Chest pain of recent onset:

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

Section 1

Full Guideline - Consultation Version

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National Clinical Guidelines Centre for Acute and Chronic Conditions

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

1 Citation

2 To be added

3

Table of Contents

Section 2 Stable Chest Pain

Is in a separate document – the Table of Contents for that Section is duplicated below for information.

The appendices are in separate documents as follows:

Preface

To be added to final document

Key Priorities for Implementation

Presentation with Acute Chest Pain

1 In people with suspected acute coronary syndrome (ACS), take a detailed clinical history if a diagnosis of ST-segment elevation myocardial infarction (MI) cannot be confirmed from the resting-12 lead ECG (that is, regional ST-segment elevation, presumed new left bundle branch block [LBBB]). Document:

- the characteristics of the pain
- other associated symptoms
- any history of coronary disease or other cardiovascular disease
- any cardiovascular risk factors, and
- details of previous investigations or treatments for similar symptoms of chest pain. (Rec. 2.1.5.2)

2. Take a resting 12-lead ECG as soon as possible. If the person is referred, ideally transmit the results to hospital before they arrive. Recording and transmission of the ECG should not delay transfer to hospital. (Rec 2.1.4.1)

3. Do not routinely administer oxygen, but monitor arterial oxygen saturation using pulse oximetry, as soon as possible, ideally before hospital admission. (Rec 2.2.1.4)

4. Be aware that there are no major differences in ACS symptoms among different ethnic groups. (Rec 2.1.3.1)

5 Be aware that the universal definition of a MI[1] is detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit, together with evidence of myocardial ischaemia with at least one of the following:

[1] Thygesen K, Alpert JS and White HD, 2007

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

The clinical classification of MI includes:

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

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

Types 3, 4 and 5 refer to the diagnosis of MI in sudden cardiac death, after percutaneous coronary intervention (PCI) and after coronary artery bypass graft (CABG) respectively.

(Rec 2.3.2.1)

Presentation with Stable Chest Pain

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

- clinical assessment alone
- clinical assessment combined with either obstructive coronary artery disease (CAD) found on anatomical testing, or myocardial ischaemia, found on functional testing, or
- all three. (Rec 3.1.1.1)

7 Before considering diagnostic investigations, estimate the likelihood of CAD (see table 1 on page 26) in people without confirmed CAD. Base the estimate on the initial clinical assessment and the ECG. (Rec 3.1.6.1)

8. After clinical assessment and a resting 12-lead ECG, offer computed tomography (CT) calcium scoring[2]. (Rec. 3.2.2.12)

9. Following calcium scoring, if the score is:

- zero, investigate other causes of chest pain
- 1–400, offer 64-slice (or above) CT coronary angiography
- greater than 400, offer invasive coronary angiography. If this is not clinically appropriate or acceptable to the person and revascularisation is not being considered, offer non-invasive functional imaging. (Rec 3.2.2.13)

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

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

[2] This recommendation is for people with a low pre-test likelihood that chest pain is caused by angina (less than 30%) and an uncertain diagnosis.

All Recommendations

1 Recommendations for Information to assist patients in decision making and support them through uncertainty.

Hyperlink to Information Chapter

1.1.1.1 Discuss the person's (and where appropriate their family's or carer/advocate's) thoughts and concerns about their condition and care. Explore any misinformation.

1.1.1.2 Offer a clear explanation of the possible causes of the person's symptoms, including the uncertainties.

1.1.1.3 Clearly explain the options and consequences at every stage of the investigative process, making joint decisions with the person and taking account of the person's preferences. The healthcare professional should:

- encourage the person to ask questions
- provide repeated opportunities for discussion
- explain test results and the need for any further investigations.

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

- their purpose and benefits
- duration
- level of discomfort and invasiveness
- risk of adverse events.

1.1.1.5 Consider and address any factors such as physical or learning difficulties, sight or hearing problems and difficulties with speaking English, which may affect the person's understanding of the information offered.

1.1.1.6 Offer information and education after diagnosis as recommended in the relevant disease management guidelines.

1.1.1.7 Recognise and address any anxiety the person may have when the cause of their chest pain is unknown.

1.1.1.8 When a person's chest pain is of non-cardiac origin, explain this clearly and refer the person for further investigation if appropriate.

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

2 Recommendations for People Presenting with Acute Chest Pain

2.1 Assessment

2.1.1 Initial assessment and referral to hospital

Hyperlink to evidence statements on initial assessment

2.1.1.1 Check immediately whether people have current chest pain. If they are pain free, check when their last episode of pain was.

2.1.1.2 Determine if chest pain or discomfort is of cardiac origin. Consider:

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

2.1.1.3 Initially assess people for any of the following symptoms and signs, which may indicate an acute coronary syndrome (ACS):

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

2.1.1.4 Do not use the person's response to glyceryl trinitrate (GTN) to make a diagnosis.

2.1.1.5 Refer people to hospital as an emergency ('blue-light' ambulance) if an ACS is suspected (see recommendation 2.1.1.3) and:

- they currently have chest pain or discomfort, 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.

2.1.1.6 Refer people urgently for same day assessment in hospital if an ACS is suspected (see recommendation 2.1.1.3) and:

- they had chest pain or discomfort in the last 12 hours, but are now pain free with a normal ECG, and there are no reasons for emergency referral

or

- the last episode of pain was 12–72 hours ago, and there are no reasons for emergency referral.

Use clinical judgement to decide on the urgency of referral.

2.1.1.7 Refer people for assessment in hospital if an ACS is suspected (see recommendation 2.1.1.3) 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 urgently for same day assessment.

2.1.1.8 If ACS is not suspected after initial assessment, consider other causes of chest pain. If chest pain may still be of cardiac origin refer to the recommendations on stable chest pain in this guideline (see Chapter 5).

2.1.1.9 If recent ACS is suspected in people whose last episode of chest pain or discomfort 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.

2.1.1.10 Refer people to hospital as an emergency ('blue-light' ambulance) if they have recent (confirmed or suspected) ACS and develop further chest pain or discomfort.

2.1.1.11 Follow the ACS guideline[3] or local protocols for ST-segment elevation MI for people who are pain free and have a confirmed diagnosis of ACS.

2.1.2 Gender differences in symptoms of acute chest pain

Hyperlink to evidence statements on gender differences

[3] The NICE clinical guideline 'Acute coronary syndromes: the management of unstable angina and non ST elevation myocardial infarction' is in development. The consultation period is 3 July–28 August 2009

2.1.2.1 Be aware that not all people with an ACS present with central chest pain as the predominant feature. The presenting symptom may be back, jaw or throat pain, breathlessness, nausea and/or vomiting, indigestion and palpitations. Such presentations are slightly more common in women.

2.1.3 Ethnic differences in symptoms of acute chest pain

Hyperlink to evidence statements on ethnicity differences

2.1.3.1 Be aware that there are no major differences in ACS symptoms among different ethnic groups.

2.1.4 Resting 12 lead ECG

Hyperlink to evidence statements on ECG

2.1.4.1 Take a resting 12-lead ECG as soon as possible. If the person is referred, ideally transmit the results to hospital before they arrive. Recording and transmission of the ECG should not delay transfer to hospital.

2.1.4.2 Follow local protocols for people with a resting 12-lead ECG showing regional ST-segment elevation or presumed new LBBB consistent with an acute ST-segment elevation MI.

2.1.4.3 Follow the ACS guideline[4] for people with a resting 12-lead ECG showing regional ST-segment depression or deep T wave inversion suggestive of a non ST-segment elevation MI or unstable angina, until a firm diagnosis is made.

2.1.4.4 Even in the absence of ST-segment changes, have an increased suspicion of ACS if there are other changes on the resting 12-lead ECG, specifically Q waves and T wave changes.

[4] The NICE clinical guideline 'Acute coronary syndromes: the management of unstable angina and non ST elevation myocardial infarction' is in development. The consultation period is 3 July–28 August 2009

2.1.4.5 Do not exclude an ACS when the person has a normal resting 12-lead ECG.

2.1.4.6 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.

Note that the results may not be conclusive.

2.1.4.7 Consider automated interpretation of the resting 12-lead ECG as an adjunctive tool, but do not use as the sole method of interpretation.

2.1.4.8 If clinical assessment (as described in recommendation 1.1.5.2), including a resting 12-lead ECG makes a diagnosis of ACS less likely, consider other life-threatening conditions such as pulmonary embolism, aortic dissection or pneumonia.

2.1.5 Early assessment in hospital

2.1.5.1 Carry out a physical examination of all people with suspected ACS to determine:

- haemodynamic status
- signs of complications
- signs of non-coronary causes of acute chest pain, such as aortic dissection.

2.1.5.2 In people with suspected ACS, take a detailed clinical history if a diagnosis of ST-segment elevation MI cannot be confirmed from the resting 12-lead ECG (that is, regional ST-segment elevation, presumed new LBBB). Document:

- the characteristics of the pain
- other associated symptoms
- any history of coronary disease or other cardiovascular disease

- any cardiovascular risk factors, and
- details of previous investigations or treatments for similar symptoms of chest pain.

2.2 Early management

Hyperlink to evidence statements on pain management

Hyperlink to evidence statements on antiplatelet therapy

Hyperlink to evidence statements on oxygen therapy

2.2.1.1 As soon as possible:

- manage pain
- give aspirin
- check oxygen saturation
- take a resting 12 lead ECG.

These should be done in the order appropriate to the circumstances, but do not delay transfer to hospital.

A blood sample for troponin measurement should be taken after arrival in hospital. Refer to recommendations 2.2.1.2–2.2.1.8 for more detail.

2.2.1.2 Offer prompt and effective pain relief. This may be achieved with GTN, but opiates such as morphine may be required, particularly if an acute MI is suspected.

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

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

2.2.1.4 Do not routinely administer oxygen, but monitor oxygen saturation using pulse oximetry as soon as possible, ideally before hospital admission.

2.2.1.5 Offer supplemental oxygen to people with oxygen saturation (SaO2) of less than 94% who are not at risk of hypercapnic respiratory failure. Aim for SaO2 of 94–98%.

2.2.1.6 In people with chronic obstructive pulmonary disease (COPD) who are at risk of hypercapnic respiratory failure, offer supplemental oxygen as necessary to achieve a target SaO2 of 88–92% until blood gas analysis is available.

2.2.1.7 Offer a single loading dose of aspirin 300 mg to people with suspected ACS as soon as possible, until further assessment can be carried out.

2.2.1.8 Manage other therapeutic interventions using appropriate guidance (ACS guideline[5] or local protocols for ST-segment elevation MI), if ACS is suspected.

2.3 Investigations and Diagnosis

Hyperlink to evidence statements on biomarkers

2.3.1 Use of biochemical markers

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

2.3.1.2 Take a second blood sample for troponin I or T measurement 10–12 hours after the onset of symptoms even if the pain has resolved.

2.3.1.3 Do not use biochemical markers such as naturetic peptides and high sensitivity C-reactive protein (hsCRP) to diagnose ACS.

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

2.3.1.5 Do not interpret troponin measurements in isolation. Take into account the clinical presentation and ECG findings.

2.3.2 Making a diagnosis

2.3.2.1 Be aware that the universal definition of an MI[6] is detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper

[5] The NICE clinical guideline 'Acute coronary syndromes: the management of unstable angina and non ST elevation myocardial infarction' is in development. The consultation period is 3 July–28 August 2009.
[6] Thygesen K, Alpert JS and White HD, 2007.

reference limit, together with evidence of myocardial ischaemia with at least one of the following:

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

The clinical classification of MI includes:

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

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

Types 3, 4 and 5 refer to the diagnosis of MI in sudden cardiac death, after percutaneous coronary intervention (PCI) and after coronary artery bypass graft (CABG) respectively.

2.3.2.2 When a raised troponin level is detected, immediately reassess to exclude other reasons for raised troponin (for example, myocarditis or pulmonary embolism) and confirm the diagnosis of ACS.

2.3.2.3 When a raised troponin level is detected in people with suspected ACS, treat using appropriate guidance (ACS guideline[7] or local protocols for ST-segment elevation MI).

[7] The NICE clinical guideline 'Acute coronary syndromes: the management of unstable angina and non ST elevation myocardial infarction' is in development. The consultation period is 3 July–28 August 2009

2.3.2.4 People with chest pain who do not have raised troponin levels (determined from appropriately-timed samples) and no acute ECG changes are unlikely to have acute MI. Reassess these people at an early stage to determine whether their chest pain is likely to be of cardiac origin, and to plan future investigation and management.

After reassessment, if cardiac ischaemia is suspected, refer to the recommendations on stable chest pain in this guideline (see section 3).

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

2.3.2.6 Do not routinely offer chest computed tomography (CT) as part of the initial assessment in the emergency department. Only consider chest CT to rule out diagnoses other than ACS, such as pulmonary embolism or aortic dissection.

3 Recommendations for People Presenting with Stable Chest Pain

These recommendations are in Section 2 where they are hyperlinked.

1 Introduction Chapter

1.1 Epidemiology

Coronary heart disease (CHD) is the most common cause of death in the UK, around one in five and one in seven women die from the disease. From 2006 to 2007 there were over 220 000 attributed to CHD (prevalence 3.7%) (http://www.heartstats.org). CHD is also the most common cause of premature death in the UK; 19% of premature deaths in men and 10% of premature deaths in women were from CHD. Although the rate from CHD has been decreasing since the early 1970's, the death rate in the UK is still higher than many countries in Western Europe. Over 2 million people are living with CHD in the UK (http://www.heartstats.org/temp/Tabsp2.9spweb08.xls)

UK estimates of angina prevalence are 4.8% of men and 3.4% of women (Health Survey for England 2003). Joint Health Survey Unit, editor. London: The Stationery Office 2004). The Quality and Outcome Framework (QOF) monitoring system recorded over 174 000 incident cases of angina in England over 2 years, an incident rate of angina of 0.33% (0.17% per annum) (The Health and Social Care Information Centre (NHS). The Quality and Outcome Framework (QOF) for April 2004 to March 2005, England Numbers on QOFR disease registers, and unadjusted prevalence rates, by Strategic Health Authority with National Summary; 2006, http://www.icservices.nhs.uk/qofdocuments/QOF0405_SHAs_Prevalence.xls. A recent systematic review of observational data (6 studies) found that the total mortality rate in angina patients was 2.8% to 6.6% per annum, compared with 1.4% to 6.5% per annum mortality rate for cardiovascular disease, and 0.3% to 5.5% per annum for non fatal MI (Jones, M., Rait, G., Falconer, J. et al , 2006). The incidence of angina and ACS has been shown to vary according to risk factors such as age, gender and ethnicity.

Chest pain is a very common symptom, from 20% to 40% of the general population will experience chest pain in their lives. Every year approximately 1.5% of the population contact their general practitioner with chest pain. Approximately 5% of visits to the emergency department are due to chest pain, and up to 40% of emergency hospital admissions are due to chest pain.

1.2 Aim of the guideline

The guideline sets out to provide guidance on the assessment and investigation of recent chest pain or discomfort of suspected cardiac origin whether or not this presents as acute pain or intermittent stable pain. This includes guidance on determining whether or not myocardial ischaemia is the cause of the chest pain (through this guideline chest pain is taken to mean both chest pain and discomfort -see glossary definition) and how to manage patients during the period when patients are being assessed and investigated.

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

1.3 Approach

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

The adverse prognostic correlates of chest pain or discomfort caused by angina or an acute coronary syndrome emphasise the importance of prompt and accurate diagnosis because treatments are available to ameliorate symptoms and prolong life. Assessing the clinical value of a diagnostic test, however, poses special difficulties that do not arise when making treatment recommendations based on the results of clinical trials. For diagnostic tests, the conventional measures of efficacy are sensitivity and specificity set against a “gold-standard” which, for tests of stable angina, is angiographic CAD. This angiographic gold standard poses immediate problems:

- CAD is variably defined across different studies, not all using the conventional ≥50% luminal obstruction.

- Coronary artery disease, while being the usual cause of angina, is neither necessary nor sufficient for diagnostic purposes (see above).

- The requirement for invasive coronary angiography to define a test's efficacy ensures a level of work-up bias that over-estimates its diagnostic value for real-world patients presenting for the first time with undifferentiated chest pain or discomfort.

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

a) Acute coronary syndromes include myocardial infarction and unstable angina which are defined in the glossary (below). They usually present acutely with chest pain or discomfort that is unprovoked and unremitting. The mortality risk is highest early after presentation, particularly in patients with myocardial infarction, in whom emergency treatment saves lives. This guideline, therefore, recommends a high threshold for excluding this diagnosis. It also recommends a low threshold for starting treatment in suspected myocardial infarction, based on the initial clinical assessment and electrocardiogram, pending the results of biomarker tests of myocardial necrosis (troponins). If the tests are positive, in the patient presenting with chest pain myocardial infarction is confirmed but if the tests are negative a diagnosis of unstable angina can often be made based on unstable symptoms and or ECG changes. In either event the patient receives no further consideration within this guideline, and their further management is informed by other treatment guidelines. However, there remains a group of troponin negative patients in whom the cause of chest pain remains unclear and who remain within the diagnostic pathway requiring additional tests described in this guideline. .

b) Diagnostic probability in suspected angina Notwithstanding the difficulties in defining the clinical value of a diagnostic test, this guideline makes recommendations for diagnosis that are cost-effective in identifying a high proportion of the at-risk population with chest pain/discomfort. It considers not only a test's diagnostic accuracy, as influenced by disease prevalence, but also its potential incremental value, recognising that in many cases a test

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

To measure the “pre-test” probability of CAD in the patient with stable chest pain undergoing initial clinical assessment, this guideline has used the Diamond and Forrester algorithm based on age, gender and the typicality of symptoms assessed by the response to 3 questions: (1) Is the pain retrosternal? (2) Is the pain precipitated by stress? (3) Is the pain relieved by rest or nitroglycerin? Patients who answer yes to all 3 questions are determined to have typical chest pain. Patients who answer yes to 2 of the questions have atypical chest pain, and patients who answer yes to only 1 question have nonanginal chest pain. Application of the Diamond and Forrester algorithm provides a probability estimate of CAD based on the disease prevalence (%) in western populations. These probability estimates may be modified by other determinants of risk apart from age and gender and this is reflected in table 1 which provides a range for each estimate from “Low” to “High” risk depending on the presence of additional factors such as diabetes, smoking, dyslipidaemia and hypertension. These additional factors should be taken into account when ascribing probability estimates of CAD in individual cases.

Table 1. Prevalence (%) of CAD in Symptomatic Patients (Adapted from Diamond and Forrester)

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

Values are percent with CAD[8]
Hi = High risk = smoking, hypertensive diabetic
Lo = Low risk = none of these 3. If there are resting ECG ST-T changes or Q waves, the likelihood of CAD is higher in each cell of the table.

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

1.4 Diagnostic pathway

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

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

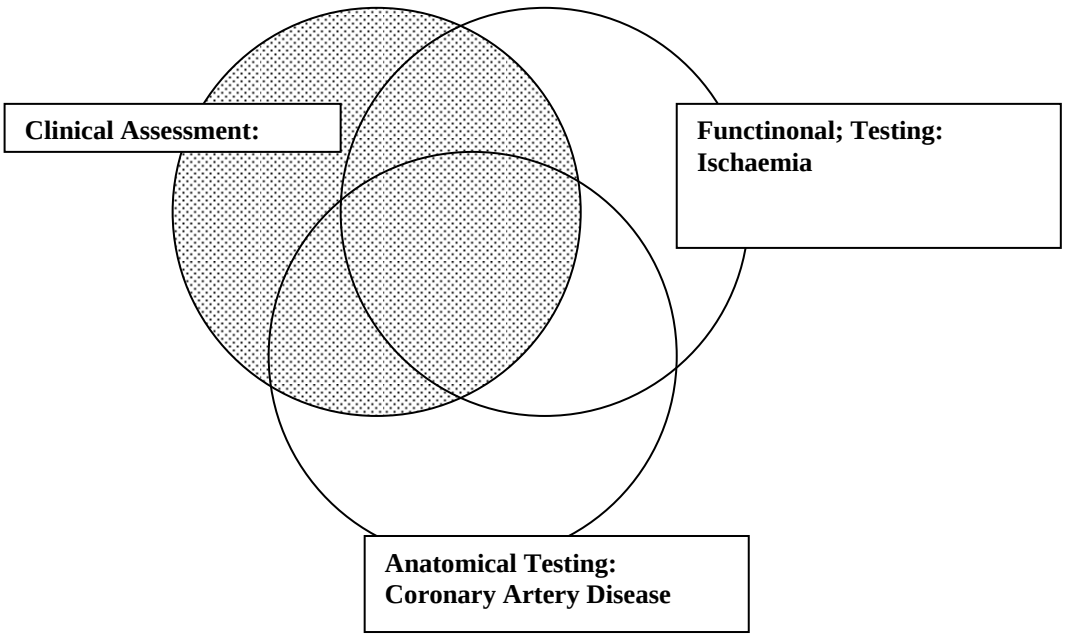
1. Clinical assessment. Application of the Diamond Forrester algorithm, as modified by consideration of additional risk factors, may permit a diagnosis of ANGINA if the probability estimate is sufficiently high (say ≥90%).

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

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

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

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



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

1.5 How the guideline is set out

This guideline is actually two separate guidelines, one for patients presenting with acute chest pain or discomfort suspected of being an acute coronary syndrome (which will be referred to as acute chest pain) and a second for patients presenting with stable chest pain suspected of being angina (which will be referred to as stable chest pain). They are different in their presentation, investigative pathways and diagnostic criteria. Therefore, there are two entirely separate, and largely unrelated, sections in the clinical chapters. One is the ‘Presentation with Acute Chest Pain’ the other is the ‘Presentation with Stable Chest Pain’. This guideline finishes, in both cases, once the likely diagnosis is determined, where the reader is referred to other relevant guidance.

The first two chapters describe the context and methods for both sections of the guideline. Chapter 3 gives guidance on information for patients with acute or stable chest pain. The evidence in this chapter was largely derived from unselected populations with acute chest pain. The view of the Guideline Development Group (GDG) was, however, that the recommendations on information are relevant to all patients presenting with chest pain.

The approach to writing a guideline, is first to pose the clinical questions that will be asked in the guideline, then to search, review and distil this evidence, from which the recommendations are derived. This is detailed in the Methods chapter. The GDG addresses each question in turn. Thus, the ‘Full Guideline’ is structured by the topics and

questions, so that the reader may follow the trail from the recommendations back to the evidence that underpins them as well as the discussion of the GDG. This means, however, that the recommendations are not in the logical order in which they should be carried out when a patient presents with chest pain. For example, all of the recommendations and evidence on the choice, timing and interpretation of biomarkers are together as that was how the evidence was reviewed.

The reader is directed to the care pathways, contained in Chapter 2 of this guideline and repeated in both the NICE guideline and the Quick Reference Guide, to view the recommendations as a patient pathway.

1.6 Scope

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

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

The guideline address assessment and investigation irrespective of setting including:

a) Assessment at initial presentation.

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

c) Choice and timing of investigations

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

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

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

1.7 Responsibility and support for guideline development

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

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

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

1.7.2 The Development Team

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

- **Guideline lead**
  who is a senior member of the Centre who has overall responsibility for the guideline

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

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

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

1.7.3 The Guideline Development Group (GDG)

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

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

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

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

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

The names of GDG members appear listed below.

Full GDG members

- Professor Adam Timmis (Chair)
  Professor of Clinical Cardiology, Barts and the London Queen Mary's School of Medicine and Dentistry, London
- Dr Jane Skinner (Clinical Advisor)
  Consultant Community Cardiologist, Royal Victoria Infirmary, Newcastle Upon Tyne
- Dr Philip Adams
  Cardiologist Consultant, Royal Victoria Infirmary, Newcastle Upon Tyne
- Dr John Ashcroft
  General Practitioner, Old Station Surgery, Ilkeston, Derbyshire
- Ms Liz Clark
  Patient Representative
- Dr Richard Coulden
  Consultant Cardiothoracic Radiologist, Glenfield Hospital, Leicester
- Professor Harry Hemingway
  Public Health Physician Epidemiologist, UCL Medical School, London
- Mrs Cathryn James
  Clinical Pathways Advisor/Emergency Care Practitioner, Yorkshire Ambulance ServiceAS HQ, Wakefield
- Ms Heather Jarman

Consultant Nurse in Emergency Care, St Georges Healthcare NHS Trust, London

- Dr Jason Kendall
  Consultant in Emergency Medicine, Frenchay Hospital, Bristol
- Mr Peter Lewis
  Chief Clinical Physiologist, Prince Charles Hospital, Merthyr, Tedfyl, Wales
- Dr Kiran Patel
  Consultant Cardiologist, Lyndon, West Bromwick, West Midlands
- Professor Liam Smeeth
  Professor of Clinical Epidemiology, London School of Hygiene and Tropical Medicine, London
- Mr John Taylor
  Patient representative

Members of the GDG from the Centre were:

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

Co-opted GDG Members

- Dr Paul Collinson

Consultant in Chemical Pathology and Head of Vascular Risk Management, St George's Hospital, London

- Dr Dorothy Frizelle
  Clinical Health Psychologist, Department of Clinical Psychology, University of Hull, Hull
- Professor Steve Goodacre
  Professor of Emergency Medicine, Medical Care Research Unit, Sheffield
- Dr Marcus Hardbord
  Consultant Physician & Gastroenterologist, Chelsea & Westminster Hospital, London
- Ms Helen Williams
  Consultant Pharmacist for Cardiovascular Disease, Southwark Health and Social Care

Observers

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

1.7.4 Guideline Development Group meetings

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

2 Methods Chapter

2.1 Introduction

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

stakeholders, the public and the NHS describes how organisations can become involved in the development of a guideline.

2.2 Developing key clinical questions (KCQs)

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

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

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

2.3 Literature search strategy

Systematic literature searches are undertaken to identify published evidence to answer the clinical questions identified by the methodology team and the GDG. The information scientist developed search strategies for each question, with guidance from the GDG, using relevant MeSH (medical subject headings) or indexing terms, and free text terms. Searches were conducted between May 2007 and November 2008. Update searches for all questions were carried out in April 2009 identify any recently published evidence. Full details of the sources and databases searched and the strategies are available in Appendix .

An initial scoping search for published guidelines, systematic reviews, economic evaluations and ongoing research was carried out on the following databases or websites: National Library for Health (NLH) Guidelines Finder, National Guidelines Clearinghouse, National Institute for Health and Clinical Excellence (NICE) Guidelines, Scottish Intercollegiate Guidelines Network (SIGN), Canadian Medical Association (CMA) Infobase (Canadian guidelines), National Health and Medical Research Council (NHMRC) Clinical Practice Guidelines (Australian Guidelines), New Zealand Guidelines Group, Guidelines International Network (GIN), OMNI, Cochrane Database of Systematic Reviews (CDSR),

Database of Abstracts of Reviews of Effects (DARE) and Heath Technology Assessment Database (HTA), NHS Economic Evaluations Database (NHSEED), TRIP, Health Evidence Bulletin Wales, BMJ Clinical Evidence, DH Data, and King's Fund.

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

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

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

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

2.4 Identifying the evidence

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

diagnosis), and if the test and the reference standard were not evaluated in all patients in the study. Diagnostic studies that did not provide test accuracy statistics (for example sensitivity, specificity) were also excluded.

2.5 Critical appraisal of the evidence

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

2.6 Health Economics

2.6.1 Health economic evidence reviews

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

Identified titles and abstracts from the economic searches were reviewed by a health economist and full papers obtained as appropriate. Retrieved papers where then reviewed by a health economist, and considered for inclusion in the Guideline. No formal inclusion or exclusion criterion was applied a priori. Each paper was considered on its own merit, and in the context of availability of relevant published economic evaluations to inform the KCQs. All valid incremental cost-utility (QALY) analyses, (including cost-consequence analyses where the incremental analyses could be calculated from the available study data), taking an NHS costing perspective, were included for all KCQs. In the absence of NHS based cost-utility analyses, incremental cost-effectiveness analyses using alternative outcome measures, (e.g. the proportion of patients correctly diagnosed), were considered. For

KCQs designated as high priority for economic evaluation, (primarily investigations for diagnosis of stable and acute chest pain), if no UK based economic evaluations were found in the literature, then non-UK economic evaluations were considered for inclusion, if it was felt that they would inform the GDG's consideration of the cost-effectiveness for the KCQ under consideration (eg where there was dominance which was likely to be replicated in a UK based analysis).

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

2.6.2 Cost-effectiveness modelling

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

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

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

- Risk of radiation from 64-slice CT coronary angiography.

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

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

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

to ensure that appropriate assumptions, model structure, and data sources were used. The results of the de novo health economic analysis are presented in Chapter 8 of this Guideline with further detail of the results and methods presented in Appendix B.

2.7 Assigning levels to the evidence

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

Table 2 Levels of evidence

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

2.8 Forming recommendations

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

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

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

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

2.9 Areas without evidence and consensus methodology

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

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

2.10 Consultation

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

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

2.11 Relationships between the guideline and other national guidance

2.11.1 Related NICE Guidance

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

Published

- Cardiovascular risk assessment: the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE clinical guideline 67 (2008). Available from http://www.nice.org.uk/guidance/CG67
- Hypertension: management of hypertension in adults in primary care. NICE clinical guideline 34 (2006). Available from: www.nice.org.uk/CG034
- Secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline 48 (2007). Available from: http://www.nice.org.uk/guidance/CG48
- Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction. NICE technology appraisal guidance 73 (2003). Available from: www.nice.org.uk/guidance/TA073
- Statins for the prevention of cardiovascular events in patients at increased risk of developing cardiovascular disease or those with established cardiovascular disease. NICE technology appraisal guidance 94 (2006). Available from: www.nice.org.uk/guidance/TA094

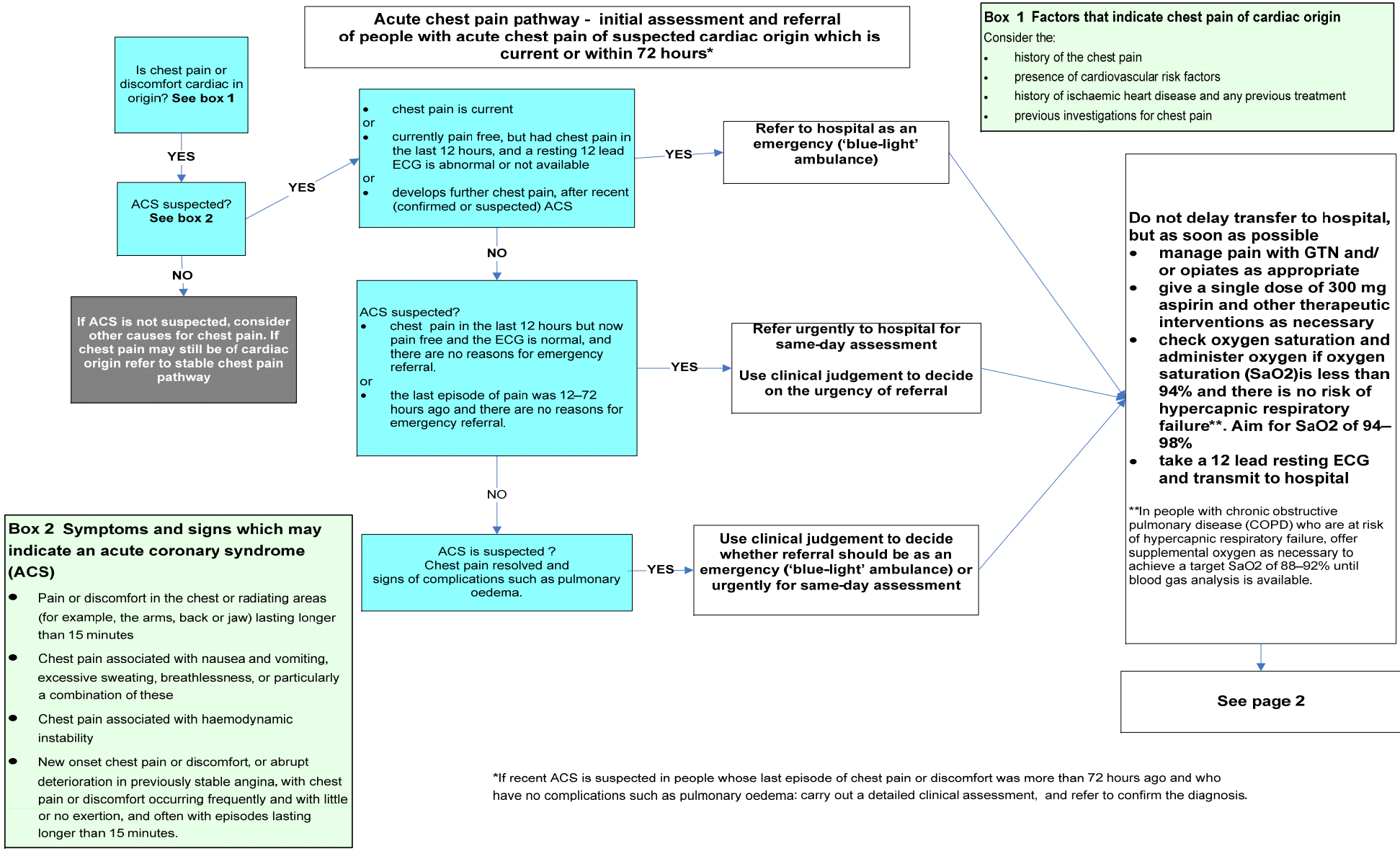
In development

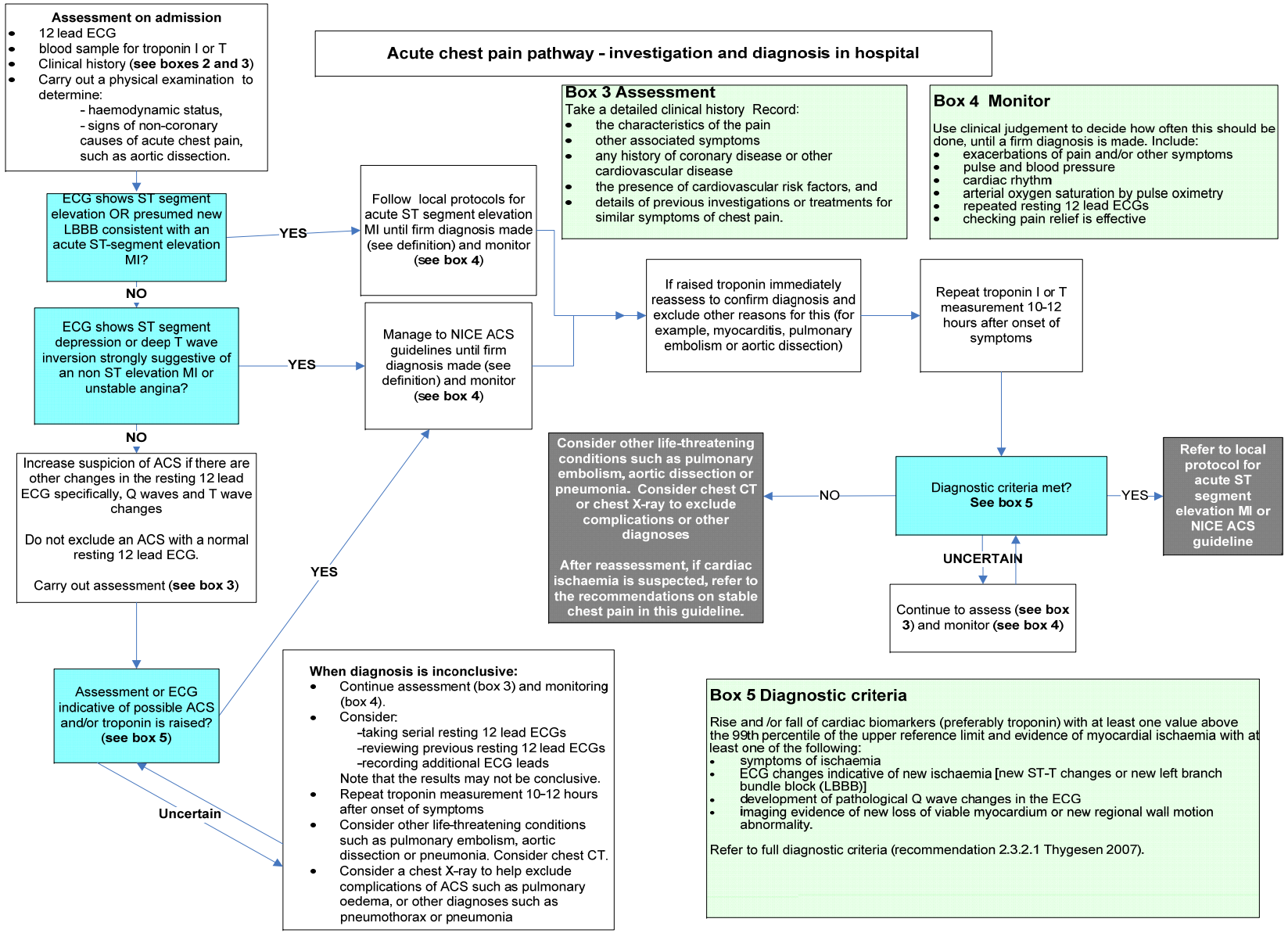
- Acute coronary syndromes: assessment and management of acute coronary syndromes. NICE clinical guideline (publication expected February 2010)
- The management of stable angina NICE clinical guideline (publication expected July 2011)

2.12 Care pathways

The acute chest pain and stable chest pain pathways are given in this section.

2.12.1 Acute Chest Pain Pathway Parts 1 & 2




Acute chest pain pathway - investigation and diagnosis in hospital
Assessment on admission
12 lead ECG
blood sample for troponin I or T
Clinical history (see boxes 2 and 3)
Carry out a physical examination to determine:
- haemodynamic status,
- signs of non-coronary causes of acute chest pain, such as aortic dissection.
ECG shows ST segment elevation OR presumed new LBBB consistent with an acute ST-segment elevation MI?
YES
Follow local protocols for acute ST segment elevation MI until firm diagnosis made (see definition) and monitor (see box 4)
NO
ECG shows ST segment depression or deep T wave inversion strongly suggestive of an non ST elevation MI or unstable angina?
YES
Manage to NICE ACS guidelines until firm diagnosis made (see definition) and monitor (see box 4)
NO
Increase suspicion of ACS if there are other changes in the resting 12 lead ECG specifically, Q waves and T wave changes
Do not exclude an ACS with a normal resting 12 lead ECG.
Carry out assessment (see box 3)
Assessment or ECG indicative of possible ACS and/or troponin is raised? (see box 5)
YES
Uncertain
When diagnosis is inconclusive:
Continue assessment (box 4) and monitoring (box 4).
Consider:
-taking serial resting 12 lead ECGs
-reviewing previous resting 12 lead ECGs
-recording additional ECG leads
Note that the results may not be conclusive.
Repeat troponin measurement 10–12 hours after onset of symptoms
Consider other life-threatening conditions such as pulmonary embolism, aortic dissection or pneumonia. Consider chest CT.
Consider a chest X-ray to help exclude complications of ACS such as pulmonary oedema, or other diagnoses such as pneumothorax or pneumonia
If raised troponin immediately reassess to confirm diagnosis and exclude other reasons for this (for example, myocarditis, pulmonary embolism or aortic dissection)
Repeat troponin I or T measurement 10-12 hours after onset of symptoms
Diagnostic criteria met? See box 5
NO
YES
UNCERTAIN
Consider other life-threatening conditions such as pulmonary embolism, aortic dissection or pneumonia. Consider chest CT or chest X-ray to exclude complications or other diagnoses
After reassessment, if cardiac ischaemia is suspected, refer to the recommendations on stable chest pain in this guideline.
Refer to local protocol for acute ST segment elevation MI or NICE ACS guideline
Continue to assess (see box 3) and monitor (see box 4)
Box 3 Assessment
Take a detailed clinical history Record:
the characteristics of the pain
other associated symptoms
any history of coronary disease or other cardiovascular disease
the presence of cardiovascular risk factors, and
details of previous investigations or treatments for similar symptoms of chest pain.
Box 4 Monitor
Use clinical judgement to decide how often this should be done, until a firm diagnosis is made. Include:
exacerbations of pain and/or other symptoms
pulse and blood pressure
cardiac rhythm
arterial oxygen saturation by pulse oximetry
repeated resting 12 lead ECGs
checking pain relief is effective
Box 5 Diagnostic criteria
Rise and /or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit and evidence of myocardial ischaemia with at least one of the following:
symptoms of ischaemia
ECG changes indicative of new ischaemia [new ST-T changes or new left branch bundle block (LBBB)]
development of pathological Q wave changes in the ECG
imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
Refer to full diagnostic criteria (recommendation 2.3.2.1 Thygesen 2007).

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2.12.2 Stable Chest Pain Pathway Parts 1-3

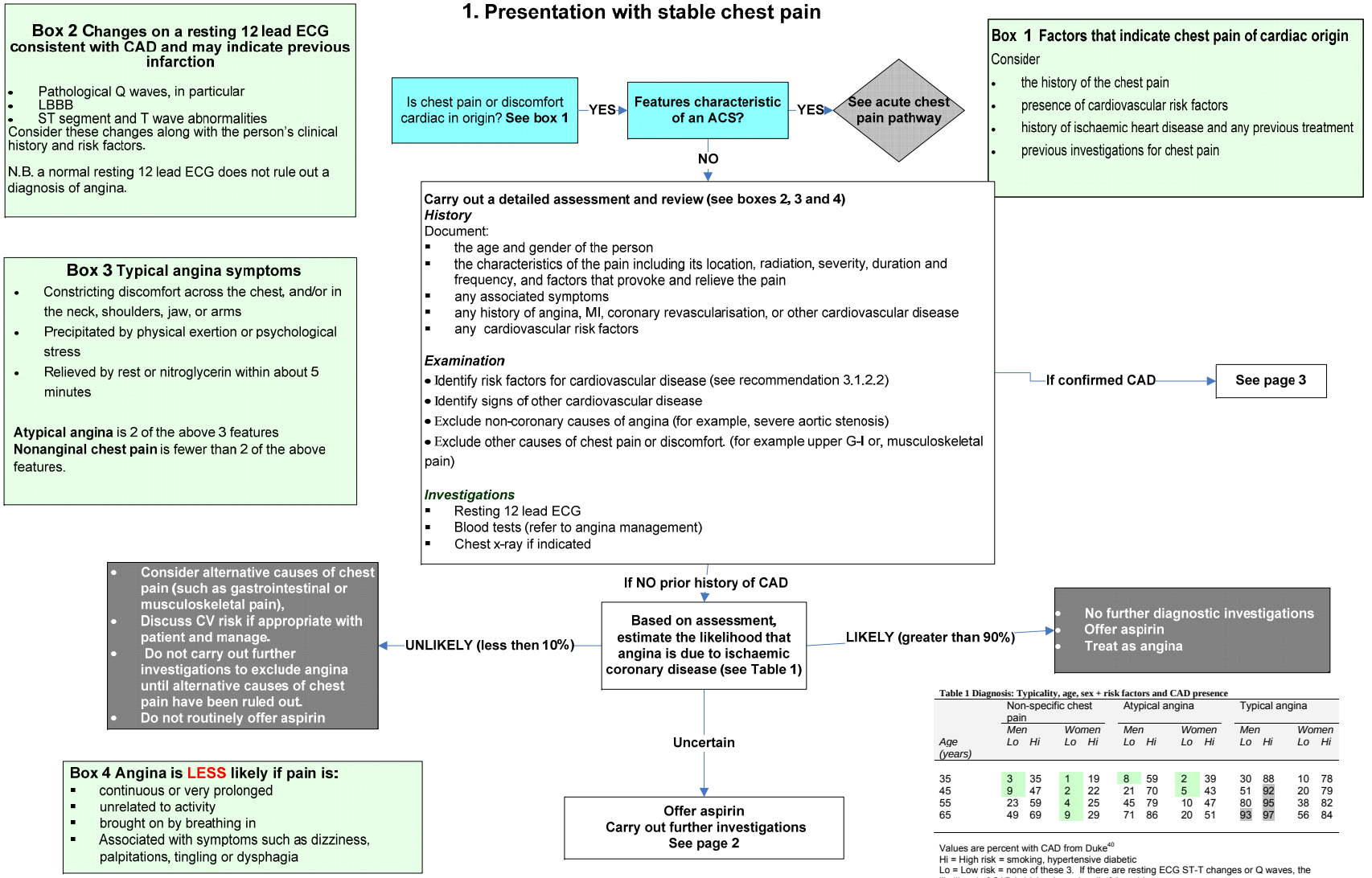


Table 1 Diagnosis: Typicality, age, sex + risk factors and CAD presence

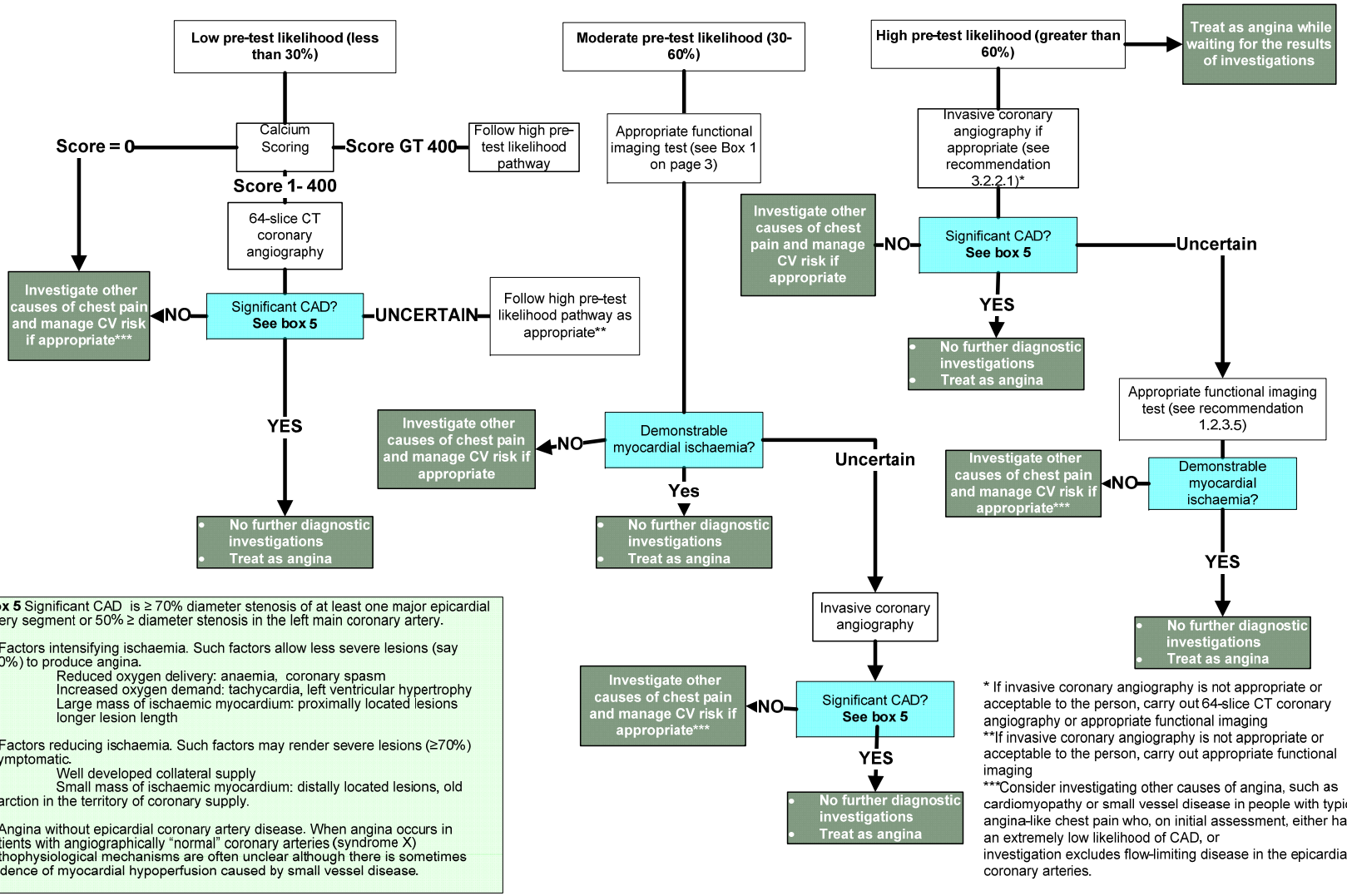
	Non-specific chest pain				Atypical angina				Typical angina			
	Men		*Women*		*Men*		*Women*		*Men*		*Women*	
Age (years)	*Lo*	*Hi*	*Lo*	*Hi*	*Lo*	*Hi*	*Lo*	*Hi*	*Lo*	*Hi*	*Lo*	*Hi*
35	3	35	1	19	8	59	2	39	30	88	10	78
45	9	47	2	22	21	70	5	43	51	92	20	79
55	23	59	4	25	45	79	10	47	80	95	38	82
65	49	69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

Values are percent with CAD from Duke[40]
Hi = High risk = smoking, hypertensive diabetic
Lo = Low risk = none of these 3. If there are resting ECG ST-T changes or Q waves, the likelihood of CAD is higher in each cell of the table.

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

The shaded areas are those that leave the pathway as ruled in or out

2. Investigations for people with no previous diagnosis of CAD and uncertain diagnosis after assessment



Box 5 Significant CAD 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
- longer lesion length

b) Factors reducing ischaemia. Such factors may render severe lesions (≥70%) asymptomatic.
- Well developed collateral supply
- Small mass of ischaemic myocardium: distally located lesions, old infarction in the territory of coronary supply.

c) Angina without epicardial coronary artery disease. When angina occurs in patients with angiographically "normal" coronary arteries (syndrome X) pathophysiological mechanisms are often unclear although there is sometimes evidence of myocardial hypoperfusion caused by small vessel disease.

* If invasive coronary angiography is not appropriate or acceptable to the person, carry out 64-slice CT coronary angiography or appropriate functional imaging
**If invasive coronary angiography is not appropriate or acceptable to the person, carry out appropriate functional imaging
***Consider investigating other causes of angina, such as cardiomyopathy or small vessel disease in people with typical angina-like chest pain who, on initial assessment, either have: an extremely low likelihood of CAD, or investigation excludes flow-limiting disease in the epicardial coronary arteries.

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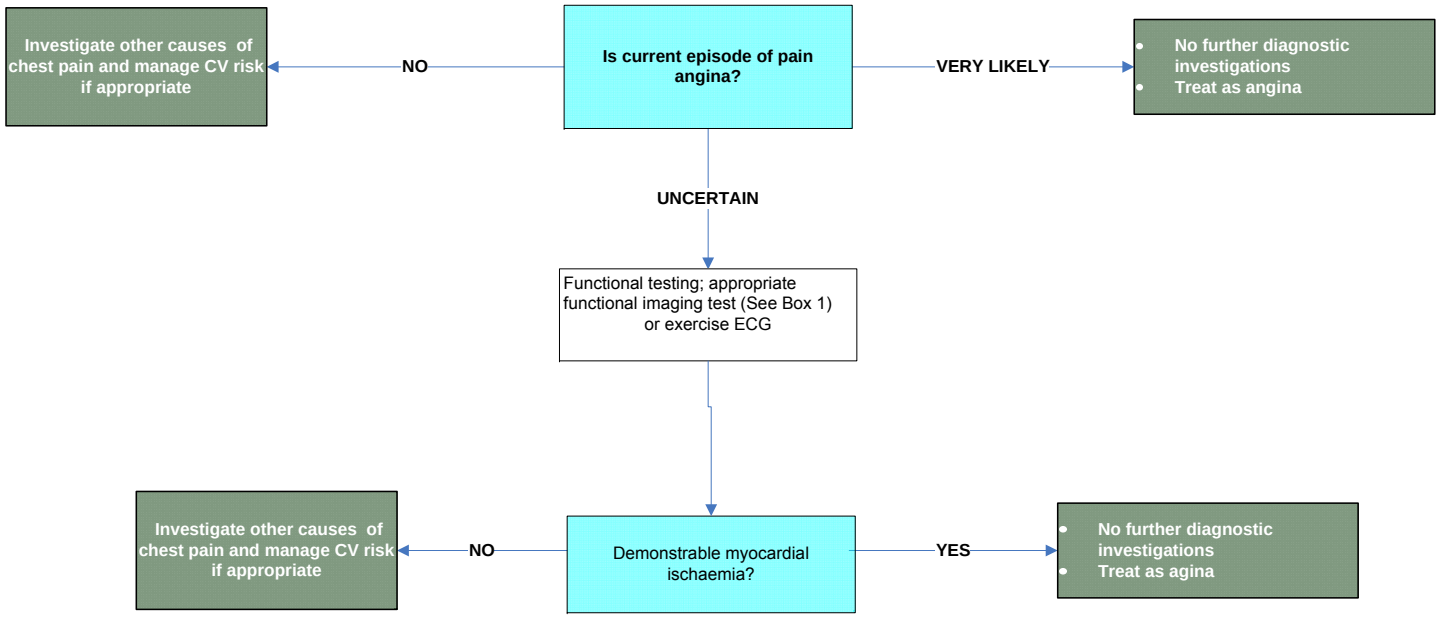
3. Established prior diagnosis of coronary artery disease



Box 1

Use:

- MPS with SPECT
- stress echocardiography
- first-pass contrast-enhanced MR perfusion, or
- MR imaging for stress-induced wall motion abnormalities.

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

1

2.13 Research Recommendations

ACUTE CHEST PAIN

2.13.1 Cost-effectiveness of multislice CT coronary angiography for ruling out obstructive CAD in patients 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 patients 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 patients with suspected troponin-negative acute coronary syndromes.

Why this is important

Current European Society of Cardiology guidelines state that in troponin-negative acute coronary syndromes, 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 patients, ensuring that a significant proportion of at-risk patients 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 patient group.

2.13.2 Novel cardiac biomarkers in patients with acute chest pain.

What is the effectiveness and cost effectiveness of new, high sensitivity troponin methods in low, medium, and high risk patients with acute chest pain?

Research recommendation

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

(b) Evaluation of other putative biomarkers in comparison with the diagnostic and prognostic performance of the most clinically-effective and cost-effective troponin assays.

Why this is important

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

2.13.3 Refining the use of telephone advice in patients with chest pain.

Research question

In what circumstances should telephone advice be given to patients calling with a symptom of chest pain? Is the appropriateness influenced by age, gender or symptoms?

Research recommendation

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

Why this is important

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

STABLE CHEST PAIN

2.13.4 Establishing a national registry for patients who are undergoing initial assessment for stable angina

Research Question and Recommendations

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

a. 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 obtained at initial assessment (history, examination, routine bloods, resting 12 lead ECG).

b. Assessment of the extent to which new circulating biomarkers add information incremental to measures made at initial assessment.

c. 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 patients with suspected stable angina prior to 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 – which 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 due to cardiac 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 patients with suspected stable angina. For example, the contributions (if any) of simple clinical measures such as body mass index, routine blood markers such as 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.

2.13.5 Cost-effectiveness of Multislice CT coronary angiography compared with functional testing in the diagnosis of angina

Research question

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

Research recommendation

Further research should be undertaken to evaluate the clinical and cost-effectiveness of multislice CT coronary angiography compared with functional testing in the diagnosis of angina in a population of patients with stable chest pain who have a moderate pre-test likelihood of CAD.

Why this is important

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

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

2.13.6 Information about presenting and explaining tests

Research question

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

Research recommendation

To establish the optimal ways of presenting information to patients on the diagnostic pathway.

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 RCTs comparing the effects of different methods of

communication on patient comprehension. 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 patients 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. Due consideration should be given to any communications problems the patient may have.

2.14 Acknowledgements

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2.15 Glossary and Definitions

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

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

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

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

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

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

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

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

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

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

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

Angina without epicardial CAD. When angina with evidence of ischaemia occurs in patients with angiographically "normal" coronary arteries (syndrome X) pathophysiological mechanisms are often unclear although there is sometimes evidence of myocardial hypoperfusion caused by small vessel disease

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

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

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

	consequences.
Emergency	Immediate request leading to an immediate response from the ambulance service with a 'blue light' ambulance
Exercise ECG (sometimes known as an exercise test or stress ECG)	An investigation which measures the electrical activity from the heart during exercise, usually used to look for signs of myocardial ischaemia.
Extended dominance	Where the incremental cost-effectiveness of an intervention is higher than that of the next, more effective, alternative.
Evidence statements	A summary of the evidence distilled from a review of the available clinical literature
Evidence-based questions (EBQs)	Questions which are based on a conscientious, explicit and judicious use of current best evidence
Health economics	The branch of economics concerned with the allocation of society's scarce health resources, between alternative healthcare treatments/programmes, in an attempt to improve the health of the population.
Health related quality of life	An attempt to summarise an individual's or the population's quality of life resulting from the combined effect of their physical, mental, and social well-being.
Haemodynamic instability	A clinical state of perfusion failure with clinical features of circulatory shock and or severe heart failure, and requiring pharmacological or mechanical support to maintain normal blood pressure and or adequate cardiac output. It may also be used to describe a clinical state when one or more physiological measurements, for example blood pressure and or pulse, are outside the normal range.
Incremental cost-effectiveness ratio (ICER)	The difference in the costs of two alternative treatment strategies/programmes, divided by the difference in the effectiveness outcomes of the treatment strategies/programmes for a defined population of interest. That is: (Cost treatment B – Cost treatment A)/ (Effectiveness treatment B - Effectiveness treatment B)
Life years	The number of years lived by an individual or a population. For example, if a population of 50 patients live for an average addition 2 years each as the result of receiving a healthcare intervention, then the intervention has provided 100 life years gained.
Meta regression Analysis	An approach for aggregating data from different clinical trials which examine the same question and report the same outcomes, and relating sources of variation in treatment effects to specific study characteristics
Multiple logistic regression	In a clinical study, an approach to examine which variables

analysis	independently explain an outcome
Multi-slice CT coronary angiography	Multi-slice CT coronary angiography is a non-invasive investigation which provides coronary calcium scoring and anatomical information about the degree of stenosis (narrowing) in the coronary arteries. The scanner has a special X-ray tube and rotation speed and as the technology has advanced the number of slices in each rotation has increased. A dual source scanner has two pairs of X-ray sources and multi-slice detectors mounted at 90 degrees to each other.
Myocardial infarction	See Acute Myocardial Infarction
Myocardial perfusion scintigraphy with SPECT (MPS)	MPS involves injecting small amounts of radioactive tracer to evaluate perfusion of the myocardium via the coronary arteries at stress and at rest. The distribution of the radioactive tracer is imaged using a gamma camera. In SPECT the camera rotates round the patient and the raw data processed to obtain tomographic images of the myocardium. Cardiovascular stress may be induced by either pharmacological agents or exercise.
Opportunity cost	The cost in terms of health benefits foregone by allocating resources to one intervention over an alternative intervention. The definition implicitly acknowledges the concept of scarcity of healthcare resources.
Probabilistic sensitivity analysis	The process of measuring the degree of uncertainty around outcomes in an economic evaluation by assigning probability distributions to all of the key parameters in the evaluation, and then simultaneously generating values from each of these distributions using techniques of random number generation such as Monte Carlo methods.
Quality adjusted life year (QALY)	An index of survival weighted to account for quality of life. The year of life is weighted by a utility value U (where $0 \leq U \leq 1$). U reflects the health related quality of life, such that a U of zero represents the worst possible quality of life (equivalent to being dead), and a U of 1 represents perfect health. For example, 1 QALY is achieved if one patient lives in perfect health for one year, or alternatively if 2 people live in perfect health for 6 months each. Alternatively, a person living with a quality of life represented by a u value of 0.5 for 2 years is also representative of 1 QALY value. QALYs have the advantage of incorporating changes in both quantity (longevity/survival) and quality of life (morbidity as represented by psychological, physical and social functioning for example). QALYs are core to cost-utility analysis where the QALY is used as the measure of effectiveness in the economic evaluation.
Relative risk reduction	The ratio of the probability of an event occurring in the treatment group compared to the control group.
Sensitivity	Sensitivity is the proportion of people with the disease who have a positive test. Sensitivity reflects how good the test is at identifying people with the disease. A measure of the diagnostic accuracy in including individuals with the condition. Number of True Positives divided by (Number of True Positives +

	Number of False Negatives) • True positive: People correctly diagnosed with the condition • False positive: Healthy people wrongly diagnosed with the condition • True negative: Healthy people correctly identified as healthy • False negative: People wrongly identified as healthy
Sensitivity analysis	A means of exploring the uncertainty in the results of an economic evaluation/model by varying the parameter values of the included variables one at a time (univariate sensitivity analysis) or simultaneously (multi-variate sensitivity analysis).
Significant coronary artery disease	Significant CAD is ≥ 70% diameter stenosis of at least one major epicardial artery segment or 50% ≥ diameter stenosis in the left main coronary artery. a). Factors intensifying ischaemia. Such factors allow less severe lesions (say ≥50%) to produce angina □ Reduced oxygen delivery: anaemia, coronary spasm □ Increased oxygen demand: tachycardia, left ventricular hypertrophy □ Large mass of ischaemic myocardium: proximally located lesions□ and longer lesion length b). Factors reducing ischaemia. Such factors may render severe lesions (≥70%) asymptomatic □ Well developed collateral supply □ Small mass of ischaemic myocardium: distally located lesions, old infarction in the territory of coronary supply. c). Angina without epicardial coronary artery disease. When angina occurs in patients with angiographically “normal” coronary arteries (syndrome X) pathophysiological mechanisms are often unclear although there is sometimes evidence of myocardial hypoperfusion caused by small vessel disease
Specialist	A healthcare professional who has expert knowledge of and skills in a particular clinical area, especially one who is certified by a higher medical educational organization.
Specificity	Specificity is the proportion of people free of disease who have a negative test. Specificity reflects how good the test is at identifying people without the disease. A measure of the diagnostic accuracy in excluding individuals without the condition. Number of True Negatives divided by (Number of True Negatives + Number of False Positives) • True positive: People correctly diagnosed with the condition • False positive: Healthy people wrongly diagnosed with the condition • True negative: Healthy people correctly identified as healthy • False negative: People wrongly identified as healthy
Stable angina	Unlike acute coronary syndromes, there are no case definitions of

	stable angina that have been agreed internationally. Working definition angina is a symptom of myocardial ischaemia that is recognized clinically by its character, its location and its relation to provocative stimuli. Relation to coronary artery disease. Angina is usually caused by obstructive coronary artery disease that is sufficiently severe to restrict oxygen delivery to the cardiac myocytes. Generally speaking angiographic luminal obstruction estimated at ≥70% is regarded as "severe" and likely to be a cause of angina, but this will depend on other factors listed below that influence ischaemia independently of lesion severity. *Factors intensifying ischaemia.* Such factors allow less severe lesions (say ≥50%) to produce angina Reduced oxygen delivery: anaemia, coronary spasm Increased oxygen demand: tachycardia, left ventricular hypertrophy Large mass of ischaemic myocardium: proximally located and longer lesions *Factors reducing ischaemia.* Such factors may render severe lesions (≥70%) asymptomatic Well developed collateral supply Small mass of ischaemic myocardium: distally located lesions, old infarction in the territory of coronary supply. *Angina without epicardial coronary artery disease.* When angina with evidence of ischaemia occurs in patients with angiographically "normal" coronary arteries (syndrome X) pathophysiological mechanisms are often unclear although there is sometimes evidence of myocardial hypoperfusion caused by small vessel disease.
Stable chest pain	Chest pain occurring intermittently, whose frequency and intensity does not vary significantly day to day and which often occurs with a predictable pattern. May also be described as a chest discomfort.
Stress echocardiograph	Echocardiography is an ultrasound examination of the heart. Exercise or pharmacological stress may be used to look for reversible systolic regional wall motion abnormalities consistent with the development of myocardial ischaemia.
Stress ECG	See exercise ECG above
Stress magnetic resonance imaging (stress MRI)	MRI is a diagnostic procedure that uses radio waves in a strong magnetic field. The pattern of electromagnetic energy released is detected and analysed by a computer to generate detailed images of the heart. Stress MRI is a specific application in which a contrast agent is used to detect myocardial blood flow at stress

	and at rest. Pharmacological stress is used to induce cardiovascular stress.
Technology appraisal	Formal ascertainment and review of the evidence surrounding a health technology, which in this publication refers to technology appraisals undertaken by NICE only.
Troponin	A complex of three regulatory proteins that is integral to muscle contraction in skeletal and cardiac muscle. The presence of the subtypes, troponin I and troponin T, in peripheral blood is very sensitive and specific for detecting myocardial damage.
Unstable angina	This often presents in the same way as myocardial infarction but without biomarker evidence of myocardial necrosis. The working definition for this guideline is: new onset chest pain/discomfort, or abrupt deterioration in previously stable angina, with chest pain/discomfort occurring frequently and with little or no exertion, and often with prolonged episodes
Unstable chest pain	Chest pain which occurs with increasing frequency, often with increasing intensity, and which occurs with no predictable pattern. May also be described as a chest discomfort.
Urgent	Requiring an early action on the same day, but not as an emergency. Usually includes additional clarification of the timescale using clinical judgement.
Utility	A variable usually taking a value between zero (death) and unity (perfect health) which reflects health related quality of life, and which is used in the calculation of QALYs.
Willingness to pay	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.

1

3 Information for Patients Chapter

Return to Recommendations

3.1.1 Introduction

In general conveying information to the patient requires good communication skills, assessment of prior knowledge and readiness to learn, and effective teaching strategies. Information giving to an acutely ill patients 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 physician.

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

Given 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 acute chest pain, or the patient is diagnosed with non cardiac chest pain, the patient exits the care pathway of this guideline. One randomised controlled trial was identified that examined the use of an information sheet in the education of patients with acute chest pain of suspected cardiac origin.

3.1.2 Evidence statements

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

chest pain of suspected cardiac origin (700 patients) found that 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 outcomes of satisfaction with care, severity of pain, prevalence of further pain, patient modification of lifestyle factors, seeking additional information, and altered planned action in the event of recurrent pain (Arnold, J., Goodacre, S., Bath, P. et al , 2009).

3.1.3 Evidence

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

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. 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).

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.

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 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.

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.

There are some limitations which may have biased the outcome of this study. The study was not blinded; there was a 30% non response rate to the questionnaire; there was potential for contamination between groups by the nurses giving the information on the information sheet verbally to the control group.

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.

3.1.4 Evidence to recommendations

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

4 People Presenting with Acute Chest Pain Chapter

4.1 Introduction

This section 4.1 examines the assessment of patients presenting with acute chest pain of suspected cardiac origin and is intended for patients presenting in both the primary and secondary healthcare settings. Importantly the initial assessment is aimed at identifying those patients with acute MI or ACS and in whom very early therapeutic interventions will make a substantial difference to patient outcomes. This encompasses determining risk factors for CAD, obtaining a clinical history, physical examination, resting ECG recording, and cardiac biomarker measurement. In reviewing this evidence and making recommendations the GDG emphasized the importance of early recognition of patients with acute MI or ACS, and adopted a high threshold for ruling out these diagnoses. If an acute MI or ACS has been ruled out, patients may still have chest pain of cardiac origin (for example patients with risk factors for CAD and troponin negative results), and these patients have been identified for further assessment according to the stable chest pain recommendations in Chapter 5.

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

4.2 Assessment

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

4.2.1.1 Evidence statements for initial assessment and referral to hospital

1 There is considerable heterogeneity in the patient characteristics and study settings between cohort studies and within the studies selected for meta-analyses, and there may have been incorporation bias, for the diagnosis of acute MI / ACS.

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

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

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

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

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

7 One cohort study that 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, PTCA, CADG, angiographic CAD, atypical; absence of CAD history
- risk factors of CAD (having 2 or more) typical; smoking obesity, hypertension, diabetes, hyperlipideamia, family history, atypical absence or only 1 risk factor

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 was diagnostically unhelpful.

Increasing numbers of atypical criteria was associated with increasing PPV for excluding acute MI and major coronary adverse events at six months. (Schillinger, Martin, Sodeck, Gottfried, Meron, Giora et al , 2004)

8 One cohort study of limited power in patients with acute chest pain of suspected cardiac origin and normal serial troponin I levels found that an increased chest pain score ≥ 10 (based on chest pain location, radiation, character and severity, influenced by GTN, stature or breathing, dyspnoea, nausea / vomiting, diaphoresis and history of angina), ≥ 2 chest pain episodes in the last 24 hours, age ≥ 67 years, insulin-dependent diabetes mellitus, and prior PCI were associated with increased risk of the composite outcome of all cause mortality or nonfatal MI at 1 year follow up. (Sanchis, J., Bodí, V., Llácer, A. et al , 2005)

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

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

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

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

Three systematic reviews (Swap, Clifford J. and Nagurney, John T., 2005) (Bruyninckx, R., Aertgeerts, B., Bruyninckx, P. et al , 2008) (Mant, J., McManus, R. J., Oakes, R.-A. L. et al , 2004), and three cohort studies (Schillinger, Martin, Sodeck, Gottfried, Meron, Giora et al , 2004) (Sanchis, J.,

Bodí, V., Llácer, A. et al , 2005) (Sanchis, Juan, Bodí, Vicent, Núñez, Julio et al , 2005) 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 chest pain history in the evaluation of patients with suspected MI or acute coronary syndrome (search date 2005) (Swap, Clifford J. and Nagurney, John T., 2005). Prior systematic reviews and prospective and retrospective observational 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 ischemic episodes. The following factors that precipitated or aggravated chest pain were also examined; pleuritic, positional, palpable, exercise, emotional stress, relieving factors, and associated symptoms (Swap, Clifford J. and Nagurney, John T., 2005).

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

Table 3
Value of specific components of chest pain history for the diagnosis of acute MI

Pain Descriptor	Number of patients	PLR (95% CI)
Increased likelihood of acute MI		
Radiation to right arm or shoulder	770	4.7 (1.9-12)
Radiation to both arms or shoulders	893	4.1 (2.5-6.5)
Associated with exertion	893	2.4 (1.5-3.8)
Radiation to left arm	278	2.3 (1.7-3.1)
Associated with diaphoresis	8426	2.0 (1.9-2.2)
Associated with nausea or vomiting	970	1.9 (1.7-2.3)
Worse than previous angina or similar to previous MI	7734	1.8 (1.6-2.0)
Described as pressure	11504	1.3 (1.2-1.5)
Decreased likelihood of acute MI		
Described as pleuritic	8822	0.2 (0.1-0.3)
Described as positional	8330	0.3 (0.2-0.5)
Described as sharp	1088	0.3 (0.2-0.5)
Reproducible with palpation	8822	0.3 (0.2-0.4)
Inflammatory location	903	0.8 (0.7-0.9)
Not associated with exertion	893	0.8 (0.6-0.9)

Permissions granted from original source (Swap, Clifford J. and Nagurney, John T., 2005).

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

3 in primary care, and 1 was in a chest pain observational unit (Bruyninckx, R., Aertgeerts, B., Bruyninckx, P. et al , 2008).

Table 4 and Table 5 detail the results of meta-analyses for the utility of components of the clinical history in the diagnosis of acute MI and acute coronary syndrome, 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 acute coronary syndrome, 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 acute coronary syndrome (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 on the likelihood of an acute MI. Other symptoms had even less influence on the likelihood of an acute MI indicating that they could not be used to exclude an acute MI or acute coronary syndrome. Presentation with pain on palpation was found to be the only symptom that may rule out the probability of an acute MI or acute coronary syndrome, as indicated by NLRs of 0.23 and 0.17, respectively). However, 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 acute coronary syndrome (Bruyninckx, R., Aertgeerts, B., Bruyninckx, P. et al , 2008).

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Table 4

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

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

= number of studies, LR = likelihood ratio, OR = odds ratio

Permissions granted from original source (Bruyninckx, R., Aertgeerts, B., Bruyninckx, P. et al , 2008)

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Table 5
Pooled sensitivity, specificity, positive and NLRns, odds ratios of signs and symptoms for ACS in patient groups

				ACS					*ACS*	
Symptom				*Non-selected patients*					*Selected patients*	
		#		*95% CI*	*I^{2a} (%)*		*#*		*95% CI*	*I^{2a} (%)*
Pain in left arm	Sensitivity	3	38	18.6 to 59.5	95		0		No studies	
and/or shoulder	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	Sensitivity	1	18	9.6 to 26.2	Only one		1	23	10.6 to 35.9	Only one
and/or shoulder	Specificity		95	93.8 to 96.1	study			94	87.2 to 100	study
	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		0		No studies	
	Specificity		76	72.2 to 79.1	study					
	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
	Specificity		76	26.7 to 98.6	98			49	35.0 to 63.0	study
	PLR		1.49	0.62 to 3.56	80			0.57	0.33 to 0.99	

Table 5
Pooled sensitivity, specificity, positive and NLRns, odds ratios of signs and symptoms for ACS in patient groups

				ACS					*ACS*	
Symptom				*Non-selected patients*					*Selected patients*	
		#		*95% CI*	*I^{2a} (%)*		#		*95% CI*	*I^{2a} (%)*
	NLR		0.93	0.77 to 1.13	87			1.44	1.02 to 2.04	
	OR		1.59	0.58 to 4.37	80			0.4	0.17 to 0.90	
Epigastric pain	Sensitivity	4	12	5.4 to 20.8	97		0		No studies	
	Specificity		89	82.9 to 94.1	98					
	PLR		1.05	0.35 to 3.20	97					
	NLR		0.98	0.88 to 1.08	97					
	OR		1.08	0.31 to 3.74	97					
Oppressive pain	Sensitivity	1	56	49.7 to 62.1	Only one		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					

Table 5
Pooled sensitivity, specificity, positive and NLRns, odds ratios of signs and symptoms for ACS in patient groups

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

= number of studies

Selected patients = patients recruited by coronary care units and cardiologists

LR = likelihood ratio

OR = odds ratio

I^{2a} = test for heterogeneity

Permissions granted from original source Bruyninckx et al 2008

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

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

Table 6

Positive and NLRs for individual components of the clinical history and signs and symptoms for the assessment of acute chest pain

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

Table 6
Positive and NLRs 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*
	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	

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

There was considerable heterogeneity in the results, particularly (although not exclusively) for the NLRs, indicating that the pooled summary statistics should be interpreted with caution. Nevertheless, there is no evidence that any single symptom or sign taken in isolation is of much value in the diagnosis of acute chest pain (Mant, J., McManus, R. J., Oakes, R.-A. L. et al , 2004).

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

Seven pre-defined factors were evaluated and designated as either typical or atypical, location of chest pain (typical: left sided, atypical: right sided), character of pain (typical: crushing / sneezing / 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 / diaphoreis, atypical: absence of vegetative signs), history of CAD (typical: MI / PTCA / CABG, atypical: none) and risk factors for CAD namely; smoking, obesity, hypertension, diabetes, hyperlipidemia, and family history all typical, atypical was defined as absence or only one risk factor (Schillinger, Martin, Sodeck, Gottfried, Meron, Giora et al , 2004).

Thirteen percent of patients (168 patients) had an acute MI and 19% (240 patients) had a major adverse event at 6 month follow up (defined as either cardiovascular death, percutaneous coronary interventions, coronary artery bypass surgery or MI. The LRs to predict or exclude an acute MI and major adverse coronary events at 6 months are shown in Table 7. The presence of four or more typical criteria was associated with a positive predictive value (PPV) of 0.21 (95% CI 0.17 to 0.25) to indicate an acute MI and 0.30 (95% CI 0.25 to 0.35) for a major adverse event. Increasing numbers of atypical chest pain criteria were associated with increasing PPVs for excluding an acute MI and major adverse event at 6 months. The presence of four or more atypical criteria was associated with a PPV of 0.94 (95% CI 0.92 to 0.96) to exclude acute MI, and a PPV of 0.93 (95% CI 0.90 to 0.96) for 6 month exclusion of major adverse coronary event. 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 (Schillinger, Martin, Sodeck, Gottfried, Meron, Giora et al , 2004).

Table 7

Likelihood ratios of increasing numbers of typical and atypical symptoms and history of chest pain, acute myocardial infarction and 6 month cardiac adverse effects (myocardial infarction, need for percutaneous transluminal angioplasty or coronary artery bypass surgery, cardiac death)

	PLR to predict	
	Acute myocardial infarction	6 Months cardiac adverse effects
1 typical symptom or history	1.15	1.15
2 typical symptoms and/or history	1.32	1.34
3 typical symptoms and/or history	1.48	1.58
4 typical symptoms and/or history	1.77	1.87
5 typical symptoms and/or history	1.88	2.11
6 typical symptoms and/or history	1.85	1.54
	PLR to exclude	
	Acute myocardial infarction	6 Months cardiac adverse effects
1 atypical symptom or history	1.05	1.04
2 atypical symptoms and/or history	1.25	1.29
3 atypical symptoms and/or history	1.76	1.85
4 atypical symptoms and/or history	2.22	3.02
5 atypical symptoms and/or history	3.19	4.87
6 atypical symptoms and/or history	3.34	4.58

Permissions requested from original source (Schillinger, Martin, Sodeck, Gottfried, Meron, Giora et al , 2004).

The second cohort study assessed the risk stratification of patients with acute chest pain and with normal serial troponin I concentrations (Sanchis, J., Bodí, V., Llácer, A. et al , 2005). The study recruited consecutive patients with acute chest pain during a 28 month period. A total of 609 patients were included in the study, the mean age was 64±12 years and 67% were men (Sanchis, J., Bodí, V., Llácer, A. et al , 2005).

Patients underwent a chest pain score assessment, an ECG, and an exercise stress test. The chest pain score was based on: location (substernal) = +3, location (precordial) = +2, location (neck, jaw or epigastrium) = +1, location (apical) = -1; radiation (either arm) = +2, radiation (shoulder, back, neck or jaw) = +1; character (crushing, pressing or squeezing) = +3, character (heaviness or tightness) = +2, character (sticking, stabbing, pinprick or catching) = -1; severity (severe) = +2, (moderate) = +1; influenced by glyceryl trinitrate = +1, influenced by stature = -1, influenced by breathing = -1; associated symptoms dyspnoea = +2, nausea or vomiting = +2, diaphoresis = +2; history of exertional angina = +3. Risk factors were recorded, namely; age, smoking, hypertension, hypercholesterolemia, diabetes, family history of ischaemic heart disease, history of ischaemic heart disease, and previous coronary surgery (Sanchis, J., Bodí, V., Llácer, A. et al , 2005).

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 coronary event (acute MI in the case of a new episode of chest pain or cardiac death). Multivariate analysis found that the following were independent factors in predicting an acute MI; higher chest pain score (per point, odds ratio (OR) 1.2, 95% CI 1.1 to 1.4, *P* = 0.009), older age (per year, OR 1.04, 95% CI 1.01 to 1.09, *P* = 0.04), male sex (OR 3.7, 95% CI 1.2 to 11.1, *P* = 0.02), and diabetes (OR 2.5, 95% CI 1.1 to 5.7, *P* = 0.02) (Table 8). For the prediction of major coronary events, the following were independent predictors; higher chest pain score (OR 1.2, 95% CI 1.1 to 1.4, *P* = 0.01), diabetes (OR 2.3, 95% CI 1.1 to 4.7, *P* = 0.03), ST-segment depression (OR 2.8, 95% CI 1.13 to 6.3, 95%, *P* = 0.003), and previous coronary surgery (OR 3.1, 95% CI 1.3 to 7.6, *P* = 0.01) (Table 9). The patient population was stratified according to these 4 independent predictors, and the continuous variable chest pain score was transformed into a categorical variable by receiver operating characteristic test to define the best cut off value (≥ 11). This categorical variable persisted as an independent predictor in the multivariate model (OR 2.4, 95% CI 1.1 to 5.5, *P* = 0.04) (Sanchis, J., Bodí, V., Llácer, A. et al , 2005).

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Table 8

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
Hypercholersterolaemia	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

Permissions granted from original source (Sanchis, J., Bodí, V., Llácer, A. et al , 2005).

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Table 9

Predictors of major events (acute myocardial infarction or cardiac death) by univariate and multivariate analyses

	Univariate *P* value	Multivariate *P* value	OR	95% CI
Clinical history				
Pain score (per point)	0.002	0.001	1.2	1.1 to 1.4
Age (per year)	0.01	NS	NA	NA
Men	0.2	NA	NA	NA
Smoking	0.5	NA	NA	NA
Hypertension	0.2	NA	NA	NA
Hypercholersterolaemia	1	NA	NA	NA
Diabetes	0.03	0.03	2.3	1.1 to 4.7
Family History of IHD	1	NA	NA	NA
History of IHD	0.007	NS	NA	NA
Coronary surgery	0.01	0.01	3.1	1.3 to 7.6
ECG				
ST depression	0.003	0.01	2.8	1.3 to 6.3
T Wave inversion	0.7	NA	NA	NA
CI, confidence interval; NA, not applicable; NS, not significant; OR, odds ratio				
Permissions requested from original source (Sanchis, J., Bodí, V., Llácer, A. et al , 2005).				

The third cohort study assessed a new risk score for patients with acute chest pain, no ST-segment deviation and with normal serial troponin I concentrations (Sanchis, Juan, Bodí, Vicent, Núñez, Julio et al , 2005). The study recruited 646 consecutive patients during a 34 month period. Patients were included if they had acute chest pain of possible cardiac origin and patients were excluded if the initial ECG showed ST-segment deviation (≥1mm elevation or depression) or if they had any elevated troponin I measurements. The primary end point was a composite of all cause mortality or nonfatal MI at 1 year follow up; the secondary end point was all cause mortality, nonfatal MI or urgent revascularisation at 14 day follow up. Of the total of 646 patients included in the study, 68% were men and the mean age was 64±12 years.

Patients underwent a chest pain score assessment based on: location (substernal) = +3, location (precordial) = +2, location (neck, jaw or epigastrium) = +1, location (apical) = -1; radiation (either arm) = +2, radiation (shoulder, back, neck or jaw) = +1; character (crushing, pressing or squeezing) = +3, character (heaviness or tightness) = +2, character (sticking, stabbing, pinprick or catching) = -1; severity (severe) = +2, severity (moderate) = +1; influenced by glyceryl trinitrate = +1, influenced by stature = -1, influenced by breathing = -1; associated symptoms (dyspnoea) = +2, (nausea or vomiting) = +2, (diaphoresis) = +2; history of exertional angina = +3. The following risk factors were recorded: gender, age, smoking, arterial hypertension, diabetes mellitus, insulin-dependant diabetes mellitus (IDDM), hypercholesterolemia, at least 3 risk factors for CAD combined (from the following; family history of ischaemic heart disease, hypertension, hypercholesterolaemia, diabetes or being a current smoker), ≥ 2 chest pain episodes in last 24 hours, Killip class>1 at presentation, evidence of prior coronary stenosis ≥ 50%, use of aspirin in the last 7 days, prior PCI, prior CABG, and a history of heart failure. An ECG was recorded in the emergency department (Sanchis, Juan, Bodí, Vicent, Núñez, Julio et al , 2005).

At 1 year follow up, the primary end point (all-cause mortality or non-fatal MI) occurred in 43 patients (6.3%). At a 14 day follow up, the secondary end point

(all-cause mortality or nonfatal MI or urgent revascularisation) occurred in 35 patients (5.4%). Multivariate analysis found that the following were independent factors in predicting all cause mortality or nonfatal MI; a chest pain score ≥ 10 points (hazard ratio (HR) 2.5, 95%CI 1.2 to 5.6, *P* = 0.02), ≥ 2 chest pain episodes in last 24 hours (HR 2.2, 95% CI 1.2 to 4.2, *P* = 0.01), age ≥ 67 years (HR 2.3, 95% CI 1.2 to 4.4, *P* = 0.01), IDDM (HR 4.2, 95% CI 2.1 to 8.4, *P* = 0.0001), and prior PCI (HR 2.2, 95% CI 1.1 to 4.8, *P* = 0.04) (Sanchis, Juan, Bodí, Vicent, Núñez, Julio et al , 2005).

The study constructed a risk score from 5 variables which were shown to be independently related to the primary end point. The variables with similar HR (chest pain score ≥ 10, ≥ 2 chest pain episodes in the last 24 hours, age ≥ 67 years and prior PCI) were assigned a 1 point value. IDDM was assigned a 2 point value as the HR value was twice the HR value of the other variables. This risk score gave the following patient population distribution: 0 points: n=111 (17.2%), 1 point: n=198 (30.7%), 2 points: n=206 (31.9%), 3 points: n=103 (15.9%), 4 points: n=16 (2.5%), 5 points: n=11 (1.7%), 6 points: n=1 (0.2%). The study combined 4-6 points due to the low number of patients giving the distribution: 4-6 points: n=25 (4.3%). The study then distinguished the 5 points values as: very low-risk (0 points, primary end point = 0%), low-risk (1 points, primary end point = 3.1%), intermediate-risk (2 points, primary end point = 5.4%), high-risk (3 points, primary end point = 17.6%) and very high-risk (≥ 4 points, primary end point = 29.6%). The statistical significance for the trend was *P* = 0.00001. The differences between the groups were also significant (comparing very low-, low-, intermediate-risk to very high-risk *P* = 0.0001, *P* = 0.0001, *P* = 0.0001 respectively; comparing very low-, low-, intermediate-risk to high-risk *P* = 0.002, *P* = 0.0001, *P* = 0.0001 respectively) (Sanchis, Juan, Bodí, Vicent, Núñez, Julio et al , 2005).

The new risk score was then compared with (Antman, E. M., Cohen, M., Bernink, P. J. L. et al , 2000) The new risk score had an accuracy C index of 0.78 (*P* = 0.0001) compared with the TIMI score C index of 0.66 (*P* = 0.0001), and the accuracy of the new score was significantly greater compared with the TIMI score (*P* = 0.0002).The accuracy of both risk scores was also tested for

the secondary endpoint of death MI or urgent revascularization at 14 days as the TIMI score was originally designed for this outcome. The new risk score (C index of 0.70, *P* = 0.0001) and the TIMI score (C index of 0.66, *P* = 0.002) were both correlated with the secondary endpoint without significant differences between them (Sanchis, Juan, Bodí, Vicent, Núñez, Julio et al , 2005).

4.2.1.3 Health economic evidence

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

4.2.1.4 Evidence to recommendations

Methodologically all three systematic reviews were of high quality with a low risk of study incorporation bias with respect the methodology of study selection. 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 acute coronary syndrome in the analyses conducted in the systematic reviews, none of elements alone or in combination identified a group of patients that could be safely discharged without further diagnostic investigation. The three cohort studies were well conducted with a low risk of bias. They demonstrated that some risk factors and symptoms were associated with an increased probability of acute MI; however, the cohort studies 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 recruitment bias likely. There was little evidence in patients presenting to primary care. However, whilst the results of the systematic reviews, further supported by the results of two cohort studies, found that the characteristics of the chest pain and associated symptoms, the presence of risk factors and a past history of coronary disease

influence the likelihood of whether a patient with chest pain is suffering an acute MI / ACS, and the GDG agreed that this was insufficient from which to reach a definitive diagnosis. Irrespective of whether a patient presents to emergency services, an emergency department, primary care or other healthcare settings, additional testing is always necessary if an acute MI/ACS is suspected.

The GDG also recognised that patients with acute chest pain of suspected cardiac origin might also have other causes for their symptoms. In some cases, these may be due to other life threatening conditions and early diagnosis is important and potentially life saving. Searching for the evidence for symptoms associated with these was not part of this guideline, but the GDG felt it was important to emphasise the importance of considering other possible diagnoses during a clinical assessment (see section starting on page 70).

4.2.2 Gender differences in symptoms

4.2.2.1 Evidence statements for differences in presentation by gender

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

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

3 One systematic review found that women presenting with ACS were more likely to experience middle or upper back pain, neck pain, jaw pain, shortness of breath, nausea or vomiting, loss of appetite, weakness and fatigue, cough, paroxysmal nocturnal dyspnoea,

indigestion and dizziness (Canto, J. G., Goldberg, R. J., Hand, M. M. et al , 2007)

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

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

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

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

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

9 One cohort study in patients presenting with acute MI or unstable angina found that women compared with men were more likely to have hypertension and diabetes, whereas men were more likely

than women to have a past history of MI, previous CABG surgery and history of smoking. (Chua, T. P., Saia, F., Bhardwaj, V. et al , 2000),

4.2.2.2 Clinical evidence

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

Introduction

Historically, the descriptions of chest pain symptoms associated with ACS have been based on the presentation characteristics of men. Studies from the Framingham cohort have shown that there are important gender differences in the initial presentation of CAD; women tend to present with angina while for men the commonest presentation is MI, and in the Framingham cohort women were found to present with cardiac symptoms approximately 10 years later than men (Lerner, D. J. and Kannel, W. B., 1986). The Framingham Offspring Study (participants aged 30 to 74 years at the start of the study and a follow up of 16 years) assessed 6 risk factors and the relationship between them (lowest quantile high-density lipoprotein, highest quantile cholesterol, body mass index, systolic blood pressure, triglycerides and plasma glucose). The study showed that about one third of people had a single risk factor, and 17% had 3 of the risk factors. With 16 years of follow up for coronary events defined as MI or sudden death, the event rate among all enrollees was compared with the event rate among those with 3 or more risk factors. The coronary events noted among those with 3 or more risk factors were 48% in women and 20% in men, indicating that risk factor determination is an important component in the evaluation of women with suspected CAD (Wilson, P. W., Kannel, W. B., Silbershatz, H. et al , 1999).

Women with ischaemic heart disease have more adverse outcomes compared with men (Vaccarino, V., Parsons, L., Every, N. R. et al , 1999) despite the repeated documented lower angiographic disease burden and more often preserved left ventricular function compared with men (Nabel, E. G., Selker, H. P., Califf, R. M. et al , 2004). Hence the recognition that clinical

presentation and risk factors differ between men and women is important in the initial assessment of chest pain to determine the need for further evaluation.

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

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

Analysis of the 4 studies in patients presenting with acute coronary syndrome found that women were more likely to experience back pain, nausea and / or vomiting, dyspnoea, indigestion and palpitations compared with men. Table 2 details the proportion of studies that reported the gender differences compared with the total number of studies identified in the systematic review. No gender differences were reported for the following symptoms; presence of chest pain (2 studies), arm and shoulder pain (2 studies), neck pain (2 studies), dizziness (3 studies) (Patel, H., Rosengren, A., and Ekman, I., 2004).

Analysis of the 11 studies in patients presenting with acute MI found that women are more likely to have back, jaw, and neck pain, and nausea and / or vomiting, dyspnoea, palpitations, indigestion, dizziness, fatigue, loss of appetite and syncope. The following symptoms were not associated with gender differences in the presentation of acute MI in some of the studies; arm and shoulder pain (4 studies), epigastric discomfort, heartburn or abdominal

pain (7 studies), throat pain (2 studies) (Patel, H., Rosengren, A., and Ekman, I., 2004).

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 comorbid conditions. Some studies evaluated only a small number of symptoms, and may have missed other statistically significant symptoms (Patel, H., Rosengren, A., and Ekman, I., 2004).

Table 2

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

Acute coronary syndrome		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

Permissions requested from original source (Patel, H., Rosengren, A., and Ekman,

Table 2

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

Acute coronary syndrome		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
I., 2004).			

The second systematic review (search date 2005) examined the gender differences in the presenting symptoms of ACS (Canto, J. G., Goldberg, R. J., Hand, M. M. et al , 2007). 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 without chest pain are frequently labeled as 'atypical' and included pain or discomfort in locations other than the chest, such as pain localised to the arm(s), shoulder, middle back, jaw or epigastrum. Atypical chest pain has also been described as not severe, not prolonged, and not classic in presentation, where classic cardiac chest pain is described as burning, sharp, pleuritic, positional pain or discomfort that is reproducible on palpitation of the chest wall.

The review included studies from large cohorts or registries, single-centre reports, or studies based on personal interviews that compared symptom presentation in men versus women. In the studies identified there was a lack of standardisation on data collection and reporting on principal or associated symptoms. Given the considerable heterogeneity of the studies analysed, there were no formal meta-analyses performed, and results were reported as

a descriptive narrative with simple descriptive statistics (Canto, J. G., Goldberg, R. J., Hand, M. M. et al , 2007).

The review identified 9 large cohort studies, and 20 smaller cohort studies or personal interview studies that provided information on ACS presentation with and without typical chest pain or discomfort according to sex.

Analysis of the nine large cohort studies found that approximately one third of all patients presented without acute chest pain / discomfort (32%, 149 039 of 471 730 patients), and the absence of chest pain was more common in women than in men (38%, 73 003 of 19 4797 women versus 27%, 76 036 of 27 6933 men). One of the large studies had significantly greater patient numbers (National Registry of MI Report) (Canto, J. G., Shlipak, M. G., Rogers, W. J. et al , 2000)) which could have dominated the results, hence the analysis was repeated excluding this study and showed that almost one quarter of women with ACS did present with typical chest pain (Canto, J. G., Goldberg, R. J., Hand, M. M. et al , 2007).

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

The review identified a number of studies that demonstrated that the frequency of other ACS-associated symptoms differed according to sex. Compared with men, 8 studies found that women are more likely to experience middle or upper back pain, 4 studies found that women are more likely to have neck pain, and 2 studies found that women are more likely to have jaw pain. Five studies found that women are more likely to have shortness of breath and 5 studies showed women are more likely to have

nausea or vomiting. Loss of appetite, weakness and fatigue, and cough were identified as more common in women versus men in 2 studies each. Paroxysmal nocturnal dyspnoea, indigestion and dizziness were reported as more common in women versus men in 1 study each (Canto, J. G., Goldberg, R. J., Hand, M. M. et al , 2007).

The first cohort study compared symptoms of acute MI in women versus men (Isaksson, R. M., Holmgren, L., Lundblad, D. et al , 2008). The study was part of the Multinational Monitoring of Trends and Determinants in Cardiovascular disease (MONICA), a population-based registry which included all acute events rather than only events recorded in hospital. According to the MONICA criteria (based on the World Health Organisation (WHO) definitions) typical symptoms of MI were defined as the presence of typical chest pain and characterised by duration of more than 20 min, 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 min, 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±6.8 years for men and 56.6±6.68 years for women (Isaksson, R. M., Holmgren, L., Lundblad, D. et al , 2008).

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

The second cohort study examined sex-related differences in the clinical history and risk factors associated with ST-segment elevation acute MI (Kosuge, M., Kimura, K., Ishikawa, T. et al , 2006). Five hundred and ten consecutive patients admitted to a coronary care unit were identified, and off 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 h of admission. Acute MI was diagnosed on the basis of typical chest pain lasting ≥ 30 min, ST-segment elevation of ≥ 2 mm at least 2 contiguous precordial leads or ST-segment elevation of ≥ 1 mm in at least 2 inferior leads (II, III, or a VF), and a typical increase in serum creatine kinase (Kosuge, M., Kimura, K., Ishikawa, T. et al , 2006).

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

The third study was a multicentre case-control study, the CAD Offspring of Year 2000 CARDIO2000 study, and examined cardiovascular risk factors and their relationship with gender (Chrysohoou, C., Panagiotakos, D. B., Pitsavos, C. et al , 2003). The study randomly selected patients who were admitted to a

hospital with a first acute MI or unstable angina event. After selection of cardiac patients, 1078 cardiovascular disease-free subjects (controls) were randomly selected and matched to the patients by age (±3 years), gender and region. Controls were mainly individuals who visited the outpatient clinics of the same hospital in the same period as the coronary patients for routine examinations or minor surgical operations. All control subjects had no clinical symptoms or evidence of cardiovascular disease in their medical history. A total of 848 cardiac patients were included in the study and 1078 controls (Chrysohoou, C., Panagiotakos, D. B., Pitsavos, C. et al , 2003).

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

Women experiencing their first cardiac event were significantly older than men ($P < 0.01$). Univariate analysis found that women were significantly more likely to have hypertension, hypercholesterolemia and diabetes, whereas men were significantly more likely to smoke, do physical activity and have higher alcohol consumption. This difference was found in both the cardiac patient group and the control group (see Table 3) (Chrysohoou, C., Panagiotakos, D. B., Pitsavos, C. et al , 2003).

Table 3
Risk factors' distribution (% within sex) of the study's population by gender

	Acute coronary syndrome group		Control group		
	Men	Women	Men	Women	*P* Value †
Number of participants	701(82%)	147 (18%)*	862 (80%)	216 (20%)*	-
Smoking habit	525 (75%)	44 (30%)**	500 (58%)	54 (25%)**	<0.001
Hypertension	308 (44%)	101 (69%)**	216 (25%)	69 (32%)*	<0.001
Hypercholesterolemia	414(59%)	100 (68%)*	233(27%)	67 (31%)	<0.01
Diabetes mellitus	168(24%)	46 (31%)*	78 (9%)	17 (8%)	<0.001
Family history of premature CHD	308(44%)	76(52%)*	129 (15%)	39 (18%)	<0.001
Body mass index (kg/m^2)	27.4±4	27.1±4	26.7±3	26.1±4	<0.05
Physical activity	253 (36%)	37 (25%)*	371 (43%)	84 (39%)*	<0.01
Alcohol consumption (w/day)‡	1.97±1	0.5±0.2*	1.34±1	0.2±0.2*	<0.05

Comparisons between men and women, by group of subjects

ACS=acute coronary syndromes; CHD=coronary heart disease; † comparisons between patients and controls, after taking into account the effect of gender (stratified analysis); ‡ alcohol intake was measured in wine glasses (100 ml, concentration 12%) per day; **P* < 0.05; ***P* < 0.01

Permissions requested from original source (Chrysohoou, C., Panagiotakos, D. B., Pitsavos, C. et al , 2003).

When adjusting for age, multivariate analysis found that for women hypertension was associated with a higher risk of CAD compared with men (odds ratio 4.86 versus 1.66 *P* < 0.01, respectively).

Family history of CAD and hypercholesterolemia were associated with a higher risk of CAD in men than in women with odds ratios of 5.11 versus 3.14, *P* < 0.05 for family history, respectively, and odds ratios of 3.77 versus 2.19 *P* < 0.05 for hypercholesterolemia, respectively. Details of the results of the multivariate analysis are given in Table 4 (Chrysohoou, C., Panagiotakos, D. B., Pitsavos, C. et al , 2003).

Table 4

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

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

OR = odds ratio; CI = confidence interval; CHD = coronary heart disease; **p* value for the different effect (men vs. women) of the investigated factor on coronary risk; ** alcohol intake was measured in wine glasses (100mL, concentration 12%) per day.

Permissions requested from original source (Chrysohoou, C., Panagiotakos, D. B., Pitsavos, C. et al , 2003).

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

The results for the differences in risk factors showed that women were more likely to have diabetes mellitus (23% in women versus 11% in men, *P* = 0.007), and a history of hypertension (52% in women versus 32% in men, *P* = 0.001). Men were more likely to have a history of prior MI (51% in men versus 39% in women *P* = 0.06), history of previous coronary artery bypass graft operation (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). As this study recruited a highly selected population that was transferred to the tertiary centre, there is a high risk of bias in the study, and as such, the results should be interpreted with caution (Chua, T. P., Saia, F., Bhardwaj, V. et al , 2000).

4.2.2.3 Health economic evidence

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

4.2.2.4 Evidence to recommendations

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

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

4.2.3 Ethnic differences in symptoms

4.2.3.1 Evidence statements for differences in presentation by ethnicity

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

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

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

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

5 One cohort study in patients presenting with acute chest pain found that African American women were more likely to have diabetes

compared with Caucasian women. (Maynard, C., Beshansky, J. R., Griffith, J. L. et al , 1997)

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

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

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

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

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

11 No health economic evidence was identified.

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4.2.3.2 Clinical evidence

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

Introduction

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

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

after adjustment. A number of studies have shown that Afro 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 Afro Americans are more likely to have renal insufficiency and CHF.

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

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

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

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

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

The study found that African American patients with a final diagnosis of acute MI had similar presenting signs and symptoms compared with the Caucasian patients. The odds ratios were all > 1.0 for all symptoms examined in both Caucasians and African Americans, and there was no significant difference in the odds ratios in two groups for the following; chest pain ≥ 30 min (Caucasian OR 4.2 (95%CI 1.9 to 9.3) versus African American 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 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 1.9 (95%C 1.4 to 2.6), *P* > 0.2), diaphoresis (Caucasian 2.4 (95%C 1.5 to 3.9) versus African American 3.2 (95%C 2.4 to 4.4) *P* > 0.2) and rales on physical examination (Caucasian 3.8 (95%C 2.3 to 6.4) versus African American 2.4 (95%C 1.8 to 3.4), *P* > 0.15) (Johnson, P. A., Lee, T. H., Cook, E. F. et al , 1993).

While it was found that African American patients were less likely to have a final diagnosis of acute MI (*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 odds ratio for acute MI outcomes for African Americans compared with Caucasians was 0.77 (95% CI 0.54 to 1.1) (Johnson, P. A., Lee, T. H., Cook, E. F. et al , 1993).

The second cohort study assessed the causes of chest pain and presenting symptoms in African American patients and Caucasian patients presenting to the emergency department (Maynard, C., Beshansky, J. R., Griffith, J. L. et al , 1997). Patients were included if they presented with chest or left arm pain, shortness of breath or other symptoms suggestive of acute cardiac ischemia. A total of 10 001 patients were included, of which 3401 were African American and 6600 were Caucasian. The mean age for male African Americans was 52±14 years and was 55±15 years for female African Americans. The mean age for Caucasian males was 60±15 years and for Caucasian females the mean age was 65±16 years. The study compared risk factors and signs and symptoms of the patients and these are detailed in Table 5 (Maynard, C., Beshansky, J. R., Griffith, J. L. et al , 1997).

1

Table 5
Medical History and Clinical Characteristics of patients on admission

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

Table 5
Medical History and Clinical Characteristics of patients on admission

	Men			Women		
Variable	% Caucasian*	% African American†	*P*	% Caucasian ‡	% African American§	*P*
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 requested from original source (Maynard, C., Beshansky, J. R., Griffith, J. L. et al , 1997)

The study found that there were differences in patients' medical history dependant upon racial background. African Americans were more likely to smoke and have hypertension compared with Caucasians, and African American women were more likely to have diabetes than Caucasian women. Caucasian patients were more likely to have a history of angina or MI and to take cardiac medications. There was no difference in the number of African Americans and Caucasian male patients who had chest pain as a primary symptom. There were a higher number of African American female patients than Caucasian female patients who had chest pain as a primary symptom. African American patients were more likely to report additional symptoms of shortness of breath, abdominal pain, nausea, vomiting and dizziness. African Americans were more likely to have a diastolic blood pressure of > 90mmHg when admitted to hospital compared to Caucasian patients (Maynard, C., Beshansky, J. R., Griffith, J. L. et al , 1997).

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

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

The third cohort study compared the medical history and the risk factors of African Americans with Caucasian patients admitted with suspected acute MI to an emergency department chest pain unit within 48 h of pain onset (Klingler, Diane, Green, Weir Robbya, Nerenz, David et al , 2002). The study also examined patient perception of chest pain by race. The study identified patients through a floor census and screened through a brief review of their medical charts. Patients were approached to participate based on their medical record number. Five hundred patients were approached and 215 met the inclusion criteria. Patients were included if English was their primary language and they could recall pre-hospital events. Patients were excluded if they were of a race other than African American or Caucasian, were aged < 18 years, had known mental impairment, were pregnant, had a MI subsequent to admission, had a previous interview prior to admission, or had significant emergency data missing from their medical records. The study recruited 157 African American patients (73%) and 58 Caucasian patients (27%). The mean age for African American patients was 59±14 years and for Caucasian

patients was 62±15 years, 46% of the African American patients were male compared to 57% of the Caucasian patients (Klingler, Diane, Green, Weir Robbya, Nerenz, David et al , 2002).

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

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

Symptoms were assessed through open ended questions and a close ended check off of symptoms. Patients answered yes or no. The patients had no differences in frequency of symptoms according to race. No significant differences were found between African American and Caucasian patients in the objective symptoms (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 objective symptoms but were marginally more likely to attribute their symptoms to a gastrointestinal source rather than

a cardiac source (*P* = 0.05). Of 157 African American patients, 11 patients were diagnosed as having had an acute MI (11%), while 27 out of 58 Caucasian patients (47%) were diagnosed with acute MI (*P* < 0.001). However of those patients with a final diagnosis of MI, 61% of African Americans attributed their symptoms to a gastrointestinal source and 11% to a cardiac source versus 26% and 33%, respectively for Caucasian patients. Hence although the proportion of objectively defined typical symptoms were similar, self attribution was more likely to be non cardiac in African American patients compared with Caucasian patients ((Klingler, Diane, Green, Weir Robbya, Nerenz, David et al , 2002).

The fourth cohort study compared the symptom presentation in Asian and Caucasian patients with ACS (Teoh, M., Lalondrelle, S., Roughton, M. et al , 2007). Consecutive patients requiring hospital admission for ACS were recruited by a senior cardiac nurse. The final diagnosis was decided by a cardiologist based upon the results of ECG, exercise testing 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 elevation MI, and MI associated with ST-segment elevation (Teoh, M., Lalondrelle, S., Roughton, M. et al , 2007).

Of 3000 patients surveyed, 95 (3.2%) were of neither Caucasian nor Asian race, or were of mixed racial origins. Of the remaining 2905 patients, 604 (21%) were Asian and 2301 (79%) were Caucasian. The demographic details and type of ACS are detailed in Table 6. 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), with no statistically significant difference in the proportion of Caucasians (21%) versus Asians (18%) being diagnosed with ST-segment elevation MI (table 14) (Teoh, M., Lalondrelle, S., Roughton, M. et al , 2007).

Table 6
Demographics and cardiac diagnosis of presentation in the Asian and Caucasian groups

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

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

The distribution of reported discomfort for Asians and Caucasians is detailed in Table 7 for all patients admitted to the emergency department. Frontal upper body discomfort was reported by 94% of Asian patients versus 89% of Caucasian patients (*P* < 0.001), while almost twice as many Asian patients reported pain on the rear of their body compared with Caucasian patients (46% versus 25%, respectively, *P* < 0.001) (Teoh, M., Lalondrelle, S., Roughton, M. et al , 2007).

Table 7
Comparison of pain characteristics between Asian and Caucasian groups

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

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

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

There was a small but statistically significant difference in the intensity of discomfort reported, with Asian patients reporting a median pain rating of 7.5 compared with 7.0 in Caucasian patients ($P < 0.002$). Twenty four percent of Asian patients rated their discomfort at the maximum value of 10 compared with 19% of Caucasian patients. A smaller percentage of Asian patients (6%) reported feeling no discomfort at presentation (silent MI) compared with Caucasian patients (13%) ($P = 0.002$). These patients were identified by a

combination of symptoms, including fatigue, shortness of breath, collapse and resuscitation following cardiac arrest. Logistic regression analysis was performed to determine which factors contributed to patients reporting a silent episode, and the most significant factor was a patients diabetic status, they were more than twice as likely to report that they felt no pain during presentation compared with non-diabetics (odds ratio 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 (odds ratio 1.61, 95% CI 1.08 to 1.10). Analysis with age as a continuous variable was also associated with silent episodes. Overall Asian patients were younger, more likely to be diabetic and they tended to report greater intensity of pain over a greater area of the body, and more frequent discomfort over the rear of their upper thorax compared with Caucasian patients (Teoh, M., Lalondrelle, S., Roughton, M. et al , 2007).

The filth cohort study assessed the differences in presentation of acute MI between Bangladeshi patients and Caucasian patients (Barakat, K., Wells, Z., Ramdhany, S. et al , 2003). Inclusion criteria was acute MI as defined by the presence of cardiac chest pain with ST 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 years and for Caucasian patients was 68±19 years, 87% of the Bangladeshi group were male compared to 70% of the Caucasian group. One third of the Bangladeshi patients were fluent in English (Barakat, K., Wells, Z., Ramdhany, S. et al , 2003).

The study examined the patients age, sex, smoking status, history of hypertension, diabetes, family history of ischaemic heart disease, previous MI, the nature of the chest pain (central pain, left sided pain or other pain) the character of the pain typical (heaviness, tightness, weight, pressure, band-like, gripping) or non-classical (sharp, stabbing, pinching, burning), how the

pain was interpreted and what the patients initial response was. The study also adjusted any significant results with respect to the patients age, sex, risk factors and proficiency in English (Barakat, K., Wells, Z., Ramdhany, S. et al , 2003).

The study found that the Bangladeshi patients were younger, more often male, and more likely to be diabetic and to report a previous MI compared with Caucasian patients. However Caucasian patients were more likely to report a family history of ischaemic heart disease compared with Bangladeshi patients. The study also found that Bangladeshi patients were significantly less likely to report central chest pain (odds ratio 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) (odds ratio 0.25, 95% CI 0.09 to 0.74; *P* = 0.0118). Again these differences remained after adjustment for the patients' age, sex, risk factor profiles and fluency in English (Barakat, K., Wells, Z., Ramdhany, S. et al , 2003).

4.2.3.3 Health economic evidence

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

4.2.3.4 Evidence to recommendations

The review of the evidence found two well conducted cohort studies with a low risk of bias which found that African Americans had a similar clinical presentation of acute MI compared with Caucasians, while one well conducted cohort study reported that African American patients were more likely to report additional symptoms of shortness of breath, abdominal pain, nausea, vomiting and dizziness compared with Caucasians. One well

conducted cohort study and a second study that may have incorporation bias (because it cited 'cardiac chest pain' as an inclusion criterion) indicated that Asian patients may present with more atypical symptoms compared with Caucasian patients, and that Asian patients are more likely to be younger, to be diabetic and to have had a prior MI. The GDG concluded that whilst there may be differences between different ethnic groups in the symptomatic presentation of ACS/MI, these are small.

4.2.4 Use of nitrates in the diagnosis of acute chest pain

4.2.4.1 Evidence statements for nitrates

1 In 3 prospective observational studies and one retrospective cohort studies, nitrates were of no diagnostic value in patients with acute chest pain.

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4.2.4.2 Clinical evidence

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

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

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

ECGs, 2 troponin tests, and chest X ray) (Steele, R., McNaughton, T., McConahy, M. et al , 2006).

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

Of a total of 278 patients that 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, were not admitted to hospital and required medical management only. The final 270 patients were followed up for 4 weeks after hospital discharge to determine repeat hospitalisations, cardiac events, death, new medical diagnoses after discharge and other cardiac testing. Twelve patients (4.4%) were lost to follow up (Steele, R., McNaughton, T., McConahy, M. et al , 2006).

Of the 270 patients studied, 177 patients (66%) showed a positive response to nitroglycerin, while 93 out of 270 patients had a negative response (34%). In the positive pain relief with nitroglycerin group, 60 out of 177 patients (34%)

had defined cardiac chest pain and 117 out of 177 patients (66%) had non cardiac chest pain. In the negative pain relief group 23 out of 93 patients (25%) had cardiac chest pain and 70 out of 93 patients (75%) had non cardiac chest pain. For patients diagnosed with acute MI, 20 were in the pain relief with nitroglycerin group, and 15 were in the no pain relief group. There were 3 deaths in the group which experienced pain relief and 6 deaths in the group with no pain relief (Steele, R., McNaughton, T., McConahy, M. et al , 2006).

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

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

The second cohort study examined the change in numeric description of pain after sublingual nitroglycerin administration to patients presenting to the emergency department with suspected cardiac chest pain (Diercks, D. B., Boghos, E., Guzman, H. et al , 2005). An 11 point numeric descriptive scale was used to assess pain before and 5 min 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 min after administration of nitroglycerin (Diercks, D. B., Boghos, E., Guzman, H. et al , 2005).

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

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

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

In the total patient population, 125 (19%) patients had no change in pain, 206 (31%) patients had minimal pain reduction, 145 (22%) had moderate pain

reduction, and 188 (28%) patients had significant or complete pain reduction. A change in the numeric descriptive scale score was not associated with a diagnosis of cardiac-related chest pain (as defined as all cause mortality, MI, or diagnostic testing confirming the presence of CAD) in any of these 4 subgroups using Pearson χ^2 statistic $P = 0.76$) (Diercks, D. B., Boghos, E., Guzman, H. et al , 2005).

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

Chest pain was rated on a score from 1 (mild pain) to 10 (severe pain), and the pain score was recorded immediately before and approximately 5 min 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 min of administration of 0.4 mg sublingual nitroglycerin either as a tablet or a spray (Henrikson, C. A., Howell, E. E., Bush, D. E. et al , 2003).

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

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

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

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

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

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

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

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

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

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

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

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

4.2.4.3 Health economic evidence

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

4.2.4.4 Evidence to recommendations

Three well conducted cohort studies with a low risk of bias found that patients with acute cardiac chest pain had equivalent rates of pain relief compared with patients with non cardiac causes of their pain. The results of the retrospective study were similar to the other studies, although it had a high risk of

incorporation bias. The GDG concluded that response to nitroglycerin is not helpful as a diagnostic tool in differentiating cardiac chest pain, from non cardiac chest pain, but may nevertheless be useful as a therapeutic agent for pain relief.

4.2.5 Resting 12 lead ECG

4.2.5.1 Evidence statements for ECG

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

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

3 One systematic review that examined the use of a pre-hospital ECG and advanced notification of the ECG found that the door to treatment interval decreased with use of a pre-hospital ECG and advanced notification compared with no pre-hospital notification of ECG. There was heterogeneity in the studies identified. (Morrison, L. J., Brooks, S., Sawadsky, B. et al , 2006)

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

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

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

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

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

9 One retrospective cohort study in patients with suspected acute MI, that compared automated QT dispersion and ST-segment measurements to that of physician interpretation of ECG found that independent classification by QT-end and QT-peak dispersions was not superior to physician consensus. Automated assessment of ST-segment deviation gave a higher sensitivity but a lower specificity for the diagnosis of acute MI compared with the physicians'

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

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

4.2.5.2 Clinical evidence

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

Four systematic reviews (Ioannidis, J. P., Salem, D., Chew, P. W. et al , 2001) (Morrison, L. J., Brooks, S., Sawadsky, B. et al , 2006) (Chun, Andrea Akita and McGee, Steven R., 2004) (Mant, J., McManus, R. J., Oakes, R.-A. L. et al , 2004), and six cohort studies (Sanchis, J., Bodí, V., Llácer, A. et al , 2005), (Conti, Alberto, Paladini, Barbara, Toccafondi, Simone et al , 2002) (Fesmire, F. M., 2000) (Ohlsson, M., Ohlin, H., Wallerstedt, S. M. et al , 2001) (Aufderheide, T. P., Xue, Q., Dhala, A. A. et al , 2000) (Diercks, D. B., Kontos, M. C., Chen, A. Y. et al , 2009) were identified in patients with acute chest pain. Two of the systematic reviews examined studies in both acute and stable patients with chest pain (Chun, Andrea Akita and McGee, Steven R.,

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

The first systematic review examined the utility of ECG changes in patients with acute chest pain (Mant, J., McManus, R. J., Oakes, R.-A. L. et al , 2004). The reference standards used for MI were combinations of ECG changes, enzyme changes and typical clinical features and in some cases radionucleotide scanning results. 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. 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.

As detailed in Table 8, 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 elevation, depression, Q waves and/ or T wave changes (PLR 5.30 95%CI 3.66 to 7.70) (Table 16). A completely normal ECG was reasonably helpful at ruling out a MI (PLR 0.14, 95%CI 0.11 to 0.20, $P = 0.007$) in patients with

acute chest pain. There was significant heterogeneity in the studies, nevertheless, the results indicated that a single ECG gave important diagnostic information in the evaluation of patients with acute chest pain (Mant, J., McManus, R. J., Oakes, R.-A. L. et al , 2004).

Table 8
Resting ECG for acute chest pain

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

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

A further number of studies were identified that examined an ECG in addition to some or all of the following evaluations that had been used in the emergency department: signs, symptoms, and investigations. These were defined as 'black box' studies. There were fifteen studies evaluating real time decision making on the initial information available to physicians. Analysis of black box studies was divided into 4 subgroups; interpretation of admission ECG for MI and acute coronary syndrome, interpretation of clinical data other than ECG, A&E initial diagnoses for MI and acute coronary syndrome, 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 LR–. Of 0.08 (95% CI 0.05 to 0.18). Full details are shown in Table 9 (Mant, J., McManus, R. J., Oakes, R.-A. L. et al , 2004).

Table 9
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	0.87 (95% CI	3.28 (95% CI	0.66 (95% CI

Table 9
Black Box Studies

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

Table 9
Black Box Studies

	Studies	Sensitivity	Specificity	PLR	NLR
		(95% CI 0.94 to 0.96)	0.56)	(95% CI 1.87 to 3.47)	(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 (i.e. a decision by a front-line physician, not an outside expert) and adequate follow up.

AMI, acute MI.

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

The second systematic review identified 8 studies that examined the use of an ECG in the identification of acute MI in patients presenting to the emergency department with chest pain (Chun, Andrea Akita and McGee, Steven R., 2004). Pooled estimates were calculated for PLRs and NRLs. Based on the PLR and its 95%CI, ST-segment elevation was the most useful ECG change for the diagnosis of acute MI (sensitivity range 31 to 49%, specificity range 97 to 100%, PLR 22 (95%CI 16 to 30) and NLR 0.6 (95% CI 0.6 to 0.6)) The second most useful was the presence of Q wave (sensitivity of 10 to 34%, and a specificity of 96 to 100%, PLR 22 (95%CI 7.6 to 62) and NLR 0.8 (95% CI 0.8 to 0.9)). For ST-segment depression the sensitivity was 20 to 62%, specificity was 88 to 96%, PLR 4.5 (95%CI 3.6 to 5.6) and NLR 0.8 (95% CI 0.7 to 0.9). T wave inversion had a sensitivity of 9 to 39%, specificity of 84 to 94%, PLR 2.2 (95%CI 1.8 to 2.6) and NLR 0.9 (95% CI 0.8 to 1.0) (Chun, Andrea Akita and McGee, Steven R., 2004).

The diagnostic utility of the ECG was compared with other assessments including classification of chart pain, associated symptoms (nausea, diaphoresis, dyspnoea), risk factors (gender, age, hypertension, diabetes, smoking status, family history of CAD, hypercholestoraemia, prior MI, angina,

obesity). A normal ECG was by far the most discriminatory feature for ruling out a diagnosis of acute MI (sensitivity from 1 to 13%, specificity from 48 to 77%, PLR 0.20 (95%CI 0.1 to 0.3) and NRL 1.4 (95% CI 1.4 to 1.6)) (Chun, Andrea Akita and McGee, Steven R., 2004).

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

The fourth systematic review investigated the accuracy and clinical effect of out-of-hospital ECG in the diagnosis of acute MI and acute cardiac ischemia (defined in the publication as both unstable angina and acute MI) (Ioannidis, 2001 198 /id}. 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 odds ratio (which compared an out of hospital ECG with a hospital ECG) (Ioannidis, J. P., Salem, D., Chew, P. W. et al , 2001).

Analysis of the diagnostic performance for acute MI in the eight studies evaluating an out of hospital ECG found that the diagnostic odds ratio 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 odds ratio 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 acute coronary syndrome). 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 min) and angioplasty (92 min versus 115 min) compared with an in hospital ECG (Ioannidis, J. P., Salem, D., Chew, P. W. et al , 2001).

The first cohort study assessed the risk stratification of patients with acute chest pain presenting to the emergency department with normal serial troponin I concentrations (Sanchis, J., Bodí, V., Llácer, A. et al , 2005). This study has been described in detail in section 1.2.2 (Clinical history, risk factors and physical examination). A total of 609 patients were consecutively recruited; the mean age was 64±12 years and 67% were men (Sanchis, J., Bodí, V., Llácer, A. et al , 2005).

Patients underwent an ECG in the emergency department, a chest pain score assessment, clinical history and an exercise test. Of 609 patients with a normal troponin test, 70 (12%) had ST-segment depression and 54 (9%) had T wave inversion. During a 6 month follow up, 25 patients (4.1%) had an acute MI, 9 (1.5%) died of cardiac causes and 29 (4.8%) had a major event (acute MI or cardiac death). Univariate analysis found that ST-segment depression was an independent factor in predicting an acute MI ($P < 0.004$, odds ratio 2.9, 95%CI 1.2 to 6.8, and also in predicting major cardiac events (acute MI and / or cardiac death) ($P = 0.003$, odds ratio 2.8, 95%CI 1.3 to 6.3). Multivariate analysis found that ST-segment depression was an independent factor in predicting an acute MI ($P = 0.02$, odds ratio 2.9, 95%CI 1.2 to 6.8,),

and also in major events (acute MI and / or cardiac death) (*P* = 0.003, odds ratio 2.8, 95%CI 1.3 to 6.3). 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 6). Multivariate analysis for T wave inversion was not applicable as univariate analysis found that it was not significant (*P* = 0.5) for acute MI and major events (*P* = 0.7) (Sanchis, J., Bodí, V., Llácer, A. et al , 2005).

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

The chest pain score was based on the elements of the clinical history, each of which was given a value. These included; location of pain (substernal or precordial) = +3, left chest, neck, lower jaw or epigastrium)= +1, apex = -1; radiation of pain (arm, shoulder, back, neck or lower jaw) = +1; character of pain (crushing, pressing or heaviness) = +2, character of pain (sticking, pleuritic or pinprick) = -1; associated symptoms (dyspnoea, nausea or diaphoresis) = +2; history of angina = +3

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 ±standard deviation for high, intermediate and low probability was 63±10, 64±11 and 38±15 years, respectively. The proportion of men in the high,

intermediate and low probability groups was 67%, 62% and 66%, respectively. The proportion of smokers in the high, intermediate and low probability groups was 35%, 33% and 12%, respectively. The proportion of people with diabetes in the high, intermediate and low probability groups was 25%, 28% and 8%, respectively (Conti, Alberto, Paladini, Barbara, Toccafondi, Simone et al , 2002).

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

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

The third cohort study examined which patients with acute chest pain could potentially benefit from continuous 12-lead ST-segment monitoring with automated serial ECG (Fesmire, F. M., 2000). The study included 706 consecutive patients from a convenience population who presented to an emergency department. Patients had an initial history, physical examination and ECG, and were subsequently classed in four different categories. Category I were patients with acute coronary syndrome 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 acute coronary syndrome,

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 PTCA or alternatively for a maximum of 2 hours. The average age for category II was 57.3±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 PTCA / CABG. The average age for category III was 54.6±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 PTCA / CABG. The average age for category IV was 52.6±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 PTCA / CABG (Fesmire, F. M., 2000).

Patients were diagnosed with acute MI if they met WHO diagnostic criteria (Gillum, R. F., Fortmann, S. P., Prineas, R. J. et al , 1984). Unstable angina was diagnosed if the admitted patient received that discharge diagnosis by the physician, or if the patient had a 30 day adverse event outcome (death, PTCA, CABG, post emergency department acute MI, cardiogenic shock, ventricular fibrillation, sustained ventricular tachycardia, third degree AV block, bradycardic or asystolic arrest). The final diagnosis according to initial category was as follows; category II acute MI 24.1%, completed acute MI 1.5%, unstable angina 46.0% and non cardiac chest pain 28.5%; category III acute MI 3.9%, completed acute MI 0.3%, unstable angina 19.2% and non cardiac chest pain 76.6%; category IV acute MI 1.0%, completed acute MI 1.9%, unstable angina 2.4% and non cardiac chest pain 94.7% (Fesmire, F. M., 2000).

Sensitivity and specificity of serial ECG diagnostic for new injury or new / evolving ischemia and 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 new injury or new / evolving ischemia

was 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).

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 PTCA, 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%, $P < 0.001$). .

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±31min (Fesmire, F. M., 2000).

The fourth cohort study was a retrospective study that examined whether the utilization of artificial neural networks in the automated detection of an acute MI was improved by using a previous ECG in addition to the current ECG (Ohlsson, M., Ohlin, H., Wallerstedt, S. M. et al , 2001). In total 902 ECG-confirmed acute MIs were reviewed. If a patient presented more than once to the emergency department and had an ECG, the final ECG was used in the study. For each ECG included, a previous ECG for the same patient was selected from the clinical electrocardiographic database. Artificial neural networks were then programmed to detect the acute MI based on either the current ECG only or on the combination of the previous and current ECG if available. The average age of the patients was 74±11 years, and 60% were men (Ohlsson, M., Ohlin, H., Wallerstedt, S. M. et al , 2001).

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

The study used ROC curves to evaluate the difference in interpretation and diagnosis of the acute MI when both ECGs were analysed compared to only the current ECG. The ROC curve showed that the neural network performance in the diagnosis of an acute MI was improved when both ECGs were present (area under ROC with current ECG only = 0.85, area under ROC with both ECGs = 0.88; $P = 0.02$). The intern performed better when both ECGs were present (area under ROC with current ECG = 0.71, area under ROC with both ECGs = 0.78; $P < 0.001$) and made a diagnosis of acute MI more frequently when both ECGs were analysed, compared with the current ECG only. In contrast, the cardiologists performance was not significantly improved when both ECGs were analysed (area under ROC with current ECG = 0.79, area under ROC with both ECGs = 0.81; $P = 0.36$). The study indicated the diagnostic performance of an artificial neural network and that of an intern was improved when there was access to a previous ECG from the same patient (Ohlsson, M., Ohlin, H., Wallerstedt, S. M. et al , 2001).

The fifth cohort study examined the added diagnostic value of automated QT-dispersion measurements and automated measurements of ST-segment deviation in the interpretation of the ECG by emergency department physicians who did not have cardiology training or expertise in the electrocardiographic diagnosis of acute cardiac ischemia (Aufderheide, T. P.,

Xue, Q., Dhala, A. A. et al , 2000). The study included 1568-patient ECGs. Patients were included if they were aged over 18 years, sought paramedic evaluation for suspected cardiac chest pain and their chest pain was classed as stable (a systolic blood pressure of 90mmHg or more, absence of second- or third-degree heart block, ventricular fibrillation or ventricular tachycardia on initial examination). Patients were excluded if the paramedic thought a pre-hospital ECG would affect treatment, if they had atrial fibrillation or flutter, heat block, or fully paced rhythms, and based on QRS duration criteria although the study did not specify the duration. The pre-hospital ECGs were sent by mobile phone and were interpreted by a physician. The median age of patients was 62 years and 55% were men (Aufderheide, T. P., Xue, Q., Dhala, A. A. et al , 2000).

The study assessed the sensitivity and specificity for diagnosing an acute MI by two physicians examining the ECG recording and the automated independent classification of ST-segment changes (both elevation and depression), QT-end dispersion and QT-peak dispersion measurements (Aufderheide, T. P., Xue, Q., Dhala, A. A. et al , 2000). The study found that for physician interpretation of the ECG the average sensitivity was 48% and specificity was 99%. Independent assessment of ST-segment deviation using the automated computer gave a higher sensitivity of 90% but a lower specificity of 56% compared with the physicians' 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 physicians consensus and the automated classification of ST-segment deviations increased the sensitivity compared with the physician consensus alone by 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 by 35% compared with physician consensus alone (65% versus 48%, respectively $P < 0.001$) and the specificity remained comparable (96% versus 99%, respectively). This study suggests that the addition of automated computer interpretation of the ECG to physicians interpretation of the ECG may improve the identification of patients with acute MI (Aufderheide, T. P., Xue, Q., Dhala, A. A. et al , 2000).

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

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

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

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

With respect to clinical outcomes in the total population, there was a trend for a decrease in mortality for pre-hospital ECG patients versus in-hospital ECG, 6.7% versus 9.5%, respectively, adjusted odds ratio 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 odds ratio 0.75, 95%CI 0.56 to 1.01, *P* = 0.06) (Diercks, D. B., Kontos, M. C., Chen, A. Y. et al , 2009).

4.2.5.3 Health economic evidence

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

GDG were of the opinion that an ECG was mandatory in all patients with acute chest pain of suspected cardiac origin, and did not request further economic analysis.

4.2.5.4 Evidence to recommendations

Two high quality systematic reviews with a low risk of study incorporation bias with respect to the studies selected for the meta-analyses 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 (Aufderheide, T. P., Xue, Q., Dhala, A. A. et al , 2000).

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 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 elevation MI, pending confirmation of the diagnosis. Other ECG abnormalities are less diagnostic, but may be useful when part of the initial assessment, which includes the clinical history, to reach a provisional diagnosis pending confirmation. A normal ECG makes the diagnosis of an acute MI / ACS less likely, but is not definitive and the GDG emphasized that a normal ECG alone should not be used to exclude a diagnosis of MI / ACS without further evaluation and testing. In patients with normal or equivocal ECG findings on presentation, serial ECG testing may be helpful.

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

4.2.6 Early assessment in hospital

4.2.6.1 Other causes of chest pain

The differential diagnosis of patients presenting with chest pain is extensive, ranging from relatively benign musculoskeletal etiologies and l of 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. The Table 10 details the symptoms of some of the causes of non ischamic cardiac chest pain as published by The European Society of Cardiology Task Force Report (Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction, 2000).

Table 10
Non-ischaemic causes of chest pain
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

Table 10 **Non-ischaemic causes of chest pain** **Eur Heart J, Vol. 23, issue 15, August 2002.**	
Disease	Differentiating symptoms and signs
	A common cause of chest pain
Pulmonary embolism	Tachypnoea, hypoxaemia, hypocarbia No pulmonary congestion on chest X ray May resemble inferior wall infarction: ST elevation (II, III, aVF) Hyperventilation PaO_2 and $PaCO_2$ decreased
Hyperventilation	The main symptom is dyspnoea, as in pulmonary embolism Often a young patient Tingling and numbness of the limbs, dizziness $PaCO_2$ decreased, PaO_2 increased or normal An organic disease may cause secondary hyperventilation
Spontaneous pneumothorax	Dyspnoea is the main symptom Auscultation and chest X ray One sided pain and bound to respiratory movements
Aortic dissection	Severe pain with changing localization In type A dissection sometimes coronary ostium obstruction, usually right coronary with signs of inferoposterior infarction Sometimes broad mediastinum on chest X ray New aortic valve regurgitation
Pericarditis	Change of posture and breathing influence the pain Friction sound may be heard ST-elevation but no reciprocal ST depression
Pleuritis	A jabbing pain when breathing A cough is the most common symptom Chest X ray

Table 10 **Non-ischaemic causes of chest pain** **Eur Heart J, Vol. 23, issue 15, August 2002.**	
Disease	Differentiating symptoms and signs
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 requested from (Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction, 2000).	

Use of chest X ray

4.2.6.2 Evidence statements for chest X ray

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

Return to Recommendations

4.2.6.3 Clinical evidence for chest X ray

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

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

4.2.6.4 Health economic evidence

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

4.2.6.5 Evidence to recommendations

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

4.3 Early Management

4.3.1 Introduction

This section 4.2 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 that have a very highly likelihood of an acute MI or ACS, nor patients diagnosed with acute MI or ACS as these patients are not part of this guideline. Such patients should be managed according to other relevant guidelines. Studies in unselected acute chest pain populations were selected, with the exception of aspirin for which no literature was identified in patients with acute chest pain and a study in patients with acute MI in the emergency department was reviewed. There was a paucity of literature in patients with acute chest pain, and the studies in this population had very low patient numbers relative to the many studies in patients with acute MI and ACS.

4.3.2 Oxygen

4.3.2.1 Evidence statements for oxygen

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

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

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

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

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4.3.2.2 Clinical evidence

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

One systematic review was reviewed (Nicholson, Christopher, 2004). A second more recent systematic review (Meme Wijesinghe, Kyle Perrin, Anil Ranchord et al , 2008) identified 2 randomised controlled trials in addition to the studies identified by the first systematic review (Nicholson, Christopher, 2004). Rather than appraise the second systematic review it was decided to appraise the 2 randomised controlled trials individually (Wilson, A. T. and Channer, K. S., 1997) (Rawles, J. M. and Kenmure, A. C., 1976).

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

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

Five of the 9 studies reported metabolic data. Lactate levels were measured in 2 studies; one found oxygen reduced lactate levels in the patients tested, while the second study found no change with oxygen. Two studies examined lactate extraction ratios; 1 showing oxygen had no effect and the other indicating that ratios were worse with oxygen administration. Another study

found oxygen administration resulted in an increase in the cardiac enzyme aspartate aminotransferase (Nicholson, Christopher, 2004).

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

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

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

The first randomised controlled trial examined oxygen administration in patients who had had a suspected acute MI within the previous 24 hours and who were under 65 years (Rawles, J. M. and Kenmure, A. C., 1976). Patients were excluded if they had the following; clinical evidence of right or left heart failure, chronic bronchitis or emphysema or breathlessness from any other cause, transferred from other wards for treatment of arrhythmias, undergone cardiac arrest before admission, suffered from cardiogenic shock. One hundred and five consecutive patients were randomised to receive oxygen and 95 to receive air. Myocardial infarction was not confirmed in 25 patients in the oxygen group and 18 patients in the air group, and these patients were

excluded from subsequent analysis. Oxygen or compressed air was given through an MC mask at a flow rate of 6 l/min for 24 hours. The mean PaO_2 was higher in the oxygen group compared with the air group (18.2±1.56 versus 8.7±2.9 IU/ml, $P < 0.001$) (Rawles, J. M. and Kenmure, A. C., 1976).

During the study there was one death in the oxygen group and two deaths in the air group. Overall there were nine deaths in the oxygen group compared with three in the air group (9/80 patients (11%) in the oxygen patients versus 3/77 patients (4%) in the air group), although this difference was not significant 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±7.1 IU/ml for the oxygen group versus 80.7±6.6 IU/ml in the control group ($P < 0.05$). Oxygen administration increased sinus tachycardia compared with air ($P < 0.05$) (Rawles, J. M. and Kenmure, A. C., 1976).

The randomised controlled trial found that oxygen administration did not reduce the incidences of the following arrhythmias: atrial ectopics, atrial tachycardia, atrial flutter, atrial fibrillation, sinus bradycardia, junctional rhythm, accelerated idoventricular rhythm, ventricular ectopics, ventircular tachycardia, ventricular fibrillation, heart block. Systolic ejection times did not differ between the two groups on the first or second day. The study indicated that oxygen treatment had no benefit for patients with acute MI; rather the evidence suggests that there may be potential harm with oxygen treatment in patients with normal oxygen saturation levels (Rawles, J. M. and Kenmure, A. C., 1976).

The second randomised controlled trial examined the use of supplementary oxygen therapy and the role of pulse oximetry in 50 consecutive patients with acute MI admitted to the coronary care unit within six hours of the onset of thrombolytic therapy (Wilson, A. T. and Channer, K. S., 1997). Patients with central cyanosis, pulmonary disease requiring oxygen independent of the cardiac status or those in whom blood gas estimation showed a $PCO_2 > 5.5$ kPa and patients with left ventricular failure requiring inotropic support were excluded. Forty two subjects completed the study. Twenty two received

continuous oxygen at 4 l/min by face mask; 20 received no supplemental oxygen except for central cyanosis or respiratory distress. Patients were studied for the first 24 hours following admission to the coronary care unit (Wilson, A. T. and Channer, K. S., 1997).

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

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

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

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

- If hypoxaemic, the initial oxygen therapy is nasal cannulae at 2 to 6 l/min or simple face mask at 5 to 10 l/min unless oxygen saturation is < 85% (use reservoir mask) or if at risk from hypercapnia
- The recommended initial target saturation range, unless stated otherwise, is 94 to 98%
- If oximetry is not available, give oxygen as above until oximetry or blood gas results are available
- If patients have COPD or other risk factors for hypercapnic respiratory failure, aim at a saturation of 88 to 92% pending blood gas results but adjust to 94 to 98% if the $PaCO_2$ is normal (unless there is a history of respiratory failure requiring NIV or IPPV) and recheck blood gases after 30 to 60 min

4.3.2.3 Health economic evidence

No health economic evidence reporting the incremental value of oxygen use in the early management of the relevant patient group was found in the literature. Oxygen is in routine use and not expensive, (BP composite cylinder with integral headset to specification, 1360 litres costs £9.48).

4.3.2.4 Evidence to recommendations

No evidence was found which examined the efficacy of supplementary oxygen in unselected patients with chest pain of suspected cardiac origin, and the GDG appraised the evidence in patients with acute MI. The British Thoracic Society had also recently reviewed the evidence on this topic. Rather unexpectedly, given current clinical practice to administer oxygen routinely to patients with acute chest pain of suspected cardiac origin, the conclusion drawn from the available evidence from one well conducted systematic review and one well conducted randomised controlled trial, and further confirmed by the recommendations in the BTS 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 BTS guideline were used to inform the thresholds at which oxygen should be administered, and the target oxygen saturation to be achieved.

4.3.3 Pain Management

4.3.3.1 Evidence statements for pain management

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

2 One small randomised controlled trial in patients with suspected acute MI or unstable angina with chest pain that had been unresponsive to nitroglycerine found that morphine (10 mg) and nalbuphine (20 mg) reduced pain within 5 minutes after intravenous administration. Pain relief increased during the observed 120 minutes. There was no difference in the pain relief between the morphine and nalbuphine groups. There was no difference in respiration rate, systolic or diastolic blood pressure between the two groups nor in the side effects of nausea, dizziness or drowsiness. (Hew, E., Haq, A., and Strauss, H., 1987)

3 One small randomised controlled trial in patients with chest pain and suspected acute MI found that there was no difference in degree pain relief between nalbuphine (≤ 20 mg) and intravenous diamorphine (≤ 5 mg) plus metoclopramide (10 mg). Pain relief

occurred within 10 minutes of administration and up to the observed 120 minutes. No differences were reported in the side effects of nausea, vomiting or dizziness, nor in systolic diastolic blood pressure, heart rate between the two groups. (Jamidar HA, Crooks SW Adgey AA, 1987)

4 One small randomised controlled trial in patients with chest pain and suspected acute MI found that intravenous diamorphine (5 mg) was associated with greater complete pain relief compared with morphine (10 mg) and pentazocine (30 mg) 10 minutes after initial injection, pain relief with diamorphine (5 mg) and methadone were similar. Complete pain relief at 30, 60 and 13 min was similar in all four pain management groups. (Scott, M. E. and Orr, R., 1969).

5 One cohort study in patients with chest pain and suspected acute MI found that intravenous morphine administration (5 mg) reduced pain within 20 min and pain reduction remained for the observed 8 hours. Higher morphine requirement (5 mg repeated if necessary) was associated with the following; female gender, history of angina pectoris, previous chronic heart failure, initial degree of suspicion of acute MI, presence of ST-segment elevation on entry ECG, presence of ST-segment depression on entry ECG, and Q wave on entry ECG. In addition, morphine requirement was highest in patients with the greatest suspicion of MI, rather than patients with possible myocardial ischaemia. (Everts, B., Karlson, B. W., Herlitz, J. et al , 1998)

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

4.3.3.2 Clinical evidence

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

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

The first randomised controlled trial examined buprenorphine and diamorphine for pain relief in patients with suspected or ECG proven acute MI (Hayes, M. J., Fraser, A. R., and Hampton, J. R., 1979). There were three separate studies in 3 separate patient groups. Ten patients in study group 1 received buprenorphine (0.3 mg) and were monitored for haemodynamic changes. Seventy patients in study group 2 were randomised to receive either intravenous buprenorphine (0.3 mg) (50 patients) or sublingual buprenorphine 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±10 years, 49 men) or intravenous diamorphine (5 mg) (59 patients, 55±10 years, 42 men). The mean duration of chest pain was 5.5±7.3 hours. The time, degree and duration of pain relief were measured using an unmarked visual analogue scale which was scored by the patient, and scoring was expressed as a percentage of the initial score (Hayes, M. J., Fraser, A. R., and Hampton, J. R., 1979)

In the study group 1 all 10 patients had ECG-proven acute MI, and had had prior diamorphine treatment but required further analgesia for recurrent pain. The patients were all given intravenous buprenorphine (0.3 mg), and the systemic blood pressure, heart rate, and pulmonary artery pressure were monitored. Intravenous buprenorphine led to no significant change in heart rate, systemic diastolic blood pressure or systemic arterial systolic pressure.

There was a sustained fall in systemic arterial systolic pressure of about 10 mm Hg, however this did not reach statistical significance (at 1 h, t = 1.14191, P < 0.1). For study group 2 in patients with suspected acute MI, pain relief was measured for 45 min. The intravenous buprenorphine (0.3 mg) group achieved considerably faster pain relief compared with the sublingual buprenorphine (0.4 mg) group (Hayes, M. J., Fraser, A. R., and Hampton, J. R., 1979).

Pain relief in patients in study group 3 was monitored for 6 hours. Measurements from the visual analogue scale found that the mean starting pain score was similar in the two groups. Of the 59 patients in the intravenous buprenorphine (0.3 mg) group, 49% of patients did not require further analgesia after an initial dose compared with 42% in the diamorphine group (5 mg). At 5 min the percentage pain relief in the buprenorphine group was lower compared with diamorphine group (P < 0.01), however at 15 min the pain relief was similar in the two groups. There was no significant difference in the subsequent analgesia requirement for pain relief between the two groups during the 6 hour study period. No major side effects were reported in either group. Twelve patients in the buprenorphine group and 7 patients in the diamorphine group vomited in the 6 hour study period, but this difference between the two groups was not statistically significant. Twelve patients in the buprenorphine group and 15 patients in the diamorphine group were subsequently found to have inconclusive evidence of acute MI (Hayes, M. J., Fraser, A. R., and Hampton, J. R., 1979).

The second randomised controlled trial in patients with moderately severe or severe chest pain due to a suspected MI or unstable angina compared intravenous nalbuphine (20 mg) with intravenous morphine (10 mg) for pain relief (Hew, E., Haq, A., and Strauss, H., 1987). Patients were included if their pain was unresponsive to sublingual nitroglycerin. The exclusion criteria were; heart rate was less than 50 beats per min, 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, 21 men) or morphine (10 mg) (29 patients, mean age 62 years, 21 men) (Hew, E., Haq, A., and Strauss, H., 1987).

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

The mean pain scores for the nalbuphine group were consistently lower compared with morphine group, with the difference greatest at 5 minutes, (nalbuphine = 1.88, morphine = 3.48, $P = 0.08$). However the overall therapeutic response was not significant ($P = 0.10$). Pain relief in the nalbuphine group was consistently lower compared with morphine group (greatest at 5 minutes) however the overall therapeutic response was not significant ($P = 0.10$). Neither group had significant changes in systolic or diastolic blood pressure or heart rate. Respiration rate were similar in both groups and there was no clinically significant depression in respiration rate for either group. There was no significant difference in nausea, dizziness or drowsiness reported in the two groups. Neither group had a significant change in either systolic or diastolic blood pressure over the 120 minute observation period. Mean heart rate did not change significantly in either group during the observation period (Hew, E., Haq, A., and Strauss, H., 1987).

The third randomised controlled trial compared nalbuphine with diamorphine plus metoclopramide for pain relief in patients with suspected acute MI (Jamidar HA, Crooks SW Adgey AA, 1987). One hundred and seventy six patients met the inclusion criteria of moderate or severe chest pain due to suspected acute MI and no previous administration of analgesia. Of the 176 patients, 87 patients received nalbuphine (≤ 20 mg) (mean age 61 years, 51 men), and 89 patients received intravenous diamorphine (≤ 5 mg) with

metoclopramide (10 mg) (mean age 62 years, 30 men). Patients were withdrawn from the trial if they required further pain relief after 15 to 20 minutes (12.6% of patients in the nalbuphine group and 6.7% of patients in the diamorphine group) (Jamidar HA, Crooks SW Adgey AA, 1987).

The study reported pain relief at 10, 30, 60 and 120 minutes, any side effects, blood pressure and heart rate. The pain score rated by observers was; no pain (grade = 0), moderate pain defined as chest discomfort not associated with sweating or distress (grade = 2) and severe pain defined as severe pain accompanied by obvious distress (grade = 3). Seventy seven percent of patients in the morphine group and 69% of patients in the nalbuphine group had satisfactory pain relief at 10 minutes (grade = 0 or 1). Forty four percent of patients in the nalbuphine group and 39% of patients in the morphine group had total pain relief at 10 minutes (grade = 0), and the mean pain score was similar for both the nalbuphine and diamorphine group at each time assessment. There was no difference in the 2 groups in the number of drug doses or the overall summation of pain score at all time points. Pain relief reoccurred in 5 patients in the nalbuphine group and 2 patients in the diamorphine group but this difference was not significant (Jamidar HA, Crooks SW Adgey AA, 1987).

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

The fourth randomised controlled trial examined the pain relief effects of diamorphine, methadone, morphine and pentazocine all administered intravenously in 118 patients with suspected acute MI and severe or moderate chest pain (Scott, M. E. and Orr, R., 1969). The age range in the total study population was 30 to 79 years (79% of patients were aged between 50 to 69 years) and 89 patients were male. Patients received one dose of diamorphine (5 mg) (30 patients), methadone (10 mg) (31 patients), morphine (10 mg) (29

patients) or pentazocine (30 mg) (25 patients). Patients were excluded if they had cardiac shock, cardiac failure, severe nausea, pronounced bradycardia, had received potent analgesic or anti-emetic in previous 4 hours. The study reported pain relief at 10, 30, 60 and 120 minutes after drug administration. Pain was assessed as severe, moderate, mild, or absent following drug administration (Scott, M. E. and Orr, R., 1969).

The study reported that all four drugs gave pain relief to some extent in approximately 90% of the total study population at 10 and 30 minutes after administration. At the 10 minute time point, patients who received diamorphine had greater complete pain relief compared with both the morphine group ($P < 0.05$) and the pentazocine group ($P < 0.05$), while pain relief with methadone and diamorphine were similar. At 30 minutes complete pain relief was not significantly different in any of the groups and approximately 40% of patients in each group reported complete pain relief. Severe nausea requiring subsequent administration of an anti-emetic was needed in 8, 11, 4 and 7 patients in the diamorphine, methadone, morphine and pentazocine groups, respectively (no significant differences). Only patients in the pentazocine group had an increase in blood pressure from baseline compared with the other groups ($P < 0.05$), the other groups had no or little appreciable change in blood pressure compared with initial blood pressure (Scott, M. E. and Orr, R., 1969)..

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

Pain administration was 6.6±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 (Everts, B., Karlson, B. W., Herlitz, J. et al , 1998).

The study also examined patient characteristics that were associated with higher morphine requirement in 2988 patients over 3 days of hospitalisation. The following were independent predictors of higher morphine requirement ; male gender, history of angina, history of chronic heart failure, initial degree of suspicion of acute MI, presence of ST-segment elevation on entry ECG, presence of segment ST 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±0.2 mg. The study reported that after intravenous morphine administration there was a reduction in the diastolic blood pressure and a similar trend in systolic blood pressure but this was not significant. After intravenous morphine the heart rate was reduced, but respiratory frequency remained the same before and after intravenous morphine in all patients (Everts, B., Karlson, B. W., Herlitz, J. et al , 1998).

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

hundred and fifteen patients were male (Herlitz, J., Richter, A., Hjalmarson, A. et al , 1986).

Of ninety eight percent of patients that had chest pain at home, only 51% had pain on arrival at the coronary care unit. 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 congestive heart failure did not alter the pattern of pain. Patients with higher pain intensity at home had more pain in the first 24 hours, and a longer duration of pain compared with patients with a lower home pain intensity score, despite receiving more morphine. Pain course was not affected by initial heart rate, however higher initial systolic blood pressure was associated a more severe pain course, a longer pain duration, and a greater morphine requirement (Herlitz, J., Richter, A., Hjalmarson, A. et al , 1986)..

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

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

the pain score was not validated within the study or against other known pain scores.

4.3.3.3 Health economic evidence

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

4.3.3.4 Evidence to recommendations

The GDG considered that prompt and effective management of chest pain was an important priority in the management of patients with acute chest pain of suspected cardiac origin and that patients should be treated to be completely pain free. The GDG's appraisal of the evidence starting on page 117, 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 opiates should be used if nitroglycerin is not effective in achieving complete pain relief.

4.3.4 Anti-platelet therapy

4.3.4.1 Evidence Statements for anti-platelet therapy

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

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

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

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4.3.4.2 Clinical evidence

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

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

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

Cumulative mortality rates at 7 and 30 days were assessed from medical charts. There was a lower mortality rate in patients who received aspirin before admission to hospital compared with those post admission at 7 days (2.4% versus 7.3%, $P < 0.002$) and 30 days (4.9% versus 11.1%, $P < 0.001$). After adjustments for baseline and prognosis-modifying factors (age, gender, history of MI, diabetes mellitus, hypertension, Killip Class on admission and

primary reperfusion) the result remained significant at 7 days (OR 0.43 95%CI 0.18 to 0.92), and was reported as significant at 30 day follow up (OR 0.60 95%CI 0.32 to 1.08). Compared with post hospital aspirin therapy, pre hospital administration of aspirin was associated with a reduction in the following in-hospital complications; asystole ($P < 0.001$), resuscitation ($P < 0.001$) and ventilation ($P < 0.002$) (Barbash, Israel M., Freimark, Dov, Gottlieb, Shmuel et al , 2002).

A subgroup analysis was conducted of both patients selected for primary reperfusion (thrombolysis or primary PTCA) (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 elevation MI (Barbash, Israel M., Freimark, Dov, Gottlieb, Shmuel et al , 2002).

4.3.4.3 Health Economic Evidence

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

4.3.4.4 Evidence to recommendations

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

in high risk patients, 2002) and in one cohort study in patients with acute MI found that pre hospital administration was associated with a lower mortality compared with administration at or during admission hospital admission. The GDG concluded that a single loading dose of aspirin, in a dose consistent with that recommended in guidelines for acute MI or ACS, should be given as soon as possible to patients with acute chest pain of suspected cardiac origin, pending further assessment. However, the GDG were of the opinion that other anti-platelet agents, such as clopidogrel, should only be given following an initial assessment which had refined the diagnosis, and that management of those with acute MI or ACS be informed by other relevant guidelines.

4.4 Investigations and Diagnosis

4.4.1 Introduction

Cardiac biomarkers are proteins that are released into the cardiac interstitium due to the compromised integrity of myocyte cell membranes as a result of myocardial ischaemia. Up to the1980s, there were only a few assays available for the retrospective detection of cardiac tissue necrosis, such as the enzymatic methods for creatine kinase and lactate dehydrogenase catalytic activities. However, in the last 20 years highly sensitive and specific assays for the detection of myocardial necrosis have been developed including troponin I, troponin T and myoglobin. Assays for markers of myocardial function, including cardiac natriuretic peptides, have also become available. The measurement of some of these newer biomarkers has been incorporated into internationally recognised diagnostic criteria for acute MI because of their greater diagnostic accuracy compared with older markers. The WHO traditionally defined acute MI as requiring the presence of at least 2 of 3 diagnostic criteria; an appropriate clinical presentation, typical ECG changes, and raised cardiac enzymes essentially total CK or its MB isoenzyme (CK-MB) activities (Gillum, R. F., Fortmann, S. P., Prineas, R. J. et al , 1984). The Joint European Society of Cardiology (ESC) and the American College of Cardiology (ACC) committee published a consensus document in 2000 for a new definition of MI (Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology

Committee for the redefinition of myocardial infarction, 2000). The ESC / ACC definition of acute MI required the rise and fall of a biomarker of myocardial necrosis (unlike the WHO definition which did not stipulate a fall) together with other criteria; ischaemic symptoms, development of pathological Q waves. The ECC / ACC definition was updated in 2007 owing to considerable advances in the diagnosis and management of MI since the its original publication, and it has been adopted as a universal definition of myocardial infarction (Thygesen, K., Alpert, J. S., and White, H. D., 2007) The full definition is given in section XXX. Specifically for biomarkers it states;

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

Troponin I and T

Troponin is a complex of three polypeptides found in muscle fibres. One polypeptide (troponin I) binds to actin, another (troponin T) binds to tropomyosin, and the third (troponin C) binds to calcium ions. Calcium ions bind to troponin, the troponin changes shape, forcing tropomyosin away from the actin filaments. Myosin cross-bridges then attach onto the actin resulting in muscle contraction. Skeletal and cardiac forms are structurally distinct, and antibodies have been developed that react only with the cardiac forms of troponin I and troponin T. Troponin I and T are first detected 3 to 4 hours after an acute MI, and duration of detection of troponin I may be 7 to 10 days, duration of detection of troponin T may be up to 7 to 14 days.

Creatinine kinase (CK)

Creatinine kinase is an enzyme responsible for transferring a phosphate group from ATP to creatinine. CK enzyme consists of two subunits, which can be either B (brain type) or M (muscle type). There are, therefore, three different isoenzymes: CK-MM, CK-BB and CK-MB. Total CK (the activity of the MM, MB, and BB isoenzymes) is not myocardial-specific. However, the MB isoenzyme (also called CK-2) comprises about 40% of the CK activity in cardiac muscle, and 2% or less of the activity in most muscle groups and

other tissues. MB usually becomes abnormal 3 to 4 hours after an MI, peaks in 10 to 24 hours, and returns to normal within 72 hours.

Myoglobin

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

4.4.2 Use of biomarkers

4.4.2.1 Evidence statements for biomarkers

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

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

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

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

5 The sensitivity of troponins achieves a maximum 10 to12 hours after onset of symptoms or 6-9 hours after presentation. (Ebell, M. H., Flewelling, D., and Flynn, C. A., 2000),

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

8 There is health economic evidence to show that biomarker measurement at presentation, and at 6 hours after onset of pain, is also cost-effective (£18,567/QALY in 2000) compared with a strategy of testing at presentation only (Goodacre, S. and Calvert, N., 2003).

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

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

Return to Recommendations

4.4.2.2 Clinical evidence

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

The following biomarkers were assessed troponin I, troponin T, creatine kinase (CK), creatine kinase-MB (CKMB), creatine kinase-MB isoforms (CKMB isoforms) and myoglobin. Appendix C summarizes the statistical results of the cardiac biomarkers' diagnostic performance for all the studies identified.

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

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

The systematic review identified 7 studies that evaluated the performance of a single troponin I test in the diagnosis of acute MI. However, 3 studies did not report specificity data and were excluded from analyses. Two of the 4 included studies were of all eligible emergency department patients, while the other 2 studies were in patients admitted to the hospital from the emergency department. Reported troponin I testing for all studies was at time of presentation with acute chest pain. From meta-analyses, the sensitivity of troponin I was 39% (95%CI 10% to 78%) and the specificity was 93% (95%CI 88% to 97%). The prevalence of acute MI in the 4 studies ranged from 6% to 39% with a total number of 1149 patients. Detail of the timing of the troponin I test from onset of symptoms was not given for the individual studies, except that it was reported that in one study where patients had a mean duration of symptoms of 2 hours the sensitivity was 23%, while in a second study where patients had a average of 7 hours of symptoms the sensitivity was 100%. This marked variation in test sensitivity was attributed to the heterogeneity in study participants. No studies were identified that examined the use of single troponin I for the identification of partients with ACS (Balk, E. M., Ioannidis, J. P., Salem, D. et al , 2001).

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

The systematic review identified 9 studies that evaluated the diagnostic performance of a single troponin T test; however 3 studies were excluded due to insufficient data reporting. Of the remaining 6 studies, 4 studies recruited all eligible patients in the emergency department, 1 study drew blood prior to arrival to the emergency department, and 1 study only included patients admitted to the hospital. The prevalence of acute MI ranged from 6% to 39% in the 6 studies. The study that only included patients admitted to the hospital had an acute MI prevalence of 15%. Reported troponin T testing for all studies was at time of presentation with acute chest pain, however, information on the timing of the single troponin T test from onset of symptoms was not given. The sensitivity range for troponin T in the 6 studies was 15% to 53% (1348 patients), and the specificity range was 89% to 98%. The sensitivity and specificity for the study that only included patients admitted to the hospital were 15% and 97%, respectively. Meta-analyses for all six studies gave a troponin T sensitivity of 39% (95% CI 26% to 53%) and a specificity of 93% (95% CI 90% to 96%). Meta-analyses for the 5 studies that recruited all eligible patients in the emergency department (1171 patients) gave a troponin T sensitivity of 44% (95% CI 32% to 56%) and a specificity of 92% (95% CI 88% to 95%). No studies were identified that examined the use of single troponin T for the identification of partients with ACS (Balk, E. M., Ioannidis, J. P., Salem, D. et al , 2001).

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

reported sensitivities of 31% and 45% for the diagnosis of ACS, respectively, and specificities of 98% and 97%, respectively (Balk, E. M., Ioannidis, J. P., Salem, D. et al , 2001).

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

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

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

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

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

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

gave a sensitivity of 49% (95%CI 41% to 57%) and a specificity of 93% (95%CI 88% to 96%) (in total). No information on the timing of the test from onset of symptoms was given. One study was identified that examined the single myoglobin test for the diagnosis of ACS. Eighty six patients were enrolled, and the prevalence of acute coronary syndrome, sensitivity and specificity were 52%, 16% and 100%, respectively.

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

The second systematic review (search date 1999) evaluated the use of troponin I and troponin T in the diagnosis of acute MI in patients presenting to the emergency department with acute chest pain (Ebell, M. H., Flewelling, D., and Flynn, C. A., 2000). Six studies were identified that evaluated the diagnostic performance of troponin I Prevalence of acute MI in the identified studies was not reported. Meta analyses for the sensitivity and specificity of troponin I at 1, 2, 3, 4, 5 and 6 hours from onset of pain are detailed in Table 11. The most accurate test performance was at 6 hours from onset of pain with a sensitivity of 90% and a specificity of 95% (Ebell, M. H., Flewelling, D., and Flynn, C. A., 2000).

Fourteen studies were identified that evaluated the diagnostic performance of troponin T in the identification of patients with acute MI. Prevalence of acute MI in the identified studies was not reported. Sensitivity and specificity values are detailed in Table 11 for troponin T at 2 assay cutoff off values of; > 0.1 ng/ml and > 0.2 ng/ml at the following time points; 1, 2, 3, 4, 6, 8 and 10 hours

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

Table 11

Summary of Data for Troponin T and I Tests for Diagnosing AMI					
	Hours from onset of chest pain	Sensitivity	Specificity	PLR	NLR
Troponin T>0.1*					
	1	0.47	0.87	3.7	0.6
	2	0.53	0.87	3.9	0.5
	3	0.58	0.86	4.1	0.5
	4	0.64	0.85	4.2	0.4
	6	0.74	0.83	4.4	0.3
	8	0.84	0.81	4.5	0.2
	10	0.93	0.80	4.6	0.1
Troponin T>0.2†					
	1	0.14	0.87	1.1	1.0
	2	0.33	0.87	2.5	0.8
	3	0.50	0.86	3.5	0.6
	4	0.65	0.85	4.3	0.4
	6	0.86	0.83	5.1	0.2
	8	0.96	0.81	5.2	0.05
	10	0.96	0.80	4.7	0.05

Table 11

Summary of Data for Troponin T and I Tests for Diagnosing AMI					
Troponin 1>0.1‡					
	1	0.13	0.95	2.7	0.9
	2	0.34	0.95	6.8	0.7
	3	0.52	0.95	10	0.5
	4	0.67	0.95	13	0.34
	5	0.80	0.95	16	0.2
	6	0.90	0.95	18	0.1

NOTE: Values are calculated from the best-fit curve for sensitivity and specificity. While troponin 1 appears to be more accurate, these data are based on the results of a single relatively small study and should be interpreted with caution.

AMI denotes acute myocardial infarction; PLR PLR; NLR NLR.

Permissions requested from original source respectively (Ebell, M. H., Flewelling, D., and Flynn, C. A., 2000).

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

range), and urgent revascularization during admission or up to 30 days post admission, and length of stay in the coronary care unit (Alp, N. J., Bell, J. A., and Shahi, M., 2001).

Table 12 details the outcome results for the standard management and troponin I protocol groups based upon ECG findings and troponin I findings. As shown Table 12 the troponin I protocol allowed earlier discharge of the low risk group (normal ECG) compared with the standard management group (mean10 hours versus mean 30 hours, respectively) without an increased incidence of adverse events. The troponin I protocol had a greater accuracy compared with the standard management protocol for identification of the moderate risk of cardiac events group (troponin negative / ECG indicative of ischaemia; 15% major adverse event rate during admission and 30 day follow up), and the high risk group (troponin I positive; 75% major adverse event rate) (Alp, N. J., Bell, J. A., and Shahi, M., 2001).

Table 12
Combined pre-discharge and 30-day follow-up outcomes

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

MI, non-fatal myocardial infarction; IQR, interquartile range, iECG, ischaemic ECG; nECG, normal ECG; TnI, troponin I.

Permission requested from original source (Alp, N. J., Bell, J. A., and Shahi, M., 2001)55(Alp, N. J., Bell, J. A., and Shahi, M., 2001).

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

Of the 502 patients, ECG findings identified 111 patients with ST elevation acute MI and 35 patients with non ST elevation acute MI. One hundred and thirty nine troponin T positive patients and 7 troponin T negative patients were diagnosed as having either an ST elevation or non ST elevation acute MI (the 7 troponin negative patients were diagnosed based on ECG changes and ischaemic symptoms alone). Sensitivity, specificity, positive predictive value and negative predictive values for the use of elevated troponin T in the diagnosis of acute MI were 95% , 94%, 87% and 98%, respectively (Guo, Xiaobi, Feng, Jianzhang, and Guo, Hengshan, 2006).

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

and a specificity of 100%. The sensitivity and specificity of serial troponin T were 90% and 91%, respectively. The sensitivity and specificity of serial CK-MB were 90% and 90%, respectively. The serial CK-MB isoforms test had the lowest sensitivity compared with the other biomarkers at 70% with a specificity of 99%. The serial myoglobin test had the lowest specificity compared with other biomarkers at 75%, with a sensitivity of 80%. Additional statistical diagnostic performance results are given in (Kost, G. J., Kirk, J. D., and Omand, K., 1998).

The third study determined sensitivities of troponin I, CK-MB, myoglobin and a combined triple test of troponin I, myoglobin and CK-MB, at 0 up to > 72 hours from the onset of chest pain (Chiu, A., Chan, W. K., Cheng, S. H. et al , 1999). The diagnostic thresholds for troponin I, CK-MB, myoglobin were < 2.0 ng/ml, < 0.5 ng/ml and < 90 ng/ml, respectively. Patients were included in the study if an initial diagnosis of acute MI was made based on two of the three criteria; (1) development of Q wave, (2) ST depression or elevation (3) serial changes in CPK. Eighty seven patients were recuruited from the emergency department with a mean age of 67±years, and 59 were men (Chiu, A., Chan, W. K., Cheng, S. H. et al , 1999).

The sensitivities of the biomarkers for the diagnosis of acute MI at the different time points are detailed in Table 13. Specificity values were not determined. None of the biomarkers had good sensitivity within the first 4 hours after an acute MI. Both myoglobin and CK-MB had greatest sensitivity between 4 to 8 hours, while troponin I and CKMB were had greatest sensitivity between 8 hours to 24 hours. The combined triple test of troponin I, myoglobin and CK-MB had excellent sensitivity from 4 to 72 hours (Chiu, A., Chan, W. K., Cheng, S. H. et al , 1999).

Table 13

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

Hours since infarct	0-4	4-8	8-12	12-24	24-48	48-72	>72
Patients (n)	34	26	41	76	76	69	67

Table 13

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

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

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

The fourth study examined the diagnostic performance of the serial measurement of biomarkers in patients with acute chest pain of suspected cardiac origin admitted to a coronary care unit (Eggers, Kai Marten, Oldgren, Jonas, Nordenskjöld, Anna et al , 2004). Patients were included if chest pain was > 15 min duration in the previous 12 hours; patients with evidence of pathological ST-segment elevation on admission ECG requiring immediate perfusion therapy were excluded. The study recruited 197 patients with a median age of 66 years (range 55 to 75 years) and 130 were male. Troponin I, CK-MB and myoglobin were measured at presentation and 6 and 12 hours after presentation; the assay cut off value for diagnosis for troponin I was 0.1 μg/l, for CK-MB was 3.5 μg/l and for myoglobin in men was 98 μg/l and for women was 56 μg/l. The index event was classified by an independent end point evaluator. Acute MI was diagnosed if one on the following was fulfilled in addition to the acute chest pain; development of Q wave with 24 hours, or elevated troponin I levels within 24 hours. Acute coronary syndrome was diagnosed if new ST-segment depression or T wave inversion occurred within 24 hours (Eggers, Kai Marten, Oldgren, Jonas, Nordenskjöld, Anna et al , 2004).

The median time from onset of chest pain to the first blood sample in the study participants was 5.5 hours (interquartile range 3.4 to 9.6 hours). The cause of admission was as follows in the 197 patients; acute MI 43 patients (22%), acute coronary syndrome 30 patients (15%), other heart disease 43 patients (10%), and unspecified chest pain 19 patients (32%). Table 14 details sensitivities of the biomarkers for the diagnosis of acute MI at a given specificity of 95%. Troponin I gave the highest sensitivity at all time points, although an acceptable high sensitivity of ≥ 95% was not found before 12 hours post admission. CK-MB and myoglobin had poorer diagnostic performance compared with troponin I. The cumulative sensitivities at 2 hours for troponin I, CK-MB and myoglobin were 93%, 79% and 67%, respectively. The cumulative specificities at 2 hours for troponin I, CK-MB and myoglobin were 81%, 88% and 86%, respectively. At 6 hours the cumulative sensitivities for troponin I and CK-MB were 98% and 81%, and the corresponding specificities were 76% and 88% respectively (Eggers, Kai Marten, Oldgren, Jonas, Nordenskjöld, Anna et al , 2004).

Table 14
Sensitivities of single markers at a given specificity of 95%

	0 Hours (n=176)	6 Hours (n=180)	12 Hours (n=172)
Troponin I	79 (63-92)	89 (73-97)	100 (90-100)
Cutoff	0.20 µg/L	0.19 µg/L	0.16 µg/L
CK-MB	66 (48-81)	81 (65-93)	77 (61-90)
Cutoff	4.3 µg/L	3.6 µg/L	3.5 µg/L
Myoglobin	63 (45-79)	43 (27-62)	
Cutoff (men)	120 µg/L	142 µg/L	
Cutoff (women)	68 µg/L	81 µg/L	

Permissions requested from original source (Eggers, Kai Marten, Oldgren, Jonas, Nordenskjöld, Anna et al , 2004).

The fifth study examined the diagnostic performance of troponin I and CK-MB in the identification of acute MI (Falahati, Alireza., Sharkey, Scott W.,

Christensen, Dane. et al , 1999). Three hundred and twenty seven consecutive patients were recruited; inclusion and exclusion criteria were not reported. The diagnosis of acute MI was according to World Health Organisation criteria (Gillum, R. F., Fortmann, S. P., Prineas, R. J. et al , 1984). The assay cut off point for diagnosis of acute MI was 0.8 μg/l for troponin I, and 5.0 μg/l for CK-MB. The study reported one result for both sensitivity and specificity based on the “peak concentration” results for each biomarker; for troponin I this was between 12 to 18 hours, and for CK-MB this was between 6 to 12 hours (Falahati, Alireza., Sharkey, Scott W., Christensen, Dane. et al , 1999).

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

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

Acute MI was diagnosed in 44 of the 975 study participants (4.5%). The sensitivity and specificity of myoglobin at admission were 22% and 88%, respectively. The sensitivity and specificity of myoglobin at 2 hours were 22% and 88%, respectively. The sensitivity and specificity of CK-MB at admission

were 0 and 98%, respectively. The sensitivity and specificity of CK-MB at 2 hours were 91% and 78%, respectively (Fesmire, Francis M., Christenson, Robert H., Fody, Edward P. et al , 2004).

The seventh diagnostic study evaluated a rapid qualitative beside immunoassay for troponin T in the pre hospital setting for the diagnosis of acute MI (Gust, R., Gust, A., Böttiger, B. W. et al , 1998). Sixty eight patients with acute, central, crushing chest pain strongly suspected to be acute MI were included. The chest pain had to be radiating to the neck or one or both shoulders and not be relieved by rest or sublingual glyceryl trinitrate. The mean age of study participants was 69±12 years, and 47 were male. The assay troponin T cut of value for diagnosis of acute MI was 0.2μg/l (Gust, R., Gust, A., Böttiger, B. W. et al , 1998).

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

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

Cardiology Committee criteria and recorded at hospital discharge (Planer, David, Leibowitz, David, Paltiel, Ora et al , 2006).

A total of 238 patients (68%) were sent home by the primary care physician, and 111 patients (38%) were referred to the emergency department. Of these 111 patients, 4 had positive troponin tests. A diagnosis of acute MI was confirmed in-hospital in all 4 patients. Of the remaining 107 troponin negative patients that had been referred to the emergency department, only 42 were hospitalised (39%), one of which was diagnosed with acute MI after a troponin T elevation 48 hours after hospital admission. A further 17 patients were diagnosed with acute coronary syndrome. Follow up at 2 months of the 238 patients that were sent home by the primary care physician found that 1 patient had an acute MI and 1 patient had unstable angina. The positive predictive value of the primary care physician to predict hospitalization was 41%, and the negative predictive value was 94%. The overall prevalence of acute MI was 1.7%. The sensitivity and specificity of community troponin T testing for the diagnosis of acute MI within 72 hours were 83% and 100%, respectively (Planer, David, Leibowitz, David, Paltiel, Ora et al , 2006).

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

Of the 267 patients, 60 patients had a final diagnosis of acute MI based on World Health Organization criteria, and 26 patients had acute coronary artery syndrome based on class III criteria in the Braunwald classification (Braunwald, E., 1989). The sensitivity and specificity for troponin T were 87%

and 94%, respectively. The sensitivity and specificity for CK-MB were 47% and 83%, respectively. The sensitivity and specificity for serial CK-MB were 95% and 87%, respectively (Zarich, Stuart W., Qamar, Asad U., Werdmann, Michael J. et al , 2002).

The tenth study evaluated establishing a gradient of risk in patients with acute coronary syndrome using serial troponin I measurements (al Harbi, Khalid., Suresh, C. G., Zubaid, Mohammad. et al , 2002). The study included 124 patients, 86 patients in group 1 who had suspected acute MI or acute coronary syndrome, and 38 control subjects who were healthy and age-matched with no history of cardiovascular disease or any other chronic disease. Group 1 patients were admitted to a coronary care unit for further evaluation. Only Group 1 patients had serial troponin testing at presentation and 8 and 16 hours after presentation. Group 2 subjects had a single troponin I test. The assay cut off value was 0.05 ng/ ml (al Harbi, Khalid., Suresh, C. G., Zubaid, Mohammad. et al , 2002).

Of the 86 patients in group 1, 51 patients were diagnosed with acute MI based on classical clinical symptoms and development of Q wave and 35 patients were diagnosed with acute coronary syndrome based on Braunwald classification (Braunwald, E., 1989) and absence of ST-segment abnormalities on ECG. Table 15 details the diagnostic performance results for troponin I. Only 1 healthy control of 38 had a troponin I value > 0.1 ng/ml, which was 0.121 ng/ml. Thirty two healthy control subjects (84%) had troponin I values < 0.05 ng/ml. The 99^{th} percentile value in the healthy study population was estimated to be 0.05 ng/ml (al Harbi, Khalid., Suresh, C. G., Zubaid, Mohammad. et al , 2002).

Table 15
Diagnostic sensitivity and specificity for troponin I measurements

	Acute MI		Acute coronary syndrome		
	>0.05 ng/ml	>0.3 ng/ml	>0.05 ng/ml	<0.3ng/ml	>0.05 & <0.3 ng/ml
Sensitivity, %					
TnI-1 admission	60	38	38	85	35
TnI-2 8 hours	88	80	62	74	50
TnI-3 16 hours	93	87	61	76	41
Specificity, %					
TnI-1 admission	82	93	55	21	84
TnI-2 8 hours	72	86	13	45	90
TnI-3 16 hours	79	88	6	47	92

Permissions requested from original source (al Harbi, Khalid., Suresh, C. G., Zubaid, Mohammad. et al , 2002).

The eleventh study compared the diagnostic performance of troponin T, CK and myoglobin in patients with acute chest pain presenting to the emergency department (Vatansever, S., Akkaya, V., Erk, O. et al , 2003). Thirty three patients diagnosed with acute MI based on ST elevation and 27 healthy control subjects were included in the study. The mean age in the acute MI group was 51±11 years, and 28 patients were male, and the mean age in the control group was 51±12 years, and 25 subjects were male. The assay threshold values for diagnosis for the biomarkers were not given (Vatansever, S., Akkaya, V., Erk, O. et al , 2003).

Troponin T, myoglobin and CK testing was performed presentation and 2 hours after presentation in the acute MI patients and one single test was performed on the controls. Sensitivity and specificity values for CK were 64% and 90% at admission, respectively, and 79% and 90% at 2 hours after admission, respectively. Sensitivity and specificity values for troponin T were 76% and 90% at admission, respectively, and 97% and 90% at 2 hours after admission, respectively. Sensitivity and specificity values for myoglobin were 85% and 90% at admission, respectively, and 97% and 90% at 2 hours after admission, respectively. The biomarker levels in the control subjects were not

reported numerically, but shown graphically to be less than those of the acute MI patient group at the 2 time points for all 3 (Vatansever, S., Akkaya, V., Erk, O. et al , 2003).

The twelfth study examined the diagnostic performance of myoglobin, troponin T, troponin I and CK-MB subforms, total CK-MB activity and total CK-MB mass for the identification of patients with acute MI (Zimmerman, J., Fromm, R., Meyer, D. et al , 1999).Testing was performed at presentation to the emergency department and at 1, 2, 4, 6, 10, 18 and 22 hours after presentation. The assay cut off point values for acute MI diagnosis, for troponin I was 1.5 ng/ml, for troponin T was 0.1 ng/ml, for CK-MB subforms was MB2 to MB1 ratio of 1.6, for total CK-MB activity was 9 IU/l, for total CK-MB mass was ≥7 ng/ml, and for myoglobin was 85 ng/ml. Nine hundred and fifty five were included. The inclusion criteria were; chest pain lasting for 15 minutes or longer, and occurring within the previous 24 hours, and age > 21 years. The mean age was 55 ±13 years and 571 were male. The diagnostic criteria for acute MI was a CK-MB mass ≥7 ng/ml and a CK-MB index (CK-MB mass/CK) ≥2.5% determined by the results of the core laboratory in ≥ 2 samples obtained in the first 24 hours after hospital arrival or in 1 sample if only one was available for analysis (Zimmerman, J., Fromm, R., Meyer, D. et al , 1999).

Acute MI was confirmed in 119 of 955 patients (13%) based on CK-MB mass criteria. ST elevation on ECG was only found in 45% of these patients. Thirty six patients had Q wave infarcts and 83 patients had non Q wave infarcts. As detailed in Table 16 CK-MB subforms was most sensitive and specific (91% and 89%, respectively) within 6 hours of chest pain onset, followed by myoglobin. For late diagnosis, total CK-MB activity was the most sensitive and specific (96% and 98%, respectively) at 10 hours from onset, followed by troponin I (Zimmerman, J., Fromm, R., Meyer, D. et al , 1999).

Table 16

Early Diagnosis				Late Diagnosis			
Marker	2h	4h	6h	10h	14h	18h	22h
CK-MB subforms							
Sensitivity	21.1	46.4	91.5	96.2	90.6	80.9	53.1
Specificity	90.5	88.9	89.0	90.2	90.0	89.9	92.2
Myoglobin							
Sensitivity	26.3	42.9	78.7	86.5	62.3	57.5	42.9
Specificity	87.3	89.4	89.4	90.2	88.3	88.8	91.3
Troponin T							
Sensitivity	10.5	35.7	61.7	86.5	84.9	78.7	85.7
Specificity	98.4	98.3	96.1	96.4	96.1	95.7	94.6
Troponin I							
Sensitivity	15.8	35.7	57.5	92.3	90.6	95.7	89.8
Specificity	96.8	94.2	94.3	94.6	92.2	93.4	94.2
Total CK-MB activity							
Sensitivity	21.2	40.7	74.5	69.2	98.1	97.9	89.8
Specificity	100.0	98.8	97.5	97.5	96.1	96.9	96.2
Total CK-MB mass							
Sensitivity	15.8	39.3	66.0	90.4	90.5	95.7	95.7
Specificity	99.2	98.8	100.0	99.6	98.9	99.6	99.1

Permissions requested from original source (Zimmerman, J., Fromm, R., Meyer, D. et al , 1999).

Values are percentages

4.4.2.3 Universal definition of acute MI

The universal definition of an MI is;

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

- Symptoms of ischaemia

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

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

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

4.4.2.4 Health Economic Evidence

Four papers have been included in the review of the health economics literature. The first study (Mant, J., McManus, R. J., Oakes, R.-A. L. et al , 2004) was an HTA that included a Monte Carlo decision analytic simulation model to evaluate the cost-effectiveness of four diagnostic strategies for suspected ACS. The model was used to assess the incremental cost-effectiveness of adding hospital point of care troponin-T testing to determine whether to administer thrombolytic therapy to patients with negative A&E resting ECGs. The model structure facilitates two sub-analyses which

consider the incremental benefit of troponin-T testing for patients with and without pre-hospital telemetry ECG.

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

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

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

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

used in the analysis, but the modelled test sensitivities and specificities are included in Table 17.

Table 17
Sensitivities and specificities of testing strategies (range used for sensitivity analysis)

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

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

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

Base case results were insensitive to variation of prevalence of acute myocardial infarction or unstable angina; AMI or UA health utility values; mortality estimates; treatment effect estimates; costs of treating AMI and UA; cost of terminal care; and cost of long term treatment of survivors. Results

were sensitive to variation in the cost of each strategy, the cost of ruling out false positives, and the effect of false positive diagnosis on quality of life.

The authors conclude that strategies based on short periods of observation are likely to represent a more efficient use of resources than those requiring overnight admission. However, it is notable that the costs of cardiac biomarkers have come down considerably since this study was published in 2003. Therefore, if the analysis were adjusted to reflect this reduction in unit prices, the current estimate of incremental cost per QALY gained of single and serial biomarker measurements compared with no testing is likely to be considered even more cost-effective.

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

Patients randomised to the intervention group (n = 447) received a standard clinical evaluation of serial ECG and CK-MB determinations with the addition of serial Troponin-T determinations measured at presentation and 3 and 12 hours post presentation. The control group (n=409) received standard clinical evaluation without serial Troponin-T measurements. Primary study endpoints were emergency department and hospital length of stay and total charges. Secondary endpoints included death and nonfatal MI at 30 days post-discharge.

Within the group of patients presenting with chest pain, the authors reported a stronger trend toward a reduced length of stay and significant reduction in total charges in the intervention group compared with the control group. In patients with ACS, both length of stay and total charges were significantly lower in the intervention group. Amongst patients without ACS, fewer

intervention group patients were admitted to hospital compared with the controls and there was a significant reduction in length of stay. The authors indicate that Troponin-T determinations appear to be particularly useful in patients who have a falsely elevated CKMB values. Cardiac events at 30 days occurred in 3.1% of patients and did not differ between intervention and control groups for the whole cohort and subgroups.

The authors conclude by saying that the utilisation of Troponin-T led to a 20-25% reduction in length of stay and total charges in high and low risk patients with and without ACS and a 7-11% reduction in unnecessary admissions. On average, total charges for patients in the intervention group were $1,540 less than for those in the control group. This represents a potential cost savings of $920 per patient. The authors assert that the annual savings to the hospital based on this analysis were estimated at $4 million in total charges ($2.4 million in costs). Savings are predominantly due to reduced length of stay in patients with and without ACS and to reduced admissions for patients without ACS in the Troponin-T group.

Finally, a prospective study (Choi, Y. F., Wong, T. W., and Lau, C. C., 2004) was undertaken to assess the value and cost saving potential of three cardiac biomarkers – CKMB, myoglobin and Troponin-T – in the diagnosis of patients with chest pain presenting to a Hong Kong emergency department. The final diagnosis was defined as either acute MI, ischaemic heart disease with no proven infarction or atypical chest pain without ischaemic heart disease. The study presents a simple cost-benefit analysis, with effectiveness measured as the cost of resources not used when unnecessary admission was avoided and when future acute MIs were prevented through diagnosis with cardiac biomarkers.. The perspective was unclear, but only direct medical costs measured in current (assumed 2003/04) Hong Kong dollars were included.

In terms of diagnostic value, the performance of Troponin-T was superior to CK-MB and myoglobin. The sensitivity and specificity of Troponin-T was 100% and 99% respectively. For CK-MB, sensitivity was 57% and specificity was 94%. Myoglobin had a very low sensitivity of 29% and specificity of 89%.

Results of the economic analysis showed that testing for Troponin-T would yield a cost savings of an estimated of HK$171,000 compared with testing for CK-MB. This was attributed to the superior sensitivity and specificity of Troponin-T over CK-MB. Although the Troponin-T test was about HK$20 more expensive per unit, the savings generated by avoiding unnecessary hospital admissions (HK$142,000) and from correctly diagnosing significant CAD and thus avoiding future AMI (HK$53,200) made it a cost saving option. The study deemed myoglobin to be of no value due to its lack of specificity. No sensitivity analysis was undertaken.

The authors admit that theirs was an over-simplified analysis for the reason that many costs and/or savings were not included. They suspect their estimation of savings to be conservative given their crude approximation of the cost of a future AMI.

Although the cost-benefit study by Choi et al. (2001) and the costing study by Zarich et al (2003) are non-UK NHS based studies, the strong results in terms of net savings are almost certainly replicable if NHS based costings were substituted.

4.4.2.5 Evidence to recommendations

The evidence for the use of biochemical markers of myocardial necrosis such as troponins and CK-MB to aid diagnosis in patients with acute chest pain is well established. This is not so for markers of ischaemia and for other markers such as BNP.

The majority of patients presenting to the emergency department with acute chest pain do not have MI or ACS and expert opinion in GDG was that about 5% of unselected patients would do so. Patients with an MI or ACS must be identified effectively and in a timely manner to ensure they receive appropriate treatment as early as possible. Others, who do not have MI or ACS, may be discharged, providing other conditions do not require admission.

Troponin is a more sensitive and specific marker for myocardial necrosis than other biochemical markers, including CK-MB and myoglobin, although the GDG acknowledged that the biomarkers being evaluated in the studies were often part of the definition to make a diagnosis of acute MI. In addition to being clinically effective troponin was also found to be to be cost-effective. During the appraisal of the evidence the GDG noted that one study examining the cost-effectiveness of troponin testing was linked to the decision to administer thrombolytic therapy, and queried the authors assumption that the decision to administer thrombolytic therapy could be based on a positive troponin T test when the resting ECG was negative, given that it does not reflect current clinical practice. However, the conclusion of the GDG was that whilst this is not current practice, the overall conclusions from the study that troponin testing is cost effective were still likely to be valid, and had been confirmed by other studies. It was further noted that troponin was the preferred marker recommended in the 'Universal Definition of MI', and that troponin levels also provide prognostic information, although many studies analysing their prognostic value were studies evaluating a particular therapeutic intervention in patients with ACS and unstable angina, rather than in unselected patients with acute chest pain.

Myocardial necrosis and troponin release may occur due to reasons other than ACS and the GDG emphasised the importance of interpreting the results in an individual patient, taking into consideration the overall clinical and ECG findings, to identify those with non-ACS causes for myocardial necrosis. However, this distinction is not always straightforward as some conditions other than ACS, which result in troponin release, may also present with chest pain. In some patients further specialist assessment and diagnostic testing will be required, before a conclusion can be reached.

The GDG discussed the timing of troponin testing. The diagnostic criteria for an acute MI, includes "detection of rise and /or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit" and thus a baseline troponin measurement is recommended. The timing of the second sample was discussed as earlier

testing could potentially lead to the earlier discharge of many patients. However, having appraised the evidence the GDG agreed that the second sample be taken 10 to 12 hours after the onset of symptoms, for optimal sensitivity. The GDG noted that earlier rule out protocols, including one with testing 6 hours after admission, had been evaluated, but felt that the adverse consequences of a false negative test were substantial, and recommended a more cautious approach routinely. However, the GDG recognized that troponin assays were evolving and the highly sensitive assays currently being developed and evaluated, are likely to lead to opportunities for earlier testing.

4.4.3 Multislice CT coronary angiography for emergency department triage of patients with acute chest pain

In the past few years a number of pilot studies have examined the utility of multislice CT in the emergency department in the differential diagnosis of acute chest pain. To date these studies consist of small numbers of patients (around 100 patients), they have been conducted primarily in the USA, and they are limited in scope because each represents the experience of one centre. There are differences in study protocols, patient recruitment, scanners used, angiography protocols and angiographic analyses. This makes direct comparison of these studies difficult with respect to reviewing and interpretation. The authors of these studies while stating the potential promise of multislice CT, they do emphasise that further evaluation needs to be done. There are other considerations as given below;

- Currently the use of multislice CT coronary angiography in the emergency would reduce diagnostic time, however this becomes less important with the evolving technology of reduce waiting time for biomarker assay results.

- Multislice CT coronary angiography will identify a group of patients with sub clinical CAD i.e. disease that is not the cause of the current chest pain episode. The significance of this will need to be evaluated in large studies in the recruitment of unselected consecutive chest pain patients.

- It has not been established if the patient in the emergency department should receive a dedicated CT coronary angiogram, or have an entire thoracic scan. A dedicated coronary CT coronary angiogram would give the best possible images of the coronary arteries, but allows limited visualisations of other structures that may be responsible for chest pain. The benefit of an entire scan is that it would rule out pulmonary embolism and aortic dissection, however, this would involve increased radiation dose, increased scanning time, and possible less than optimal visualisation of coronary arteries.

- The best use of the multislice CT scanner in the emergency department has not been established. Images could be obtained as soon as possible after initial assessment (history, risk factors, examination) and the first set of cardiac enzymes. In which case the multislice CT coronary angiography results would be used as a component of the decision to discharge or admit the patient. Alternatively multislice CT coronary angiography could be used to aid in determining what further monitoring and treatment is indicated after a decision has been made to admit the patient. Hence it is unclear at which point multislice CT coronary angiography would fit into an algorithm used in the emergency department, and what would be the most cost-effective use of multislice CT coronary angiography in the emergency department. This may have implications on cost-effectiveness.

- Current preliminary findings indicate that multislice CT coronary angiography in the emergency department has potential for the ruling out of CAD. When stenosis of > 50% is detected the patient would undergo further non invasive or invasive testing, but the precise course of further evaluation is uncertain at this stage due to the limited literature. Resolving this could potentially be a large piece of work, and would impact on the current care pathway.

- Owing to the limited number of studies, health economic evaluation of multislice CT coronary angiography in the emergency department may

be difficult, particularly as there is no information regarding the subsequent testing of patients when stenosis is > 50%.

To illustrate the current literature four studies were reviewed (Hoffmann, U., Nagurney, J. T., Moselewski, F. et al , 2006), (Coles, D. R., Wilde, P., Oberhoff, M. et al , 2007), (Johnson, T. R., Nikolaou, K., Wintersperger, B. J. et al , 2007), (Rubinshtein, R., Halon, D. A., Gaspar, T. et al , 2007).

The first study recruited consecutive patients presenting to the emergency department with acute chest pain that had an inconclusive clinical evaluation (Hoffmann, U., Nagurney, J. T., Moselewski, F. et al , 2006). Patients were included if they had no or non-diagnostic ECG changes, normal initial cardiac biomarkers, sinus rhythm, the ability to perform a breath hold of 10 to15 sesonds and were > 18 years. Patients were excluded if they had elevated troponin-I or creatine kinase-MB levels, new diagnostic ECG changes (ST-segment elevation or depression > 1 mm or T-wave inversion > 4 mm in > 2 anatomically contiguous leads), a serum creatinine > 1.3 mg/dl, haemodynamic or clinical instability (systolic blood pressure < 80 mm Hg, clinically significant atrial or ventricular arrhythmias, persistent chest pain despite therapy). The study recruited 103 patients that underwent 64-slice CT coronary angiography; 83 Caucasians, 20 African American, 66% were men and the mean age was 53.8±12.2 years. A panel of experts blinded to the results of the 64-slice CT coronary angiogram determined the absence or presence of acute coronary syndrome based upon the evidence accumulated during the index hospitalization and at 5 month follow up. Diagnosis was according to the American College of Cardiology / American Heart Association guidelines) (Hoffmann, U., Nagurney, J. T., Moselewski, F. et al , 2006).

A final diagnosis of acute coronary syndrome was made in 14 patients (14%), 5 had an acute MI and 9 had unstable angina pectoris. Acute coronary syndrome was ruled out in the remaining 89 patients (86%). Telephone follow-up was completed in 81 of the 89 patients (91%) who did not have an acute coronary syndrome during the index hospitalization. None of these patients reported suffering a major cardiovascular adverse event. Table 18 details the results of the diagnostic accuracy of 64-slice CT coronary angiography based

on detection of significant stenois of > 50% (Hoffmann, U., Nagurney, J. T., Moselewski, F. et al , 2006).

Table 18

Diagnostic accuracy of 64-slice CT coronary angiography based detection of significant coronary artery stenosis (> 50%) and presence of any coronary plaque to predict ACS during index hospitalization

	Sensitivity	Specificity	PPV	NPV
All patients (n=103)				
Plaque	1.00	0.46	0.23	1.00
95% CI	0.81-1.00	0.35-0.57	0.13-0.35	0.93-1.00
n of N	14/14	41/89	14/62	41/41
Stenosis*	1.00	0.82	0.47	1.00
95% CI	0.81-1.00	0.72-0.89	0.28-0.66	0.96-1.00
n of N	14/14	73/89	14/30	73/73
Excluding patients with a proven history of CAD (prior stenting or bypass grafting) (n=93)				
Plaque	1.00	0.49	0.19	1.00
95% CI	0.74-1.00	0.38-0.60	0.09-0.32	0.93-1.00
n of N	10/10	41/83	10/52	41/41
Stenosis	1.00	0.85	0.46	1.00
95% CI	0.74-1.00	0.76-0.92	0.24-0.68	0.96-1.00
Permissions requested from original source % (Hoffmann, U., Nagurney, J. T., Moselewski, F. et al , 2006).				

The second study included patients with acute chest pain within 24 hours of admission, in sinus rhythm and with symptoms suggestive of ACS but with a clinical evaluation (Coles, D. R., Wilde, P., Oberhoff, M. et al , 2007). Patients were excluded if they had ST-segment elevation, were haemodynamically unstable or needed immediate coronary angiography. One hundred and twenty patients were included in the study with a mean age of 61.9±10.7 years and 65% were men. One hundred and three patients underwent 16-slice CT coronary angiography. Invasive coronary angiography was the reference standard (Coles, D. R., Wilde, P., Oberhoff, M. et al , 2007).

In the patient based analysis of all native vessels, 16-slice CT coronary angiography correctly identified 77 out of 84 patients with at least ≥ 50% stenosis. 16-slice CT coronary angiography correctly excluded CAD in 16 patients. The sensitivity was 92% (95%CI 83 to 87%), specificity 55% (95%CI 35 to 74%), positive predictive value of 86% (95%CI 76 to 93%), and negative

predictive value of 70% (95%CI 47 to 87%). The accuracy of 16-slice CT coronary angiography to diagnose significant disease depending on calcium score is given in Table 19 (Coles, D. R., Wilde, P., Oberhoff, M. et al , 2007).

Table 19
Influence of total calcium score and heart rate on patient based analysis

	N	TP	TN	FP	FN	Prevalence %	Sensitivity %	Specificity %	NPV %
Total calcium score									
<100	41	16	16	8	1	41 (26-58)	94 (71-100)	67 (45-84)	94 (71-100)
100-400	32	24	0	4	4	88 (71-97)	86 (67-96)	0 (0-60)	0 (0-60)
>400	40	37	0	1	2	98 (87-100)	95 (83-99)	0 (0-98)	0 (0-84)
MSCTCA *heart rate*									
HR ≤65	74	56	9	6	3	80 (69-88)	95 (86-99)	60 (32-84)	75 (43-95)
HR >65	39	21	7	7	4	64 (47-79)	84 (64-96)	50 (23-77)	63.6 (31-89)

TP = True positive, TN = True negative, FP = False positive, FN = False negative

Permissions requested from original source % (Coles, D. R., Wilde, P., Oberhoff, M. et al , 2007).

The third study recruited 55 consecutively patients with acute chest pain (35 men, aged 67 ± 10 years) that were referred from the emergency department by cardiologists or emergency physicians (Johnson, T. R., Nikolaou, K., Wintersperger, B. J. et al , 2007). Patients were referred if ECG findings were absent or inconclusive and cause of their chest pain was unclear. 64-slice CT coronary angiography determined that cause of chest pain in 37 patients as detailed in Table 20. In 14 patients, 16-slice CT coronary angiography findings did not explain the chest pain and this was in agreement with the clinical follow-up findings, which also did not reveal a diagnosis (Johnson, T. R., Nikolaou, K., Wintersperger, B. J. et al , 2007).

Table 20
Imaging findings in study population

Diagnosis	No of patients
Pulmonary embolism	10
High-grade coronary artery stenosis	9
Aortic aneurysm	6

Table 20 **Imaging findings in study population**	
Bypass graft occlusion	2
Pneumonic consolidation	2
Atelectasis	2
Mediastinal mass	2
Aortic dissection	1
Cardiac tumour	1
Lung tumour	1
Large hiatal hernia	1
Pulmonary metastasis	1
Permissions requested from original source % (Johnson, T. R., Nikolaou, K., Wintersperger, B. J. et al , 2007).	

Twenty four patients had signs of athleroschleosis of the coronary arteries. The diagnostic accuracy of 16-slice CT coronary angiography was compared with coronary angiography as the reference standard for the detection of significant (> 50%) stenosis in 20 patients. There were 16 true-positive results, including eight cases of occlusion, three false-positive results, and one false-negative. Thus sensitivity and specificity were 94% and 77%, respectively. The positive predictive value was 84%, and the negative predictive value was 91% (Johnson, T. R., Nikolaou, K., Wintersperger, B. J. et al , 2007).

The fourth study included 58 patients with a mean age 56±10 years, and 64% were men) (Rubinshtein, R., Halon, D. A., Gaspar, T. et al , 2007). One third of the group (22 patients, 38%) had previously diagnosed CAD. Patients were included if they were considered to be at intermediate-risk; normal baseline ECG, normal initial biomarkers, no exclusion criteria such as clinical suspicion of pulmonary embolism, aortic dissection, or pericarditis), clinical symptoms of definite ischemic origin but without high-risk features (not included in the study because of clear diagnosis) or symptoms of uncertain origin but compatible

with possible acute coronary syndrome (Rubinshtein, R., Halon, D. A., Gaspar, T. et al , 2007).

64-slice CT coronary angiography findings were positive in 23 of the 58 patients (40%) (≥ 50% stenosis), 11 of whom (48%) had a prior history of myocardial revascularisation (7 PCI, 4 CABG). In the 35 64-slice CT coronary angiography-negative patients, 2 patients had a non coronary cause of chest pain (1 chronic aortic dissection, 1 pancreatic tumor). One other patient had subclavian artery stenosis proximal to a functional left internal mammary artery bypass graft (Rubinshtein, R., Halon, D. A., Gaspar, T. et al , 2007).

Acute coronary syndrome was diagnosed in 20 out 23 of the multislice CT coronary angiography positive patients. Coronary angiography was performed in 17 patients (74%) and confirmed obstructive CAD in 16, with 1 false-positive with multislice CT coronary angiography. The 64-slice CT coronary angiography sensitivity for diagnosis of acute coronary syndrome was 100% (20/20 patients) (95% confidence interval 100 to 100%), specificity 92% (35/38) (95% CI, 83 to 100%), positive predictive value 87% (20/23) (95% CI, 72 to 100%), and negative predictive value 100% (35/35) (95% CI, 100% to 100%). There were no deaths or MIs in the follow-up period in the 35 patients who were discharged from the emergency department (Rubinshtein, R., Halon, D. A., Gaspar, T. et al , 2007).

4.4.3.1 Cost-Effectiveness of MSCT for acute chest pain in the emergency department

The health economics update search identified two decision analytic model cost-effectiveness analyses from the United States.(Ladapo, J. A., Hoffmann, U., Bamberg, F. et al , 2009) (Khare, R. K., Courtney, D. M., Powell, E. S. et al , 2008) Both assess the cost-effectiveness of 64-slice CT coronary angiography in low risk patients presenting with chest pain in the emergency department. Ladapo and colleagues(Ladapo, J. A., Hoffmann, U., Bamberg, F. et al , 2009) define their low risk acute chest pain patients as having presented to an emergency department and having no history of heart disease, negative initial troponins, and normal or non-diagnostic ECGs. Ladapo models a hypothetical cohort of 55 year old men and women

separately, whilst Khare(Khare, R. K., Courtney, D. M., Powell, E. S. et al , 2008) models a hypothetical cohort of 55 year old men and an assumed CAD prevalence of 2%, 6%, and 10%.

In Ladapo et al.(Ladapo, J. A., Hoffmann, U., Bamberg, F. et al , 2009) the comparator is a Standard of Care (SoC) option involving biomarkers and stress testing (either MPS with SPECT, stress echocardiography or exercise ECG). In Khare et al(Khare, R. K., Courtney, D. M., Powell, E. S. et al , 2008) the comparators are stress echocardiography or stress ECG. The models are similar in structure, and they both appear to take a US healthcare payer perspective, despite Ladapo's indication of having taken a societal perspective. Both models assess QALY outcomes using published estimates of quality adjusted survival. Both studies based their estimates of test characteristic on the outcomes of a clinical trial by Goldstein et al(Goldstein, J. A., Gallagher, M. J., O'Neill, W. W. et al , 2007).

Both models produce favourable results for 64-slice CT coronary angiography, with base case and sensitivity analyses results which are either cost-effective or more often cost-saving. 64-slice CT coronary angiography was cost-saving in women and cost-effective in men in Ladapo's model, whilst it was cost saving for a wide range of modelled scenarios in the Khare model.

4.4.3.2 Evidence to recommendations

The GDG appraised the evidence for the use of multislice CT coronary angiography in unselected patients with chest pain of suspected cardiac origin and was of the opinion that there was insufficient evidence currently on which make a recommendation for its use in the emergency department in such patients. They acknowledged that this was an evolving area, which was the subject of on-going research, but the published evidence found to date was in small cohorts of patients and further research is required. The GDG noted the results of two recently published decision analytic model analyses from the United States examining the cost-effectiveness of 64 slice CT coronary angiography in low risk patients with acute chest pain.(ref Khare et al and

Ladapo et al) However, before CT coronary angiography be incorporated into an acute chest pain pathway, the GDG considered that de novo, NHS based, economic evaluation should be undertaken, in unselected acute chest pain patients, when better evidence from comparative clinical trials becomes available. In particular, this should be when there is greater clarity on the relative costs, and test accuracies, of the emerging highly sensitive biomarkers. The cost-effectiveness of multislice CT angiography for rule out of obstructive CAD in patients with troponin negative ACS has been included as a recommendation for future research. The GDG recognised that CT imaging has an established role in current clinical practice to investigate selected patients with chest pain, for example those with suspected pulmonary embolism or aortic dissection, but it was beyond the scope of this guideline to appraise the evidence or make recommendations for this group of patients.

Return to Recommendations

End of Section 1 – Go to Section 2 for Chapter 5 - Patients Presenting with Stable Chest Pain

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