction; UA, unstable angina									

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making

(a) Risk of bias was assessed using the QUADAS-2 checklist.

(b) Inconsistency was assessed by inspection of the sensitivity and specificity forest plots (based on the primary measure), or summary area under the curve (sROC) plots across studies, using the point estimates and confidence intervals.

(c) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability: downgraded because studies used a combined reference standard (invasive angiography and major cardiac adverse events)

(d) The judgement of precision was based on visual inspection of the confidence region in the diagnostic meta-analysis if a diagnostic meta-analysis was conducted. Where a diagnostic meta-analysis was not conducted imprecision was assessed according to the range of point estimates. A rating of serious imprecision was given if the confidence intervals for sensitivity crossed 2 areas; <50%, 50% to 90% and 90% or very serious imprecision for three areas

Table 45: Clinical evidence profile: dual source computed tomography (DSCT)

Index test (Threshold)	Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (median/ range/ 95% CI)	Specificity % (median/ range/ 95% CI)	Quality
Index test									
DSCT: prevalence of NSTEMI/UA ≤10%	1	109	Serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness[c]	Very serious imprecision[d]	1.00 (0.29 to 1.00)	0.99 (0.94 to 1.00)	VERY LOW
DSCT: prevalence of NSTEMI/UA 10% to 20%	1	89	Serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness[c]	Serious imprecision[d]	1.00 (0.78 to 1.00)	0.96 (0.89 to 0.99)	LOW
DSCT: prevalence of NSTEMI/UA >20% to 50%	No studies identified								
DSCT: prevalence of NSTEMI/UA >50%	No studies identified								
; DSCT, dual source computed tomography; NSTEMI, non-ST elevation myocardial infarction; UA, unstable angina									

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making

(a) Risk of bias was assessed using the QUADAS-2 checklist.

(b) Inconsistency was assessed by inspection of the sensitivity and specificity forest plots (based on the primary measure), or summary area under the curve (sROC) plots across studies, using the point estimates and confidence intervals.

(c) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability: downgraded because studies used a combined reference standard (invasive angiography and major cardiac adverse events)

(d) The judgement of precision was based on visual inspection of the confidence region in the diagnostic meta-analysis if a diagnostic meta-analysis was conducted. Where a diagnostic meta-analysis was not conducted imprecision was assessed according to the range of point estimates. A rating of serious imprecision was given if the confidence intervals for sensitivity crossed 2 areas; <50%, 50% to 90% and 90% or very serious imprecision for three areas

Table 46: Clinical evidence profile: rest and stress single photon emission computed tomography (SPECT)

Index test (Threshold)	Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (median/ range/ 95% CI)	Specificity % (median/ range/ 95% CI)	Quality
Index test									
Rest SPECT: prevalence of	1	40	Serious risk	No serious	Serious	Very serious	1.00 (0.16 to	0.71 (0.54 to	VERY LOW

Index test (Threshold)	Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (median/ range/ 95% CI)	Specificity % (median/ range/ 95% CI)	Quality
NSTEMI/UA ≤10%			of bias[a]	inconsistency[b]	indirectness[c]	imprecision[d]	1.00)	0.85)	
Rest SPECT: prevalence of NSTEMI/UA >10% to 20%	No studies identified								
Rest SPECT: prevalence of NSTEMI/UA >20% to 50%	1	80	Serious risk of bias[a]	No serious inconsistency[b]	Serious indirectness[c]	Serious imprecision[d]	0.94 (0.71 to 1.00)	0.75 (0.62 to 0.85)	VERY LOW
Rest SPECT: prevalence of NSTEMI/UA >50%	No studies identified								
Stress SPECT: prevalence of NSTEMI/UA ≤10%	2	420	Serious risk of bias[a]	No serious inconsistency[b]	Serious indirectness[c]	Serious imprecision[d]	(i) 0.60 (0.41 to 0.77) (ii) 0.71 (0.29 to 0.96)	(i) 0.95 (0.92 to 0.97)[d] (ii) 0.90 (0.81 to 0.95)[d]	VERY LOW
Stress SPECT: prevalence of NSTEMI/UA >10% to 20%	4	1772	Serious risk of bias[a]	No serious inconsistency[b]	Serious indirectness[c]	Serious imprecision[d]	Pooled 0.86 (0.62 to 0.95)	Pooled 0.86 (0.72 to 0.94)	VERY LOW
Stress SPECT: prevalence of NSTEMI/UA >20% to 50%	No studies identified								
Stress SPECT: prevalence of NSTEMI/UA > 50%	No studies identified								

, non-ST elevation myocardial infarction; SPECT, single photon emission computed tomography; UA, unstable angina

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making

a) *Risk of bias was assessed using the QUADAS-2 checklist.*
b) *Inconsistency was assessed by inspection of the sensitivity and specificity forest plots (based on the primary measure), or summary area under the curve (sROC) plots across studies, using the point estimates and confidence intervals.*
c) *Indirectness was assessed using the QUADAS-2 checklist items referring to applicability: downgraded because studies used a combined reference standard (invasive angiography and major cardiac adverse events)*
d) *The judgement of precision was based on visual inspection of the confidence region in the diagnostic meta-analysis if a diagnostic meta-analysis was conducted. Where a diagnostic meta-analysis was not conducted imprecision was assessed according to the range of point estimates. A rating of serious imprecision was given if the confidence intervals for sensitivity crossed 2 areas; <50%, 50% to 90% and 90% or very serious imprecision for three areas*

Table 47: Clinical evidence profile: stress echocardiography

Index test (Threshold)	Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (median/range /95% CI)	Specificity % (median/range /95% CI)	Quality
Index test									
Stress ECHO: prevalence of NSTEMI/UA ≤10%	3	1068	Serious risk of bias[a]	No serious inconsistency[b]	Serious indirectness[c]	Very serious imprecision[d]	Pooled 0.75 (0.18 to 0.96)	Pooled 97 (0.88 to 0.99)	VERY LOW
Stress ECHO: prevalence of NSTEMI/UA 10% to 20%	2	691	Serious risk of bias[a]	No serious inconsistency[b]	Serious indirectness[c]	Serious imprecision[d]	(i) 0.85 (0.76 to 0.92) (ii) 0.60 (0.36 to 0.81)	(i) 0.95 (0.93 to 0.97)[d] (ii) 0.96 (0.92 to 0.99)[d]	VERY LOW
Stress ECHO: prevalence of NSTEMI/UA >20% to 50%	2	592	Serious risk of bias[a]	No serious inconsistency[b]	Serious indirectness[c]	Serious imprecision[d]	(i) 0.90 (0.82 to 0.95) (ii) 0.63 (0.47 to 0.76)	(i) 0.92 (0.89 to 0.95)[d] (ii) 0.82 (0.73 to 0.89)[d]	VERY LOW
Stress ECHO: prevalence of NSTEMI/UA >50%	3	179	Serious risk of bias[a]	Serious inconsistency[b]	No serious indirectness[c]	Very serious imprecision[d]	Pooled 0.75 (0.26 to 0.95)	Pooled 70 (0.32 to 0.91)	VERY LOW

ECHO, echocardiography; ECG, electrocardiogram; NSTEMI, non-ST elevation myocardial infarction; UA, unstable angina

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making

(a) Risk of bias was assessed using the QUADAS-2 checklist.

(b) Inconsistency was assessed by inspection of the sensitivity and specificity forest plots (based on the primary measure), or summary area under the curve (sROC) plots across studies, using the point estimates and confidence intervals.

(c) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability: downgraded because studies used a combined reference standard (invasive angiography and major cardiac adverse events)

(d) The judgement of precision was based on visual inspection of the confidence region in the diagnostic meta-analysis if a diagnostic meta-analysis was conducted. Where a diagnostic meta-analysis was not conducted imprecision was assessed according to the range of point estimates. A rating of serious imprecision was given if the confidence intervals for sensitivity crossed 2 areas; <50%, 50% to 90% and 90% or very serious imprecision for three areas

Table 48: Clinical evidence profile: rest and stress magnetic resonance imaging (MRI)

Index test (Threshold)	Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (median/ range/ 95% CI)	Specificity % (median/ range/ 95% CI)	Quality
Index test									
Rest MRI: prevalence of NSTEMI/UA ≤10%	No studies identified								
Rest MRI: prevalence of NSTEMI/UA 10% to 20%	1	171	Serious risk of bias[a]	No serious inconsistency[b]	Serious indirectness[c]	Serious imprecision[d]	0.89 (0.72 to 0.98)	0.86 (0.79 to 0.91)	VERY LOW
Rest MRI: prevalence of NSTEMI/UA >20% to 50%	No studies identified								
Rest MRI: prevalence of NSTEMI/UA >50%	No studies identified								
Stress MRI: prevalence of NSTEMI/UA ≤10%	1	1068	Serious risk of bias[a]	No serious inconsistency[b]	Serious indirectness[c]	Very serious imprecision[d]	1.00 (0.03 to 1.00)	0.90 (0.77 to 0.97)	VERY LOW
Stress MRI: prevalence of NSTEMI/UA 10% to 20%	1	900	Serious risk of bias[a]	No serious inconsistency[b]	Serious indirectness[c]	Very serious imprecision[d]	1.00 (0.48 to 1.00)	0.96 (0.80 to 1.00)	VERY LOW
Stress MRI: prevalence of NSTEMI/UA >20% to 50%	No studies identified								
Stress MRI: prevalence of NSTEMI/UA >50%	No studies identified								
; MRI, magnetic resonance imaging; NSTEMI, non-ST elevation myocardial infarction; UA, unstable angina									

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making

(a) Risk of bias was assessed using the QUADAS-2 checklist.

(b) Inconsistency was assessed by inspection of the sensitivity and specificity forest plots (based on the primary measure), or summary area under the curve (sROC) plots across studies, using the point estimates and confidence intervals.

(c) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability: downgraded because studies used a combined reference standard (invasive angiography and major cardiac adverse events)

(d) The judgement of precision was based on visual inspection of the confidence region in the diagnostic meta-analysis if a diagnostic meta-analysis was conducted. Where a diagnostic meta-analysis was not conducted imprecision was assessed according to the range of point estimates. A rating of serious imprecision was given if the confidence intervals for sensitivity crossed 2 areas; <50%, 50% to 90% and 90% or very serious imprecision for three areas

Table 49: Clinical evidence profile: exercise electrocardiogram (ECG)

Index test (Threshold)	Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (median/ range/ 95% CI)	Specificity % (median/ range/ 95% CI)	Quality
Index test									
Exercise ECG: prevalence of NSTEMI/UA ≤10%	2	1005	Serious risk of bias[a]	No serious inconsistency[b]	Serious indirectness[c]	Serious imprecision[d]	(i) 0.94 (0.81 to 0.99) (ii) 0.80 (0.28 to 0.99)	(i) 0.87 (0.85 to 0.90)[d] (ii) 00.91 (0.86, 0.94)[d]	VERY LOW
Exercise ECG: prevalence of NSTEMI/UA >10% to 20%	2	151	Serious risk of bias[a]	No serious inconsistency[b]	Serious indirectness[c]	Serious imprecision[d]	(i) 0.70 (0.47 to 0.87) (ii) 0.28 (0.10 to 0.53)	(i) 0.90 (0.85 to 0.94)[d] ii) 0.95 (0.89 to 0.98)[d]	VERY LOW
Exercise ECG: prevalence of NSTEMI/UA >20% to 50%	No studies identified								
Exercise ECG: prevalence of NSTEMI/UA >50%	1	47	Serious risk of bias[a]	No serious inconsistency[b]	Serious indirectness[c]	Serious imprecision[d]	0.65 (0.43 to 0.84)	0.75 (0.53 to 0.90)	VERY LOW
ECG, electrocardiogram; NSTEMI, non-ST elevation myocardial infarction; UA, unstable angina									

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making

(a) Risk of bias was assessed using the QUADAS-2 checklist.

(b) Inconsistency was assessed by inspection of the sensitivity and specificity forest plots (based on the primary measure), or summary area under the curve (sROC) plots across studies, using the point estimates and confidence intervals.

(c) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability: downgraded because studies used a combined reference standard (invasive angiography and major cardiac adverse events)

(d) The judgement of precision was based on visual inspection of the confidence region in the diagnostic meta-analysis if a diagnostic meta-analysis was conducted. Where a diagnostic meta-analysis was not conducted imprecision was assessed according to the range of point estimates. A rating of serious imprecision was given if the confidence intervals for sensitivity crossed 2 areas; <50%, 50% to 90% and 90% or very serious imprecision for three areas

Table 50: Predictive values: 64-slice or higher multi-detector computed tomography (MDCT)

Index test (Threshold)	Number of studies	n	Negative predictive values/median (rang)	Positive predictive values/median (range)

Index test (Threshold)	Number of studies	n	Negative predictive values/median (rang)	Positive predictive values/median (range)
MDCT: prevalence of NSTEMI/UA ≤10%	9	2616	0.98 (0.98-1.00)	0.80 (0.13-0.95)
MDCT: prevalence of NSTEMI/UA 10% to 20%	3	473	Could not be calculated	0.80 (0.80-0.90)
MDCT: prevalence of NSTEMI/UA >20% to 50%	4	208	0.95 (0.95-0.97) 0.95-1.0	0.84 (0.73-0.91)
MDCT: prevalence of NSTEMI/UA >50%	4	374	0.90 (0.90-0.94)	0.90 (0.80-0.96)

Table 51: Predictive values: dual source computed tomography (DSCT)

Index test (Threshold)	Number of studies	n	Negative predictive value	Positive predictive value
DSCT: prevalence of NSTEMI/UA ≤10%	1	109	0.97	0.84
DSCT: prevalence of NSTEMI/UA 10% to 20%	1	89	1.0	0.34

Table 52: Predictive values: rest and stress single photon emission computed tomography (SPECT)

Index test (Threshold)	Number of studies	n	Negative predictive value/ median (range)	Positive predictive value/median (range)
Rest SPECT: prevalence of NSTEMI/UA ≤10%	1	40	1.00	0.15
Rest SPECT: prevalence of NSTEMI/UA >20% to 50%	1	80	0.99	0.45
Stress SPECT: prevalence of NSTEMI/UA ≤10%	2	420	0.96 (0.50-0.99))	0.38 (0.38-0.56)
Stress SPECT: prevalence of NSTEMI/UA >10% to 20%	4	1772	0.96(0.92-0.99)	0.53 (0.45-0.56

Table 53: Predictive values: stress echocardiography

Index test (Threshold)	Number of studies	n	Negative predictive value/median (rnge)	Positive predictive value/median (range)
Stress ECHO: prevalence of NSTEMI/UA ≤10%	3	1068	0.99 (0.96-1.0)	0.44 (0.43-0.88)
Stress ECHO: prevalence of NSTEMI/UA 10% to 20%	2	691	0.95 (0.95-0.97)	0.67 (0.67-0.81)
Stress ECHO: prevalence of NSTEMI/UA >20% to 50%	2	592	0.83 (0.83-0.97)	0.60 (0.60-0.75)
Stress ECHO: prevalence of NSTEMI/UA >50%	3	179	0.46 (0.31-0.87)	0.86 (0.71-0.95)

Table 54: Predictive values: rest and stress magnetic resonance imaging (MRI)

Index test (Threshold)	Number of studies	n	Negative predictive value	Positive predictive value
Rest MRI: prevalence of NSTEMI/UA 10% to 20%	1	171	Could not be calculated	0.57
Stress MRI: prevalence of NSTEMI/UA ≤10%	1	1068	1.0	0.17
Stress MRI: prevalence of NSTEMI/UA 10% to 20%	1	900	1.0	0.83

Table 55: Predictive values: exercise electrocardiogram (ECG)

Index test (Threshold)	Number of studies	n	Negative predictive value	Positive predictive value
Exercise ECG: prevalence of NSTEMI/UA ≤10%	2	1005	Range 1.0	0.15(0.15-0.26)

Index test (Threshold)	Number of studies	n	Negative predictive value	Positive predictive value
Exercise ECG: prevalence of NSTEMI/UA >10% to 20%	2	151	0.91 (0.91-0.96)	0.42 (0.42-0.47)
Exercise ECG: prevalence of NSTEMI/UA >50%	1	47	0.67	0.71

Update 2016

7.4.2.2.3 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in Appendix G.

Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

The sections below detail the costs borne by the NHS for introducing routine non-invasive coronary computerised tomographic angiography (CCTA) scanning at emergency department index visits into the diagnostic pathway of ACS for low risk people presenting with acute chest pain.

The large majority of the evidence found from the diagnostic review was for CCTA. The evidence found that all the other tests in the protocol had either similar or lower diagnostic accuracy compared to CCTA. The costs in Table 56 show that CCTA has the lowest unit cost per test. The GC therefore decided to focus the economic analysis on routine CCTA testing versus standard of care (SOC). Current standard of care after initial triage can include any of the non-invasive tests listed in the guideline protocol.

Table 56: Unit costs of tests

Item	Description	Source	Cost
CCTA	RD28Z, complex computerised tomography scan	NHS Reference Costs 2014–15	£122.11
Rest SPECT	RN20Z, myocardial perfusion scan	NHS Reference Costs 2014–15	£300.00
Stress SPECT	RN21Z, myocardial perfusion scan, stress only	NHS Reference Costs 2014–15	£367.29
ECHO	EY50Z, complex echocardiogram	NHS Reference Costs 2014–15	£271.31
CMR	RA67Z, cardiac magnetic resonance imaging scan, pre- and post-contrast	Enhanced Tariff Option 2015–16	£515.00
Exercise ECG	EY51Z, electrocardiogram monitoring or stress testing	NHS Reference Costs 2014–15	£153.00

Update 2016

The introduction of highly sensitive troponin assays has dramatically changed how people with acute chest pain are managed in UK emergency departments. Test results can be analysed a lot earlier than with the standard troponin assays, as they reach peak diagnostic accuracy in a significantly shorter time frame (4 hours compared to 12 hours). This allows for a more rapid discharge than was previously possible. For this reason, any studies conducted prior to the high-sensitivity troponin era were considered not applicable to what NICE recommends as best practice in the UK. The clinical review found one test-and-treat study on CCTA that was relevant to the population, [55] which had been conducted after the introduction of high-sensitivity troponin assays.

The BEACON study was conducted in the Netherlands and compared 30-day outcomes of routine CCTA testing at ED index visits versus standard of care for low risk people presenting to the emergency department with acute chest pain or symptoms suggestive of ACS warranting further diagnostic investigation. [55] Standard care consisted of some CCTA testing, however this was not routine and people in this group were more likely to receive an exercise ECG test. Some people in the routine CCTA group did not receive a CCTA as for some people the test could not be performed, for example for people with insufficient ability to hold their breath. The results found that CCTA and SOC clinical outcomes were the same. The study also gave a detailed breakdown of the resource use over 30 days for each arm of the trial, which is given below. It concluded that the average cost per patient was lower in the CCTA group than the SOC group (£284 versus €431)[f].

Resource use breakdown: [55]

*Average cost per patient in the CCTA group = [cost of initial ED evaluation] + [cost CCTA] + 0.13 * [cost XECG] + 0.01 * [cost SPECT] + 0.004 * [cost CMR] + 0.17 * [cost ICA] + 0.09 [cost PCI] + 0 * [cost CABG] + 0.05 [cost repeat ED evaluation] + 0.03 [repeat hospital admission] =* ***£284***

*Average cost per patient in the SOC group = [cost of initial ED evaluation] + 0.58 * [cost XECG] + 0.07 * [cost SPECT] + 0.01 * [cost CMR] + 0.13 * [cost ICA] + 0.05 [cost PCI] + 0.02 * [cost CABG] + 0.08 [cost repeat ED evaluation] + 0.06 [repeat hospital admission] =* ***£431***

Cost analysis comparing CCTA to SOC

As results from the clinical review and the BEACON study both reported that clinical outcomes were the same between CCTA and SOC, routine CCTA can only be considered cost effective if it has equal or lower average costs per patient compared to SOC. To determine the cost-effectiveness of CCTA, a de novo cost analysis was conducted that was based on the resource use reported in the BEACON study, however unit costs from the UK NHS were applied. The unit costs that were included in the analysis are listed in Table 57.

Update 2016

Table 57: UK unit costs

				Probabilistic Sensitivity Analysis[(a)]		
Item	**Code and Description**	**Source**	**Cost**	**Dist**	**Alpha**	**Beta**
CCTA	RD28Z, complex computerised tomography scan	NHS Reference Costs 2014–15	£122.11	Gamma	3.42	35.67
Stress SPECT	RN21Z, myocardial perfusion scan, stress only	NHS Reference Costs 2014–15	£367.29	Gamma	5.27	69.70
CMR	RA67Z, cardiac magnetic resonance imaging scan, pre- and post-contrast	Enhanced Tariff Option 2015–16	£515.00	Gamma	60.89	8.46
Exercise ECG	EY51Z, electrocardiogram monitoring or stress testing	NHS Reference Costs 2014–15	£153.00	Gamma	11.06	13.83
ICA	EY43A to EY43F, standard cardiac catheterisation with CC score 0–13+	NHS Reference Costs 2014–15, weighted average	£1,141.26	Gamma		

[f] Converted from Euros using OECD purchasing power parities (PPPs).

				Probabilistic Sensitivity Analysis[a]		
Item	Code and Description	Source	Cost	Dist	Alpha	Beta
PCI	EY40A to EY41D, standard or complex percutaneous transluminal coronary angioplasty with CC score 0–12+	NHS Reference Costs 2014–15, weighted average	£2,242	Gamma		
CABG	ED28A to ED28B, standard coronary artery bypass graft with CC score 0–10+	NHS Reference Costs 2014–15, weighted average	£7,303.00	Gamma		
ED visit (admitted)	VB09Z, emergency medicine, category 1 investigation with category 1–2 treatment	NHS Reference Costs 2014–15	£132.00	Gamma	15.07	8.76
ED visit (non-admitted)	VB09Z, emergency medicine, category 1 investigation with category 1–2 treatment	NHS Reference Costs 2014–15	£107.00	Gamma	5.84	126.48
Repeat hospital admission	EB10A to EB10E, actual or suspected myocardial infarction, with CC score 0–13+	NHS Reference Costs 2014–15, weighted average	£280.00	Gamma		

(a) The alpha and beta values were estimated using the upper and lower quartiles listed in the NHS reference costs. For the costs where the distribution values are not reported, alpha and beta values were estimated for each NHS reference cost category (e.g. CS Score +13) to estimate the probabilistic probabilities for each category. Then weighted averages were calculated to estimate the probabilistic probabilities of the overall cost item.

Update 2016

The analysis was split into 3 sections: cost of tests during index visit, cost of tests after index visit, and treatment and repeat admission costs. This was done in order to gain a better understanding of where costs are likely to occur.

Cost of tests during index visit

Table 58 gives details on the average costs of each test at the index visit per patient for both the CCTA and SOC groups. There were 245 people followed up in each group of the study, therefore the proportions were estimated by dividing the number of tests reported to have been carried out during index visits by 245.

Table 58: Cost of tests during index visit per patient

						Values used in probabilistic sensitivity analysis[b]				
Test	Unit cost	Proportion[g] *(n/total n)*		Average cost per patient *(unit cost * proportion)*		Dist	Alpha		Beta	
		CCTA	SOC	CCTA	SOC		CTCA	SOC	CTCA	SOC
ExECG	£153.00	0.09 (23/245)	0.53 (130/245)	£13.77	£81.09	Beta	22	130	223	115
CCTA	£122.11	0.971	0.004 (1/245)	£118.62	£0.49	Beta	238	1	7	244

[g] Proportions were sourced from the BEACON study 55. Dedic A, Lubbers MM, Schaap J, Lammers J, Lamfers EJ, Rensing BJ et al. Coronary CT Angiography for Suspected ACS in the Era of High-Sensitivity Troponins: Randomized Multicenter Study. Journal of the American College of Cardiology. 2016; 67(1):16-26.

						Values used in probabilistic sensitivity analysis[b]				
Test	**Unit cost**	**Proportion[g]** *(n/total n)*		**Average cost per patient** *(unit cost * proportion)*		**Dist**	**Alpha**		**Beta**	
		(238/245)								
SPECT	£367.29	0.008 (2/245)	0.03 (7/245)	£2.94	£11.02	Beta	2	7	243	238
CMR	£515.00	0.004 (1/245)	0.004 (1/245)	£2.06	£2.06	Beta	1	1	244	244
ICA (no PCI)	£1141.26	0.088 (21.52/245) (a)	0.059 (14.52/245) (a)	£100.43	£67.62	Beta	21.52	14.52	223.48	230.48
			Total	**£237.82**	**£162.28**					

(a) The NHS reference cost for a PCI is likely to include the cost of an ICA. The probability of requiring an ICA in each group was adjusted to only include those that received an ICA with no PCI, to ensure the cost of an ICA was not double counted[h]

(b) Alpha and beta values were calculated using the resource utilisation values reported in the BEACON study.

Cost of tests after index visit

Table 59: Cost of tests after index visit per patient

						Values used in probabilistic sensitivity analysis				
Test	**Unit cost**	**Proportion[i]** *(n/total n)*		**Average cost per patient** *(unit cost * proportion)*		**Dist**	**Alpha**		**Beta**	
		CCTA	**SOC**	**CCTA**	**SOC**		**CTCA**	**SOC**	**CTCA**	**SOC**
ExECG	£153.00	0.036 (9/245)	0.052 (13/245)	£5.51	£7.96	Beta	9	13	236	232
CCTA	£122.11	0.004 (1/245)	0.008 (2/245)	£0.49	£0.98	Beta	1	2	244	243
SPECT	£367.29	0 (0/245)	0.036 (9/245)	0	£13.22	Beta	0	9	245	236
CMR	£515.00	0 (0/245)	0.008 (2/245)	0	£4.12	Beta	0	2	245	243
ICA (no PCI)	£1141.26	0.018 (4.41/245)[(a)]	0.014 (3.48/245)[(a)]	£20.54	£16.23	Beta	4.41	3.48	240.59	241.52
			Total	**£26.54**	**£42.50**					

(a) The NHS reference cost for a PCI is likely to include the cost of an ICA. The probability of requiring an ICA in each group was adjusted to only include those that received an ICA with no PCI, to ensure the cost of an ICA was not double counted[j]

Update 2016

[h] Invasive coronary angiography (ICA), percutaneous coronary intervention (PCI)

[i] Proportions were sourced from the BEACON study 55. Dedic A, Lubbers MM, Schaap J, Lammers J, Lamfers EJ, Rensing BJ et al. Coronary CT Angiography for Suspected ACS in the Era of High-Sensitivity Troponins: Randomized Multicenter Study. Journal of the American College of Cardiology. 2016; 67(1):16-26

[j] Invasive coronary angiography (ICA), percutaneous coronary intervention (PCI)

(b) Alpha and beta values were calculated using the resource utilisation values reported in the BEACON study.

Table 59 gives details on the estimated average cost of receiving each test after the index visit per person for both groups.

Costs of treatments and repeat admissions

Table 60 gives details of the average cost of treatments, repeat ED visits and hospital admissions per patient for both groups. These were calculated using the numbers reported in the study, UK costs and results from the test-and-treat clinical review.

Table 60: Costs of treatment and repeat admissions per patient

						Values used in probabilistic sensitivity analysis[(b)]				
Test	**Unit cost**	**Proportion[k]** *(n/total n)*		**Average cost per patient** *(unit cost * proportion)*		**Dist**	**Alpha**		**Beta**	
		CCTA	**SOC**	**CCTA**	**SOC**		**CTCA**	**SOC**	**CTCA**	**SOC**
ED visit non-admitted	£107.00	0.024 (6/245)	0.02 (5/245)	£2.57	£2.14	Beta	6	5	239	240
ED visit admitted	£132.00	0.029 (7/245)	0.057 (14/245)	£3.70	£7.52	Beta	7	14	238	231
Hospital admission	£280.00	0.029 (7/245)	0.057 (14/245)	£8.12	£15.95	Beta	7	14	238	231
PCI (inc. ICA)	£2242.00	0.0615[(a)]	0.0368[(a)] (31/842)	£137.84	£82.54	Beta		31		811
CABG	£7303.00	0.0085[(a)]	0.0095[(a)] (8/842)	£61.76	£69.39	Beta		9		834
			Total	**£214.11**	**£177.55**					

(a) Probabilities estimated using results from the test-and-treat clinical review

(b) Alpha and beta values were calculated using the resource utilisation values reported in the BEACON study. For PCI (inc ICA) and CABG the probabilistic proportions were calculated using the risk ratios reported in the clinical review.

Most probabilities in **Table 60** were calculated from the BEACON study results, except for the probabilities of requiring PCI or CABG treatment. These were estimated using the meta-analysed results from the test-and-treat clinical review. The meta-analysed results were calculated from the results of three studies (including the BEACON study) [55 ,82 ,102] on 1,687 people in total, therefore they are likely to be more accurate than the results of the Netherlands study alone. As the costs of these

[k] Proportions were sourced from the Netherlands study 55. Dedic A, Lubbers MM, Schaap J, Lammers J, Lamfers EJ, Rensing BJ et al. Coronary CT Angiography for Suspected ACS in the Era of High-Sensitivity Troponins: Randomized Multicenter Study. Journal of the American College of Cardiology. 2016; 67(1):16-26

Update 2016

treatments are significantly higher than any other unit costs included in the analysis, it was considered more appropriate to use the meta-analysed results in order to reduce the level of bias in the average costs. In the Netherlands study, no one in the CCTA group received a CABG, but four people in the SOC group did. As the GC felt that the probability of a patient receiving a CABG is not likely to be affected by whether they received a CCTA at their ED index visit or not, but instead determined by their underlying condition, they believed using the original results would have led to an unfair bias in favour of CCTA.

Base case results

Table 61 shows the base case results of the cost analysis.

Table 61: Base case results – average cost per patient

	SOC	CCTA
Test at index visit (Table 58)	£162.28	£237.82
Tests after index visit (**Table 59**)	£42.50	£26.54
Treatment and admissions (**Table 60**)	£177.55	£214.11
Total	**£382.33**	**£478.47**

The results in Table 61 show that in a UK setting, the SOC group is estimated to have lower average costs over 30 days than the CCTA group: **£382.33** compared to **£478.47.** This is the opposite result to the results reported in the BEACON study, where the SOC group appeared to have higher average patient costs (£284 versus £430). The study reported that a reason for the CCTA group having lower costs was due to less outpatient testing occurring in that group. Although this is the case, the results above imply that the costs of tests after the index visit are relatively low in both groups. Significantly higher costs occur from the index visit tests and treatment and admissions.

Update 2016

The primary reason that the results of our analysis conflicted with the results from the original study is that the BEACON study only reported the median costs, not the mean costs. The distribution of costs in the study was extremely skewed as many people were discharged straight from the ED with low costs while a few people had very high costs due to expensive treatments. These high costs would not be captured in a median cost statistic. Another reason is that the costs used in the study were from the Netherlands not the UK, where there is likely to be some variation. Finally, the probabilities of requiring PCI or CABG treatment were taken from the clinical review and included the combined results of 3 studies.

Probabilistic sensitivity analysis

To account for parameter uncertainty and to see how robust the base case results were to changes in resource use or costs, a probabilistic sensitivity analysis (PSA) was undertaken. The GC acknowledged that NHS reference costs are average costs and that the costs of tests, treatments, ED visits and hospital admissions vary by different hospitals and geographically. They also acknowledged that most of the probabilities in the analysis were based on only 1 study that was not conducted in the UK, therefore they also have a degree of uncertainty and in reality will vary.

For the PSA, beta distributions were attached to all of the proportions and gamma distributions were attached to all of the costs. To define the distributions around the proportions, alpha and beta parameters were calculated from the events recorded in the study. To define the distributions around the costs, parameters were calculated from the interquartile ranges. For the costs that were calculated as weighted averages (for example the cost of a PCI treatment), distributions were

attached to each individual cost, and then new probabilistic weighted averages were calculated from the probabilistic costs. Ten-thousand simulations were run, with each simulation simultaneously randomly selecting a value from each distribution and calculating the average cost results. Averages were then taken of the 10,000 simulation results to give the probabilistic results shown in Table 62.

Table 62: Probabilistic results (averages of 10,000 simulations) – average cost per patient

	SOC	CCTA
Test at index visit	£162.02	£237.64
Tests after index visit	£43.01	£26.80
Treatment	£177.50	£224.62
Total	**£382 (CI £272, £493)**	**£489 (CI £286, £692)**
Number of simulations with the lowest cost	8883 (88.83%)	1117 (11.17%)

The results in Table 62 show that the base case results are robust to changes in the parameter values. On average, the SOC group total costs were **£382** compared to **£489** for the CCTA group. The PSA results also show that for 8,883 (89%) of the 10,000 simulations, the SOC group had the lowest costs per person.

Economic considerations

Evidence from the literature suggests that routine CCTA for low to intermediate risk people with acute chest pain can lower costs by increasing emergency department discharge rates or decreasing hospital length of stay. [81,102,135] The studies that report these findings were conducted before the routine use of high-sensitivity troponin assays, therefore their results are not considered applicable. One study conducted after the introduction of high sensitivity troponin [55] found that CCTA had lower median costs after 30 days than SOC. However, when UK costs were applied, more accurate estimates for the proportion of people that would require expensive treatments were used, and mean costs were reported, the CCTA group became the group with the highest average costs over 30 days. These results are robust to changes in parameter values.

The cost analysis results suggest that CCTA is likely to be more costly than standard care and therefore not likely to be cost effective for a low risk population, however the GC acknowledged that it might be cost effective for other populations, for example an intermediate risk population.

Other considerations

The GC acknowledged that the outcomes reported in the clinical review and in the BEACON study were only 30-day outcomes and that no long-term health outcomes were reported. The cost analysis also only included costs that would occur over a 30-day time horizon. Although the GC felt that 30 days may be long enough to capture all the important costs and outcomes, they were aware of the limitations a short time horizon has on the results.

The BEACON study reported that the mean radiation dose in the CCTA group was higher than the SOC group (7.3 6.6 mSv versus 2.6 6.5 mSv). As 30-day outcomes are estimated to be the same and average costs are estimated to be higher with CCTA, it should be considered whether it is worth putting patients at increased risk through the use of CCTA testing.

Update 2016

7.4.2.2.4 Evidence statements

Clinical effectiveness

Clinical

Multi-detector CT angiography compared to standard practice:

Seven studies comprising 576 to 2946 people per outcome suggested that there was no clinically significant effect on the critical outcomes of all-cause mortality, cardiovascular mortality and non-fatal MI at 30 days (Very low to Low quality). There was no clinically significant effect for the important outcomes of readmission due to cardiac cause, PCI and CABG.

One study comprising 699 people suggested that there was no clinically significant effect on the critical outcomes of all-cause mortality, non-fatal MI, PCI and CABG at 30 days (Low to Very low quality).

One study comprising 562 people suggested that there was no clinically significant effect on the critical outcome of all-cause mortality at 30 days (Low quality).

One study comprising 562 people suggested that there was no clinically significant effect on the critical outcome of all-cause mortality at 1 year (Very low quality).

Resting SPECT compared to standard practice:

One study comprising 2475 people suggested that there was no clinically significant effect on the critical outcome of all-cause mortality, PCI and CABG at 30 days (Very low quality).

Update 2016

Stress SPECT compared to standard practice:

One study comprising 1508 people suggested that there was no clinically significant effect on the critical outcome of cardiac mortality at 30 days (Very low quality).

One study comprising 1508 people suggested that there was no clinically significant effect on the critical outcome of cardiac mortality at one year (Very low quality).

Stress MRI compared to standard practice:

Two studies comprising 105 to 110 people suggested that there was no clinically significant effect on the critical outcomes of all-cause mortality, cardiac mortality, non-fatal MI, PCI and stress testing adverse events at 30 days (Very low to Low quality).

Economic

- No relevant economic evaluations were identified.

Diagnostic test accuracy

Clinical

Eighteen studies examined the diagnostic tests accuracy of 64-slice or higher multi-detector CT angiography:

- Very low quality evidence from nine studies of 2616 adults showed a pooled sensitivity of 95% and a pooled specificity of 95% at a prevalence of 10% or less.

- Very low quality evidence from three studies of 473 adults showed a pooled sensitivity of 95% and a pooled specificity of 97% at a prevalence of between 10 and 20%.
- Very low quality evidence from four studies of 4208 adults showed a pooled sensitivity of 98% and a pooled specificity of 92% at a prevalence of greater than 20% and less than 50%.
- Low quality evidence from four studies of 374 adults showed a pooled sensitivity of 99% and a pooled specificity of 82% at a prevalence of greater than 50%.

Two studies examined the diagnostic test accuracy of dual source computed tomography (DSCT) angiography:

- Very low quality evidence from one study of 40 adults showed a sensitivity of 100% and specificity of 99% at a prevalence of 10% or less.
- Low quality evidence from one study of 89 adults showed a sensitivity of 100% and specificity of 96% at a prevalence of between 10 and 20%.

Seven studies examined the diagnostic test accuracy of single photon emission computed tomography (SPECT):

- Very low quality evidence from one study of 40 adults showed a sensitivity of 100% and specificity of 71% at a prevalence of 10% or less.
- Very low quality evidence from one study of 80 adults showed a sensitivity of 94% and specificity of 75% at a prevalence of between 10 and 20%.
- Very low quality evidence from two studies of 420 adults showed a sensitivity of 60 and 71% and a specificity of 90 and 95% at a prevalence of less than 10%.
- Very low quality evidence from four studies of 1772 adults showed a pooled sensitivity of 86% and a pooled specificity of 96% at a prevalence of between 10 and 20%.

Update 2016

Twelve studies examined the diagnostic test accuracy of stress echocardiography:

- Very low quality evidence from three studies of 1068 adults showed a pooled sensitivity of 75% and a pooled specificity of 97% at a prevalence of 10% or less.
- Very low quality evidence from two studies of 691 adults showed a sensitivity of 60 and 85% and specificity of 95 and 96% at a prevalence of between 10 and 20%.
- Very low quality evidence from two studies of 592 adults showed a sensitivity of 63 and 90% and specificity of 82 and 92% at a prevalence of between 20 and 50%.
- Very low quality evidence from three studies of 779 adults showed a pooled sensitivity of 75% and a pooled specificity of 70% at a prevalence of greater than 50%.

Three studies examined the diagnostic test accuracy of cardiac magnetic resonance imaging (MRI):

- Very low quality evidence from one study of 171 adults showed a sensitivity of 89% and specificity of 96% at a prevalence of between 10 and 20%.
- Very low quality evidence from one study of 1068 adults showed a sensitivity of 100% and specificity of 96% at a prevalence of 10% or less.
- Very low quality evidence from one study of 900 adults showed a sensitivity of 100% and specificity of 96% at a prevalence of between 10 and 20%.

Five studies examined the diagnostic test accuracy of exercise ECG:

- Very low quality evidence from two studies of 1005 adults showed a sensitivity of 80 and 94% and specificity of 87 and 91% at a prevalence of 10% or less.

- Very low quality evidence from two studies of 151 adults showed a sensitivity of 28 and 70% and specificity of between 90 and 95% at a prevalence of between 10 and 20%.
- Very low quality evidence from one study of 765 adults showed a sensitivity of 66% and specificity of 75% at a prevalence of greater than 50%.

Economic

- No relevant economic evaluations were identified.

7.4.2.2.5 Recommendations and link to evidence

Recommendations	**1.2.6.6 Do not routinely offer non-invasive imaging or exercise ECG in the initial assessment of acute cardiac chest pain.**
Relative values of different diagnostic measures and outcomes	Clinical effectiveness review The GC considered the critical outcomes were: all-cause mortality, cardiovascular mortality, myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), hospitalisation during 30-day follow-up period for cardiac causes and non-cardiac causes, quality of life, incidence of MACE (mortality, myocardial infarction and revascularisation combined) and adverse events. The committee also considered process outcomes such as time to discharge as important. No data were reported on quality of life, MACE, adverse events or any of the process outcomes. Diagnostic test accuracy review The GC considered sensitivity to be critical for decision making. High sensitivity indicates that the test correctly identifies people with the condition. If a condition is treatable and the consequences of missing a case are serious, high sensitivity is required. Missing a case of non-ST elevation (NSTEMI) or unstable angina (UA) may have serious consequences including death and future major adverse cardiac events (MACE). The GC also considered specificity to be important. The higher the specificity the greater the confidence that an individual without NSTEMI will have a negative finding. Low specificity means that more people without the condition might stay in hospital longer than necessary, have more diagnostic tests, receive unnecessary procedures and treatments with increased anxiety for both the individual and family members. Negative and positive predictive values were considered useful by the GC. These values indicate the probability that a person does not have the condition given that the test result is negative, or that a person does have the condition if the test result is positive. Unlike sensitivity and specificity, negative and positive predictive values vary according to prevalence and should only be considered in this context.
Quality of the clinical evidence	Clinical effectiveness Most outcomes were Low to Very low quality across all of the comparisons and prevalence categories. Outcomes were downgraded due to methodological reasons, for example including unclear or no explanation of allocation concealment and randomisation, blinding and missing data. The majority of results were imprecise. Furthermore, many studies did not provide details of 'standard care', including medication. The studies were

Update 2016

	also underpowered for all outcomes with the exception of mortality. Diagnostic test accuracy review Assessment of overall quality of the evidence using GRADE resulted in quality ratings of Low for most of the non-invasive tests at the 4 prevalence categories. Most studies used a combined reference standard of ICA and MACE at 30 days follow-up, however in most studies ICA was only performed in people with positive initial test finding. This is likely to have implications for the observed diagnostic test accuracy for all the non-invasive imaging studies with the exception of the two studies assessing dual-source CT in which ICA alone was the reference standard. Lack of blinding of the study investigators performing ICA and investigators collecting data for MACE may also have had an influence on the results. Imprecision was evaluated according to the width of confidence intervals across the 3 following categories: <50%, ≥50% and >90%. Imprecision was identified in a few instances. All studies had populations consistent with those specified in the review protocol. The GC noted that both functional and anatomical tests were being compared with an anatomical reference standard of angiography. It is unclear how this impacts on the diagnostic accuracy of the functional tests.
Trade-off between clinical benefits and harms	While diagnostic cohort studies indicated a high sensitivity for multi-slice CT angiography this does not tell us whether adopting a particular diagnostic strategy improves patient outcomes. Evidence on patient outcomes comparing two diagnostic interventions is ideally provided by the RCTs. Clinical effectiveness review Eleven RCTs were identified comparing multi-slice CT angiography with standard care, multi-slice CT angiography with exercise ECG, SPECT with standard care and MRI with standard care. Overall the results of the RCTs were consistent with no benefit for all outcomes including all-cause and cardiovascular mortality and myocardial infarction, although very limited data were available for all of the tests except for multi-slice CT angiography. Conversely, there was no evidence that using these investigations was associated with any adverse consequences. MRI was associated with a clinically important increase in CABG compared to standard practice. Diagnostic accuracy review Sensitivity and specificity: The majority of evidence was on multi-slice and dual-source CT angiography. This technique yielded a sensitivity of over 95% and a specificity of over 82% across the different prevalence categories. Limited evidence on resting SPECT and stress MRI suggested a sensitivity of between 94 and 100%. The sensitivities for the other tests were all below 90%. However, study sizes were small and the results varied across studies. A lower level of sensitivity may be acceptable if a combination of tests were used such that patients with a false negative test result still underwent further testing.

Update 2016

	Negative and positive predictive values For MDCT, DSCT, SPECT and MRI across all of the prevalence groups the negative predictive values were 95% or above but the positive predictive values were much lower, ranging between 15 and 80%. With the exception of the lowest risk group, stress ECHO yielded lower negative predictive values of between 46 and 95% and positive predictive values of between 60 and 86%. Exercise ECG had a negative predictive value of 100% in the lowest prevalence group but between 67 and 91% in the highest two groups. Positive predictive values were low for all groups. As the majority of study data were in the low prevalence populations, the added value of a high negative predictive value is low. The GC discussed that although the sensitivity of multi-slice and dual-source CT angiography was high, the test-and-treat RCT data showed that this non-invasive imaging strategy did not improve patient outcomes. The GC considered that the potential current role of these tests would be to assist in the assessment of patients where the diagnosis was still equivocal after the results of high sensitivity troponin tests. However, all of the studies except one on multi-slice CT angiography (BEACON) were conducted before the use of high-sensitivity troponins, and so are difficult to interpret in this context.
Trade-off between net clinical effects and costs	The large majority of the evidence found from the diagnostic accuracy and test-and-treat clinical reviews were for multi-slice CT angiography. The evidence found that all the other tests in the protocol had either similar or lower diagnostic accuracy compared to CT. The unit costs presented to the GC (see section 6.4.2.2.3) showed that CT has the lowest unit cost per test. The GC therefore decided to focus the economic analysis on routine CT testing. The results of the economic analysis for CT could then be extrapolated to consider the cost effectiveness of the other tests. The economic analysis undertaken was a costing analysis (see section 6.4.2.2.3). The CT-STAT, ACRIN-PA and ROMICAT-2 trials all found that CTCA safely reduced time to diagnosis, increased discharge rates or reduced hospital length of stay, suggesting that the use of early CTCA might reduce medical costs without impacting health outcomes. These trials were conducted before the introduction of high-sensitivity troponin assays which has considerably changed standard of care and length of stay in the ED. Current NICE guidance (DG15) recommends the use of high-sensitivity troponin assays. The results from these trials were therefore considered not applicable to what NICE currently recommends as best practice in the UK and they were not included in the economic evidence sections of this guideline. One study from the clinical effectiveness review was directly relevant to the population, post- the routine use of high-sensitivity troponin assays. The study was conducted in the Netherlands and found that, although there were no differences in clinical outcomes, CT was associated with lower (median) direct medical costs than standard of care (£284 versus £431), after 30 days of follow-up. The study found no difference in discharge rates or length of stay after CT.

Update 2016

	A cost analysis was conducted (see section 6.4.2.2.3), using the resource use results from the Netherlands paper, attaching UK costs, and calculating the mean cost for each strategy. The proportion of individuals who ended up requiring PCI or CABG treatment was re-calculated using the meta-analysed results as presented in the clinical review. The results from this analysis estimated that CT was associated with higher direct medical costs than standard optimal care (£487 versus £382), contradicting the results of the original study. Probabilistic analysis showed the base case results to be robust to changes in costs and resource use parameters, showing that CT had higher mean costs in 88% of the simulations. Across 10,000 simulations the mean cost of standard optimal care was £383 and CT was £489. Due to the conflicting results of the cost analysis in section 6.4.2.2.3, compared to that of the BEACON study, the GC were not confident that the use of routine CT would lower costs, as the BEACON study had suggested. One reason that could explain the difference is that the BEACON study only reported the median costs for each group. As the distribution of costs was likely to be skewed, the committee were uncertain whether the routine CT group would still have had lower costs had the mean costs of each group in the trial been reported. The GC felt that the cost analysis results in section 6.4.2.2.3 were likely to better reflect the true UK cost estimates and that routine CT was more likely to lead to higher costs. The GC therefore decided that it should not be routinely offered. The cost analysis in section 6.4.2.2.3 was conducted for a low risk group. The GC considered that CT might be cost effective in an intermediate risk population but at present there is not enough evidence to determine if this is the case.
Other considerations	Although the committee did not routinely recommend non-invasive tests in the initial assessment of ACS, they recognised the role of these tests in excluding complications of ACS and to rule out other causes of chest pain. The 2010 guideline already had recommendations that highlighted this and the committee considered that without any further evidence to recommend non-invasive tests, and in particular multi slice CT angiography, the recommendations in the use of CT and chest X-ray were still relevant. The GC noted that the value of multi-slice CT angiography may be higher in higher risk groups. This is currently being investigated in higher risk people in the RAPID-CTCA study. With the exception of one study (BEACON), the tests were conducted without the use of high sensitivity troponin and that is the current practice for clinical decision making.

Update 2016

8 People presenting with stable chest pain

8.1 Assessment

Introduction

A universal definition for stable angina has not been agreed internationally, in contrast to that which has been developed for MI[209].

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.

8.1.1 Review question: What is the accuracy, clinical utility and cost effectiveness of clinical prediction models/tools (clinical history, cardiovascular risk factors, physical examination) in evaluating people with stable chest pain of suspected cardiac origin?

8.1.1.1 Clinical evidence review

8.1.1.1.1 Methods

A systematic review of the literature search was conducted as specified in the review protocol (Appendix D). The protocol was developed in consultation with the topic experts and reviewed by the core committee members before the review was carried out. The following outcomes were considered important for decision making: area under the ROC curve (AUC, c-statistic, c-index), sensitivity and specificity.

A number of protocol refinements (see Appendix D) were made during the evidence review phase in consultation with the topic experts. The refinements were informed by the committee discussions on the diagnostic test accuracy question and were made to ensure that the evidence base was not restricted by study design nor based solely on higher prevalence populations, for example, those selected for invasive coronary angiography. To this end, we also included studies that used computed tomography coronary angiography (CTCA) as a reference standard to more closely reflect the population in whom pre-test probability scoring is most appropriate. We have presented the results in separate subgroups based on the reference standard used.

Update 2016

It was also agreed with the committee to restrict the literature search to studies published from 2009. This was because the previous guideline development group had reviewed evidence for clinical prediction of CAD and selected a model adapted from the Duke Clinical Score as the best available model for inclusion in NICE CG95 (2010). That model was developed in the USA in 1993 in a cohort of patients aged 30-70 years undergoing invasive coronary angiography for investigation of chest pain. Its applicability in a contemporary UK setting may be questionable, given changes in the distribution of coronary risk factors over the past 20 years. It was therefore felt important to focus the review on identifying and evaluating the performance of different clinical prediction models which have been validated in recent studies published since the original guideline was developed. The reason for this decision is detailed in Appendix D. On this basis, a systematic search (see Appendix H) identified 7,985 articles. The titles and abstracts were screened and 48 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (Appendix D). Of these, 24 were excluded as they did not meet the criteria and 24 met the criteria and were included.

A review flowchart is provided in Appendix F and the excluded studies (with reasons for exclusion) are shown in Appendix N. Data from the included studies were extracted into standardised evidence tables.

8.1.1.1.2 Results

The 24 studies meeting the review inclusion criteria are summarised in Table 63. Extracted data for each study are presented in the evidence tables in Appendix I. A total of 39 different prediction models were evaluated across these studies. Evidence synthesis and appraisal was restricted only to those validated models in common use (reported in 2 or more studies), or to novel models (single study reported with development and validation cohorts). Table **64** summarises the 15 validated models included in the review in terms of the patient data required for their computation and the number of studies that evaluated the model. Some studies compared the performance of more than one model within the same patient cohort. Evidence for the predictive accuracy of each model was evaluated separately.

Update 2016

Table 63: Summary of included studies

Study reference (including study design)	Study population	Validated prediction models	Non-validated prediction models (included in evidence tables but not appraised in GRADE tables)	Reference standard for CAD diagnosis	Accuracy measures	Setting
Caselli 2015(a)[32] Cross-sectional	N=429 Stable chest pain and intermediate probability of CAD	FRS	Bio-humoral Euro-SCORE	'CTA risk score' (based on CTCA images and calcium scoring)	AUC	14 European centres (part of EVINCI study), including UK
Caselli 2015(b)[33] Cross-sectional	N=527 Stable chest pain and intermediate probability of CAD	Updated D-F (Genders) EVINCI model (integrated clinical + bio-humoral model)	Bio-humoral model 2	Functional testing (+ coronary angiography in subsample)	AUC Sensitivity and specificity	14 European centres (part of EVINCI study), including UK
Cetin 2014[34] Cross-sectional	N=407 Symptoms of CAD and / or abnormal stress test		$CHADS_2$ CHA_2DS_2-VASc CHA_2DS_2-VASc-HS score	Invasive coronary angiography (ICA)	AUC	Turkey (single centre)
Chen 2014[40] Cross-sectional	N=551 Exertional chest tightness / pain referred for elective ICA	Severe Predicting Score D-F		ICA	AUC	China (single centre)
Dharampal (2013)[56] Cross-sectional	N=1,975 Stable chest pain or referred for ICA for suspected CAD		Clinical evaluation model Clinical evaluation model plus CT coronary calcium score	ICA (and/or CTCA)	AUC	The Netherlands (single centre)
Gaibazzi (2015)	N=445	FRS	FRS + Echocardiographic	ICA	AUC	Italy (8 centres)

Update 2016

Study reference (including study design)	Study population	Validated prediction models	Non-validated prediction models (included in evidence tables but not appraised in GRADE tables)	Reference standard for CAD diagnosis	Accuracy measures	Setting
[74] Cross-sectional	Chest pain or abnormal stress test referred for ICA	Diagnostic Imaging in Coronary Artery Disease (DICAD) score	calcium score (eCS) FRS + Carotid intima-media thickness (cIMT) FRS + Carotid plaques (cPL)			
Genders (2010) [77] Cross-sectional	N=254 Chest pain or abnormal functional test referred for ICA	D-F Duke Clinical Score (Pryor et al. 1993) Morise 1994 Morise 1997	D-F + CT calcium score (CTCS) Duke Clinical Score + CTCS Morise 1994 + CTCS Morise 1997 + CTCS	ICA	AUC	The Netherlands (single centre)
Genders (2011) [78] Cross-sectional	N=2,260 Chest pain suggestive of CAD, referred for ICA	D-F Updated D-F (Genders)		ICA	AUC	10 countries (14 centres), including UK
Genders (2012) [79] Cross-sectional	N=4,426 Stable chest pain referred for CTCA (97%) or ICA for suspected CAD	Duke Clinical Score Updated D-F (Genders) Clinical model (updated D-F + risk factors) Diagnostic Imaging in Coronary Artery Disease (DICAD) score		ICA (or imputed data from CTCA)	AUC	11 countries (18 centres), including UK
Hong (2012) [105]	N=140 Women with chest	Morise 1997 D-F		CTCA	AUC Sensitivity and	USA (single centre)

Update 2016

Study reference (including study design)	Study population	Validated prediction models	Non-validated prediction models (included in evidence tables but not appraised in GRADE tables)	Reference standard for CAD diagnosis	Accuracy measures	Setting
Cross-sectional	pain referred for CTCA				specificity	
Hwang (2012)[107] Cross-sectional	N=252 Underwent CTCA for atypical or non-anginal chest pain	FRS		CTCA	AUC Sensitivity and specificity	Korea (single centre)
Jensen (2012) [116] Cross-sectional	N=633 Referred for ICA with chest pain suggestive of CAD	D-F Updated D-F (Genders) Duke Clinical Score Morise 1997 CORSCORE		ICA	AUC	Denmark (single centre)
Kotecha (2010) [127] Cross-sectional	N=539 Referred for ICA (76% with chest pain)	FRS SCORE – high risk regions	Conventional risk factors model (Risk) Conventional risk factors + hs-CRP and BNP (Risk+)	ICA	AUC	Australia (3 centres)
Kumamaru (2014) [129] Cross-sectional	N=3,996 Referred for CTCA with chest pain suggestive of CAD	Duke Clinical Score		CTCA / ICA	AUC	Japan (single centre)
Park (2011) [165] Cross-sectional	N=138 Referred for ICA with stable chest pain or abnormal stress test; aged	Age-adjusted FRS (AFRS)	AFRS + inverse-Flow-mediated dilation (iFMD; an ultrasound parameter) AFRS + Brachial ankle pulse wave velocity (baPWV)	ICA	AUC	Korea (single centre)

Update 2016

Study reference (including study design)	Study population	Validated prediction models	Non-validated prediction models (included in evidence tables but not appraised in GRADE tables)	Reference standard for CAD diagnosis	Accuracy measures	Setting
	30-75yrs		AFRS + baPWV + iFMD			
Pickett (2013) [169] Cross-sectional	N=1,027 Referred for CTCA (75% with chest pain)	D-F Morise 1997		CTCA	AUC	USA (single centre)
Rademaker (2014) [175] Cross-sectional	N=178 Women with chest pain referred for CTCA	D-F Duke Clinical Score Updated D-F (Genders) Morise 1997	Updated D-F + gestational diabetes + oestrogen status	CTCA	AUC	The Netherlands (single centre)
Rosenberg (2010) [183] Cross-sectional	N=526 Referred for ICA with history of chest pain / anginal equivalent symptoms	D-F Combined D-F + Gene expression algorithm		ICA	AUC Sensitivity and specificity	USA (39 centres)
Shmilovich (2014)[199] Cross-sectional	N=199 Referred for CTCA with chest pain	D-F	D-F + Diagonal earlobe crease (DELC)	CTCA	AUC Sensitivity and specificity	USA (single centre)
Versteylen (2011) [217] Cross-sectional	N=1,296 Patients with chest pain who had CTCA	D-F FRS PROCAM risk score SCORE		CTCA	AUC	The Netherlands (one centre)

Update 2016

Study reference (including study design)	Study population	Validated prediction models	Non-validated prediction models (included in evidence tables but not appraised in GRADE tables)	Reference standard for CAD diagnosis	Accuracy measures	Setting
Wasfy (2012) [221] Cross-sectional	N=114 Patients referred for CTCA with chest pain	D-F Duke Clinical Score		CTCA	AUC	USA (one centre)
Winther (2016)[226] Cross-sectional	N=228 Referred for CTCA or ICA for suspected CAD (84% had typical or atypical chest pain)	Updated D-F (Genders)	D-F + CAD-score (acoustic measure) D-F + CAD score (acoustic measure) + coronary calcium score	ICA (and/or CTCA)	AUC	Denmark (single centre)
Yalcin (2012) [227] Cross-sectional	N=350 Patients who had ICA (chest pain not reported)	FRS Modified FRS (MFRS) PROCAM SCORE - high-risk regions SCORE – low-risk regions		ICA	AUC Sensitivity and specificity	Turkey (one centre)
Yang (2015)[228] Cross-sectional	N=7,333 Referred for CTCA for suspected CAD (approximately 70% had typical or atypical chest	Updated D-F (Genders) HRA score		CTCA	AUC	12 sites across 6 countries: USA, Canada, Korea, Austria, Italy, Switzerland, Germany.

Update 2016

Study reference (including study design)	Study population	Validated prediction models	Non-validated prediction models (included in evidence tables but not appraised in GRADE tables)	Reference standard for CAD diagnosis	Accuracy measures	Setting
	pain)					

CAD = coronary artery disease; FRS = Framingham Risk Score; CTCA = computed tomography coronary angiography; AUC = area under the curve; D-F = Diamond and Forrester model; ICA = invasive coronary angiography; HRA score =high risk anatomy score

Studies not in bold were excluded from evidence synthesis and appraisal because they either assessed the predictive accuracy only of a non-validated model(s) or because they used a threshold for diagnosing CAD which differed from that used in the majority of studies (≥50% stenosis in any major epicardial artery assessed using CTCA or ICA).

Table 64: Summary of validated probability models in the included studies

		Patient data required to assess CAD probability score								
CAD probability model (date published/ updated; development setting)	**No. of included studies in which model was used**	**Age**	**Sex**	**Chest pain symptoms / typicality**	**Smoking status**	**Family history of CAD**	**Diabetes**	**Hypertension / BP**	**Cholesterolaemia / blood lipids**	**Other variables**
Diamond-Forrester[1] (1979; USA)	11	✓ (30-69yrs)	✓	✓						
Framingham Risk Score[2] (2008; USA)	7	✓ (20-79yrs)	✓		✓		✓ (Version-specific)	✓	✓	

Update 2016

CAD probability model (date published/ updated; development setting)	No. of included studies in which model was used	Patient data required to assess CAD probability score								
		Age	Sex	Chest pain symptoms / typicality	Smoking status	Family history of CAD	Diabetes	Hypertension / BP	Cholesterolaemia / blood lipids	Other variables
Duke Clinical Score[3] (1993; USA)	6	✓ (30-70yrs)	✓	✓	✓		✓		✓	• History of MI; • ECG
Updated D-F (Genders) (2011;10 countries inc. UK)[4]	6	✓	✓	✓						
Morise[5] (1997; USA)	5	✓	✓	✓	✓	✓	✓	✓	✓	• Oestrogen status (women) • Obesity (BMI>27)
SCORE[6] (2012;12 European countries)	3	✓	✓		✓			✓	✓	
DICAD (2012; 11 countries inc. UK)[7]	2	✓	✓	✓	✓		✓	✓	✓	• BMI • CT coronary calcium score

Update 2016

CAD probability model (date published/ updated; development setting)	No. of included studies in which model was used	Patient data required to assess CAD probability score								
		Age	Sex	Chest pain symptoms / typicality	Smoking status	Family history of CAD	Diabetes	Hypertension / BP	Cholesterolaemia / blood lipids	Other variables
PROCAM[8] (2002) Germany	2	✓ (35-65)	✓ (Male only)		✓		✓	✓	✓	• Family history of MI
Morise[9] (1994; USA)	1	✓	✓	✓			✓		✓	
CORSCORE (2012; Denmark)[10]	1	✓	✓	✓	✓			✓	✓	• History of MI
SPS[11] (2014; China)	1	✓	✓				✓		✓	• AVC on echo • ECG
EVINCI[12] (2015; 14 European centres, including UK)	1	✓	✓	✓					✓	• AST • hs-CRP
Combined D-F + Gene expression algorithm[13]	1	✓	✓	✓						• Blood-based test for expression values for 23

Update 2016

CAD probability model (date published/ updated; development setting)	No. of included studies in which model was used	Patient data required to assess CAD probability score								
		Age	Sex	Chest pain symptoms / typicality	Smoking status	Family history of CAD	Diabetes	Hypertension / BP	Cholesterolaemia / blood lipids	Other variables
(2010; USA)										genes
HRA score[14] (2015; 6 countries across N. America, Europe & Asia)	1	✓	✓	✓	✓	✓	✓	✓	✓	• History of peripheral vascular disease
Updated D-F (Genders) + risk factors (2011; 10 countries inc. UK)[15]	1	✓	✓	✓	✓		✓	✓	✓	• BMI

✓ = information required to compute patient's probability of CAD
Dark shading = variable not included in the prediction model

1. *D-F: Derived from symptomatic patients referred for ICA and autopsy studies; applicable to patients aged 30-69yrs; developed to predict CAD ≥50% stenosis (Diamond and Forrester, 1979)*
2. *FRS: Developed to estimate the 10-year risk of developing cardiovascular disease events; studies that used modified or age-adjusted versions are included (Wilson et al. 1998; D'Agostino et al. 2008)*
3. *Duke Clinical Score: Established and validated in symptomatic patients referred for ICA; developed to predict CAD ≥75% stenosis (Pryor et al. 1993)*
4. *Updated D-F: Developed in symptomatic patients referred for ICA or CTCA to update D-F for application in contemporary adult patient cohorts,(including >69 years (included study: Genders et al. 2011)*
5. *Morise 1997: updated version of Morise 1994, refining adjustment for gender in the original model.*

Update 2016

6. SCORE: Developed to predict 10-year risk of fatal CVD in non-diabetic asymptomatic populations based on data from 12 European cohorts (Conroy et al. 2003; Perk et al. 2012)
7. Diagnostic Imaging in Coronary Artery Disease (DICAD): developed to examine the incremental diagnostic value of adding coronary calcium score to probability model based on risk factors (- included study: Genders 2012)
8. PROCAM: Developed for predicting 10-year risk of acute coronary events; based on cohort of mean aged 35-65 (Assmann et al. 2002)
9. Morise 1994: developed to predict probability of coronary artery disease, including diabetes and dyslipidaemia in addition to the variables used in D-F.
10. CORSCORE: a novel risk scoring system for predicting CAD (included study: Jensen 2012)
11. SPS: a novel risk scoring system to guide early invasive coronary angiography in angina patients using analysis of clinical risk factors, electrocardiography (ECG), and echocardiography (included study: Chen 2014)
12. EVINCI: developed to assess the incremental value of circulating biomarkers over the Genders model to predict functionally significant CAD(included study: Casselli 2015b)
13. Combined D-F and gene expression algorithm (included study: Rosenberg 2010).
14. HRA score: Developed to predict patients' pre-test probability of high-risk coronary anatomy (as opposed to obstructive CAD) using large, prospective international registry of patients referred for CTCA (- included study: Yang 2015)
15. Updated D-F (Genders) + risk factors model: developed to examine incremental diagnostic value of adding additional independent risk factors to the extended D-F mode (- included study: Genders 2012)

Update 2016

8.1.1.1.3 Evidence synthesis and quality appraisal

Area under the curve (AUC)

The included studies all reported the area under the ROC curve (AUC) statistic for each model. A ROC curve plots the sensitivity of a model against its specificity across the full range of possible thresholds scores. Accuracy, in terms of being able to discriminate between cases and non-cases, is measured by the area under the ROC curve (AUC). An area of 1 represents a perfect prediction; an area of 0.5 represents a worthless prediction (equivalent to 'chance'). An area under the curve (AUC) value of 0.7 to 0.8 indicates acceptable model discrimination; values of 0.8 to 0.9 indicate excellent discrimination, and values greater than 0.9 indicate outstanding discrimination (Hosmer 2000). [106] For the purpose of this review, we made the assumption that a model for predicting CAD in unselected patients with stable chest pain would have acceptable clinical utility if it had an AUC of 0.7 or above.

Where a model was examined in two or more studies, we have reported the individual AUC with 95%CIs reported by each study, and a summary median and range of AUCs for the study sample. Where a model was examined in a single study we have reported the AUC with 95%CIs.

Some studies also reported an overall sensitivity and specificity for a model, but it was not usually possible to verify these figures with reference to the relevant 2x2 data as it was not clear what threshold level had been used to dichotomise probability scores to indicate presence or absence of CAD. Therefore only AUC data were included in the evidence synthesis. These data are shown in the GRADE profiles in Appendix K.

Update 2016

CAD threshold

The most common threshold to define a diagnosis of obstructive CAD in the evidence base was ≥50% stenosis in any major epicardial coronary artery, as determined by invasive coronary angiography (ICA) or computed tomography coronary angiography (CTCA). Because CTCA may be considered a less robust diagnostic reference standard than ICA, evidence for the different probability models is presented separately according to the reference standard used (GRADE table for studies using ICA-based studies, GRADE table for CTCA-based studies).

Quality assessment

The QUADAS-2 quality assessment checklist for diagnostic studies was used to evaluate the quality of each included study, as recommended in the NICE guideline manual (2014). [155] Because applicability to the review question varied between models depending on the variables included, and the likelihood of that information being available at a typical index clinic visit, QUADAS-2 ratings were applied on a model-by-model basis within studies.

The rating strategy used to derive a rating is shown in Table 70. An overall summary rating for each study of 'no serious', 'serious' or 'very serious' for both 'risk of bias' and 'applicability' was derived from the QUADAS-2 ratings for each domain as follows:

- No serious: 0 or 1 domain rated as 'unclear', no domains rated as 'high'.
- Serious: 2 domains rated as 'unclear' or 1 domain rated as 'high'.
- Very serious: 3 or more domains rated as unclear or 2 or more domains rated as 'high'.

The rationale for the ratings for each study can be found in the comments section of individual evidence tables (Appendix I). A summary individual study quality ratings for each domain, and summary ratings for 'risk of bias' and 'applicability' are shown in Appendix J.

8.1.1.1.4 GRADE quality assessment

A GRADE quality assessment was carried out for each model applying a modification of the principles for assessing evidence on diagnostic test accuracy described by the GRADE working group (see: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3364356/). Evidence from cross sectional studies begins with a quality rating of high and is 'downgraded' to moderate, low or very-low quality according to serious or very serious sources of uncertainty in four domains: risk of bias, indirectness, inconsistency and imprecision. 'No serious', 'serious' or 'very serious' judgements were made in each domain as follows:

Risk of bias: Risk of bias was rated according to the most common summary rating (see Section 2.3.1.3) derived from the QUADAS 'risk of bias' elements for the studies contributing to the effect estimate.

Indirectness: Indirectness was rated according to the most common summary rating (see Section 2.3.1.3) derived from the QUADAS 'applicability' elements for the studies contributing to the effect estimate.

Inconsistency: As we did not statistically pool the reported AUC data, it was not possible to statistically assess the degree of heterogeneity of contributing studies. We have therefore set this as 'Not applicable' in the GRADE profiles.

Imprecision: The GRADE working group has not published criteria for assessing imprecision in relation to AUC statistics. For the current review, the AUC classification categories referred to above were used. Arbitrary minimal important difference levels of 0.7 and 0.8 were chosen for the assessment of imprecision, to be applied to the range of AUC scores reported across contributing studies (or to the 95% confidence interval where a model was evaluated by a single study).

- If AUC range (or 95% CIs around AUC for a single study) crossed one MID (0.7 or 0.8) – downgrade one level (serious imprecision)
- If AUC range (or 95% CIs around AUC for a single study) crossed both MIDs (0.7 and 0.8) – downgrade 2 levels (very serious imprecision).

For full GRADE profiles please see Appendix K.

An overall summary of findings for the five most evaluated probability models is presented in Appendix M.

Update 2016

8.1.1.2 Health economics evidence review

8.1.1.2.1 Methods

Economic literature search

The evidence was identified by conducting a broad search relating to diagnostic strategies stable chest pain of suspected cardiac origin in the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment database (HTA). The search also included Medline and Embase databases using an economic filter. Studies published in languages other than English were not reviewed. The search was conducted on 2 June 2015. The health economic search strategies are detailed in Appendix H.

The health economist also sought out relevant studies identified by the surveillance review or Committee members.

8.1.1.2.2 Results of the economic literature review

1464 articles were identified in the search. 1464 of these were excluded based on title and abstract alone. 0 full text articles were obtained.

The flowchart summarising the number of studies included and excluded at each stage of the review process can be found in Appendix G.

Update 2016

8.1.1.2.3 Economic modelling

Economic modelling was not prioritised for this review question

8.1.1.3 Evidence statements

8.1.1.3.1 Clinical evidence statements

Invasive coronary angiography to diagnose CAD at 50% stenosis

Twelve cross-sectional studies evaluated 15 different prediction models. Accuracy of all the models that were validated in more than one study was in the AUC range 0.7 and 0.8 (indicating good overall discrimination between CAD and non-CAD)

Moderate quality evidence was found for the following prediction models:

- Genders (updated Diamond-Forrester) model: over 3 studies (5,287 patients) the median AUC was 0.77 (range: 0.71 to 0.79);
- Age-adjusted Framingham Risk Score: a single study reported an AUC of 0.86 (95%CI 0.80 to 0.93).

Low quality evidence was found for the following prediction models:

- Framingham Risk Score: over 3 studies (1,334 patients) the median AUC was 0.74 (range: 0.67 to 0.76);
- Modified Framingham Risk Score: a single study (350 patients) reported an AUC of 0.73 (95%CI 0.67 to 0.79)
- SCORE model: over 2 studies (889 patients) the median AUC was 0.70 (range: 0.65 to 0.75);
- PROCAM: a single study (350 patients) reported an AUC of 0.69 (95%CI 0.62 to 0.75);
- Morise 1994: a single study (254 patients) reported an AUC of 0.83 (95%CI 0.78 to 0.88)
- Genders model + risk factors ('Clinical model'): a single study (4,426 patients) reported an AUC of 0.79 (95%CI not reported)

Very low quality evidence was found for the following prediction models:

- Diamond-Forrester model: over 5 studies (3,473 patients) the median AUC was 0.73 (range: 0.64 to 0.81);
- Duke Clinical Score: over 2 studies (6,242 patients) the median AUC was 0.75 (range: 0.59 to 0.84);
- Morise 1997 model: over 2 studies (887 patients) the median AUC was 0.76 (range: 0.68 to 0.84);
- Diagnostic Imaging for CAD (DICAD) model: over 2 studies (4,871 patients) the median AUC was 0.78 (range 0.67 to 0.88);
- CORSCORE: a single study (633 patients) reported an AUC of 0.73 (95%CI not reported);
- Severe Predicting Score (SPS): a single study (204 patients) reported an AUC of 0.71 (95%CI not reported);
- Combined Diamond-Forrester plus gene algorithm score: a single study (525 patients) reported an AUC of 0.72 (95%CI 0.68 to 0.76).

Update 2016

Computed tomography coronary angiography to diagnose CAD at 50% stenosis

Eight cross-sectional studies evaluated 7 different prediction models. Accuracy of all the models that were validated in more than one study was in the AUC range 0.6 and 0.7 (indicating reasonable overall discrimination between CAD and non-CAD).

High quality evidence was found for the following prediction models:

- PROCAM: a single study (1,296 patients) reported an AUC of 0.64 (95%CI 0.61 to 0.78).

Moderate quality evidence was found for the following prediction models:

- Diamond-Forrester model: over 5 studies (2,800 patients) the median AUC was 0.61 (range 0.56 to 0.72);
- Framingham Risk Score: over 2 studies (1,548 patients) the median AUC was 0.69 (range: 0.68 to 0.71);
- SCORE: a single study (1,296 patients) reported an AUC of 0.64 (95%CI 0.61 to 0.68)

Low quality evidence was found for the following prediction models:

- Duke Clinical Score: over 2 studies (1,385 patients) the median AUC was 0.65 (range: 0.59 to 0.71);
- Genders (updated Diamond-Forrester) model: over 2 studies (632 patients) the median AUC was 0.69 (0.61 to 0.76);
- Morise 1997 model: over 3 studies (1,345 patients) the median AUC was 0.68 (range: 0.67 to 0.77)

8.1.1.3.2 Health economic evidence statements

No studies were included in the economic systematic review.

8.1.1.4 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The committee agreed that area under the ROC curve (AUC) was the best measure of the overall performance of the probability models, because it is an index of how well a model discriminates between a positive or negative diagnosis of coronary artery disease (CAD), as measured by the reference standard. The committee acknowledged that AUC was preferable to sensitivity and specificity reported for a single threshold score since the models in question are not intended to be used as diagnostic tests but for estimating diagnostic likelihood.
Quality of evidence	The committee agreed with the decision to evaluate accuracy at the threshold level of 50% stenosis (measured by ICA or CTCA), as reported in the majority of studies. Pre-test probability models are not primarily intended to estimate likelihood of more severe disease (≥70% stenosis). They also agreed with the decision not to pool AUC data given the small number of studies assessing the same model, lack of consistent reporting of 95% confidence intervals (required for meta-analysis) and differences in study population that may be a potential source of heterogeneity (for example, prevalence of CAD diagnosed by ICA, ranged from 34% to 80% in studies evaluating the original Diamond-Forrester model). They acknowledged that, while an imperfect summary measure, the median and range of AUCs reported for the most commonly validated models were all very similar across studies (see Appendix M). This indicated that the models all performed reasonably well (AUCs between 0.7 and 0.8) and with similar consistency in contemporary cohorts of patients with chest pain where ICA was used as the reference standard. The committee discussed the lower discriminatory performance of the same models in studies where CTCA was the reference standard (AUCs between 0.6 and 0.7). These studies differ from the ICA studies not only in terms of the diagnostic reference standard used abut also the types of patients in which the models are applied (that is, a more diverse prevalence population). It is unclear whether these

Update 2016

	Committee discussions
	or other unmeasured differences are responsible for the variation in performance of the models. Evidence for relatively high AUCs reported for some less commonly validated models was discussed and discounted. This was because they were either based on single study data, so replication of findings could not be assessed (e.g. the AFRS and Morise 1994 model), or the model was not directly applicable to the review protocol because it requires information that would not be routinely available at the typical index clinic visit (e.g. the DICAD model incorporates CT calcium score data). External validity concerns, relating to the study populations in which models were tested, were accounted for in GRADE ratings of 'indirectness' (QUADAS concerns about population applicability were judged 'serious' if studies had recruited patients on the basis of referral for ICA, 'unclear' if recruited patients had all been referred for CTCA). However, the committee expressed concern about the external validity of the most commonly validated models themselves. Those specifically developed to predict CAD were all derived from high prevalence cohorts (that is, patients referred for invasive coronary angiography). This limits their generalisability to the unselected population of patients referred from primary care, in which the models are all likely to over-estimate true rates of prevalence. In support of this, a topic expert cited a study by Cheng et al. (2011) [41] which found that the original Diamond-Forrester model significantly over-estimated actual prevalence of CAD in an international multicentre register of patients referred for CTCA across all three categories of chest pain type (typical, atypical and non-anginal chest pain), and all sex and age subgroups.
Trade-off between benefits and harms	A pre-test probability model has clinical utility if it identifies subgroups in whom the need for further testing can be discounted; that is, when a diagnosis of CAD can be accurately ruled out (<10% probability) or ruled in (>90% probability) on the basis of clinical assessment alone. Where there is diagnostic uncertainty (probabilities between 10-90%), and testing strategies are known to be differentially cost-effective at different levels of risk, an accurate model provides a useful means for stratifying patients to ensure appropriate testing. The committee identified potential negative consequences of using a model that systematically over-estimates the probability of CAD relative to its true prevalence. Decisions about further testing based on inflated estimates may result in too many patients undergoing unnecessary tests and in overuse of more aggressive testing than is clinically warranted.
Trade-off between net health benefits and resource use	No studies were included in the economic systematic review. The cost difference between clinical prediction tools is thought to be minimal because they all involve a few simple questions based on readily available information from the patient.
Other considerations	The committee reviewed a table of probability data generated using the updated Diamond-Forrester model developed by Genders et al. (2011), [78] as published in the European Cardiology Society guidelines (The Task Force on the management of stable coronary artery disease of the European Society of Cardiology, 2013) – see **Table 65** below.

Update 2016

Committee discussions

Table 65: The probability of coronary artery disease in differing categories of chest pain (adapted from Genders 2011, published with author's permission by The Task Force on the management of stable coronary artery disease in the European Society of Cardiology guidelines 2013).

	Non-anginal pain		Atypical angina		Typical angina	
Age	Men	Women	Men	Women	Men	Women
30-39	18	5	29	10	59	28
40-49	25	8	38	14	69	37
50-59	34	12	49	20	77	47
60-69	44	17	59	28	84	58
70-79	54	24	69	37	89	68
≥80	65	32	78	47	93	76

It was agreed that the Genders model showed an overall good level of discrimination in the review of evidence (median 0.77), performing relatively consistently across 3 recent studies (range: 0.71 to 0.79). The committee acknowledged that the model is likely to provide more realistic probability estimates than the one currently recommended in CG95 because:

- it was derived using sophisticated logistic regression techniques in a large contemporary multicentre cohort which included UK patients;
- it extends the age range to include probability estimates for patients over 70 years of age.

However, the Committee considered it unnecessary and potentially confusing to include the Genders probability table in the amended guideline in the same way that a table of pre-test probabilities was included in CG95 for the following reasons:

- the data table shows that the only age and sex subgroups with a probability <10% (indicated in green in **Table 65**) are patients with non-anginal chest pain features in whom further diagnostic testing would not be routinely undertaken;
- in patients with typical or atypical angina, only one subgroup (men with typical angina over the age of 80) has a pre-test probability >90% (indicated in red in **Table 65**);

in patients with typical or atypical angina, all other age and sex subgroups fall within the 'uncertain' (10-90%) range, so would all be appropriate for further

Update 2016

	Committee discussions
	diagnostic testing; the evidence for the review question on the accuracy, clinical utility and cost effectiveness of tests for diagnosing coronary artery disease in people with stable chest pain of suspected cardiac origin (see section 7.2.2) strongly favoured CTCA as the first line testing strategy for all patients with 10-90% probability of CAD, negating the need for low / intermediate / high risk pre-test stratification. The committee agreed that it would not be necessary to make a separate recommendation for no further testing in male patients with typical angina over 80 years of age. This is because the Genders model is likely to over-estimate probabilities of CAD across all patient subgroups for the reasons noted above. True prevalence in this subgroup will therefore be lower than the 93% noted in the data table and so CTCA should be performed to establish a definitive diagnosis. The committee discussed the diagnostic management of patients younger than 30 years of age (outside the lower age range included in the pre-test probability studies reviewed). Topic experts noted that there is a risk in clinical practice of over-investigating younger patients with stitch-like pain brought on by exercise and relieved by rest (technically 'atypical angina', according to the accepted definition). However, it was acknowledged that a recommendation specifically relating to younger patients could not be made as no evidence was available for review. The topic experts were keen to clarify in the updated recommendations that patients with non-anginal chest pain on clinical assessment should not be investigated routinely for CAD regardless of pre-test probability, unless there are indications to suggest the chest pain may in fact be of cardiac origin. Currently this information is noted only in small print beneath the probability table included in CG95 and covers information on resting ECG ST-T changes or Q waves. As the committee are recommending deletion of this table with no replacement data table, a clear recommendation is required or this accompanying guidance would also be removed. The committee deliberated on this. The topic experts advised that, in their experience, resting ECG ST-T changes or Q waves would warrant further testing in people assessed as having non-anginal chest pain, with CTCA as the first line strategy. The resulting recommendation (see recommendation 1.3.3.12 listed in section 7.1.1.5) may therefore be considered consensus-based rather than evidence-based. However, it clarifies advice included in the original guideline and reflects accepted clinical practice. The committee considered the impact of basing a diagnostic testing strategy on the description of the pain and the implications for those who have poor language or communication skills as well as non-English speakers or communication disorders but considered that the current recommendations (recommendation 1.1.1.6) would cover these situations. The committee concluded that diagnostic testing for all patients assessed as having typical or atypical angina should be offered. This was because the best available contemporary evidence (from Genders et al. 2011), [78] taking into account limitations in external validity of the model, suggests that all patients in these two chest pain categories will have 'uncertain' probabilities of CAD in the 10-90% range. The committee agreed that it is clinically inappropriate to rule in (>90%) or out (<10%), with certainty, a diagnosis of stable angina in patients who either have typical or atypical angina-type chest pain on assessment. The wording of recommendations from the original guideline should be changed to make clear

Update 2016

	Committee discussions
	that it is not possible to diagnose stable angina on the basis of clinical assessment alone without further diagnostic testing. Conversely, a diagnosis may only be excluded where patients are assessed as having non-anginal chest pain and have a normal resting ECG.

8.1.1.5 Recommendations

1.3 People presenting with stable chest pain

Update 2016

1.3.1.1 Exclude a diagnosis of stable angina if clinical assessment indicates non-anginal chest pain (see recommendation 1.3.3.1) and there are no other aspects of the history or risk factors raising clinical suspicion. [new 2016]

1.3.1.2 If clinical assessment indicates typical or atypical angina (see recommendation 1.3.3.1), offer diagnostic testing (see sections 1.3.4, 1.3.5 and 1.3.6). [new 2016]

1.3.2 Clinical assessment

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. [2010]**

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. [2010]**

1.3.3 Making a diagnosis based on clinical assessment

1.3.3.1 Assess the typicality of chest pain as follows:

- **Presence of three of the features below is defined as typical angina.**
- **Presence of two of the three features below is defined as atypical angina.**
- **Presence of one or none of the features below is defined as non-anginal chest pain.**

Update 2016

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. [2010, amended 2016]**

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. [2010]**

1.3.3.3 **Do not define typical and atypical features of anginal chest pain and non-anginal chest pain differently in ethnic groups. [2010]**

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:**

- **Age**
- **whether the person is male**
- **cardiovascular risk factors including:**
  - **a history of smoking**
  - **diabetes**
  - **hypertension**
  - **dyslipidaemia**
  - **family history of premature CAD**
  - **other cardiovascular disease**
- **history of established CAD, for example, previous MI, coronary revascularisation. [2010]**

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). 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). [2010]

1.3.3.6 **Consider investigating other causes of angina, such as hypertrophic cardiomyopathy, in people with typical angina-like chest pain and a low likelihood of CAD. [2010, amended 2016]** Update 2016

1.3.3.7 **Arrange blood tests to identify conditions which exacerbate angina, such as anaemia, for all people being investigated for stable angina. [2010]**

1.3.3.8 **Only consider chest X-ray if other diagnoses, such as a lung tumour, are suspected. [2010]**

1.3.3.9 **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 the NICE guideline on cardiovascular disease and the NICE guideline on hypertension in adults. [2010]**

1.3.3.10 For people in whom stable angina cannot be excluded on the basis of the clinical assessment alone, take a resting 12-lead ECG as soon as possible after presentation. [2010, amended 2016] Update 2016

1.3.3.11 Do not rule out a diagnosis of stable angina on the basis of a normal resting 12-lead ECG. [2010]

1.3.3.12 Do not offer diagnostic testing to people with non-anginal chest pain on clinical assessment (see recommendation 1.3.3.1) unless there are resting ECG ST-T changes or Q waves. [new 2016]

Update 2016

1.3.3.13 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. [2010]

1.3.3.14 For people with confirmed CAD (for example, previous MI, revascularisation, previous angiography) in whom stable angina cannot be excluded based on clinical assessment alone, see recommendation 1.3.4.4 about functional testing. [2010, amended 2016]

Update 2016

1.3.3.15 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. [2010]

1.3.3.16 Follow local protocols for stable angina[l] while waiting for the results of investigations if symptoms are typical of stable angina. [2010]

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

1.3.4.1 Include the typicality of anginal pain features (see recommendation 1.3.3.1) in all requests for diagnostic investigations and in the person's notes. [2010, amended 2016]

Update 2016

1.3.4.2 Use clinical judgement and take into account people's preferences and comorbidities when considering diagnostic testing. [2010]

1.3.4.3 Offer 64-slice (or above) CT coronary angiography if:

- **clinical assessment (see recommendation 1.3.3.1) indicates typical or atypical angina, or**
- **clinical assessment indicates non-anginal chest pain but 12-lead resting ECG has been done and indicates ST-T changes or Q waves. [new 2016]**

Update 2016

1.3.4.4 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 the section on non-invasive functional imaging for myocardial ischaemia for further guidance on non-invasive functional testing. An exercise ECG may be used instead of functional imaging [2010]

1.3.5 Additional diagnostic investigations

Update 2016

[l] Stable angina. NICE guideline CG126 (2011).

1.3.5.1 Offer non-invasive functional imaging (see section 1.3.6) for myocardial ischaemia if 64-slice (or above) CT coronary angiography has shown CAD of uncertain functional significance or is non-diagnostic. [2016]

1.3.5.2 Offer invasive coronary angiography as a third-line investigation when the results of non-invasive functional imaging are inconclusive. [2016]

Update 2016

1.3.6 Use of non-invasive functional testing for myocardial ischaemia

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 (for example, disabilities, frailty, limited ability to exercise) when deciding on the imaging method. [This recommendation updates and replaces recommendation 1.1 of Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction (NICE technology appraisal guidance 73)]. [2016]

Update 2016

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. [2010]

1.3.6.3 Use exercise or dobutamine for stress echocardiography or MR imaging for stress-induced wall motion abnormalities. [2010]

1.3.6.4 Do not use MR coronary angiography for diagnosing stable angina. [2010]

1.3.6.5 Do not use exercise ECG to diagnose or exclude stable angina for people without known CAD. [2010]

1.3.7 Making a diagnosis following investigations

Box 1 Definition of significant coronary artery disease

- Significant coronary artery disease (CAD) found during CT 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 which 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. **[2016]**

Update 2016

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

- **significant CAD (see box 1) is found during invasive or 64-slice (or above) CT coronary angiography, or**
- **reversible myocardial ischaemia is found during non-invasive functional imaging. [2016]**

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, or**
- **reversible myocardial ischaemia is not found during non-invasive functional imaging [2016]**

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. [2010]

8.1.2 Research recommendations

The committee did not make any research recommendations for this review question.

Update 2016

[m] Stable angina. NICE guideline CG126 (2011).

8.1.3 Differences in presentation by gender

8.1.3.1 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.[89]

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.[230]

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.[122]

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.[59]

8.1.3.2 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%)[89]. 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[89].

Women with ischaemic heart disease have more adverse outcomes compared with men[213] despite the repeated documented lower angiographic disease burden and more often preserved left ventricular function compared with men[153]. 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.

8.1.3.3 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[230] and two studies were in patients with stable angina[59,122].

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[230]. 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 7.1.4[230].

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[59], 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[230].

Of 11 082 patients seen at the rapid access chest pain clinics the following patients were 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[230].

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[230].

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[122]. 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[144] 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)[144].

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[122].

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[122].

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[59]. 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[59].

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[59].

Estimates of pre-test likelihood of CAD varied widely according to age, 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[59].

8.1.3.4 Health economic evidence

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

8.1.3.5 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.

8.1.4 Differences in presentation by ethnicity

8.1.4.1 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.[230]

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.[230]

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.[230]

8.1.4.2 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[26] and the disparity in cardiovascular mortality has not been attributed to differences in traditional risk factors[65]. 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[230]. 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[230].

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[230].

Of 11 082 patients seen at the rapid access chest pain clinics the following patients were 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[230].

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[230].

8.1.4.3 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.

8.1.4.4 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.

8.1.5 12-Lead resting ECG

8.1.5.1 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.[136].

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.[46]

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.[172]

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.[173]

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

8.1.5.2 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[46,136], and two studies utilizing logistic regression modelling for the prediction of significant CAD[172,173] were reviewed. The two systematic reviews[46,136] also examined the use of ECG in patients presenting with acute chest pain and they have been discussed in section 6.2.5 of the guideline.

The first systematic review identified 12 studies that examined the use of ECG for the diagnosis of CAD[136]. 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 66 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[136].

Table 66			
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[136].			

The second systematic review (search date 2003) 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[46]. 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[46].

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[172]. 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[35].

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[173]. 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[173].

8.1.5.3 Health economic evidence

No health economic evidence was identified for this question.

8.1.5.4 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.

8.1.6 Chest X ray

8.1.6.1 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.[172,173]

2 In one study cardiomegaly as shown on chest X ray was a significant predictor of survival at 3 years.[173]

3 No health economic evidence was found for this question.

8.1.6.2 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[172,173].

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[172]. 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[35]. 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[172].

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[173]. 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[173].

8.1.6.3 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.

8.1.6.4 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.

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

8.2.1 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.

8.2.2 Review question: In people with stable chest pain of suspected cardiac origin, what is the accuracy, clinical utility and cost effectiveness of:

- **non-invasive diagnostic tests**
- **invasive diagnostic tests**
- **calcium scoring**

8.2.2.1 Clinical evidence review

8.2.2.1.1 Methods and results

A systematic review of the literature search was conducted as specified in the review protocol (Appendix D). The protocol was developed in consultation with the topic experts and then reviewed by the core committee members before the review was carried out. The following outcomes were considered important for decision making: true positive, false positive, false negative, true negative, sensitivity, specificity. A number of protocol refinements were made during the evidence review phase. These were informed by the advice of topic experts due to the complexity and variation in the technology of the included diagnostic tests and because of the large body of evidence. Refinements were subsequently agreed by the standing committee and can be viewed in Appendix D.

Update 2016

A systematic search (see Appendix H) identified 10,637 articles. The titles and abstracts were screened and 749 articles were identified as potentially relevant. An additional 3 articles were identified from the existing guideline which were not retrieved in the searches. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (Appendix D). Of these 693 were excluded as they did not meet the criteria and 60 met the criteria and were included.

A review flowchart is provided in Appendix F and the excluded studies (with reasons for exclusion) are shown in Appendix N.

Ten different diagnostic tests were identified as of current diagnostic importance. Invasive coronary angiography (ICA) is the gold standard for establishing the presence, location, and severity of coronary artery disease, but the technique is invasive, costly and associated with a small but definite

risk of morbidity and mortality. Using ICA as the reference standard, evidence for each of the nine alternative identified testing strategies was evaluated separately. These nine index tests are listed in **Table 68**.

Sixty cross-sectional, diagnostic studies were included, with a total of 9,780 participants. Data from each included study were extracted into evidence tables (Appendix I). A summary of key characteristics of each study are shown in Table 67. Population was classified as one of the following 4 categories:

- A: Population had suspected coronary artery disease (CAD), but there was no breakdown of numbers with chest pain, or the numbers with chest pain was less than 50%.
- B: Population had suspected CAD and 50% or more had chest pain.
- C: All participants had suspected CAD and chest pain (combination of types e.g. typical angina, atypical angina, non-cardiac)
- D: All participants had suspected CAD and typical chest pain of suspected cardiac origin

Table 67: Summary of included studies

Study (author/year)	Total sample size	Age Mean (SD)	Study population category	Index test (a)	Location
Arnold et al 2010[6]	65	64 (9)	A: Suspected CAD	4a, 4b, 4a+4b	Unclear (?UK, Australia, Poland)
Bettencourt et al 2011[15]	90	62 (8)	B: Suspected CAD, 92% with chest pain	2,9, 2+9	Portugal
Budoff et al 1998[23]	33	55 (9)	C: 100% with chest pain (combination of types)	7	USA
Budoff et al 2007[25]	30	54 (9)	A: Suspected CAD	7	USA
Budoff et al 2008[22]	230	57 (10)	C: 100% with chest pain (combination of types)	2	USA
Budoff et al 2013[24]	230	57 (10)	C: 100% with chest pain (combination of types)	3	USA
Cademartiri et al 2007[28]	72	54 (8)	C: 100% with chest pain (combination of types)	2	Italy
Cademartiri et al 2008[27]	145	63 (10)	B: Suspected CAD, 81% with chest pain	2	Italy
Carrascosa et al 2010[31]	50	62 (13)	B: Suspected CAD, 82% with chest pain	2	Argentina
Chen et al 2011 [37]	113	62 (SD not reported)	C: 100% with chest pain (combination of types)	2	Taiwan
Cramer et al 1997[54]	78	58 (SD not reported)	D: 100% stable chest pain of suspected cardiac origin	7	The Netherlands
Di Bello et al 1996a[58]	45	53 (7)	C: 100% with chest pain (combination of types)	4b,7	Italy
Di Bello et al 1996b[57]	45	53 (7)	C: 100% with chest pain (combination of types)	4b,7	Italy
Donati et al 2010[62]	52	64 (10)	C: 100% with chest pain (combination of types)	2	Switzerland/USA (unclear)
Fleming et al 1992[68]	44	57 (11)	A: Suspected CAD	7	USA
Fujitaka et al	125	70 (11)	C: 100% with chest pain	2, 2+7	Japan

Update 2016

2009[71]			(combination of types)		
Hennessy et al 1998[90]	157	59 (11)	C: 100% with chest pain (combination of types)	4b	UK
Herzog et al 2007[96]	40	61 (8)	A: Suspected CAD	2	USA
Herzog et al 2008[94]	30	59 (10)	B: Suspected CAD, 63% with chest pain	2	Switzerland
Herzog et al 2009[95]	42	62 (8)	B: Suspected CAD, 62% with chest pain	2	Switzerland
Hoffmann et al 1993[99]	66	57 (10)	A: Suspected CAD	4b	Germany
Javadrashid et al 2009[115]	158	58 (10)	A: Suspected CAD	3	Iran
Kaminek et al 2015[120]	164	61 (12)	A: Suspected CAD	7	Czech Rep.
Kawase et al 2004[121]	50	67 (12)	A: Suspected CAD	6	Japan
Klein et at 2008[123]	54	60 (10)	B: Suspected CAD, 83% with chest pain	6	Germany
Klem et al 2006[124]	92	58 (12)	A: Suspected CAD	6	USA
Krittayaphong et al 2009[128]	66	61 (12)	B: Suspected CAD, 52% with chest pain	6	Thailand
Marangelli et al 1994[137]	82	68 (8)	C: 100% with chest pain (combination of types)	4b	Italy
Marwick et al 1993 [138]	217	58 (10)	B: Suspected CAD, >=65% with chest pain	4b,7	Belgium
Mazeika et al 1992[140]	55	55 (9)	A: Suspected CAD	4b	UK
Meng et al 2009[145]	109	63 (9)	A: Suspected CAD	2	China
Miszalaski-Jamka et al 2012[148]	61	57 (12)	A: Suspected CAD	4a	Poland
Muhlenbruch et al 2007[150]	51	59 (8)	A: Suspected CAD	2	Germany
Nagel et al 1999[154]	208	60 (9)	A: Suspected CAD	4b, 5	Germany
Nazeri et al 2009	168	58 (11)	A: Suspected CAD	2	Iran
Nieman et al 2009[157]	98	56 (10)	C: 100% with chest pain (combination of types)	2	Holland
Nixdorff et al 2008[159]	71	62 (SD not reported)	A: Suspected CAD	4b	Unclear (Europe)
Onishi et al 2010[163]	59	64 (11)	A: Suspected CAD	4a	Japan
Overhus et al 2010[164]	100	61 (9)	B: Suspected CAD, 80% with chest pain	2	Denmark
Parodi et al 1999[166]	101	55 (9)	D: 100% stable chest pain of suspected cardiac origin	4b	Italy
Piers et al 2008[170]	60	64 (SD not reported)	A: Suspected CAD	2	The Netherlands
Pontone et al 2014[171]	91	Not reported	A: Suspected CAD	2	Italy
Pugliese et al	204	59 (11)	A: Suspected CAD	2	The Netherlands

Update 2016

2008[174]					
Raff et al 2005[176]	70	59 (11)	A: Suspected CAD	2	USA
Rixe et al 2009[181]	76	68 (9)	B: Suspected CAD, 80% with chest pain	2	Germany
Ropers et al 2006[182]	84	58 (10)	A: Suspected CAD	2	Germany
San Roman et al 1996[187]	102	64 (11)	D: 100% stable chest pain of suspected cardiac origin	4b	Spain
San Roman et al 1998[186]	102	64 (10)	D: 100% stable chest pain of suspected cardiac origin	4b,7	Spain
Santoro et al 1998[190]	60	Not reported	C: 100% with chest pain (combination of types)	4b, 7	Italy
Schepis et al 2007[191]	77	66 (9)	B: Suspected CAD, 57% with chest pain	7, 3+7	Switzerland
Senior et al 2004[195]	55	median 61 (range 47-61)	C: 100% with chest pain (combination of types)	4b, 7	UK/Germany
Severi et al 1993[196]	429	55 (4)	C: 100% with chest pain (combination of types)	4b	Italy
Shaikh et al 2014[197]	45	61 (7)	A: Suspected CAD	4b	USA
Sheikh et al 2009[198]	73	60 (9)	C: 100% with chest pain (combination of types)	2	Kuwait
Stolzmann et al 2011[203]	60	64 (10)	B: Suspected CAD, 65% with chest pain	6, 3+6	Switzerland
Swailam et al 2010[204]	30	53 (6)	C: 100% with chest pain (combination of types)	2	Egypt
Thomassen et al 2013[207]	44	66 (9)	C: 100% with chest pain (combination of types)	2,7,2+7	Denmark
Van Werkhoven et al 2010	61	57 (9)	C: 100% with chest pain (combination of types)	2	The Netherlands
Von Ziegler et al 2014[219]	4,137	61 (12)	C: 100% with chest pain (combination of types)	3	Germany
Yao et al 2004[229]	73	53 (11)	A: Suspected CAD	7	China

All studies were cross-sectional diagnostic studies.
Mean/SD are rounded to whole numbers.
Index tests 2=CTCA, 3=Calcium Scoring, 4a=Stress Echo (perfusion), 4b=Stress Echo (wall motion), 5=CMR (wall motion), 6=CMR (Perfusion), 7=MPS SPECT/PET, 8=CT FFR, 9=CT Perfusion, 10=PET
All studies had invasive coronary angiography as the reference standard. Studies reporting combined analyses are indicated by (+)

Forest plots are shown in Appendix M and illustrate the sensitivity and specificity reported for each study arranged by index test. The forest plots include individual (rather than pooled) study data and no overall point estimates are shown. In addition they illustrate covariates of interest, including stenosis level for diagnosis according to invasive coronary angiography (ICA; 50% or 70% stenosis level) and population categories for each study (A, B, C or D).

Covariates relating to specifics of a test are also shown where appropriate (e.g. method of inducing stress for stress echocardiography, calcium threshold for calcium scoring).

In addition to diagnostic data, side-effects or minor or major adverse events associated with either test were extracted and reported in the evidence tables. No studies reported stroke or death in

Update 2016

relation to ICA or any index test. One study reported coronary artery dissection in relation to ICA (Budoff et al 2008). [22] Three studies reported a total of 4 cardiac events in relation to administration of index tests. These are:

- Cardiac arrest (n=1) Mazeika et al 1992[140] (stress echo for wall motion).
- Left heart failure (n=1) San Roman et al 1998[186] (after administration of dobutamine)
- Left heart failure (n=1) San Roman et al 1998[186] (after administration of dipyridamole)
- Left heart failure (n=1) San Roman et al 1996[187] (after dobutamine-atropine infusion).

Update 2016

8.2.2.1.2 Evidence synthesis

In instances where more than one study evaluated the same index text, a meta-analysis was considered. Decisions on whether to undertake meta-analysis, and for which subsets of studies were taken in conjunction with committee members, based on the clinical heterogeneity of the included studies and following preliminary examination of the data. The strategy for evidence synthesis is shown for each test in Table 68 and compared with the reference test (invasive coronary angiography) listed in row 1. The committee agreed that data for 50% and 70% stenosis should be analysed and considered separately for each test.

Table 68: Evidence synthesis strategy

Index test	Subgroups for analysis		Number of studies	Synthesis method	Notes
1. Invasive coronary angiography (ICA)					Reference standard
2. Computed tomography coronary angiography (CTCA)	50% sten.		25	Meta-analysis	
	70% sten.		3	Meta-analysis	
3. Calcium score	50% sten.	Threshold: 0	2	Meta-analysis	
		Threshold: 400	2	Meta-analysis	
	70% sten.	Threshold: 0	1	Single study	
		Threshold: 400	1	Single study	
4a. Stress echocardiography (echo) - perfusion	50% sten.		3	Meta-analysis	Despite variation in stress inducing methods, all serve to achieve coronary vasodilatation, and so pooling is justified.
	70% sten.		1	Single study	
4b. Stress echo - wall motion	50% sten.	Stress method: vasodilatation	5	Meta-analysis	Studies induced stress by modifying vasodilation or heart rate: analysis is based on these categories.
		Stress method: heart rate modification	8	Meta-analysis	

Update 2016

Index test	Subgroups for analysis		Number of studies	Synthesis method	Notes
	70% sten.	Stress method: vasodilatation	7	Meta-analysis	
		Stress method: heart rate modification	4	Meta-analysis	
5. Cardiac magnetic resonance (CMR) - wall motion	50% sten.		1	Single study	
	70% sten.		0	N/A	
6. CMR - perfusion	50% sten.		5	Meta-analysis	The topic experts advised that delayed enhancement is not usually used in isolation, so data using this method in isolation were excluded. When data was reported for perfusion imaging alone and perfusion + delayed enhancement, the later was used in the meta-analysis.
	70% sten.		3	Meta-analysis	
7a. Myocardial perfusion scintigraphy - single-photon emission computed tomography (MPS - SPECT)	50% sten.		11	Meta-analysis	Despite variation in stress inducing methods, all serve to achieve coronary vasodilatation, and so pooling is justified.
	70% sten.		3	Meta-analysis	
7b. MPS – positron emission tomography (MPS - PET)	50% sten.		0	N/A	
	70% sten.		1	Single study	
8. Computed tomography fractional flow reserve (CT FFR)			0	N/A	
9. Computed tomography (CT) - perfusion	50% sten.		1	Single study	
	70% sten.		1	Single study	

Meta-analysis

Meta-analysis was performed using the statistical software package 'R'. The 'reitsma' function from the 'mada' R library (https://cran.r-project.org/web/packages/mada/index.html) was used to produce pooled estimates for sensitivity and specificity, together with 95% confidence intervals. This function implements the bivariate model of Reitsma et al. (2005), [179] which takes into account the paired nature of sensitivity and specificity values. Chi^2 and I^2 values were calculated in order to assess heterogeneity. The results of the analyses are shown in **Table 69** and plotted in Appendix M. A sensitivity analysis was also performed, in order to assess the impact of low quality studies on the

Update 2016

overall effect estimates. Studies with very serious concerns over risk of bias or applicability according to the QUADAS-2 checklist (see Section 8.2.2.1.3) were excluded from the sensitivity analysis. The results of the sensitivity analysis are shown in **Table 69** ('-' indicates that no studies had very serious risk of bias or applicability concerns, so a sensitivity analysis was not performed).

Table 69: Diagnostic test accuracy meta-analysis results

	Main analysis				Sensitivity analysis			
Index test	**Sensitivity (95% CI)**	**I^2**	**Specificity (95% CI)**	**I^2**	**Sensitivity (95% CI)**	**I^2**	**Specificity (95% CI)**	**I^2**
CTCA – 50% stenosis	0.96 (0.94 to 0.97)	0%	0.79 (0.72 to 0.84)	80%	0.96 (0.94 to 0.97)	0%	0.79 (0.73 to 0.85)	79%
CTCA – 70% stenosis	0.96 (0.88 to 0.99)	0%	0.72 (0.55 to 0.85)	79%	-	-	-	-
Calcium score – 50% stenosis, threshold:0	0.99 (0.97 to 0.99)	0%	0.49 (0.36 to 0.63)	92%	-	-	-	-
Calcium score – 50% stenosis, threshold:400	0.54 (0.52 to 0.57)	0%	0.88 (0.87 to 0.88)	0%	-	-	-	-
Stress echocardiography, Perfusion – 50% stenosis	0.84 (0.76 to 0.90)	28%	0.79 (0.69 to 0.86)	0%	-	-	-	-
Stress echocardiography, Wall motion – 50% stenosis, vasodilators	0.77 (0.69 to 0.83)	50%	0.86 (0.68 to 0.95)	77%	-	-	-	-
Stress echocardiography, Wall motion – 50% stenosis, heart rate modifiers	0.76 (0.72 to 0.79)	0%	0.80 (0.71 to 0.88	65%	-	-	-	-
Stress echocardiography, Wall motion – 70% stenosis, vasodilators	0.64 (0.49 to 0.76)	85%	0.90 (0.86 to 0.93)	0%	-	-	-	-
Stress echocardiography, Wall motion – 70% stenosis, heart rate modifiers	0.75 (0.62 to 0.85	64%	0.88 (0.79 to 0.93)	0%	-	-	-	-
CMR, Perfusion – 50% stenosis	0.84 (0.76 to 0.90)	18%	0.85 (0.77 to 0.90)	0%	-	-	-	-
CMR Perfusion – 70% stenosis	0.93 (0.84 to 0.97)	0%	0.81 (0.56 to 0.93)	83%	-	-	-	-
MPS-SPECT – 50% stenosis	0.81 (0.74 to 0.86)	75%	0.78 (0.70 to 0.85)	45%	0.78 (0.68 to 0.85)	74%	0.81 (0.70 to 0.89)	60%
MPS-SPECT – 70% stenosis	0.76 (0.44 to 0.93)	88%	0.76 (0.58 to 0.88)	0%	-	-	-	-

Update 2016

8.2.2.1.3 Quality assessment

QUADAS-2 checklist

The QUADAS-2 quality assessment checklist for diagnostic studies was used to evaluate each included study, as recommended in the NICE guideline manual (2014). [155] The rating strategy used to derive a rating for each quality parameter is shown in Table 70.

Table 70: QUADAS-2 Quality rating strategy by quality parameter

Quality Parameter	Rating strategy

Quality Parameter	Rating strategy
Domain 1 Patient Selection A. Risk of bias 1) Consecutive/random sample. 2) Case-control study design 3) Avoid inappropriate exclusions *(3 signalling questions, rate Yes/No/Unclear)*	Could the selection of patients have introduced bias? Rating: LOW/HIGH/UNCLEAR (3/3 Yes) rate as LOW risk, (1/3 unclear) rate as UNCLEAR risk, (≥1 unclear or No) rate as HIGH risk.
B. Concerns regarding applicability *(1 signalling question rate concern as low/high/unclear)*	Considerations relating to population were: 1) The population in the review protocol is defined as people with suspected CAD with or without chest pain. The desired population for informing guideline recommendations is one of chest pain but agreement was made in conjunction with topic experts that if suspected CAD formed the entire population (no breakdown provided) we would rate as UNCLEAR applicability. If suspected CAD with a breakdown of sub categories (including chest pain at a rate of at least 50%), we rated as LOW. 2) Pre-test probability stated as LOW, MODERATE/INTERMEDIATE OR HIGH defining the entire study population was rated as HIGH risk of bias. If a study provided analysis by each risk level this is would not be rated down as this would reflect a real-world population and would have been desired. 3) Whether recruitment into the study was based on referral for coronary angiography. If so we rated as HIGH concern re applicability since the study population was likely to reflect a higher prevalence population.
Domain 2 Index Tests A Risk of Bias *(2 signalling questions rate as Yes/No/Unclear)*	Overall rating if both Yes, rated as LOW risk, if ≥1 are no or unclear, rated as HIGH risk.
B Concern regarding applicability *(1 signalling question)*	Concern rated as LOW/HIGH/UNCLEAR.
Domain 3 Reference Standard A Risk of Bias *(2 signalling questions, rate concern as Yes/No/Unclear)*	Overall rating if both yes rated as LOW, if ≥1 unclear/no rate as High.
B Concern regarding applicability *(1 signalling question)*	Concern rated as LOW/HIGH/UNCLEAR
Domain 4 Flow and Timing A Risk of Bias *(4 signalling questions, rate concern as Yes/No/Unclear)*	Overall rating if ≥2 of the 4 with UNCLEAR or NO rate as HIGH risk of bias. If 1 of 4 is NO/UNCLEAR rate as low. 1) Time limit up to 3 months rated as YES (per protocol inclusion). If no time limit specified rate as UNCLEAR. 2) Drop outs/exclusions – If exceeded 20% (arbitrary figure) then rate as NO.

Update 2016

An overall summary rating for each study of 'no serious', 'serious' or 'very serious' for 'risk of bias' and 'applicability' was derived from the QUADAS-2 ratings for each domain as follows:

- **No serious:** 0 or 1 domain rated as 'unclear', no domains rated as 'high'.
- **Serious:** 2 domains rated as 'unclear' or 1 domain rated as 'high'.
- **Very serious:** 3 or more domains rated as unclear or 2 or more domains rated as 'high'.

The rationale for ratings for each study can be found in the comments section of individual evidence tables (Appendix I). A summary individual study quality ratings for each domain, and summary ratings for 'risk of bias' and 'applicability' are shown in Appendix J.

GRADE quality assessment

GRADE quality assessment was carried out for each index test according to the methods for assessing a body of evidence on diagnostic test accuracy described by the GRADE working group (see: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3364356/) and outlined in section 4.2.5.2.1. The stable chest pain update topic experts employed the methods detailed below for inconsistency and imprecision.

Inconsistency: This criterion applied only when meta-analysis had been performed. I^2 and Chi^2 statistics were calculated to assess the heterogeneity of contributing studies. Inconsistency was rated as 'serious' if there was substantial unexplained heterogeneity (I^2>50%) in either the sensitivity or specificity analysis, and very serious if there was very substantial heterogeneity (I^2>75%) in either analysis.

Imprecision:

The GRADE working group recommend downgrading if confidence intervals are wide, but what constitutes 'wide' depends on the specific review. The topic experts were consulted on maximum width of 95% CIs deemed acceptable when considering imprecision around the sensitivity and specificity. A range of >20% in either the sensitivity or specificity estimate was considered serious imprecision and a range of >40% was considered very serious.

Update 2016

8.2.2.1.4 Test and treat randomised controlled trials

In the course of development, the NICE team became aware of a number of 'test and treat' randomised controlled trials relevant to the update that had not been identified in the main review because they did not report diagnostic test accuracy outcomes. A supplementary narrative review was therefore conducted to identify test and treat randomised controlled trials that included one of more of the index tests identified in the main diagnostic test accuracy review. The search strategy, review flowchart, list of excluded studies, and evidence tables for this supplementary review can be found in Appendices H, F, N and I respectively.

The search identified 9200 records. Of these 995 were articles that were also identified in the main diagnostic test accuracy review, and so were not examined further, and 8194 were excluded on the basis of title and abstract. Eleven full text articles were examined and 8 were excluded (for a list of excluded studies and reasons for exclusion, see Appendix N), leaving 3 included studies. Details of the included studies were extracted into evidence tables (see Appendix I), and narrative summaries are provided below.

SCOT-HEART (The SCOT-HEART team, 2015)[110]

4,146 participants with stable chest pain of suspected cardiac origin were recruited from multiple chest pain clinics in Scottish hospitals between 2010 and 2014 (mean age 57.1 years, 56% male). Participants were randomised to standard diagnostic care (which included clinical assessment, calculation of cardiovascular risk, exercise electrocardiography and further testing at the discretion

of the clinician) or standard care with additional CT coronary angiography (CTCA). At 6 weeks, CTCA reclassified the diagnosis of coronary heart disease in 558 (27%) patients and the diagnosis of angina due to coronary heart disease in 481 (23%) patients. This changed planned investigations (15% vs 1%; p<0·0001) and treatments (23% vs 5%; p<0·0001) but did not affect 6-week symptom severity or subsequent admittances to hospital for chest pain. After 1·7 years, CTCA was associated with a 38% reduction in fatal and non-fatal myocardial infarction (26 vs 42, HR 0·62, 95% CI 0·38–1·01; p=0·053), but this was not statistically significant.

PROMISE (Douglas et al. 2015) [63]

10,003 participants with suspected coronary artery disease from several centres in the USA were recruited between 2010 and 2014 (mean age 60.8 years, 53% male). Participants were randomised to CTCA or functional testing (which could include exercise electrocardiography, nuclear stress testing or stress echocardiography). Over a median follow-up period of 25 months, a primary end-point event (death, myocardial infarction, hospitalisation for unstable angina, major complication of cardiovascular or diagnostic testing procedure) occurred in 164 of 4996 patients in the CTCA group (3.3%) and in 151 of 5007 (3.0%) in the functional-testing group (adjusted hazard ratio, 1.04; 95% confidence interval, 0.83 to 1.29; p=0.75). CTCA was associated with fewer catheterizations showing no obstructive CAD than was functional testing (3.4% vs. 4.3%, p=0.02).

CAPP trial (McKavanagh et al. 2015) [141]

500 participants with stable chest pain but without known coronary artery disease were recruited from several chest pain clinics in Northern Ireland (mean age 58.4 years, 55% male). Participants were randomised to CTCA or exercise electrocardiography as the initial diagnostic investigation and followed up for 12 months. More participants in the CTCA group were diagnosed with significant CAD (128 vs 72), and more were treated both medically and surgically (136 vs 54). Fewer hospital admissions were recorded for the CTCA group than the exercise electrocardiography group. There was a significantly greater improvement in quality of life, measured by the Seattle angina questionnaire at 12 months in the CTCA group than the exercise electrocardiography group (mean difference, 24.9, 95% confidence interval 29.6 to 20.2, p=0.04).

Update 2016

8.2.2.2 Health economic evidence review

8.2.2.2.1 Results of the economic literature review

2438 articles were identified in the search. 2360 of these were excluded based on title and abstract alone. 78 full text articles were obtained. 76 full text articles were excluded. Because there was a cost-utility analysis using UK costs included, studies were selectively excluded if they used non-UK costs. Studies were included if they used UK costs and any type of health benefit such as QALYs or correct diagnoses. Two studies from the published literature were included as well as the 2 cost-effectiveness analyses from the original guideline for a total of 4 included models. Table 71 contains the economic evidence profile for this review question summarising the results of the studies included in the systematic review, modelling conducted for the previous guideline and the economic model developed for the present update. Full economic evidence tables are contained in Appendix L.

The flowchart summarising the number of studies included and excluded at each stage of the review process can be found in Appendix G. Appendix O contains a list of excluded studies and the reason for their exclusion.

A 2015 cost-utility analysis (Genders et al.)[76] investigated the cost effectiveness of CTCA, CMR, ECHO, SPECT; and CTCA followed by CMR, ECHO or SPECT after positive CTCA results. With additional options for conservative or invasive diagnostic workups, there were a total of 16 diagnostic strategies compared in the model. A lifetime time horizon was adopted and a markov state-transition model

was used for lifetime prognoses. The populations were 60 year old males and females with no history of coronary artery disease. The perspective was the NHS for costs and the person with stable chest pain for health benefits. The cost year was 2011 and a discount rate of 3.5% was used. Sensitivity and specificity of tests were taken from meta-analyses available in the published literature. The authors found that health benefits in terms of QALYs were very similar for all strategies, CTCA prior to ICA increased effectiveness, and ECHO was consistently more effective and less expensive than other imaging tests. For the men with a 30% pre-test likelihood CTCA+ECHO was the optimal strategy with an ICER of £7,000 per QALY. For women with a 30% pre-test likelihood, the invasive version of ECHO was the optimal strategy with an ICER of £8,000 per QALY. For both men and women with pre-test likelihoods of 50%, 70% and 90%, either the conservative or invasive versions of ECHO were the optimal strategies. These results were robust to one way sensitivity analysis. Probabilistic sensitivity analysis was carried out but not well reported. This study was directly applicable with minor limitations.

The 2010 economic model developed for the original guideline was a short term model comparing 10 strategies of various combinations of exercise ECG, SPECT, CT calcium scoring, CTCA and ICA. ECHO and CMR were not included in the model. Incremental analysis of results was repeated for this update excluding strategies containing exercise ECG as one of the tests because this was excluded as an index test in the clinical review. The structure of the model was a decision tree that reported results in terms of cost per correct diagnosis and also identified total true positives, false negatives, true negatives and false positives for each strategy. The perspective was the NHS for costs. The model was rerun for 5 levels of pre-test likelihood: 5%, 20%, 40%, 60% and 80%. CT calcium scoring followed by CTCA was the least cost per correct diagnosis for all pre-test likelihoods. Both CTCA and ICA were potentially cost effective for pre-test likelihoods greater than 40% although there was no threshold for cost per correct diagnosis. For the 5% and 20% pre-test likelihoods, two strategies, CT calcium scoring followed by CTCA followed by ICA, and CTCA followed by ICA, were potentially cost effective with relatively low costs per correct diagnosis and ICA was unlikely to be cost effective. This study was directly applicable with potentially serious limitations due to the lack of long term modelling. Probabilistic sensitivity analysis was not programmed into the model.

Update 2016

A second 2010 model was conducted for the original guideline comparing SPECT with ICA for people with a pre-test likelihood of 20-60%. This analysis had potentially serious limitations due to the lack of including all relevant comparators.

A 2007 cost-utility analysis by Hernandez et al.[93] compared 4 strategies: ECG, SPECT then ICA; ECG then ICA; SPECT then ICA; and ICA. The first two strategies including ECG were excluded and results incrementally reanalysed for this update. The reanalysis found that CA was not cost effective with an ICER of £44,444 per QALY compared with SPECT+ICA for the 10.5% pre-test likelihood. ICA was cost effective for 30%, 50% and 85% pre-test likelihoods with ICERs well below £20,000 per QALY compared with SPECT+ICA. This analysis was only partially applicable because costs and evidence on diagnostic accuracy are now different compared with when this analysis was carried out and there were many relevant comparators not in the analysis.

8.2.2.2.2 Economic modelling

De novo economic modelling was carried out for this review question. Please refer to Appendix P for full details of this analysis. Economic modelling conducted for this update found that CTCA had the lowest cost per correct diagnosis for all levels of pre-test likelihood due to the low cost of the test, high sensitivity, and low probability of fatal and non-fatal complications. The addition of ECHO or CMR after positive CTCA results had the potential to be considered cost effective for lower levels of pre-test likelihood but the optimal strategy was unknown without a cost-effectiveness threshold for cost per correct diagnosis. The average costs per correct diagnosis for strategies of functional testing following CTCA (4, 5 and 6) were very close together for lower pre-test likelihoods, so one functional test could not be chosen above others with certainty. When a 70% stenosis threshold was used for

sensitivity and specificity in a sensitivity analysis, the results were similar to the base case. The cost of CTCA had to triple before it ceased to be the least cost per correct diagnosis. When the cost of CMR was reduced, CTCA remained the lowest cost per correct diagnosis, but CTCA+ECHO was dominated. This analysis was directly applicable with potentially serious limitations because it was a short term model.

Update 2016

Table 71: Economic evidence profile for the review question on the accuracy, clinical utility and cost effectiveness of tests for diagnosing coronary artery disease in people with stable chest pain of suspected cardiac origin

Study	Applicability	Limitations	Other comments	Incremental Cost	Uncertainty Effect	ICER	
NICE 2016 1. ICA 2. CTCA 3. CTCA+ICA 4. CTCA+SPECT 5. CTCA+ECHO 6. CTCA+CMR 7. SPECT+ICA 8. ECHO+ICA 9. CMR+ICA 10. SPECT+CTCA 11. ECHO+CTCA 12. CMR+CTCA 13. CTCA-SPECT 14. CTCA-ECHO 15. CTCA-CMR 16. no testing (where '+' indicates 2nd test occurs after positive 1st test and '–' indicates 2nd test occurs after negative 1st test) United Kingdom	Directly applicable	Potentially serious limitations 1	Short term diagnostic decision tree 45% pre-test likelihood (see Appendix P for full results): 16. no testing 2. CTCA 5. CTCA+ECHO 6. CTCA+CMR 1. ICA	- £122.49 £99.59 £88.00 £1,384.84	- 81.95% 9.09% 2.37% 5.77% (correct diagnoses)	- £149 £1,096 £3,707 £23,983 (per correctly diagnosis)	SA1: sensitivity and specificity based on 70% stenosis level: similar results SA2: Cost of CTCA: had to triple before it ceased to be the least cost per correct diagnosis SA3: Cost of CMR: strategy CTCA+CMR became more cost effective PSA: 100% likelihood that CTCA was the least cost per correct diagnosis at all pre-test likelihoods; cost-effectiveness acceptability curves and scatterplots provided

Update 2016

Study	Applicability	Limitations	Other comments	Incremental Cost	Uncertainty Effect	ICER	
Genders et al. 2015[76] No imaging ECHO CTCA +ECHO ECHO-i CTCA+SPECT-i CTCA +ECHO-i CTCA CTCA +CMR CTCA +SPECT-i CTCA +CMR-i CTCA -i SPECT SPECT-i CMR CMR-i CAG United Kingdom, The Netherlands, United States	Directly applicable	Minor limitations	Decision tree for short term diagnostic outcomes and markov model for long term prognoses Results for men, 30% pre-test likelihood (see Appendix L for full evidence tables): No imaging ECHO CTCA +ECHO CTCA +ECHO-i Results for women, 30% pre-test likelihood (see Appendix L for full evidence tables): No imaging ECHO CTCA +ECHO ECHO-i CTCA +ECHO-i	- £1,140 £46 £90 - £1,157 £37 £19 £64	- 0.22 QALYs 001 QALYs 0.00 QALYs (rounding) - 0.23 QALYs 0.00 QALYs 0.00 QALYs 0.01 QALYs (rounding)	- £5,000/QALY £7,000/QALY £32,000/QALY - £5,000/QALY £7,000/QALY £8,000/QALY £53,000/QALY	The following parameters were tested in one way sensitivity analysis: Pre-test likelihood of CAD (reported in full evidence tables) False negative results returned to physician in 3 years rather than 1: increased the cost effectiveness of CTCA No QALY reduction for false positives taking unnecessary medication: CTCA+ECHO became more favourable Probabilistic sensitivity analysis: credible intervals for all ICERs cross; otherwise poorly reported.
NCGC 2010a ECG, SPECT, ICA ECG, CTCA, ICA ECG, ICA SPECT, ICA CTCA, ICA	Directly applicable	Potentially serious limitations 2	Decision tree for short term diagnostic outcomes Results for 20% pre-test likelihood: Ca+CTCA Ca+CTCA+ICA CTCA+ICA	- £1,722.26 £882.99	- 4.98% 1.73%	- £3,458 £5,104	No PSA The original Guideline Committee made the following determinations about what constituted cost effective in the absence of a threshold for the following one way sensitivity analyses.

Update 2016

Study	Applicability	Limitations	Other comments	Incremental	Uncertainty		
				Cost	Effect	ICER	
ICA ECG, CTCA CTCA CaScore, CTCA CaScore, CTCA, ICA United Kingdom			ICA	£4,204.19	3.91% (correct diagnoses)	£10,752 (per correct diagnosis)	Reducing the specificity of CTCA to 67% from 89%: At 5% CAD prevalence, Ca+CTCA+ICA is still likely to be cost-effective although with a higher ICER than base case At 20% CAD prevalence, the ICER for Ca+CTCA+ICA compared with Ca+CT is lower than the base case because the number of correct diagnoses is higher At 40% CAD prevalence and above, the most cost-effective strategy is still sending all patients directly for invasive coronary angiography Increasing the calcium score threshold from >0 to >100, the sensitivity of calcium scoring decreases to 72% but the specificity increases to 81% Ca+CTCA remains the least cost option at all levels of CAD prevalence but Ca+CTCA+ICA is less cost effective compared to the base case. At 5% CAD prevalence, Ca+CTCA+ICA is still likely to be cost effective with an increased ICER of £2183 At 20% CAD prevalence,

Update 2016

Study	Applicability	Limitations	Other comments	Incremental Cost	Uncertainty Effect	ICER	
							Ca+CTCA+ICA is ruled out due to extended dominance so CTCA+ICA is likely to be the cost effective option with an ICER of $4764 compared with Ca+CTCA. At 40% CAD prevalence and greater, the strategy of sending all patients directly to ICA is still likely to be cost effective.
NCGC 2010b SPECT ICA United Kingdom	Partially applicable	Potentially serious limitations 3, 4	Decision tree for short term diagnostic outcomes	Not reported	Not reported	£21,549 per correct diagnosis (ICA vs. SPECT)	Not conducted
Hernandez et al. 2007[93] ECG, SPECT, ICA ECG, ICA SPECT, ICA ICA United Kingdom	Partially applicable 5	Potentially serious limitations 6	Decision tree for short term diagnostic outcomes followed by Markov model for long term consequences All results ICA vs. SPECT for 30% pre-test likelihood (full results in Appendix P)	£329	0.042 QALYs	£7,833/QALY	Probabilistic sensitivity analysis was conducted. Interpretation of CEACs: At a CAD prevalence of 10.5%, SPECT-CA has a 90% likelihood of being the optimal strategy. At 30% CAD prevalence, SPECT-CA is most optimal up to a threshold of £20,000 per QALY when CA takes over. For higher levels of CAD prevalence and thresholds over £10,000 per QALY, coronary angiography is the optimal strategy.

Update 2016

Acronyms

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; PSA: probabilistic sensitivity analysis

1 *No long term modelling*
2 *No long term modelling*
3 *No long term modelling*
4 *Only 2 comparators, excludes many relevant alternatives*
5 *Costs and diagnostic accuracy now different to when the analysis was conducted*

Update 2016

8.2.2.3 Evidence statements

8.2.2.3.1 Clinical evidence statements

Evidence for the accuracy of different diagnostic tests (compared with the gold standard of invasive coronary angiography, ICA) was evaluated for two different diagnostic thresholds. No evidence meeting the review protocol inclusion criteria was found for CT FFR.

Diagnosis of coronary artery disease - 50% stenosis threshold

High quality evidence was found for the following tests:

- CMR (wall motion analysis): a single study (172 patients) reported a sensitivity of 0.86 (95%CI 0.78 to 0.92) and a specificity of 0.86 (95%CI 0.75 to 0.93).

Moderate quality evidence was found for the following tests:

- Calcium scoring at a threshold level of 400 Hounsfield units: a meta-analysis of 2 studies (8,504 patients) had a pooled sensitivity of 0.54 (95%CI 0.52 to 0.57) and specificity of 0.88 (95%CI 0.87 to 0.88);
- Stress echocardiography (perfusion analysis): a meta-analysis of 3 studies (182 patients) had a pooled sensitivity of 0.84 (95%CI 0.76 to 0.90) and specificity of 0.79 (95%CI 0.69 to 0.86);
- Stress echocardiography (wall motion analysis) - using heart rate modification to induce stress: a meta-analysis of 8 studies (899 patients) had a pooled sensitivity of 0.76 (95%CI 0.72 to 0.79) and specificity of 0.80 (95%CI 0.71 to 0.88);
- CMR (perfusion analysis): a meta-analysis of 5 studies (331 patients) had a pooled sensitivity of 0.84 (95%CI 0.76 to 0.90) and specificity of 0.85 (95%CI 0.77 to 0.90).
- Combined CTCA and Myocardial perfusion scintigraphy: a single study (125 patients) reported a sensitivity of 0.94 (95%CI 0.84 to 0.99) and a specificity of 0.95 (95%CI 0.87 to 0.99)

Low quality evidence was found for the following tests:

- CT perfusion: a single study (90 patients) reported a sensitivity of 0.54 (95%CI 0.39 to 0.69) and specificity of 1.00 (95%CI 0.92 to 1.00).
- Combined CTCA and Myocardial perfusion scintigraphy: a single study (44 patients) reported a sensitivity of 0.91 (95%CI 0.71 to 0.99) and a specificity of 1.00 (95%CI 0.85 to 1.00)
- Combined CTCA and CT Perfusion: a single study (90 patients) reported a sensitivity of 0.83 (95% CI 0.70 to 0.93) and a specificity of 0.98 (95%CI 0.87 to 1.00)
- Combined Calcium scoring and Stress CMR: a single study (60 patients) reported a sensitivity of 0.89 (95%CI 0.74 to 0.97) and a specificity of 0.83 (95%CI 0.63 to 0.95)
- Combined Calcium Scoring and Myocardial Perfusion Scintigraphy (SPECT): a single study (77 patients) reported a sensitivity of 0.86 (95%CI 0.71 to 0.95) and a specificity of 0.86 (95%CI 0.70 to 0.95)
- Combined Stress Echo Perfusion and Wall motion: a single study (62 patients) reported a sensitivity of 0.85 (95%CI 0.71 to 0.94) and a specificity of 0.76 (95%CI 0.53 to 0.92)

Very low quality evidence was found for the following tests:

Update 2016

- CTCA: A meta-analysis of 25 studies (2,058 patients) had a pooled sensitivity of 0.96 (95%CI 0.94 to 0.97) and specificity of 0.79 (95%CI 0.72 to 0.84);
- Calcium scoring at a threshold level of 0 Hounsfield units: a meta-analysis of 2 studies (8,504 patients) had a pooled sensitivity of 0.99 (95%CI 0.97 to 0.99) and specificity of 0.49 (95%CI 0.36 to 0.63);
- Stress echocardiography (wall motion analysis) - using vasodilators to induce stress: a meta-analysis of 5 studies (422 patients) had a pooled sensitivity of 0.77 (95%CI 0.69 to 0.83) and specificity of 0.86 (95%CI 0.68 to 0.95);
- Myocardial perfusion scintigraphy (MPS - SPECT): a meta-analysis of 11 studies (923 patients) had a pooled sensitivity of 0.81 (95%CI 0.74 to 0.86) and specificity of 0.78 (95%CI 0.70 to 0.85).

Diagnosis of coronary artery disease - 70% stenosis threshold

Moderate quality evidence was found for the following tests:

- Calcium scoring at a threshold level of 0 Hounsfield units: a single study (8,274 patients) reported a sensitivity of 0.99 (95%CI 0.98 to 0.99) and specificity of 0.42 (95%CI 0.41 to 0.43);
- Calcium scoring at a threshold level of 400 Hounsfield units: a single study (8,274 patients) reported a sensitivity of 0.84 (95%CI 0.82 to 0.87) and specificity of 0.84 (95%CI 0.83 to 0.85).
- Combined CTCA and CT Perfusion: a single study (90 patients) reported a sensitivity of 0.95 (95%CI 0.82 to 0.99) and a specificity of 0.94 (95%CI 0.84 to 0.99)

Low quality evidence was found for the following tests:

- Stress echocardiography (perfusion analysis): a single study (62 patients) reported a sensitivity of 0.90 (95%CI 0.73 to 0.98) and specificity of 0.73 (95%CI 0.54 to 0.87);
- Myocardial perfusion scintigraphy (MPS - PET): a single study (44 patients) reported a sensitivity of 0.91 (95%CI 0.71 to 0.99) and a specificity of 0.86 (95%CI 0.65 to 0.97);
- CT perfusion: a single study of (90 patients) reported a sensitivity of 0.66 (95%CI 0.49 to 0.80) and specificity of 0.98 (95%CI 0.90 to 1.00).
- Combined Stress Echo Perfusion and Wall motion: a single study (62 patients) reported a sensitivity of 0.97 (95% CI 0.82 to 1.00) and a specificity of 0.64 (95%CI 0.45 to 0.80)

Very low quality evidence was found for the following tests:

- CTCA: a meta-analysis of 3 studies (371 patients) had a pooled sensitivity of 0.96 (95%CI 0.88 to 0.99) and specificity of 0.72 (95%CI 0.55 to 0.85);
- Stress echocardiography (wall motion analysis) - using vasodilators to induce stress: a meta-analysis of 7 studies (767 patients) had a pooled sensitivity of 0.64 (95%CI 0.49 to 0.76) and specificity of 0.90 (95%CI 0.86 to 0.93);
- Stress echocardiography (wall motion analysis) - using heart rate modification to induce stress: a meta-analysis of 4 studies (257 patients) had a pooled sensitivity of 0.75 (95%CI 0.62 to 0.85) and specificity of 0.88 (95%CI 0.79 to 0.93);
- CMR (perfusion analysis): a meta-analysis of 3 studies (204 patients) had a pooled sensitivity of 0.93 (95%CI 0.84 to 0.97) and specificity of 0.81 (95%CI 0.56 to 0.93);
- Myocardial perfusion scintigraphy (MPS – SPECT): a meta-analysis of 3 studies (145 patients) had a pooled sensitivity of 0.76 (95%CI 0.44 to 0.93) and specificity of 0.76 (95%CI 0.58 to 0.88).

Update 2016

8.2.2.3.2 Health economic evidence statements

Economic modelling conducted for this update found that CTCA had the lowest cost per correct diagnosis for all levels of pre-test likelihood due to the low cost of the test, high sensitivity, and low probability of fatal and non-fatal complications. This analysis was directly applicable with potentially serious limitations because it was a short term model.

A 2015 cost-utility analysis[76] found that CTCA+ECHO was the optimal strategy for low pre-test likelihoods and ECHO was the optimal strategy for pre-test likelihoods greater than 50%. This analysis was directly applicable with minor limitations.

Cost-effectiveness analysis conducted for the original guideline found that strategies starting with CT calcium scoring and CTCA were likely to be cost effective for lower pre-test likelihoods and ICA was likely to be cost effective for higher pre-test likelihoods. This analysis was partially applicable with potentially serious limitations due to the lack of long term modelling.

A 2007 cost-utility analysis[93] found that SPECT prior to ICA was likely to be cost effective for the lowest pre-test likelihood and ICA was likely to be cost effective for pre-test likelihoods greater than 30%. This analysis was partially applicable with potentially serious limitations due to the lack of relevant comparators.

8.2.2.4 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The committee agreed to use sensitivity and specificity (with 95% CIs) as primary measures of diagnostic accuracy. Further conditional measures such as positive predictive value (PPV) and negative predictive value (NPV) were not calculated since these are strongly affected by prevalence, and the body of evidence came from multiple countries worldwide with varying prevalence rates. Thus it was felt they would be of limited interpretability. The committee did not define a minimum acceptability threshold for either sensitivity or specificity for any test (see below comments under 'Benefits and Harms'). Prior to the committee meetings, the topic experts were asked to provide their thoughts on the desirable and undesirable consequences of diagnosis using tests with varying degrees of sensitivity and specificity. These are summarised below: • True positive (desirable) – a speedy and accurate diagnosis is achieved and early detection means treatment can be instigated and deterioration can be prevented. • True negative (desirable) – reassurance on the absence of disease, unnecessary treatment and testing is avoided. • False positive (undesirable) – creates unnecessary patient anxiety and exposes them to unnecessary treatments and testing and their associated risks. Can lead to patients making unnecessary lifestyle changes such as giving up work which could negatively impact quality of life. Wasted healthcare costs. • False negative (undesirable) – high risks to patients who receive no/insufficient treatment or further testing. May go on to have preventable cardiac events and/or die. Likely to have a higher reliance on NHS at a later date and additional costs associated with misdiagnosis.

Update 2016

	Committee discussions
	In terms of incorrect diagnoses, the committee were agreed that the consequences of a false negative result (possible cardiac event or death) were likely to be more serious for the patient and the healthcare system than a false positive result.
Quality of evidence	The committee noted that only three of the included studies were conducted in the UK; however the age range of patients across the included studies was that which would be expected of people presenting in the UK with stable chest pain of recent onset. In the majority of studies, the population as reported by the investigators did not directly match that specified in the review protocol (that is, people with chest pain of suspected cardiac origin). Study populations fell into four categories: • A: Population had suspected CAD, but there was no breakdown of numbers with chest pain, or the numbers with chest pain was less than 50%. • B: Population had suspected CAD and 50% or more had chest pain • C: All participants had suspected CAD and chest pain (combination of types e.g. typical angina, atypical angina, non-cardiac) • D: All participants had suspected CAD and typical chest pain of suspected cardiac origin. The committee noted that concerns about population applicability were accounted for in the quality appraisal of individual studies. Examination of forest plots generated for each test showed no clear systematic differences in sensitivity or specificity estimates attributable to differences in population category. The topic experts noted that the study populations may be the same as that specified in the review protocol even if this is not specifically stated in the article. The committee were presented with a comparative plot of the meta-analyses of all four of the index tests that were prioritised for economic modelling (namely CTCA, Stress Echo, MPS-SPECT and CMR perfusion). The slides (included in Appendix M) incorporated a visual breakdown of the relative distribution of the population categories contributing to each dataset. On reviewing this, the committee were satisfied that population differences were unlikely to account for differences in the comparative accuracy of diagnostic testing strategies. The topic experts had advised that it was important to consider evidence for both 50% and 70% stenosis diagnostic thresholds, as the former threshold may favour anatomical testing, while the latter is more likely to favour functional tests. The comparative plot of four meta-analyses showed that CTCA outperformed the other three tests when sensitivity was considered relative to 1 minus specificity at both the 50% and 70% stenosis thresholds. However, it was noted that there was significant imprecision in the results for all tests at the 70% threshold, due to small numbers of studies and sample sizes. At the 50% stenosis level, the committee noted that the evidence for CTCA and MPS-SPECT was very low quality, while that for Stress Echo and CMR perfusion was rated moderate overall. The committee noted that differences in evidence quality may relate as much to variation in study methods and reporting over time as to the value of the different tests, favouring newer techniques evaluated using more rigorous statistical standards.

Update 2016

	Committee discussions
	The committee noted that the majority of studies MPS-SPECT and CTCA studies had recruited patients on the basis of referral for coronary angiography. The concern is that such patients are a higher prevalence population than if recruited as part of a wider inclusion strategy. This may lead to higher estimates of diagnostic accuracy than would be expected in clinical practice with an unselected population. The quality ratings for population applicability assigned to each dataset reflected these concerns. There was also very significant inconsistency in the sensitivity data for MPS-SPECT and the specificity data for CTCA. The committee discussed why a small number of studies reported very low specificities in the CTCA dataset. Topic experts noted that there have been dramatic improvements over the past 10-15 years in the technology of CTCA and radiologists' skill in interpreting the images. However, no obvious relationship with publication date was observed that might account for the observed heterogeneity. A sensitivity analysis was undertaken for the CTCA and MPS-SPECT meta-analyses to evaluate the impact of excluding studies with very serious risk of bias or applicability issues, but this made little difference to the estimated sensitivity or specificity for either index test. Topic experts noted that the results for some diagnostic tests are more subjective than others, particularly CTCA and stress echocardiography, which require considerable expertise for interpretation. Furthermore, although invasive coronary angiography (ICA) is the agreed gold standard for diagnosis of coronary artery disease (CAD), it too involves a degree of subjectivity, and variations in expertise and methods of interpretation of the reference standard may be a source of heterogeneity in the meta-analyses. Additional evidence from three test and treat RCTs was considered by the committee. While recognising the importance of searching for these study designs to ensure consistency with the review protocol, the committee felt that evidence from these trials could not be used to inform the development of the recommendations. This is because none of the studies reported the diagnostic accuracy outcomes specified in the review protocol, and not all patients underwent the reference standard (invasive coronary angiography). The prognostic value of diagnostic tests is outside the remit of this guideline.
Trade-off between benefits and harms	The Topic Experts summarised the benefits and harms of each diagnostic test as follows: Invasive Coronary Angiography • Most expensive • Highest risks (stroke, MI, death) • Radiation exposure 4-6mSv • Lengthy – takes 1.5hours • Patients dislike due to side effects • Renal failure and contrast allergy are complications CTCA • Widely available • Involves insertion of a needle • Quick to perform (20 mins)

Update 2016

	Committee discussions

	• Radiation exposure of 2-5mSv • Renal failure and contrast allergy are complications
Calcium Scoring	• Radiation exposure of around 1-3mSv
Stress Echo	• No radiation exposure but risk associated with inducing stress (death: 1 in 10,000, ventricular arrhythmia or MI: 1 in 5000, asthma) • Widely available • Patients may not be suitable (e.g. people who are obese or who have chronic lung disease) • Results dependent on operator expertise
CMR	• Lengthy procedure (1hr) • Claustrophobia, metal implants, foreign bodies and renal failure are contraindications • Stress CMR not commonly available in UK hospitals • Risks associated with inducing stress (death, MI, asthma, bronchoconstriction, heart block)
SPECT	• Prone to artefacts but reporting reproducible. • Involves radiation exposure (2-10mSv. • Time consuming (3-4 hrs) • Widely available. • Almost no contraindications. • Risks associated with stress: death (1 in 10000), other risks dependent on type of stress induction.
PET	• Very few centres use this • Involves radiation exposure of around 3mSv.

In the case of all tests involving radiation exposure, this should be considered in the context of patient age. Radiation exposure is reduced with more modern machines and testing techniques.

The method of inducing stress (as is the case for echocardiography, CMR and MPS SPECT) is important. Dobutamine is unpopular with patients as it has unpleasant side effects including a flushed feeling. Other methods of inducing stress in myocardial perfusion scanning include exercise and regadenoson.

Trade-off between net health benefits and	Four cost-effectiveness analyses were included in the economic systematic review. A 2015 cost-utility analysis[76] found that CTCA+ECHO was the optimal strategy for

Update 2016

	Committee discussions
resource use	low pre-test likelihoods, and ECHO was the optimal strategy for pre-test likelihoods greater than 50%. This analysis was directly applicable with minor limitations. Cost-effectiveness analysis conducted for the original guideline in 2008 found that strategies starting with CT calcium scoring and CTCA were likely to be cost effective for lower pre-test likelihoods and ICA was likely to be cost effective for higher pre-test likelihoods. This analysis was partially applicable with potentially serious limitations. A 2007 cost-utility analysis[93] found that SPECT prior to ICA was likely to be cost effective for the lowest pre-test likelihood and ICA was likely to be cost effective for pre-test likelihoods greater than 30%. This analysis was partially applicable with potentially serious limitations. Economic modelling was conducted for the review question on the accuracy, clinical utility and cost effectiveness of tests for diagnosing coronary artery disease in people with stable chest pain of suspected cardiac origin so that all relevant diagnostic strategies could be compared using the sensitivity and specificity calculated from the meta-analysis for each test in the clinical review. The economic modelling conducted for this update found that the testing strategy of CTCA only had the lowest cost per correct diagnosis for all population subgroups in both the base case and the sensitivity analysis based on a 70% stenosis threshold. The addition of functional testing following a positive CTCA result may be cost effective for lower pre-test likelihoods, but which specific functional test would be the most cost-effective could not be determined without a cost-effectiveness threshold. After noting that CTCA+SPECT was dominated in the 20% pre-test likelihood subpopulation and CTCA+SPECT and CTCA+ECHO were dominated in the 45% pre-test likelihood subpopulation, the committee discussed that it was difficult to clearly prefer one functional test over another after positive CTCA results because their average costs per correct diagnosis were so close together for lower pre-test likelihoods and slight changes in cost or diagnostic accuracy were likely to change whether these strategies dominate each other or not. Some committee members were concerned that the cost of CTCA may be too low and not reflect its true cost. Two comparisons were provided as to why the NHS reference cost was chosen as the base case. The 2015-16 tariffs for computerised tomography scan RA12Z, RA13Z, RA14Z and RA50Z range from £103 to £128 and therefore similar to the reference cost of £122.11. Secondly, a bottom-up micro-costing was conducted for NICE diagnostics guidance 3 to establish the cost of 64-slice CT scanners and new generation CT scanners. Westwood et al. (2013) calculated a total cost per scan of £132.62, not substantially different to the NHS reference cost 2014-15 used in the base case. The second sensitivity analysis found that the cost of CTCA had to triple before it would not be considered the least cost per correct diagnosis. The committee noted that there is local variation in the cost of tests which will depend, amongst other factors, on the daily volume of the centre. The purpose of the analysis was to establish the average cost effectiveness on a national basis so nationally representative costs from the NHS reference costs or national tariff were the most appropriate to use in the model. The topic experts advised that in clinical practice the diagnosis of coronary artery disease is often not a binary outcome like it is in the economic model. For example, there will be varying degrees of atherosclerosis that may or may not be flow limiting.

Update 2016

	Committee discussions
	The committee discussed that the results reported in terms of cost per correct diagnosis assume the avoidance of false positives and false negatives are of equal value. Topic experts advised that false negatives are more important to avoid because, generally speaking, it is important to identify disease where it exists so that it can be appropriately treated. This was recognised as a limitation of the short term model and reporting results in terms of cost per correct diagnosis. Although it is difficult to quantify (and therefore not explicitly included in the form of long term modelling), these results should be interpreted within the context of the implications for false negatives and false positives. The potential implications for false negatives include remaining symptomatic with stable chest pain, returning for additional appointments with their GP or cardiologist, further testing with the same or alternative tests which may include ICA, and the costs involved for each of these elements. Due to the ongoing chest pain symptoms, most people with false negative results would be expected to be correctly diagnosed within 12 months although this may take 2 to 3 years. The potential implications and costs for people with false positive test results are varied. Some people will be treated with medication and, because their symptoms were due to a non-cardiac, transient cause, their chest pain alleviates and the medication is assumed to have worked. Therefore, even though they don't have disease, they continue on taking this medication for many years. It is unclear whether this would have negative or positive health effects because most people of this age group have some level of atheroma. In other words, although a person may not have clinically significant CAD, the medicine may have a protective effect, benefit to both health and costs. Alternatively, the medicines may cause side effects, and a cost to the NHS, that otherwise did not need to occur because they don't have disease. Some people treated with medication would continue to experience chest pain because it is caused by something other than CAD. This could be gastrointestinal reflux or a musculoskeletal problem, for example. Because their symptoms continue, they would usually be correctly diagnosed within the space of a year. This may be via an ICA, but not necessarily. In addition to the ICA or other test, people would incur the cost of additional GP and cardiologist visits. There would be a small proportion of people that would experience complications during the ICA or other test. There could also be further complications of whatever it is they do have but this cannot be defined. Some people with false positive results would be sent for treatment with PCI or CABG. However, because ICA is always conducted prior to revascularisation, the only cost incurred would be the cost of an ICA, not the incorrect treatment with PCI or CABG. There would be a small proportion of people who experience complications during the ICA. The assumption of conditional independence may be a particular limitation of this model because the diagnosis based on functional testing after a positive CTCA result may be treated differently than after a negative CTCA result. For example, when functional testing is conducted following a positive CTCA result, the committee encountered difficulty in interpreting the importance of false negatives because they will not all strictly be false negatives: some people will have stenosis as identified by the CTCA but it may not be not flow limiting or ischaemic as identified by functional testing. The economic model for this update was compared with the studies included in the economic systematic review. The results were broadly in line with the modelling conducted for the original guideline in 2008 in terms of finding that CTCA has a low cost per correct diagnosis. This is despite some substantial differences in the models such as the 2008 model having a far lower sensitivity for

Update 2016

	Committee discussions
	CTCA, higher specificity for CTCA, and higher cost for CTCA. The 2008 model included SPECT but not ECHO or CMR. When compared with the 2015 model by Genders et al., [76] the results were similar for men with a low (30%) pre-test likelihood of disease with CTCA+ECHO as the optimal strategy, but remainder of the subpopulations favoured ECHO. The modelling conducted for this update contained different inputs for ECHO which go some way to explaining the difference in results: lower sensitivity and specificity based on the most recent meta-analysis conducted for this update; and a higher cost of testing. Overall, the committee determined that the results of the economic model conducted for this update were consistent with the findings of the clinical review in terms of favouring CTCA as a first line test.
Other considerations	The committee noted that neither functional testing nor calcium scoring were used as singular testing strategies in the economic modelling on the advice of the topic experts. Functional testing provides an assessment of the haemodynamic consequences of obstructive CAD. However, the review protocol specifies that accuracy should be measured with reference to invasive coronary angiography (ICA), which is an anatomical imaging technique for identifying the location and degree of atherosclerosis. Clinically these are different pieces of the overall diagnostic 'jigsaw'. Anatomical tests can adequately diagnose presence of CAD, but do not give any information on the haemodynamic consequences of observed coronary artery stenosis. On the other hand, stress testing will give an accurate indication of the presence of flow-limiting CAD, but not all atherosclerosis will be flow-limiting. Furthermore, decisions about whether to treat observed coronary lesions medically or more aggressively with invasive techniques will usually require prior visualisation of the coronary anatomy. Topic experts also noted that calcium scoring would not usually be undertaken as a stand-alone diagnostic test, but may be performed at the same time as a CT coronary angiography to provide supplementary prognostic information to guide treatment decision-making. This is because the patient would already be in hospital with access to the CT scanner, and the additional time and cost to do a full CTCA is minimal. While there may be a very small additional risk of an adverse reaction to contrast dye used in CTCA, and a potential cancer risk associated with increased radiation exposure, these risks are regarded as minimal considering the wealth of additional diagnostic information yielded. This advice was the basis for updating one of the recommendations from the original guideline. In clinical practice, topic experts noted that diagnostic management and treatment decisions are not made in isolation of one another. However, they acknowledged that the remit of the review is restricted to the accurate and cost-effective diagnosis of the presence (or absence) of CAD and cannot consider the prognostic value of different testing strategies. After reviewing the clinical and economic evidence, the committee were agreed that the evidence strongly favoured recommending CTCA as the first line diagnostic strategy for all patients presenting with stable chest pain who have features characteristic of typical or atypical angina. This is because CTCA has greater overall accuracy compared with Stress echo, MPS-SPECT and CMR, is appropriate and well-tolerated by the majority of patients with relatively few potential risks, and has the lowest cost per correct diagnosis at all pre-test probability thresholds. The committee were confident that these advantages outweighed possible concerns associated with CTCA having lower quality evidence than was the case for some other tests included in the review.

Update 2016

	Committee discussions
	The committee discussed in what circumstances secondary testing might be indicated. Topic experts advised that where a CTCA scan shows 50-70% stenosis, or if parts of the cardiac arterial tree cannot be clearly evaluated and a definitive diagnosis made, additional functional testing should be considered. The committee noted that the evidence was unclear as to which type of functional test is most cost-effective following CTCA. Decisions regarding second-line functional testing should take account of availability, and patients' preferences and clinical suitability. The topic experts emphasised that Stress echo perfusion analysis is not commonly available in the UK. **Equalities considerations:** **Age** • During protocol development it was agreed that no sub-group reporting of diagnostic test accuracy would be carried out. As such, potential differences in DTA by age are not reported. • Age variation within included studies was discussed. The committee were satisfied that the ages of the study participants accurately represented the age of adults who might be presenting with first episodes of stable chest pain. • The topic experts advised that age was an important factor in the interpretation of calcium scoring (index test 3). However, as the committee decided that calcium scoring should not be recommended as a standalone testing strategy, this issue is not a concern. • There was no detail on age (or any other characteristics) of people who experienced serious adverse events (n=4) therefore it is not possible to evaluate the effect of age on the risk of serious adverse events. **Gender** • No studies that solely evaluated men or women were included. Some studies included a much higher proportion of men than women. As this reflects the demographic that disease is more prevalent in men than women, it was decided that there was no inequality in the evidence base in relation to gender. • One topic expert noted that women tend to describe symptoms differently to men which should be considered when assessing and classifying type of chest pain. **Ethnicity** • As stated above, no sub-group analyses were carried out according to ethnicity. This body of evidence includes studies from all over the world and only 3 studies from the UK. It represents a diverse range of ethnicities and nationalities. This body of evidence may thus not be representative of a UK population. • In addition it was noted that many people seeking medical advice in the UK do not have English as a first language. In this group of patients, it can be harder to accurately establish clinical characteristics and symptom history. No population groups were excluded that would impact on equality. The committee also identified the following as important considerations:

Update 2016

	Committee discussions
	People with learning difficulties, conditions such as dementia and with communication impairments may also be misclassified due to the difficulties associated with determining medical history and symptoms. People who are over-weight or have a disability may be unable to access the MRI scanning machines and echocardiography may also be difficult to perform. CT often obtains poor quality images from people who are overweight. Recommendations in DG3 include reference to newer generation CT scanners for people who do not fit into standard scanners. People with disabilities, frailty or limited exercise ability that limit range of movement or manoeuvrability may not be able to undergo some diagnostic tests that involve inducing stress such as stress echocardiography or CMR. They may also require adaptions such as pharmaceutical stress instead of exercise stress tests. People with renal impairment or allergies to contrast material would be contraindicated for certain tests, including CTCA. Other relative contraindications to CTCA include congestive cardiac failure and heart rhythm disorders. People with claustrophobia or difficulty holding breath may be unable to undergo CMR. Pregnant women seldom present with stable chest pain but this would usually be managed medically and investigated after delivery. The exception would be if this became acute/unstable pain. There is known geographical variation in access to services and in turn, to diagnostic tests. The committee's view is that CTCA should be considered the first choice diagnostic test for all people assessed as having typical or atypical angina. However individual circumstances, including potential contraindications, should be taken into account when deciding the most appropriate strategy for diagnostic investigation.

Update 2016

8.2.2.5 Recommendations

1.3.4.3 Offer 64-slice (or above) CT coronary angiography if:

- **clinical assessment (see recommendation 1.3.3.1) indicates typical or atypical angina, or**
- **clinical assessment indicates non-anginal chest pain but 12-lead resting ECG has been done and indicates ST-T changes or Q waves. [new 2016]**

1.3.5.1 Offer non-invasive functional imaging (see the section on non-invasive functional imaging for myocardial ischaemia) for myocardial ischaemia if 64-slice (or above) CT coronary angiography has shown CAD of uncertain functional significance or is non-diagnostic. [2016]

8.2.2.6 Research recommendations

Update 2016

The committee did not make any research recommendations for this review question.

9 Reference list

1. Alberto C, Margherita L, Cristina N, Chiara G, Egidio C, Luca V et al. Effectiveness of nuclear scan strategy in low-risk chest pain patients: novel insights from the real world. Nuclear Medicine Communications. 2011; 32(12):1223-1230

2. Aldous SJ, Richards AM, Cullen L, Than MP. Early dynamic change in high-sensitivity cardiac troponin T in the investigation of acute myocardial infarction. Clinical Chemistry. 2011; 57(8):1154-1160

3. Aldous SJ, Richards M, Cullen L, Troughton R, Than M. Diagnostic and prognostic utility of early measurement with high-sensitivity troponin T assay in patients presenting with chest pain. CMAJ Canadian Medical Association Journal. 2012; 184(5):E260-268

4. Amsterdam EA, Kirk JD, Diercks DB, Lewis WR, Turnipseed SD. Immediate exercise testing to evaluate low-risk patients presenting to the emergency department with chest pain. Journal of the American College of Cardiology. 2002; 40(2):251-256

5. Arnold J, Goodacre S, Bath P, Price J. Information sheets for patients with acute chest pain: randomised controlled trial. BMJ. 2009; 338:b541-b546

6. Arnold JR, Karamitsos TD, Pegg TJ, Francis JM, Olszewski R, Searle N et al. Adenosine stress myocardial contrast echocardiography for the detection of coronary artery disease: a comparison with coronary angiography and cardiac magnetic resonance. JACC: Cardiovascular Imaging. 2010; 3(9):934-943

7. Atar S, Nagai T, Cercek B, Naqvi TZ, Luo H, Siegel RJ. Pacing stress echocardiography: an alternative to pharmacologic stress testing. Journal of the American College of Cardiology. 2000; 36(6):1935-1941

8. Aufderheide TP, Xue Q, Dhala AA, Reddy S, Kuhn EM. The added diagnostic value of automated QT-dispersion measurements and automated ST-segment deviations in the electrocardiographic diagnosis of acute cardiac ischemia. Journal of Electrocardiology. 2000; 33(4):329-339

9. Barakat K, Wells Z, Ramdhany S, Mills PG, Timmis AD. Bangladeshi patients present with non-classic features of acute myocardial infarction and are treated less aggressively in east London, UK. Heart. 2003; 89(3):276-279

10. Barbash IM, Freimark D, Gottlieb S, Hod H, Hasin Y, Battler A et al. Outcome of myocardial infarction in patients treated with aspirin is enhanced by pre-hospital administration. Cardiology. 2002; 98(3):141-147

11. Bedetti G, Pasanisi EM, Tintori G, Fonseca L, Tresoldi S, Minneci C et al. Stress echo in chest pain unit: the SPEED trial. International Journal of Cardiology. 2005; 102(3):461-467

12. Beigel R, Oieru D, Goitein O, Chouraqui P, Konen E, Shamiss A et al. Usefulness of routine use of multidetector coronary computed tomography in the "fast track" evaluation of patients with acute chest pain. American Journal of Cardiology. 2009; 103(11):1481-1486

13. Ben-Shlomo Y, Naqvi H, Baker I. Ethnic differences in healthcare-seeking behaviour and management for acute chest pain: secondary analysis of the MINAP dataset 2002-2003. Heart. 2008; 94(3):354-359

14. Bennett P, Dyer P. Exercise stress test utility in patients with chest pain presumed to be of cardiac origin. Acute Medicine. 2013; 12(3):146-150

15. Bettencourt N, Rocha J, Ferreira N, Pires-Morais G, Carvalho M, Leite D et al. Incremental value of an integrated adenosine stress-rest MDCT perfusion protocol for detection of obstructive coronary artery disease. Journal of Cardiovascular Computed Tomography. 2011; 5(6):392-405

16. Bholasingh R, Cornel JH, Kamp O, van Straalen JP, Sanders GT, Tijssen JG et al. Prognostic value of predischarge dobutamine stress echocardiography in chest pain patients with a negative cardiac troponin T. Journal of the American College of Cardiology. 2003; 41(4):596-602

17. Blatchford O, Capewell S, Murray S, Blatchford M. Emergency medical admissions in Glasgow: general practices vary despite adjustment for age, sex, and deprivation. British Journal of General Practice. 1999; 49(444):551-554

18. Borna C, Frostred KL, Ekelund U. Predictive role of high sensitivity troponin T within four hours from presentation of acute coronary syndrome in elderly patients. BMC Emergency Medicine. 2016; 16:1

19. Britton A, Shipley M, Marmot M, Hemingway H. Does access to cardiac investigation and treatment contribute to social and ethnic differences in coronary heart disease? Whitehall II prospective cohort study. BMJ. 2004; 329(7461):318

20. Bruyninckx R, Aertgeerts B, Bruyninckx P, Buntinx F. Signs and symptoms in diagnosing acute myocardial infarction and acute coronary syndrome: a diagnostic meta-analysis. British Journal of General Practice. 2008; 58(547):e1-e8

21. Buchsbaum M, Marshall E, Levine B, Bennett M, DiSabatino A, O'Connor R et al. Emergency department evaluation of chest pain using exercise stress echocardiography. Academic Emergency Medicine. 2001; 8(2):196-199

22. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial.[see comment]. Journal of the American College of Cardiology. 2008; 52(21):1724-1732

23. Budoff MJ, Gillespie R, Georgiou D, Narahara KA, French WJ, Mena I et al. Comparison of exercise electron beam computed tomography and sestamibi in the evaluation of coronary artery disease. The American journal of cardiology. 1998; 81(6):682-687

24. Budoff MJ, Jollis JG, Dowe D, Min J, Group VCTS. Diagnostic accuracy of coronary artery calcium for obstructive disease: results from the ACCURACY trial. International Journal of Cardiology. 2013; 166(2):505-508

25. Budoff MJ, Rasouli ML, Shavelle DM, Gopal A, Gul KM, Mao SS et al. Cardiac CT angiography (CTA) and nuclear myocardial perfusion imaging (MPI)-a comparison in detecting significant coronary artery disease. Academic Radiology. 2007; 14(3):252-257

26. Budoff MJ, Yang TP, Shavelle RM, Lamont DH, Brundage BH. Ethnic differences in coronary atherosclerosis. Journal of the American College of Cardiology. 2002; 39(3):408-412

27. Cademartiri F, Maffei E, Notarangelo F, Ugo F, Palumbo A, Lina D et al. 64-slice computed tomography coronary angiography: diagnostic accuracy in the real world. Radiologia Medica. 2008; 113(2):163-180

28. Cademartiri F, Maffei E, Palumbo A, Malago R, Alberghina F, Aldrovandi A et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography in patients with low-to-intermediate risk. Radiologia Medica. 2007; 112(7):969-981

29. Canto JG, Goldberg RJ, Hand MM, Bonow RO, Sopko G, Pepine CJ et al. Symptom presentation of women with acute coronary syndromes: myth vs reality. Archives of Internal Medicine. 2007; 167(22):2405-2413

30. Canto JG, Shlipak MG, Rogers WJ, Malmgren JA, Frederick PD, Lambrew CT et al. Prevalence, clinical characteristics, and mortality among patients with myocardial infarction presenting without chest pain. JAMA: Journal of the American Medical Association. 2000; 283(24):3223-3229

31. Carrascosa P, Capunay C, Deviggiano A, Goldsmit A, Tajer C, Bettinotti M et al. Accuracy of low-dose prospectively gated axial coronary CT angiography for the assessment of coronary artery stenosis in patients with stable heart rate. Journal of Cardiovascular Computed Tomography. 2010; 4(3):197-205

32. Caselli C, de Graaf MA, Lorenzoni V, Rovai D, Marinelli M, Del RS et al. HDL cholesterol, leptin and interleukin-6 predict high risk coronary anatomy assessed by CT angiography in patients with stable chest pain. Atherosclerosis 241 (1) (pp 55-61), 2015 Date of Publication: July 01, 2015. 2015; (1):55-61

33. Caselli C, Rovai D, Lorenzoni V, Carpeggiani C, Teresinska A, Aguade S et al. A New Integrated Clinical-Biohumoral Model to Predict Functionally Significant Coronary Artery Disease in Patients With Chronic Chest Pain. Canadian Journal of Cardiology. 2015; 31(6):709-716

34. Cetin M, Cakici M, Zencir C, Tasolar H, Baysal E, Balli M et al. Prediction of coronary artery disease severity using CHADS2 and CHA2DS2-VASc scores and a newly defined CHA2DS2-VASc-HS score. American Journal of Cardiology. 2014; 113(6):950-956

35. Chaitman BR, Bourassa MG, Davis K, Rogers WJ, Tyras DH, Berger R et al. Angiographic prevalence of high-risk coronary artery disease in patient subsets (CASS). Circulation. 1981; 64(2):360-367

36. Chang SA, Choi SI, Choi EK, Kim HK, Jung JW, Chun EJ et al. Usefulness of 64-slice multidetector computed tomography as an initial diagnostic approach in patients with acute chest pain. American Heart Journal. 2008; 156(2):375-383

37. Chen CC, Chen CC, Hsieh IC, Liu YC, Liu CY, Chan T et al. The effect of calcium score on the diagnostic accuracy of coronary computed tomography angiography. The International Journal of Cardiovascular Imaging. 2011; 27 Suppl 1:37-42

38. Chen J, Rathore SS, Radford MJ, Wang Y, Krumholz HM. Racial differences in the use of cardiac catheterization after acute myocardial infarction. New England Journal of Medicine. 2001; 344(19):1443-1449

39. Chen JH, Huang HH, Yen-David HT, Wu YL, Wang LM, Lee CH. Different clinical presentations in chinese people with acute myocardial infarction in the emergency department. Journal of the Chinese Medical Association : JCMA. 2006; 69(11):517-522

40. Chen ZW, Chen YH, Qian JY, Ma JY, Ge JB. Validation of a novel clinical prediction score for severe coronary artery diseases before elective coronary angiography. PLoS ONE [Electronic Resource]. 2014; 9(4):e94493

41. Cheng VY, Berman DS, Rozanski A, Dunning AM, Achenbach S, Al-Mallah M et al. Performance of the traditional age, sex, and angina typicality-based approach for estimating pretest probability of angiographically significant coronary artery disease in patients undergoing coronary computed tomographic angiography: results from the multinational coronary CT angiography evaluation for clinical outcomes: an international multicenter registry (CONFIRM). Circulation. 2011; 124(22):2423-2432

42. Christenson J, Innes G, McKnight D, Thompson CR, Wong H, Yu E et al. A clinical prediction rule for early discharge of patients with chest pain. Annals of Emergency Medicine. 2006; 47(1):1-10

43. Christiaens L, Duchat F, Boudiaf M, Tasu JP, Fargeaudou Y, Ledref O et al. Impact of 64-slice coronary CT on the management of patients presenting with acute chest pain: results of a prospective two-centre study. European Radiology. 2012; 22(5):1050-1058

44. Chrysohoou C, Panagiotakos DB, Pitsavos C, Kokkinos P, Marinakis N, Stefanadis C et al. Gender differences on the risk evaluation of acute coronary syndromes: The CARDIO2000 study. Preventive Cardiology. 2003; 6(2):71-77

45. Chua TP, Saia F, Bhardwaj V, Wright C, Clarke D, Hennessy M et al. Are there gender differences in patients presenting with unstable angina? International Journal of Cardiology. 2000; 72(3):281-286

46. Chun AA, McGee SR. Bedside diagnosis of coronary artery disease: a systematic review. American Journal of Medicine. 2004; 117(5):334-343

47. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002; 324(7329):71-86

48. Collinson P, Gaze D, Goodacre S, Bradburn M. RATPAC CBE (Randomised Assessment of Treatment using Panel Assay of Cardiac markers - Contemporary Biomarker Evaluation). Health Technology Assessment. 2013; 17(15):1-17

49. Conigliaro J, Whittle J, Good CB, Hanusa BH, Passman LJ, Lofgren RP et al. Understanding racial variation in the use of coronary revascularization procedures: the role of clinical factors. Archives of Internal Medicine. 2000; 160(9):1329-1335

50. Conti A, Alesi A, Aspesi G, Bigiarini S, Bianchi S, Angeli E et al. Comparison of exercise electrocardiogram and exercise echocardiography in intermediate-risk chest pain patients. American Journal of Emergency Medicine. 2015; 33(1):7-13

51. Conti A, Gallini C, Costanzo E, Ferri P, Matteini M, Paladini B et al. Early detection of myocardial ischaemia in the emergency department by rest or exercise (99m)Tc tracer myocardial SPET in patients with chest pain and non-diagnostic ECG. European Journal of Nuclear Medicine. 2001; 28(12):1806-1810

52. Conti A, Paladini B, Toccafondi S, Magazzini S, Olivotto I, Galassi F et al. Effectiveness of a multidisciplinary chest pain unit for the assessment of coronary syndromes and risk stratification in the Florence area. American Heart Journal. 2002; 144(4):630-635

53. Conti A, Sammicheli L, Gallini C, Costanzo EN, Antoniucci D, Barletta G. Assessment of patients with low-risk chest pain in the emergency department: Head-to-head comparison of

exercise stress echocardiography and exercise myocardial SPECT. American Heart Journal. 2005; 149(5):894-901

54. Cramer MJ, Van Der Wall EE, Verzijlbergen JF, Jaarsma W, Niemeyer MG, Zwindrman AH et al. SPECT versus planar 99mTc-sestamibi myocardial scintigraphy: comparison of accuracy and impact on patient management in chronic ischemic heart disease. The quarterly journal of nuclear medicine : official publication of the Italian Association of Nuclear Medicine (AIMN) [and] the International Association of Radiopharmacology (IAR). 1997; 41(1):1-9

55. Dedic A, Lubbers MM, Schaap J, Lammers J, Lamfers EJ, Rensing BJ et al. Coronary CT Angiography for Suspected ACS in the Era of High-Sensitivity Troponins: Randomized Multicenter Study. Journal of the American College of Cardiology. 2016; 67(1):16-26

56. Dharampal AS, Rossi A, Dedic A, Cademartiri F, Papadopoulou SL, Weustink AC et al. Restriction of the referral of patients with stable angina for CT coronary angiography by clinical evaluation and calcium score: impact on clinical decision making. European Radiology. 2013; 23(10):2676-2686

57. Di Bello V, Bellina CR, Gori E, Molea N, Talarico L, Boni G et al. Incremental diagnostic value of dobutamine stress echocardiography and dobutamine scintigraphy (technetium 99m-labeled sestamibi single-photon emission computed tomography) for assessment of presence and extent of coronary artery disease. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology. 1996; 3(3):212-220

58. Di Bello V, Bellina CR, Molea N, Talarico L, Boni G, Magagnini E et al. Simultaneous dobutamine stress echocardiography and dobutamine scintigraphy (99mTc-MIBI-SPET) for assessment of coronary artery disease. International Journal of Cardiac Imaging. 1996; 12(3):185-190

59. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. New England Journal of Medicine. 1979; 300(24):1350-1358

60. Diercks DB, Boghos E, Guzman H, Amsterdam EA, Kirk JD. Changes in the numeric descriptive scale for pain after sublingual nitroglycerin do not predict cardiac etiology of chest pain. Annals of Emergency Medicine. 2005; 45(6):581-585

61. Diercks DB, Kontos MC, Chen AY, Pollack CV, Wiviott SD, Rumsfeld JS et al. Utilization and impact of pre-hospital electrocardiograms for patients with acute ST-segment elevation myocardial infarction:data from the NCDR (National Cardiovascular Data Registry) ACTION (Acute Coronary Treatment and Intervention Outcomes Network) Registry. Journal of the American College of Cardiology. 2009; 53(2):161-166

62. Donati OF, Stolzmann P, Desbiolles L, Leschka S, Kozerke S, Plass A et al. Coronary artery disease: which degree of coronary artery stenosis is indicative of ischemia? European Journal of Radiology. 2011; 80(1):120-126

63. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B et al. Outcomes of anatomical versus functional testing for coronary artery disease. New England Journal of Medicine. 2015; 372(14):1291-1300

64. Eggers KM, Venge P, Lindahl B. High-sensitive cardiac troponin T outperforms novel diagnostic biomarkers in patients with acute chest pain. Clinica Chimica Acta. 2012; 413(13-14):1135-1140

65. Escobedo LG, Giles WH, Anda RF. Socioeconomic status, race, and death from coronary heart disease. American Journal of Preventive Medicine. 1997; 13(2):123-130

66. Everts B, Karlson BW, Herlitz J, Hedner T. Morphine use and pharmacokinetics in patients with chest pain due to suspected or definite acute myocardial infarction. European Journal of Pain. 1998; 2(2):115-125

67. Fesmire FM. Which chest pain patients potentially benefit from continuous 12-lead ST-segment monitoring with automated serial ECG? American Journal of Emergency Medicine. 2000; 18(7):773-778

68. Fleming RM, Gibbs HR, Swafford J. Using quantitative coronary arteriography to redefine SPECT sensitivity and specificity. American Journal of Physiologic Imaging. 1992; 7(2):59-65

69. Forberg JL, Hilmersson CE, Carlsson M, Arheden H, Bjork J, Hjalte K et al. Negative predictive value and potential cost savings of acute nuclear myocardial perfusion imaging in low risk patients with suspected acute coronary syndrome: a prospective single blinded study. BMC Emergency Medicine. 2009; 9:12

70. Freund Y, Chenevier-Gobeaux C, Bonnet P, Claessens YE, Allo JC, Doumenc B et al. High-sensitivity versus conventional troponin in the emergency department for the diagnosis of acute myocardial infarction. Critical Care (London, England). 2011; 15(3):R147

71. Fujitaka K, Nakamura S, Sugiura T, Hatada K, Tsuka Y, Umemura S et al. Combined analysis of multislice computed tomography coronary angiography and stress-rest myocardial perfusion imaging in detecting patients with significant proximal coronary artery stenosis. Nuclear Medicine Communications. 2009; 30(10):789-796

72. Gaibazzi N, Reverberi C, Badano L. Usefulness of contrast stress-echocardiography or exercise-electrocardiography to predict long-term acute coronary syndromes in patients presenting with chest pain without electrocardiographic abnormalities or 12-hour troponin elevation. American Journal of Cardiology. 2011; 107(2):161-167

73. Gaibazzi N, Reverberi C, Squeri A, De Iaco G, Ardissino D, Gherli T. Contrast stress echocardiography for the diagnosis of coronary artery disease in patients with chest pain but without acute coronary syndrome: incremental value of myocardial perfusion. Journal of the American Society of Echocardiography. 2009; 22(4):404-410

74. Gaibazzi N, Rigo F, Facchetti R, Carerj S, Giannattasio C, Moreo A et al. Differential incremental value of ultrasound carotid intima-media thickness, carotid plaque, and cardiac calcium to predict angiographic coronary artery disease across Framingham risk score strata in the APRES multicentre study. European Heart Journal Cardiovascular Imaging. 2015;

75. Gallagher MJ, Ross MA, Raff GL, Goldstein JA, O'Neill WW, O'neil B. The diagnostic accuracy of 64-slice computed tomography coronary angiography compared with stress nuclear imaging in emergency department low-risk chest pain patients. Annals of Emergency Medicine. 2007; 49(2):125-136

76. Genders TS, Petersen SE, Pugliese F, Dastidar AG, Fleischmann KE, Nieman K et al. The optimal imaging strategy for patients with stable chest pain: a cost-effectiveness analysis. Annals of Internal Medicine. 2015; 162(7):474-484

77. Genders TS, Pugliese F, Mollet NR, Meijboom WB, Weustink AC, van Mieghem CA et al. Incremental value of the CT coronary calcium score for the prediction of coronary artery disease. European Radiology. 2010; 20(10):2331-2340

78. Genders TS, Steyerberg EW, Alkadhi H, Leschka S, Desbiolles L, Nieman K et al. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. European Heart Journal. 2011; 32(11):1316-1330

79. Genders TS, Steyerberg EW, Hunink MG, Nieman K, Galema TW, Mollet NR et al. Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts. BMJ. 2012; 344:e3485

80. Gillum RF, Fortmann SP, Prineas RJ, Kottke TE. International diagnostic criteria for acute myocardial infarction and acute stroke. American Heart Journal. 1984; 108(1):150-158

81. Goldstein JA, Chinnaiyan KM, Abidov A, Achenbach S, Berman DS, Hayes SW et al. The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) trial. Journal of the American College of Cardiology. 2011; 58(14):1414-1422

82. Goldstein JA, Gallagher MJ, O'Neill WW, Ross MA, O'Neil BJ, Raff GL. A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain. Journal of the American College of Cardiology. 2007; 49(8):863-871

83. Goodacre S, Cross E, Arnold J, Angelini K, Capewell S, Nicholl J. The health care burden of acute chest pain. Heart. 2005; 91(2):229-230

84. Group GW. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group website. 2011, Issue

85. Hamilton-Craig C, Fifoot A, Hansen M, Pincus M, Chan J, Walters DL et al. Diagnostic performance and cost of CT angiography versus stress ECG--a randomized prospective study of suspected acute coronary syndrome chest pain in the emergency department (CT-COMPARE). International Journal of Cardiology. 2014; 177(3):867-873

86. Hansen M, Ginns J, Seneviratne S, Slaughter R, Premaranthe M, Samardhi H et al. The value of dual-source 64-slice CT coronary angiography in the assessment of patients presenting to an acute chest pain service. Heart, Lung & Circulation. 2010; 19(4):213-218

87. Hascoet S, Bongard V, Chabbert V, Marachet MA, Rousseau H, Charpentier S et al. Early triage of emergency department patients with acute coronary syndrome: contribution of 64-slice computed tomography angiography. Archives of Cardiovascular Diseases. 2012; 105(6-7):338-346

88. Hayes MJ, Fraser AR, Hampton JR. Randomised trial comparing buprenorphine and diamorphine for chest pain in suspected myocardial infarction. British Medical Journal. 1979; 2(6185):300-302

89. Hemingway H, Langenberg C, Damant J, Frost C, Pyorala K, Barrett-Connor E. Prevalence of angina in women versus men: a systematic review and meta-analysis of international variations across 31 countries. Circulation. 2008; 117(12):1526-1536

90. Hennessy TG, Codd MB, Kane G, McCarthy C, McCann HA, Sugrue DD. Dobutamine stress echocardiography for the assessment of patients without history or electrocardiographic evidence of myocardial infarction. Journal of Noninvasive Cardiology. 1998; 2(1):7-11

91. Henrikson CA, Howell EE, Bush DE, Miles JS, Meininger GR, Friedlander T et al. Chest pain relief by nitroglycerin does not predict active coronary artery disease. Annals of Internal Medicine. 2003; 139(12):979-NaN

92. Herlitz J, Richter A, Hjalmarson A, Holmberg S. Variability of chest pain in suspected acute myocardial infarction according to subjective assessment and requirement of narcotic analgesics. International Journal of Cardiology. 1986; 13(1):9-26

93. Hernandez R, Vale L. The value of myocardial perfusion scintigraphy in the diagnosis and management of angina and myocardial infarction: a probabilistic economic analysis. Medical Decision Making. 2007; 27(6):772-788

94. Herzog BA, Husmann L, Burkhard N, Gaemperli O, Valenta I, Tatsugami F et al. Accuracy of low-dose computed tomography coronary angiography using prospective electrocardiogram-triggering: first clinical experience. European Heart Journal. 2008; 29(24):3037-3042

95. Herzog BA, Wyss CA, Husmann L, Gaemperli O, Valenta I, Treyer V et al. First head-to-head comparison of effective radiation dose from low-dose 64-slice CT with prospective ECG-triggering versus invasive coronary angiography. Heart (British Cardiac Society). 2009; 95(20):1656-1661

96. Herzog C, Nguyen SA, Savino G, Zwerner PL, Doll J, Nielsen CD et al. Does two-segment image reconstruction at 64-section CT coronary angiography improve image quality and diagnostic accuracy? Radiology. 2007; 244(1):121-129

97. Hew E, Haq A, Strauss H. A randomized controlled trial of nalbuphine vs morphine in the treatment of ischemic chest pain. Current Therapeutic Research, Clinical and Experimental. 1987; 41(3):394-402

98. Hochholzer W, Reichlin T, Stelzig C, Hochholzer K, Meissner J, Breidthardt T et al. Impact of soluble fms-like tyrosine kinase-1 and placental growth factor serum levels for risk stratification and early diagnosis in patients with suspected acute myocardial infarction. European Heart Journal. 2011; 32(3):326-335

99. Hoffmann R, Lethen H, Kleinhans E, Weiss M, Flachskampf FA, Hanrath P. Comparative evaluation of bicycle and dobutamine stress echocardiography with perfusion scintigraphy and bicycle electrocardiogram for identification of coronary artery disease. The American journal of cardiology. 1993; 72(7):555-559

100. Hoffmann U, Bamberg F, Chae CU, Nichols JH, Rogers IS, Seneviratne SK et al. Coronary computed tomography angiography for early triage of patients with acute chest pain: the ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) trial. Journal of the American College of Cardiology. 2009; 53(18):1642-1650

101. Hoffmann U, Truong QA, Fleg JL, Goehler A, Gazelle S, Wiviott S et al. Design of the rule out myocardial ischemia/infarction using computer assisted tomography: A multicenter randomized comparative effectiveness trial of cardiac computed tomography versus alternative triage strategies in patients with acute chest pain in the emergency department. American Heart Journal. 2012; 163(3):330-338.e331

102. Hoffmann U, Truong QA, Schoenfeld DA, Chou ET, Woodard PK, Nagurney JT et al. Coronary CT angiography versus standard evaluation in acute chest pain. New England Journal of Medicine. 2012; 367(4):299-308

103. Hollander JE, Chang AM, Shofer FS, McCusker CM, Baxt WG, Litt HI. Coronary computed tomographic angiography for rapid discharge of low-risk patients with potential acute coronary syndromes. Annals of Emergency Medicine. 2009; 53(3):295-304

104. Hollander JE, Litt HI, Chase M, Brown AM, Kim W, Baxt WG. Computed tomography coronary angiography for rapid disposition of low-risk emergency department patients with chest pain syndromes. Academic Emergency Medicine. 2007; 14(2):112-116

105. Hong SN, Mieres JH, Jacobs JE, Babb JS, Patel P, Srichai MB. Assessing coronary disease in symptomatic women by the Morise score. Journal of Women's Health. 2012; 21(8):843-850

106. Hosmer D, Lemeshow S. Applied Logistic Regression. Wiley. 2000; 2nd Ed.

107. Hwang Y, Kim Y, Chung IM, Ryu J, Park H. Coronary heart disease risk assessment and characterization of coronary artery disease using coronary CT angiography: comparison of asymptomatic and symptomatic groups. Clinical Radiology. 2010; 65(8):601-608

108. Iglesias-Garriz I, Rodriguez MA, Garcia-Porrero E, Ereno F, Garrote C, Suarez G. Emergency nontraumatic chest pain: use of stress echocardiography to detect significant coronary artery stenosis. Journal of the American Society of Echocardiography. 2005; 18(11):1181-1186

109. Innocenti F, Lazzeretti D, Conti A, Zanobetti M, Vicidomini S, Pini R. Stress echocardiography in the ED: diagnostic performance in high-risk subgroups. American Journal of Emergency Medicine. 2013; 31(9):1309-1314

110. investigators S-H. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial.[Erratum appears in Lancet. 2015 Jun 13;385(9985):2354; PMID: 26088642]. Lancet. 2015; 385(9985):2383-2391

111. Ioannidis JP, Salem D, Chew PW, Lau J. Accuracy and clinical effect of out-of-hospital electrocardiography in the diagnosis of acute cardiac ischemia: a meta-analysis. Annals of Emergency Medicine. 2001; 37(5):461-470

112. Irfan A, Reichlin T, Twerenbold R, Meister M, Moehring B, Wildi K et al. Early diagnosis of myocardial infarction using absolute and relative changes in cardiac troponin concentrations. American Journal of Medicine. 2013; 126(9):781-788.e782

113. Isaksson RM, Holmgren L, Lundblad D, Brulin C, Eliasson M. Time trends in symptoms and prehospital delay time in women vs. men with myocardial infarction over a 15-year period. The Northern Sweden MONICA Study. European Journal of Cardiovascular Nursing. 2008; 7(2):152-158

114. Jamidar HA, Crooks SW, Adgey AA. Nalbuphine versus diamorphine early in the course of suspected myocardial infarction. European Heart Journal. 1987; 8(6):597-602

115. Javadrashid R, Salehi A, Tarzamni MK, Aslanabadi N, Pak N. Diagnostic efficacy of coronary calcium score in the assessment of significant coronary artery stenosis. Kardiologia Polska. 2010; 68(3):285-291

116. Jensen JM, Voss M, Hansen VB, Andersen LK, Johansen PB, Munkholm H et al. Risk stratification of patients suspected of coronary artery disease: comparison of five different models. Atherosclerosis. 2012; 220(2):557-562

117. Johnson PA, Lee TH, Cook EF, Rouan GW, Goldman L. Effect of race on the presentation and management of patients with acute chest pain. Annals of Internal Medicine. 1993; 118(8):593-601

118. Johnson TR, Nikolaou K, Becker A, Leber AW, Rist C, Wintersperger BJ et al. Dual-source CT for chest pain assessment. European Radiology. 2008; 18(4):773-780

119. Johnson TR, Nikolaou K, Wintersperger BJ, Knez A, Boekstegers P, Reiser MF et al. ECG-gated 64-MDCT angiography in the differential diagnosis of acute chest pain. AJR American Journal of Roentgenology. 2007; 188(1):76-82

120. Kaminek M, Metelkova I, Budikova M, Koranda P, Henzlova L, Havel M et al. Diagnosis of high-risk patients with multivessel coronary artery disease by combined cardiac gated SPET imaging and coronary calcium score. Hellenic Journal of Nuclear Medicine. 2015; 18(1):31-34

121. Kawase Y, Nishimoto M, Hato K, Okajima K, Yoshikawa J. Assessment of coronary artery disease with nicorandil stress magnetic resonance imaging. Osaka City Medical Journal. 2004; 50(2):87-94

122. Kimble LP, McGuire DB, Dunbar SB, Fazio S, De A, Weintraub WS et al. Gender differences in pain characteristics of chronic stable angina and perceived physical limitation in patients with coronary artery disease. Pain. 2003; 101(1-2):45-53

123. Klein C, Gebker R, Kokocinski T, Dreysse S, Schnackenburg B, Fleck E et al. Combined magnetic resonance coronary artery imaging, myocardial perfusion and late gadolinium enhancement in patients with suspected coronary artery disease. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance. 2008; 10:45

124. Klem I, Heitner JF, Shah DJ, Sketch MHJ, Behar V, Weinsaft J et al. Improved detection of coronary artery disease by stress perfusion cardiovascular magnetic resonance with the use of delayed enhancement infarction imaging. Journal of the American College of Cardiology. 2006; 47(8):1630-1638

125. Klingler D, Green WR, Nerenz D, Havstad S, Rosman HS, Cetner L et al. Perceptions of chest pain differ by race. American Heart Journal. 2002; 144(1):51-59

126. Kosuge M, Kimura K, Ishikawa T, Ebina T, Hibi K, Tsukahara K et al. Differences between men and women in terms of clinical features of ST-segment elevation acute myocardial infarction. Circulation Journal. 2006; 70(3):222-226

127. Kotecha D, Flather M, McGrady M, Pepper J, New G, Krum H et al. Contemporary predictors of coronary artery disease in patients referred for angiography. European Journal of Cardiovascular Prevention and Rehabilitation. 2010; 17(3):280-288

128. Krittayaphong R, Boonyasirinant T, Saiviroonporn P, Nakyen S, Thanapiboonpol P, Yindeengam A et al. Myocardial perfusion cardiac magnetic resonance for the diagnosis of coronary artery disease: do we need rest images? The International Journal of Cardiovascular Imaging. 2009; 25 Suppl 1:139-148

129. Kumamaru KK, Arai T, Morita H, Sekine T, Takamura K, Takase S et al. Overestimation of pretest probability of coronary artery disease by Duke clinical score in patients undergoing coronary CT angiography in a Japanese population. Journal of Cardiovascular Computed Tomography. 2014; 8(3):198-204

130. Kurz K, Giannitsis E, Becker M, Hess G, Zdunek D, Katus HA. Comparison of the new high sensitive cardiac troponin T with myoglobin, h-FABP and cTnT for early identification of myocardial necrosis in the acute coronary syndrome. Clinical Research in Cardiology. 2011; 100(3):209-215

131. Kwong RY, Schussheim AE, Rekhraj S, Aletras AH, Geller N, Davis J et al. Detecting acute coronary syndrome in the emergency department with cardiac magnetic resonance imaging. Circulation. 2003; 107(4):531-537

132. Lear JT, Lawrence IG, Burden AC, Pohl JE. A comparison of stress test referral rates and outcome between Asians and Europeans. Journal of the Royal Society of Medicine. 1994; 87(11):661-662

133. Lim SH, Anantharaman V, Sundram F, Chan EY, Ang ES, Yo SL et al. Stress myocardial perfusion imaging for the evaluation and triage of chest pain in the emergency department: A randomized controlled trial. Journal of Nuclear Cardiology. 2013; 20(6):1002-1012

134. Linde JJ, Kofoed KF, Sorgaard M, Kelbaek H, Jensen GB, Nielsen WB et al. Cardiac computed tomography guided treatment strategy in patients with recent acute-onset chest pain: results from the randomised, controlled trial: CArdiac cT in the treatment of acute CHest pain (CATCH). International Journal of Cardiology. 2013; 168(6):5257-5262

135. Litt HI, Gatsonis C, Snyder B, Singh H, Miller CD, Entrikin DW et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. New England Journal of Medicine. 2012; 366(15):1393-1403

136. Mant J, McManus RJ, Oakes R-AL, Delaney BC, Barton PM, Deeks JJ et al. Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care. Health Technology Assessment. 2004; 8(2):1-158

137. Marangelli V, Iliceto S, Piccinni G, De Martino G, Sorgente L, Rizzon P. Detection of coronary artery disease by digital stress echocardiography: comparison of exercise, transesophageal atrial pacing and dipyridamole echocardiography. Journal of the American College of Cardiology. 1994; 24(1):117-124

138. Marwick T, D'Hondt AM, Baudhuin T, Willemart B, Wijns W, Detry JM et al. Optimal use of dobutamine stress for the detection and evaluation of coronary artery disease: combination with echocardiography or scintigraphy, or both? Journal of the American College of Cardiology. 1993; 22(1):159-167

139. Maynard C, Beshansky JR, Griffith JL, Selker HP. Causes of chest pain and symptoms suggestive of acute cardiac ischemia in African-American patients presenting to the emergency department: a multicenter study. Journal of the National Medical Association. 1997; 89(10):665-671

140. Mazeika P, Nihoyannopoulos P, Joshi J, Oakley CM. Uses and limitations of high dose dipyridamole stress echocardiography for evaluation of coronary artery disease. British Heart Journal. 1992; 67(2):144-149

141. McKavanagh P, Lusk L, Ball PA, Verghis RM, Agus AM, Trinick TR et al. A comparison of cardiac computerized tomography and exercise stress electrocardiogram test for the investigation of stable chest pain: the clinical results of the CAPP randomized prospective trial. European Heart Journal Cardiovascular Imaging. 2015; 16(4):441-448

142. Meijboom WB, Meijs MF, Schuijf JD, Cramer MJ, Mollet NR, van Mieghem CA et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. Journal of the American College of Cardiology. 2008; 52(25):2135-2144

143. Melki D, Lind S, Agewall S, Jernberg T. Diagnostic value of high sensitive troponin T in chest pain patients with no persistent ST-elevations. Scandinavian Cardiovascular Journal45 (4) (pp 198-204), 2011Date of Publication: August 2011. 2011; (4):198-204

144. Melzack R. The short-form McGill Pain Questionnaire. Pain. 1987; 30(2):191-197

145. Meng L, Cui L, Cheng Y, Wu X, Tang Y, Wang Y et al. Effect of heart rate and coronary calcification on the diagnostic accuracy of the dual-source CT coronary angiography in patients with suspected coronary artery disease. Korean Journal of Radiology. 2009; 10(4):347-354

146. Miller CD, Case LD, Little WC, Mahler SA, Burke GL, Harper EN et al. Stress CMR reduces revascularization, hospital readmission, and recurrent cardiac testing in intermediate-risk patients with acute chest pain. JACC: Cardiovascular Imaging. 2013; 6(7):785-794

147. Miller CD, Hwang W, Hoekstra JW, Case D, Lefebvre C, Blumstein H et al. Stress cardiac magnetic resonance imaging with observation unit care reduces cost for patients with emergent chest pain: a randomized trial. Annals of Emergency Medicine. 2010; 56(3):209-219.e202

148. Miszalski-Jamka T, Kuntz-Hehner S, Tiemann K, Karwat K, Kostkiewicz M. Quantitative myocardial contrast supine bicycle stress echocardiography for detection of coronary artery disease. Echocardiography (Mount Kisco, N Y). 2013; 30(4):392-400

149. Morrison LJ, Brooks S, Sawadsky B, McDonald A, Verbeek PR. Prehospital 12-lead electrocardiography impact on acute myocardial infarction treatment times and mortality: a systematic review. Academic Emergency Medicine. 2006; 13(1):84-89

150. Muhlenbruch G, Seyfarth T, Soo CS, Pregalathan N, Mahnken AH. Diagnostic value of 64-slice multi-detector row cardiac CTA in symptomatic patients. European Radiology. 2007; 17(3):603-609

151. Murphy NF, MacIntyre K, Capewell S, Stewart S, Pell J, Chalmers J et al. Hospital discharge rates for suspected acute coronary syndromes between 1990 and 2000: population based analysis. BMJ. 2004; 328(7453):1413-1414

152. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. European Heart Journal. 2000; 21(18):1502-1513

153. Nabel EG, Selker HP, Califf RM, Canto JG, Cao JJ, svigne-Nikkens P et al. Women's Ischemic Syndrome Evaluation: current status and future research directions: report of the National Heart, Lung and Blood Institute workshop: October 2-4, 2002: Section 3: diagnosis and treatment of acute cardiac ischemia: gender issues. Circulation. 2004; 109(6):e50-e52

154. Nagel E, Lehmkuhl HB, Bocksch W, Klein C, Vogel U, Frantz E et al. Noninvasive diagnosis of ischemia-induced wall motion abnormalities with the use of high-dose dobutamine stress MRI: comparison with dobutamine stress echocardiography. Circulation. 1999; 99(6):763-770

155. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

156. Nicholson C. A systematic review of the effectiveness of oxygen in reducing acute myocardial ischaemia. Journal of Clinical Nursing. 2004; 13(8):996-1007

157. Nieman K, Galema T, Weustink A, Neefjes L, Moelker A, Musters P et al. Computed tomography versus exercise electrocardiography in patients with stable chest complaints: real-world experiences from a fast-track chest pain clinic. Heart (British Cardiac Society). 2009; 95(20):1669-1675

158. Nilsson S, Scheike M, Engblom D, Karlsson LG, Molstad S, Akerlind I et al. Chest pain and ischaemic heart disease in primary care. British Journal of General Practice. 2003; 53(490):378-382

159. Nixdorff U, Kufner C, Achenbach S, Stilianakis N, Voigt JU, Flachskampf FA et al. Head-to-head comparison of dobutamine stress echocardiography and cardiac computed tomography for the detection of significant coronary artery disease. Cardiology. 2008; 110(2):81-86

160. Novielli N, Cooper NJ, Abrams KR, Sutton AJ. How is evidence on test performance synthesized for economic decision models of diagnostic tests? A systematic appraisal of Health Technology Assessments in the UK since 1997. Value in Health. 2010; 13(8):952-957

161. O'Driscoll BR, Howard LS, Davison AG. BTS guideline for emergency oxygen use in adult patients. Thorax. 2008; 63 Suppl 6:vi1-68

162. Ohlsson M, Ohlin H, Wallerstedt SM, Edenbrandt L. Usefulness of serial electrocardiograms for diagnosis of acute myocardial infarction. American Journal of Cardiology. 2001; 88(5):478-481

163. Onishi T, Uematsu M, Watanabe T, Fujita M, Awata M, Iida O et al. Objective interpretation of dobutamine stress echocardiography by diastolic dyssynchrony imaging: a practical approach. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography. 2010; 23(10):1103-1108

164. Ovrehus KA, Jensen JK, Mickley HF, Munkholm H, Bottcher M, Botker HE et al. Comparison of usefulness of exercise testing versus coronary computed tomographic angiography for evaluation of patients suspected of having coronary artery disease. The American journal of cardiology. 2010; 105(6):773-779

165. Park KH, Kim MK, Kim HS, Park WJ, Cho GY, Choi YJ. Clinical significance of framingham risk score, flow-mediated dilation and pulse wave velocity in patients with stable angina. Circulation journal : official journal of the Japanese Circulation Society. 2011; 75(5):1177-1183

166. Parodi G, Picano E, Marcassa C, Sicari R, Marzullo P, Verna E et al. High dose dipyridamole myocardial imaging: simultaneous sestamibi scintigraphy and two-dimensional echocardiography in the detection and evaluation of coronary artery disease. Italian Group of Nuclear Cardiology. Coronary Artery Disease. 1999; 10(3):177-184

167. Parsonage WA, Mueller C, Greenslade JH, Wildi K, Pickering J, Than M et al. Validation of NICE diagnostic guidance for rule out of myocardial infarction using high-sensitivity troponin tests. Heart. 2016; 102(16):1279-1286

168. Patel H, Rosengren A, Ekman I. Symptoms in acute coronary syndromes: Does sex make a difference? American Heart Journal. 2004; 148(1):27-33

169. Pickett CA, Hulten EA, Goyal M, Surry L, Villines TC. Accuracy of traditional age, gender and symptom based pre-test estimation of angiographically significant coronary artery disease in patients referred for coronary computed tomographic angiography. American Journal of Cardiology. 2013; 112(2):208-211

170. Piers LH, Dikkers R, Willems TP, de Smet BJGL, Oudkerk M, Zijlstra F et al. Computed tomographic angiography or conventional coronary angiography in therapeutic decision-making. European Heart Journal. 2008; 29(23):2902-2907

171. Pontone G, Bertella E, Mushtaq S, Loguercio M, Cortinovis S, Baggiano A et al. Coronary artery disease: Diagnostic accuracy of CT coronary angiography-a comparison of high and standard spatial resolution scanning. Radiology. 2014; 271(3):688-694

172. Pryor DB, Harrell FE, Jr., Lee KL, Califf RM, Rosati RA. Estimating the likelihood of significant coronary artery disease. American Journal of Medicine. 1983; 75(5):771-780

173. Pryor DB, Shaw L, McCants CB, Lee KL, Mark DB, Harrell FE, Jr. et al. Value of the history and physical in identifying patients at increased risk for coronary artery disease. Annals of Internal Medicine. 1993; 118(2):81-90

174. Pugliese F, Mollet NR, Hunink MGM, Cademartiri F, Nieman K, van Domburg RT et al. Diagnostic performance of coronary CT angiography by using different generations of multisection scanners: single-center experience. Radiology. 2008; 246(2):384-393

175. Rademaker AA, Danad I, Groothuis JG, Heymans MW, Marcu CB, Knaapen P et al. Comparison of different cardiac risk scores for coronary artery disease in symptomatic women: do female-specific risk factors matter? European Journal of Preventive Cardiology. 2014; 21(11):1443-1450

176. Raff GL, Gallagher MJ, O'Neill WW, Goldstein JA. Diagnostic accuracy of noninvasive coronary angiography using 64-slice spiral computed tomography. Journal of the American College of Cardiology. 2005; 46(3):552-557

177. Rawles JM, Kenmure AC. Controlled trial of oxygen in uncomplicated myocardial infarction. British Medical Journal. 1976; 1(6018):1121-1123

178. Reichlin T, Irfan A, Twerenbold R, Reiter M, Hochholzer W, Burkhalter H et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. Circulation. 2011; 124(2):136-145

179. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. Journal of Clinical Epidemiology. 2005; 58(10):982-990

180. Review Manager (RevMan) [Computer program]. Version 5. Copenhagen. The Nordic Cochrane Centre, The Cochrane Collaboration, 2015. Available from: http://tech.cochrane.org/Revman

181. Rixe J, Rolf A, Conradi G, Moellmann H, Nef H, Neumann T et al. Detection of relevant coronary artery disease using dual-source computed tomography in a high probability patient series: comparison with invasive angiography. Circulation journal : official journal of the Japanese Circulation Society. 2009; 73(2):316-322

182. Ropers D, Rixe J, Anders K, Kuttner A, Baum U, Bautz W et al. Usefulness of multidetector row spiral computed tomography with 64- x 0.6-mm collimation and 330-ms rotation for the noninvasive detection of significant coronary artery stenoses. The American journal of cardiology. 2006; 97(3):343-348

183. Rosenberg S, Elashoff MR, Beineke P, Daniels SE, Wingrove JA, Tingley WG et al. Multicenter validation of the diagnostic accuracy of a blood-based gene expression test for assessing obstructive coronary artery disease in nondiabetic patients. Annals of Internal Medicine. 2010; 153(7):425-434

184. Rubinshtein R, Halon DA, Gaspar T, Jaffe R, Karkabi B, Flugelman MY et al. Usefulness of 64-slice cardiac computed tomographic angiography for diagnosing acute coronary syndromes and predicting clinical outcome in emergency department patients with chest pain of uncertain origin. Circulation. 2007; 115(13):1762-1768

185. Ruigomez A, Rodriguez LA, Wallander MA, Johansson S, Jones R. Chest pain in general practice: incidence, comorbidity and mortality. Family Practice. 2006; 23(2):167-174

186. San Roman JA, Vilacosta I, Castillo JA, Rollan MJ, Hernandez M, Peral V et al. Selection of the optimal stress test for the diagnosis of coronary artery disease. Heart (British Cardiac Society). 1998; 80(4):370-376

187. San Roman JA, Vilacosta I, Castillo JA, Rollan MJ, Peral V, Sanchez-Harguindey L et al. Dipyridamole and dobutamine-atropine stress echocardiography in the diagnosis of coronary artery disease. Comparison with exercise stress test, analysis of agreement, and impact of antianginal treatment. Chest. 1996; 110(5):1248-1254

188. Sanchis J, Bodí V, Llácer A, Núñez J, Consuegra L, Bosch MJ et al. Risk stratification of patients with acute chest pain and normal troponin concentrations. Heart. 2005; 91(8):1013-1018

189. Santalo M, Martin A, Velilla J, Povar J, Temboury F, Balaguer J et al. Using high-sensitivity troponin T: the importance of the proper gold standard. American Journal of Medicine. 2013; 126(8):709-717

190. Santoro GM, Sciagra R, Buonamici P, Consoli N, Mazzoni V, Zerauschek F et al. Head-to-head comparison of exercise stress testing, pharmacologic stress echocardiography, and perfusion tomography as first-line examination for chest pain in patients without history of coronary artery disease. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology. 1998; 5(1):19-27

191. Schepis T, Gaemperli O, Koepfli P, Namdar M, Valenta I, Scheffel H et al. Added value of coronary artery calcium score as an adjunct to gated SPECT for the evaluation of coronary artery disease in an intermediate-risk population. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2007; 48(9):1424-1430

192. Schillinger M, Sodeck G, Meron G, Janata K, Nikfardjam M, Rauscha F et al. Acute chest pain--identification of patients at low risk for coronary events. The impact of symptoms, medical history and risk factors. Wiener klinische Wochenschrift. 2004; 116(3):83-89

193. Scott ME, Orr R. Effects of diamorphine, methadone, morphine, and pentazocine in patients with suspected acute myocardial infarction. Lancet. 1969; 1(7605):1065-1067

194. Sebbane M, Lefebvre S, Kuster N, Jreige R, Jacques E, Badiou S et al. Early rule out of acute myocardial infarction in ED patients: value of combined high-sensitivity cardiac troponin T and ultrasensitive copeptin assays at admission. American Journal of Emergency Medicine. 2013; 31(9):1302-1308

195. Senior R, Lepper W, Pasquet A, Chung G, Hoffman R, Vanoverschelde JL et al. Myocardial perfusion assessment in patients with medium probability of coronary artery disease and no prior myocardial infarction: comparison of myocardial contrast echocardiography with 99mTc single-photon emission computed tomography. American Heart Journal. 2004; 147(6):1100-1105

196. Severi S, Picano E, Michelassi C, Lattanzi F, Landi P, Distante A et al. Diagnostic and prognostic value of dipyridamole echocardiography in patients with suspected coronary artery disease. Comparison with exercise electrocardiography. Circulation. 1994; 89(3):1160-1173

197. Shaikh K, Wang DD, Saad H, Alam M, Khandelwal A, Brooks K et al. Feasibility, safety and accuracy of regadenoson-atropine (REGAT) stress echocardiography for the diagnosis of coronary artery disease: an angiographic correlative study. The International Journal of Cardiovascular Imaging. 2014; 30(3):515-522

198. Sheikh M, Ben-Nakhi A, Shukkur AM, Sinan T, Al-Rashdan I. Accuracy of 64-multidetector-row computed tomography in the diagnosis of coronary artery disease. Medical principles and practice : international journal of the Kuwait University, Health Science Centre. 2009; 18(4):323-328

199. Shmilovich H, Cheng VY, Nakazato R, Smith TW, Otaki Y, Nakanishi R et al. Incremental value of diagonal earlobe crease to the Diamond-Forrester classification in estimating the probability of significant coronary artery disease determined by computed tomographic angiography. American Journal of Cardiology. 2014; 114(11):1670-1675

200. Shry EA, Dacus J, Van De Graaff E, Hjelkrem M, Stajduhar KC, Steinhubl SR. Usefulness of the response to sublingual nitroglycerin as a predictor of ischemic chest pain in the emergency department. American Journal of Cardiology. 2002; 90(11):1264-1267

201. Sonel AF, Good CB, Mulgund J, Roe MT, Gibler WB, Smith SC, Jr. et al. Racial variations in treatment and outcomes of black and white patients with high-risk non-ST-elevation acute coronary syndromes: insights from CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines?). Circulation. 2005; 111(10):1225-1232

202. Steele R, McNaughton T, McConahy M, Lam J. Chest pain in emergency department patients: if the pain is relieved by nitroglycerin, is it more likely to be cardiac chest pain? CJEM Canadian Journal of Emergency Medical Care. 2006; 8(3):164-170

203. Stolzmann P, Alkadhi H, Scheffel H, Plass A, Leschka S, Falk V et al. Combining cardiac magnetic resonance and computed tomography coronary calcium scoring: added value for the assessment of morphological coronary disease? The International Journal of Cardiovascular Imaging. 2011; 27(7):969-977

204. Swailam S, Abdel-Salam Z, Emil S, Nabil H, Nammas W. Multi-slice computed tomography: Can it adequately rule out left main coronary disease in patients with an intermediate probability of coronary artery disease? Cardiology Journal. 2010; 17(6):594-598

205. Swap CJ, Nagurney JT. Value and limitations of chest pain history in the evaluation of patients with suspected acute coronary syndromes. JAMA: Journal of the American Medical Association. 2005; 294(20):2623-2629

206. Teoh M, Lalondrelle S, Roughton M, Grocott-Mason R, Dubrey SW. Acute coronary syndromes and their presentation in Asian and Caucasian patients in Britain. Heart. 2007; 93(2):183-188

207. Thomassen A, Petersen H, Diederichsen AC, Mickley H, Jensen LO, Johansen A et al. Hybrid CT angiography and quantitative 15O-water PET for assessment of coronary artery disease: comparison with quantitative coronary angiography. European Journal of Nuclear Medicine and Molecular Imaging. 2013; 40(12):1894-1904

208. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD et al. Third universal definition of myocardial infarction. Circulation. 2012; 126(16):2020-2035

209. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. European Heart Journal. 2007; 28(20):2525-2538

210. Tsutsui JM, Xie F, O'Leary EL, Elhendy A, Anderson JR, McGrain AC et al. Diagnostic accuracy and prognostic value of dobutamine stress myocardial contrast echocardiography in patients with suspected acute coronary syndromes. Echocardiography. 2005; 22(6):487-495

211. Udelson JE, Beshansky JR, Ballin DS, Feldman JA, Griffith JL, Handler J et al. Myocardial perfusion imaging for evaluation and triage of patients with suspected acute cardiac ischemia: a randomized controlled trial.[Erratum appears in JAMA 2003 Jan 8;289(2):178]. JAMA. 2002; 288(21):2693-2700

212. Ueno K, Anzai T, Jinzaki M, Yamada M, Kohno T, Kawamura A et al. Diagnostic capacity of 64-slice multidetector computed tomography for acute coronary syndrome in patients presenting with acute chest pain. Cardiology. 2009; 112(3):211-218

213. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants. New England Journal of Medicine. 1999; 341(4):217-225

214. Van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Statistics in Medicine. 2002; 21(4):589-624

215. Van Houwelingen HC, Zwinderman KH, Stijnen T. A bivariate approach to meta-analysis. Statistics in Medicine. 1993; 12(24):2273-2284

216. van Velzen JE, de Graaf FR, Kroft LJ, de Roos A, Reiber JH, Bax JJ et al. Performance and efficacy of 320-row computed tomography coronary angiography in patients presenting with acute chest pain: results from a clinical registry. The International Journal of Cardiovascular Imaging. 2012; 28(4):865-876

217. Versteylen MO, Joosen IA, Shaw LJ, Narula J, Hofstra L. Comparison of Framingham, PROCAM, SCORE, and Diamond Forrester to predict coronary atherosclerosis and cardiovascular events. Journal of Nuclear Cardiology. 2011; 18(5):904-911

218. Vogel-Claussen J, Skrok J, Dombroski D, Shea SM, Shapiro EP, Bohlman M et al. Comprehensive adenosine stress perfusion MRI defines the etiology of chest pain in the emergency room: Comparison with nuclear stress test. Journal of Magnetic Resonance Imaging. 2009; 30(4):753-762

219. von Ziegler F, Greif M, Tittus J, Schenzle J, Becker C, Becker A. Distribution of coronary calcifications in patients with suspected coronary heart disease. American Heart Journal. 2014; 167(4):568-575

220. von Ziegler F, Schenzle J, Schiessl S, Greif M, Helbig S, Tittus J et al. Use of multi-slice computed tomography in patients with chest-pain submitted to the emergency department. The International Journal of Cardiovascular Imaging. 2014; 30(1):145-153

221. Wasfy MM, Brady TJ, Abbara S, Nasir K, Ghoshhajra BB, Truong QA et al. Comparison of the Diamond-Forrester method and Duke Clinical Score to predict obstructive coronary artery disease by computed tomographic angiography. American Journal of Cardiology. 2012; 109(7):998-1004

222. Wijesinghe M, Perrin K, Ranchord A, Simmonds M, Weatherall M, Beasley R. The routine use of oxygen in the treatment of myocardial infarction: systematic review. Heart. 2009; 95(3):198-202

223. Wilkinson P, Sayer J, Laji K, Grundy C, Marchant B, Kopelman P et al. Comparison of case fatality in south Asian and white patients after acute myocardial infarction: observational study. BMJ. 1996; 312(7042):1330-1333

224. Wilson AT, Channer KS. Hypoxaemia and supplemental oxygen therapy in the first 24 hours after myocardial infarction: the role of pulse oximetry. Journal of the Royal College of Physicians of London. 1997; 31(6):657-661

225. WinBUGS [Computer programme] version 1.4. Cambridge. MRC Biostatistics Unit UoC, 2015. Available from: http://www.mrc-bsu.cam.ac.uk/software/bugs/the-bugs-project-winbugs/

226. Winther S, Schmidt SE, Holm NR, Toft E, Struijk JJ, Botker HE et al. Diagnosing coronary artery disease by sound analysis from coronary stenosis induced turbulent blood flow: diagnostic performance in patients with stable angina pectoris. International Journal of Cardiovascular Imaging. 2016; 32(2):235-245

227. Yalcin M, Kardesoglu E, Aparci M, Isilak Z, Uz O, Yiginer O et al. Cardiovascular risk scores for coronary atherosclerosis. Acta Cardiologica. 2012; 67(5):557-563

228. Yang Y, Chen L, Yam Y, Achenbach S, Al-Mallah M, Berman DS et al. A clinical model to identify patients with high-risk coronary artery disease. JACC Cardiovascular imaging. 2015; 8(4):427-434

229. Yao ZM, Li W, Qu WY, Zhou C, He Q, Ji FS. Comparison of (99)mTc-methoxyisobutylisonitrile myocardial single-photon emission computed tomography and electron beam computed tomography for detecting coronary artery disease in patients with no myocardial infarction. Chinese Medical Journal. 2004; 117(5):700-705

230. Zaman MJ, Junghans C, Sekhri N, Chen R, Feder GS, Timmis AD et al. Presentation of stable angina pectoris among women and South Asian people. CMAJ Canadian Medical Association Journal. 2008; 179(7):659-667

10 Acronyms and abbreviations

Acronym or abbreviation	Description
2VD	Two-vessel disease
3VD	Three-vessel disease
ACER	Average cost-effectiveness ratio
ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
AUC	Area under the curve
BB	Beta-blocker
BPM	Beats per minute
CA	Coronary angiography
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
CCB	Calcium-channel blocker
CHD	Coronary heart disease
CI	Confidence interval
CMR	Cardiac magnetic resonance
cTn	Cardiac troponin
CV	Coefficient of variation
DSCT	Dual source computed tomography
DTA	Diagnostic test accuracy
DTM	Decision tree model
EBCT	Electron Beam Computed Tomography
ECG	Electrocardiogram
ECHO	Echocardiogram
ED	Emergency department
ExECG	Exercise ECG
FFR	Functional flow reserve
FN	False negative
FP	False positive
GC	Guideline committee
GRACE score	Global registry of acute coronary events score
HR	Heart rate
Hs-cTn	High-sensitivity cardiac troponin
ICA	Invasive coronary angiography
ICER	Incremental cost-effectiveness ratio
IQR	Interquartile range
LAD	Left anterior descending
LBBB	Left bundle branch block
LMS	Left main stem
LoD	Limit of detection
LR	Likelihood ratio

Acronym or abbreviation	Description
MACE	Major adverse cardiac events
MDCT	Multiple detector computed tomography
MI	Myocardial infarction
MIBI	Technetium-99m sestamibi
MP	Myocardial perfusion
MPI	Myocardial perfusion imaging
MPS	Myocardial perfusion scintigraphy
MRI	Magnetic resonance imaging
MVD	Multivessel disease
NLR	Negative likelihood ratio
NPV	Negative predictive value
NSTEMI	Non-ST segment elevation myocardial infarction
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
PLR	Positive likelihood ratio
PPV	Positive predictive value
PSA	Probabilistic sensitivity analysis
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
SA	Sensitivity analysis
SBP	Systolic blood pressure
SOC	Standard of care
SPECT	Single photon emission computed tomography
STEMI	ST segment elevation myocardial infarction
SVD	Single-vessel disease
TIMI score	Thrombolysis in myocardial infarction score
TN	True negative
TP	True positive
UA	Unstable angina
WMA	Wall motion abnormalities

11 Glossary

The NICE Glossary can be found at www.nice.org.uk/glossary.

11.1 Guideline-specific terms

Phrase	Definition
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. This update uses definitions from the American Heart Association Guidelines and the European Society of Cardiology Guidelines as reference standards.
Acute myocardial infarction	A life-threatening condition that occurs when blood flow to the heart is abruptly cut off, usually as a result of blockage of one or more coronary arteries, causing tissue damage. The Universal definition of the Joint ESC/ACCF/AHA/WHF Task Force is used in this guideline[n]. Under these conditions any one of the following criteria meets the diagnosis for MI: • Detection of rise and/or fall of cardiac biomarkers values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile of the upper reference limit (URL) with at least one of the following: • Symptoms of ischaemia • New or presumed new significant ST-segment-T wave(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. •Identification of an intracoronary thrombus by angiography or autopsy.
Angina Pectoris	A heart condition that occurs when the blood supply to the muscles of the heart is restricted, usually due to coronary artery disease.
Atherosclerosis	A build-up of plaque on the inside of blood vessels.
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.

[n] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD et al. Third universal definition of myocardial infarction. Circulation. 2012; 126(16):2020-2035

Phrase	Definition
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.
Computed tomography (CT)	Uses computer-processed combinations of X-ray images taken from different angles to produce cross-sectional images (virtual 'slices') of specific areas of a scanned object.
Computed tomography (CT) perfusion	Evaluation of blood flow to the myocardium using CT imaging.
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 (narrowings).
Coronary artery	An artery which supplies the myocardium (heart muscle).
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.
Cardiac Magnetic Resonance (CMR)	See MRI
Electrocardiogram (ECG)	An ECG records the rhythm and electrical activity of the heart. A number of electrodes (small sticky patches) are placed on limbs and chest and are connected to a machine that records the electrical signals of each heartbeat.
Echocardiography (ECHO)	A non-invasive test that uses ultrasonography to image the heart.
Emergency	Immediate request leading to an immediate response from the ambulance service with a 'blue light' ambulance.
Exercise ECG (sometimes known as an exercise test or stress ECG)	A non-invasive investigation which measures the electrical activity from the heart during exercise, usually used to look for signs of myocardial ischaemia.
Functional flow reserve (FFR)	A test that measures differences in pressure behind and after stenosis of a blood vessel.
GRACE score	A tool to help clinicians assess the future risk of death or myocardial infarction (MI), as a guide to treatment options, in a patient with an acute coronary syndrome (ACS).
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

Phrase	Definition
	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.
Ischaemia	Insufficient blood supply
Magnetic resonance imaging (MRI)	A type of scan that uses strong magnetic fields and radio waves to produce detailed images of the inside of the body
Multiple detector computed tomography (MDCT)	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 imaging	Evaluation of perfusion (blood flow) to the myocardium.
Myocardial perfusion scintigraphy (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.
Positron Emission Tomography (PET)	This is a functional imaging technique that is used to observe metabolic processes in the body. The system detects pairs of gamma rays emitted indirectly by a positron-emitting radionuclide (tracer), which is introduced into the body on a biologically active molecule.
QUADAS-2 checklist	A tool used designed to assess the quality of primary diagnostic accuracy studies. It consists of four key domains covering patient selection, index test, reference standard, and flow of patients through the study and timing of the index test(s) and reference standard.
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

Phrase	Definition
	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.
Single-photon emission computed tomography (SPECT)	A type of nuclear imaging test, which uses a radioactive substance and a special camera to create 3-D pictures. This information is typically presented as cross-sectional slices through the patient. They can be used to provide information about localised function in internal organs, such as functional cardiac imaging.
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.
Stenosis	The abnormal narrowing of a passage in the body.
Stress echocardiography	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. Not to be abbreviated to or confused with ECG.
Stress electrocardiography (ECG)	See exercise electrocardiography (ECG) above.

Phrase	Definition
Stress perfusion cardiac 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.
TIMI risk score	A tool used to categorise a patient's risk of death and ischaemic events.
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. Both high sensitivity and standard sensitivity troponins are considered in this update. The definition of a Hs-cTn assay uses 2 criteria: The total imprecision, coefficient of variation (CV), of the assay should be ≤ 10% at the 99th percentile value of a healthy reference population. The limit of detection (LoD) of the assay should be such as to allow measurable concentrations to be attainable for at least 50% (ideally > 95%) of healthy individuals
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.

11.2 General terms

Term	Definition
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in an RCT. The allocation process should be impervious to any influence by the

Term	Definition
	individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	How well the results of a study or NICE evidence review can answer a clinical question or be applied to the population being considered.
Arm (of a clinical study)	Subsection of individuals within a study who receive one particular intervention, for example placebo arm.
Association	Statistical relationship between 2 or more events, characteristics or other variables. The relationship may or may not be causal.
Base case analysis	In an economic evaluation, this is the main analysis based on the most plausible estimate of each input. In contrast, see Sensitivity analysis.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Bayesian analysis	A method of statistics, where a statistic is estimated by combining established information or belief (the 'prior') with new evidence (the 'likelihood') to give a revised estimate (the 'posterior').
Before-and-after study	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs.
Bias	Influences on a study that can make the results look better or worse than they really are. (Bias can even make it look as if a treatment works when it does not.) Bias can occur by chance, deliberately or as a result of systematic errors in the design and execution of a study. It can also occur at different stages in the research process, for example, during the collection, analysis, interpretation, publication or review of research data. For examples see selection bias, performance bias, information bias, confounding factor, and publication bias.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias. A single-blinded study is one in which patients do not know which study group they are in (for example whether they are taking the experimental drug or a placebo). A double-blinded study is one in which neither patients nor the researchers and doctors know which study group the patients are in. A triple blind study is one in which neither the patients, clinicians or the people carrying out the statistical analysis know which treatment patients received.
Carer (caregiver)	Someone who looks after family, partners or friends in need of help because they are ill, frail or have a disability.
Case–control study	A study to find out the cause(s) of a disease or condition. This is done by comparing a group of patients who have the disease or condition (cases) with a group of people who do not have it (controls) but who are otherwise as similar as possible (in characteristics thought to be unrelated to the causes of the disease or condition). This means the researcher can look for aspects of their lives that differ to see if they may cause the condition. For example, a group of people with lung cancer might be compared with a group of people the same age that do not have lung cancer. The researcher could compare how long both groups had been exposed to tobacco smoke. Such studies are retrospective because they look back in time from the outcome to the possible causes of a disease or condition.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison

Term	Definition
	(control) group of patients.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	How well a specific test or treatment works when used in the 'real world' (for example, when used by a doctor with a patient at home), rather than in a carefully controlled clinical trial. Trials that assess clinical effectiveness are sometimes called management trials. Clinical effectiveness is not the same as efficacy.
Clinician	A healthcare professional who provides patient care. For example, a doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A study with 2 or more groups of people – cohorts – with similar characteristics. One group receives a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. The study follows their progress over time and records what happens. See also observational study.
Comorbidity	A disease or condition that someone has in addition to the health problem being studied or treated.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
Confidence interval (CI)	There is always some uncertainty in research. This is because a small group of patients is studied to predict the effects of a treatment on the wider population. The confidence interval is a way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that "based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110". In such a case the 95% CI would be 110 to 150. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment – often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Confounding factor	Something that influences a study and can result in misleading findings if it is not understood or appropriately dealt with. For example, a study of heart disease may look at a group of people that exercises regularly and a group that does not exercise. If the ages of the people in the 2 groups are different, then any difference in heart disease rates between the 2 groups could be because of age rather than exercise. Therefore age is a confounding factor.
Consensus methods	Techniques used to reach agreement on a particular issue. Consensus methods may be used to develop NICE guidance if there is not enough good quality research evidence to give a clear answer to a question. Formal

Term	Definition
	consensus methods include Delphi and nominal group techniques.
Control group	A group of people in a study who do not receive the treatment or test being studied. Instead, they may receive the standard treatment (sometimes called 'usual care') or a dummy treatment (placebo). The results for the control group are compared with those for a group receiving the treatment being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the treatment group, to make it as easy as possible to detect any effects due to the treatment.
Cost-benefit analysis (CBA)	Cost-benefit analysis is one of the tools used to carry out an economic evaluation. The costs and benefits are measured using the same monetary units (for example, pounds sterling) to see whether the benefits exceed the costs.
Cost-consequences analysis (CCA)	Cost-consequences analysis is one of the tools used to carry out an economic evaluation. This compares the costs (such as treatment and hospital care) and the consequences (such as health outcomes) of a test or treatment with a suitable alternative. Unlike cost-benefit analysis or cost-effectiveness analysis, it does not attempt to summarise outcomes in a single measure (like the quality-adjusted life year) or in financial terms. Instead, outcomes are shown in their natural units (some of which may be monetary) and it is left to decision-makers to determine whether, overall, the treatment is worth carrying out.
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 (CEA)	Cost-effectiveness analysis is one of the tools used to carry out an economic evaluation. The benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life years gained (that is, the number of years by which life is extended as a result of the intervention).
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the 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 (CUA)	Cost-utility analysis is one of the tools used to carry out an economic evaluation. The benefits are assessed in terms of both quality and duration of life, and expressed as quality-adjusted life years (QALYs). See also utility.
Credible interval (CrI)	The Bayesian equivalent of a confidence interval.
Decision analysis	An explicit quantitative approach to decision-making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Deterministic analysis	In economic evaluation, this is an analysis that uses a point estimate for each input. In contrast, see Probabilistic analysis
Diagnostic odds ratio	The diagnostic odds ratio is a measure of the effectiveness of a diagnostic test. It is defined as the ratio of the odds of the test being positive if the subject has a disease relative to the odds of the test being positive if the subject does not have the disease.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs

Term	Definition
	and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Disutility	The loss of quality of life associated with having a disease or condition. See Utility
Dominance	A health economics term. When comparing tests or treatments, an option that is both less effective and costs more is said to be 'dominated' by the alternative.
Drop-out	A participant who withdraws from a trial before the end.
Economic evaluation	An economic evaluation is used to assess the cost-effectiveness of healthcare interventions (that is, to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing). The aim of an economic evaluation is to maximise the level of benefits – health effects – relative to the resources available. It should be used to inform and support the decision-making process; it is not supposed to replace the judgement of healthcare professionals. There are several types of economic evaluation: cost-benefit analysis, cost-consequences analysis, cost-effectiveness analysis, cost-minimisation analysis and cost-utility analysis. They use similar methods to define and evaluate costs, but differ in the way they estimate the benefits of a particular drug, programme or intervention.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	A measure that shows the magnitude of the outcome in one group compared with that in a control group. For example, if the absolute risk reduction is shown to be 5% and it is the outcome of interest, the effect size is 5%. The effect size is usually tested, using statistics, to find out how likely it is that the effect is a result of the treatment and has not just happened by chance (that is, to see if it is statistically significant).
Effectiveness	How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care.
Efficacy	How beneficial a test, treatment or public health intervention is under ideal conditions (for example, in a laboratory), compared with doing nothing or opting for another type of care.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example, infection, diet) and interventions.
EQ-5D (EuroQol 5 dimensions)	A standardised instrument used to measure health-related quality of life. It provides a single index value for health status.
Equivocal	Where a diagnostic test result is indeterminate because it can be interpreted in one of 2 or more ways.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals or patients).
Evidence-based questions	Questions which are based on a conscientious, explicit and judicious use of current best evidence.
Evidence statements	A summary of the evidence distilled from a review of the available clinical literature.
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical	Criteria that define who is not eligible to participate in a clinical study.

Term	Definition
study)	
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore cost-effective and should be preferred, other things remaining equal.
Extrapolation	An assumption that the results of studies of a specific population will also hold true for another population with similar characteristics.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Generalisability	The extent to which the results of a study hold true for groups that did not participate in the research. See also external validity.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available to test for or treat a disease.
GRADE, GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.
Health economics	Study or analysis of the cost of using and distributing healthcare resources.
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.
Health-related quality of life (HRQoL)	A measure of the effects of an illness to see how it affects someone's day-to-day life.
Heterogeneity or Lack of homogeneity	The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The extra cost linked to using one test or treatment rather than another. Or the additional cost of doing a test or providing a treatment more frequently.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 × QALYs gained) − Incremental cost.

Term	Definition
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Intention-to-treat analysis (ITT)	An assessment of the people taking part in a clinical trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully complied with the treatment or switched to an alternative treatment. Intention-to-treat analyses are often used to assess clinical effectiveness because they mirror actual practice: that is, not everyone complies with treatment and the treatment people receive may be changed according to how they respond to it.
Intervention	In medical terms this could be a drug treatment, surgical procedure, diagnostic or psychological therapy. Examples of public health interventions could include action to help someone to be physically active or to eat a more healthy diet.
Intraoperative	The period of time during a surgical procedure.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.
Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by (1 minus specificity).
Long-term care	Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.
Logistic regression or Logit model	In statistics, logistic regression is a type of analysis used for predicting the outcome of a binary dependent variable based on one or more predictor variables. It can be used to estimate the log of the odds (known as the 'logit').
Loss to follow-up	A patient, or the proportion of patients, actively participating in a clinical trial at the beginning, but whom the researchers were unable to trace or contact by the point of follow-up in the trial
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meta-analysis	A method often used in systematic reviews. Results from several studies of the same test or treatment are combined to estimate the overall effect of the treatment.
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.
Multivariate model	A statistical model for analysis of the relationship between 2 or more predictor (independent) variables and the outcome (dependent) variable.
Negative predictive value (NPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a negative test result who do not have the disease, and can be interpreted as the probability that a negative test result is correct. It is calculated as follows: TN/(TN+FN)

Term	Definition
Net monetary benefit (NMB)	The value in monetary terms of an intervention net of its cost. The NMB can be calculated for a given cost-effectiveness threshold. If the threshold is £20,000 per QALY gained then the NMB for an intervention is calculated as: (£20,000 × mean QALYs) − mean cost. The most preferable option (that is, the most clinically effective option to have an ICER below the threshold selected) will be the treatment with the highest NMB.
Number needed to treat (NNT)	The average number of patients who need to be treated to get a positive outcome. For example, if the NNT is 4, then 4 patients would have to be treated to ensure 1 of them gets better. The closer the NNT is to 1, the better the treatment. For example, if you give a stroke prevention drug to 20 people before 1 stroke is prevented, the number needed to treat is 20. See also number needed to harm, absolute risk reduction.
Observational study	Individuals or groups are observed or certain factors are measured. No attempt is made to affect the outcome. For example, an observational study of a disease or treatment would allow 'nature' or usual medical care to take its course. Changes or differences in one characteristic (for example, whether or not people received a specific treatment or intervention) are studied without intervening. There is a greater risk of selection bias than in experimental studies.
Odds ratio	Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in one group with the probability of the same thing in another. An odds ratio of 1 between 2 groups would show that the probability of the event (for example a person developing a disease, or a treatment working) is the same for both. An odds ratio greater than 1 means the event is more likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group. Sometimes probability can be compared across more than 2 groups – in this case, one of the groups is chosen as the 'reference category', and the odds ratio is calculated for each group compared with the reference category. For example, to compare the risk of dying from lung cancer for non-smokers, occasional smokers and regular smokers, non-smokers could be used as the reference category. Odds ratios would be worked out for occasional smokers compared with non-smokers and for regular smokers compared with non-smokers. See also confidence interval, risk ratio.
Opportunity cost	The loss of other healthcare programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Outcomes from interventions to improve the public's health could include changes in knowledge and behaviour related to health, societal changes (for example, a reduction in crime rates) and a change in people's health and wellbeing or health status. In clinical terms, outcomes could include the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, functional ability, symptoms or situation. Researchers should decide what outcomes to measure before a study begins.
P value	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that one seems

Term	Definition
	more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Perioperative	The period from admission through surgery until discharge, encompassing the preoperative and postoperative periods.
Placebo	A fake (or dummy) treatment given to participants in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to participants in the experimental group). The aim is to determine what effect the experimental treatment has had – over and above any placebo effect caused because someone has received (or thinks they have received) care or attention.
Polypharmacy	The use or prescription of multiple medications.
Posterior distribution	In Bayesian statistics this is the probability distribution for a statistic based after combining established information or belief (the prior) with new evidence (the likelihood).
Positive predictive value (PPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a positive test result who have the disease, and can be interpreted as the probability that a positive test result is correct. It is calculated as follows: TP/(TP+FP)
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Post-test probability	In diagnostic tests: The proportion of patients with that particular test result who have the target disorder (post-test odds/[1 plus post-test odds]).
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Preoperative	The period before surgery commences.
Pre-test probability	In diagnostic tests: The proportion of people with the target disorder in the population at risk at a specific time point or time interval. Prevalence may depend on how a disorder is diagnosed.
Prevalence	See Pre-test probability.
Prior distribution	In Bayesian statistics this is the probability distribution for a statistic based on previous evidence or belief.
Primary care	Healthcare delivered outside hospitals. It includes a range of services provided by GPs, nurses, health visitors, midwives and other healthcare professionals and allied health professionals such as dentists, pharmacists and opticians.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Probabilistic analysis	In economic evaluation, this is an analysis that uses a probability distribution for each input. In contrast, see Deterministic analysis.
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

Term	Definition
	generation such as Monte Carlo methods.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A research study in which the health or other characteristic of participants is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
Publication bias	Publication bias occurs when researchers publish the results of studies showing that a treatment works well and don't publish those showing it did not have any effect. If this happens, analysis of the published results will not give an accurate idea of how well the treatment works. This type of bias can be assessed by a funnel plot.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYS are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a scale of 0 to 1). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance.
Randomisation	Assigning participants in a research study to different groups without taking any similarities or differences between them into account. For example, it could involve using a random numbers table or a computer-generated random sequence. It means that each individual (or each group in the case of cluster randomisation) has the same chance of receiving each intervention.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug or treatment. One group (the experimental group) receives the treatment being tested, the other (the comparison or control group) receives an alternative treatment, a dummy treatment (placebo) or no treatment at all. The groups are followed up to see how effective the experimental treatment was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
RCT	See 'Randomised controlled trial'.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1 minus specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Reporting bias	See 'Publication bias'.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Review question	In guideline development, this term refers to the questions about

Term	Definition
	treatment and care that are formulated to guide the development of evidence-based recommendations.
Risk ratio (RR)	The ratio of the risk of disease or death among those exposed to certain conditions compared with the risk for those who are not exposed to the same conditions (for example, the risk of people who smoke getting lung cancer compared with the risk for people who do not smoke). If both groups face the same level of risk, the risk ratio is 1. If the first group had a risk ratio of 2, subjects in that group would be twice as likely to have the event happen. A risk ratio of less than 1 means the outcome is less likely in the first group. The risk ratio is sometimes referred to as relative risk.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	Selection bias occurs if: a) The characteristics of the people selected for a study differ from the wider population from which they have been drawn, or b) There are differences between groups of participants in a study in terms of how likely they are to get better.
Sensitivity	How well a test detects the thing it is testing for. If a diagnostic test for a disease has high sensitivity, it is likely to pick up all cases of the disease in people who have it (that is, give a 'true positive' result). But if a test is too sensitive it will sometimes also give a positive result in people who don't have the disease (that is, give a 'false positive'). For example, if a test were developed to detect if a woman is 6 months pregnant, a very sensitive test would detect everyone who was 6 months pregnant, but would probably also include those who are 5 and 7 months pregnant. If the same test were more specific (sometimes referred to as having higher specificity), it would detect only those who are 6 months pregnant, and someone who was 5 months pregnant would get a negative result (a 'true negative'). But it would probably also miss some people who were 6 months pregnant (that is, give a 'false negative'). Breast screening is a 'real-life' example. The number of women who are recalled for a second breast screening test is relatively high because the test is very sensitive. If it were made more specific, people who don't have the disease would be less likely to be called back for a second test but more women who have the disease would be missed.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): 2 or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo

Term	Definition
	simulation).
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$).
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	The proportion of true negatives that are correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases correctly diagnosed as non-cases. See related term 'Sensitivity'. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Stakeholder	An organisation with an interest in a topic that NICE is developing a guideline or piece of public health guidance on. Organisations that register as stakeholders can comment on the draft scope and the draft guidance. Stakeholders may be: • manufacturers of drugs or equipment • national patient and carer organisations • NHS organisations • organisations representing healthcare professionals.
State transition model	See Markov model
Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. It may include a meta-analysis.
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Transition probability	In a state transition model (Markov model), this is the probability of moving from one health state to another over a specific period of time.
Treatment allocation	Assigning a participant to a particular arm of a trial.
Univariate	Analysis which separately explores each variable in a data set.
Utility	In health economics, a 'utility' is the measure of the preference or value that an individual or society places upon a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). The most widely used measure of benefit in cost–utility analysis is the quality-adjusted life year, but other measures include disability-adjusted life years (DALYs) and healthy year equivalents (HYEs).
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.