NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

Chest pain of recent onset: assessment and investigation of recent onset chest pain/discomfort of suspected cardiac origin.

1.1 Short title

Chest pain/discomfort of recent onset

2 Background

a) The National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Primary Care to develop a clinical guideline on the assessment and investigation of recent onset chest pain/discomfort of suspected cardiac origin for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health (see appendix). The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness. NICE has commissioned the National Collaborating Centre for Chronic Conditions to develop a guideline entitled 'Assessment and management of acute coronary syndromes' in parallel with this guideline.
This guideline will give guidance on the investigation and assessment of chest pain/discomfort and any associated symptoms, and when the cause of the chest pain/discomfort is known, other guidelines should be used as appropriate.

b) The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals

published by the Institute after an NSF has been issued will have the effect of updating the Framework.

c) NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their individual needs and preferences, and ensuring that patients (and their carers and families, where appropriate) can make informed decisions about their care and treatment.

3 Clinical need for the guideline

a) CHD by itself is the most common cause of death in the UK. Around one in five men and one in six women die from the disease. CHD causes around 101,000 deaths in the UK each year[1].

b) Chest pain/discomfort is a common presenting symptom in primary and secondary care, and there are many possible causes. The most important of these with regard to mortality and morbidity is CHD, including acute coronary syndromes and myocardial infarction (MI).

c) Chest pain/discomfort is caused by CHD in only a minority of cases, and guidance on the assessment of chest pain/discomfort will aid in making an accurate diagnosis, avoiding inappropriate diagnoses and treatment, and reducing unnecessary referral and admission to secondary care. Rapid identification of people with cardiac chest pain/discomfort who require further specialist assessment and management will reduce mortality and morbidity.

4 The guideline

a) The guideline development process is described in detail in two publications that are available from the NICE website (see ‘Further information’). ‘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. ‘The

guidelines manual' provides advice on the technical aspects of guideline development.

b) This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health (see appendix).

c) The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

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

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

4.1.2 Groups that will not be covered

a) People who have traumatic chest injury without cardiac symptoms.

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

4.2 Healthcare setting

a) The guideline will cover the care received from healthcare professionals who have direct contact with, and make decisions concerning, the care of people who have recent onset chest pain/discomfort of suspected cardiac origin

b) The guideline will address care in primary and secondary healthcare settings and, where appropriate, other settings, including telephone advice prior to the arrival of any healthcare support and emergency care.

c) The guideline will also be relevant to the work, but will not specifically cover the practice, of those working in the occupational health services and voluntary sector.

4.3 Clinical assessment and investigation

4.3.1 Areas that will be covered

a) Assessment of people with recent onset chest pain/discomfort of suspected cardiac origin at initial presentation.

b) Assessment and investigation of people with recent onset of chest pain/discomfort of suspected cardiac origin at initial presentation including:

- history and physical examination
- cardiovascular risk factor assessment (such as family history, age and gender)
- communication and informed discussion of treatment options
- early biochemical markers for the diagnosis of acute coronary syndrome and MI
- cardiac investigations (such as electrocardiogram and chest X-ray) for the diagnosis of acute coronary syndrome and MI
- diagnostic tests, such as exercise testing, myocardial perfusion imaging, and other appropriate imaging modalities in patients requiring further assessment.

c) Early, initial pharmacological interventions in the management of people with recent onset chest pain/discomfort of suspected cardiac origin, such as oxygen, anti-platelet therapy and pain relief before a cause is known.

Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only where clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform their decisions for individual patients.

d) The guideline will cover education and information provision for people with recent onset chest pain/discomfort of suspected cardiac origin.

e) Where relevant and where associated with chest pain/discomfort, the special needs of people from different groups will be considered, for example:

- black and minority ethnic groups
- older people
- socio-economic groups
- women
- people with disabilities
- people who have experienced chest pain/discomfort in the past.

f) The guideline development groups will take reasonable steps to identify ineffective interventions and approaches to care. If robust and credible recommendations for re-positioning the intervention for optimal use, or changing the approach to care to make more efficient use of resources can be made, they will be clearly stated. If the resources released are substantial, consideration will be given to listing such recommendations in the 'Key priorities for implementation' section of the guideline.

4.3.2 Areas that will not be covered

a) Management and symptom control once the cause of chest pain/discomfort is known (see related NICE guidance).

b) Assessment for coronary revascularisation.

c) Management of asymptomatic people with possible ischaemic heart disease (for example, people with abnormal ECG due to left bundle branch block or left ventricular dysfunction).

4.4 Status

4.4.1 Scope

This is the final scope.

The following related NICE guidance will be referred to as appropriate.

Published

Atrial fibrillation: the management of atrial fibrillation. NICE clinical guideline 36 (2006). Available from: www.nice.org.uk/CG036

Management of chronic heart failure in adults in primary and secondary care. NICE clinical guideline 5 (2007). Available from: www.nice.org.uk/CG005

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: www.nice.org.uk/CG048

Clopidogrel in the treatment of non-ST-segment elevation acute coronary syndrome. NICE technology appraisal guidance 80 (2004). Available from: www.nice.org.uk/TA080

Glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes. NICE technology appraisal guidance 47 (2007). Available from: www.nice.org.uk/TA047

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/TA073

Implantable cardioverter defibrillators (ICDs) for the treatment of arrhythmias (review of TA11). NICE technology appraisal guidance 95 (2007). Available from: www.nice.org.uk/TA095

Bradycardia – dual chamber pacemakers. NICE technology appraisal guidance 88 (2005). Available from: www.nice.org.uk/TA088

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/TA094

Cardiac resynchronisation therapy for the treatment of heart failure. NICE technology appraisal guidance 120 (2007). Available from: www.nice.org.uk/TA120

Guidance on the use of coronary artery stents. NICE technology appraisal guidance 71 (2003). Available from: www.nice.org.uk/TA071

Alteplase for the treatment of acute ischaemic stroke. NICE technology appraisal guidance 122 (2007). Available from: www.nice.org.uk/TA122

Guidance on the use of drugs for early thrombolysis in the treatment of acute myocardial infarction. NICE technology appraisal guidance 52 (2002). Available from: www.nice.org.uk/TA052

Clopidogrel and dipyridamole for the prevention of artherosclerotic events. NICE technology appraisal guidance 90 (2005). Available from: www.nice.org.uk/TA090

In development

Acute coronary syndromes: assessment and management of acute coronary syndromes. NICE clinical guideline (publication date to be confirmed)

Cardiovascular risk assessment: the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE clinical guideline (publication expected January 2008)

Stroke: diagnosis and initial management of acute stroke and transient ischaemic attack. NICE clinical guideline (publication expected July 2008)

4.4.2 Guideline

The development of the guideline recommendations will begin in December 2007.

5 Further information

Information on the guideline development process is provided in:

- 'The guideline development process: an overview for stakeholders, the public and the NHS'
- 'The guidelines manual'.

These booklets are available as PDF files from the NICE website (www.nice.org.uk/guidelinesmanual). Information on the progress of the guideline will also be available from the website.

Appendix: Referral from the Department of Health

The Department of Health asked the Institute:

To prepare a clinical guideline for the NHS in England on the investigation, assessment and management of acute chest pain of suspected cardiac origin.

Appendix B - GDG Declaration of Interests - Acute Chest Pain

Adam Timmis (Chairman)

Professor of Clinical Cardiology, Barts and the London Queen Mary's School of Medicine and Dentistry

1. Personal specific pecuniary or personal family interest:

DOI dated 07/04/09
I sat on an ad hoc advisory board for Pfizer (5/4/09) to discuss statin prescribing in the UK, for which I will receive a small honorarium. No further meetings of this board will take place.

DOI dated 10/02/09
None

DOI dated 28/11/09
Pecuniary Interest on grants from Wellcome Trust and NIHR using electronic records to investigate causes and prognosis of chest pain angina and MI

DOI dated 12-03-08
I am giving an invited lecture on "inequity in the management of angina" at the forthcoming (June) meeting of the British Cardiac Society.

The lecture is sponsored by Cardiovascular Therapeutics Inc from whom I shall receive an honorarium. The content of the lecture will be all mine.

DOI updated 30-01-08
Asked to sit on a post MI heart failure group to develop a management protocol. Group was

sponsored by Pfizer, so received a small fee.

DOI updated 17.12.07

Servier: cardiac advisory board (resigned September 2007) ; sponsored my attendance at European Society of Cardiology meeting September 2007

Cardiovascular Therapeutics Inc: cardiac advisory board (resigned Sept 2007)
HD-Clinical: I hold shares in this medical data-basing company

DOI 20/10/07
Cardiac Advisory Board Member: Servier (resigned September 2007)
Cardiac Advisory Board Member: Cardiovascular Therapeutics (resigned September 2007)

2. Personal family interest:

DOI dated 10/02/09
None

26/01/09
None

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3. Non-personal pecuniary interest:	DOI dated 10/02/09 My department is in receipt of an NIHR Biomedical Research Unit Grant to develop an academic department of cardiovascular imaging which includes MSCT. I was lead applicant on this grant which includes capital funding for purchase of a new MSCT scanner. DOI dated 20-10-07 Siemens: sponsor my cardiac research fellow at London Chest Hospital (until April 2008) DOI dated 19-12-08 Grant application: Hemingway H, Feder G, Timmis AD, et al. NIHR Programme Grant RP-PG-0407-10314. Improving the quality of care of patients with angina and heart attack. 2008-2012 (£1.8M) Grant application: Hemingway H, Hingorani A, Smeeth L, Kivimaki M, Kalra D, Timmis A.
4. Personal non-pecuniary interest:	DOI dated 10/02/09 None 26/01/09 I have published a number of papers about chest pain clinics and the management of patients with angina. In a recent paper (BMJ 2008:337:a2240) I expressed the view that the exercise ECG had little incremental value for risk assessment of patients with suspected angina (26/01/09) . None
Declaration last renewed:	21/01/2009

Jane Skinner (Clinical Advisor)

Consultant Community Cardiologist, Royal Victoria Infirmary

1. Personal specific pecuniary or personal family interest:	DOI dated 22/11/08 No New declarations to add. DOI dated 19-11-07 Co-author for a clinical evidence review commissioned by BMJ, 'Secondary prevention of ischaemic cardiac events'; previously discussed with NICE in relation to previous guideline for secondary prevention post MI, and participation agreed. Honorarium offered to co-author article for PULSE; article already discussed with NCC-PC and NICE, and participation agreed.

2. Personal family interest:	DOI dated 22/11/08 No New declarations to add.
3. Non-personal pecuniary interest:	DOI dated 22/11/08 No New declarations to add.
	DOI dated 19-11-07 None
4. Personal non-pecuniary interest:	DOI dated 22/11/08 No New declarations to add.
	DOI dated 19-11-07 None
Declaration last renewed:	22/11/2008

Phillip Adams

Cardiologist Consultant

1. Personal specific pecuniary or personal family interest:	DOI dated 10-01-09 None
	DOI dated 20-10-07 None.
2. Personal family interest:	DOI dated 10-01-09 None
	DOI dated 20-10-07 None
3. Non-personal pecuniary interest:	DOI dated 10-01-09 None
	DOI dated 20-10-07
	Department of which I am has received funding from NICE relating to Dr Skinner's work as Clinical Advisor to the Post MI guideline. Research scientist funded from Oxford Clinical Trial Service Unit as Support for participation in current multi-centre study.
4. Personal non-pecuniary interest:	DOI dated 10-01-09 None

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	DOI dated 20-10-07
	None
Declaration last renewed:	10/01/2009

John Ashcroft

General Practitioner BM BS MRCGP

1. Personal specific pecuniary or personal family interest:	DOI dated 09/01/09
	None
	DOI 18/12/08
	None
	DOI dated 16-05-08
	None
	DOI dated 27-09-07
	None
2. Personal family interest:	DOI dated 09/01/09
	None
	DOI 18/12/08
	None
	DOI dated 16-05-08
	None
3. Non-personal pecuniary interest:	DOI dated 09/01/09
	None
	DOI 18/12/08
	None
	DOI dated 16-05-08
	None
	DOI dated 27-09-07
	None
4. Personal non-pecuniary interest:	DOI dated 09/01/09
	None
	DOI 18/12/08

None

DOI dated 16-05-08
None

DOI dated 27-09-07
None

Declaration last renewed: 09/01/2009

Liz Clark

Patient representative

1. Personal specific pecuniary or personal family interest:

DOI dated 25/04/09
I will be doing 3 or 4 days work for Mid Devon PCT to help them set up a structure for patient involvement. I will be paid a small fee.

DOI dated 28/03/09
None

DOI dated 23-03-09
None

DOI dated 16-05-08
None

DOI dated 27-09-07
None

2. Personal family interest:

DOI dated 25/04/09
None

DOI dated 28/03/09
None

DOI dated 23-03-09
None

DOI dated 16-05-08
None

3. Non-personal pecuniary interest:

DOI dated 25/04/09
None

DOI dated 28/03/09
None

	DOI dated 23-03-09
	None
	DOI dated 16-05-08
	None
	DOI 27-09-07
	None
Declaration last renewed:	09/04/1942

Richard Coulden

consultant Cardiothoracic Radiologist

1. Personal specific pecuniary or personal family interest:	DOI dated 16-05-08
	None
	DOI dated 26-09-07
	None
2. Personal family interest:	DOI dated 16-05-08
	None
3. Non-personal pecuniary interest:	DOI dated 16-05-08
	None
	DOI dated 26-09-07
	None
Declaration last renewed:	16/05/2008

Harry Hemingway

Public Health Physician Epidemiologist

1. Personal specific pecuniary or personal family interest:	DOI dated 20/02/09
	None
	DOI dated 28/11/08
	DOI dated 20-10-07
	None
2. Personal family interest:	DOI dated 20/02/09
	None
	DOI dated 20-10-07

None

3. Non-personal pecuniary interest:

DOI dated 20/02/09
None

DOI dated on 03/04/09

Grant application 2007-2009: Evaluating the effectiveness of biomarkers in prioritising coronary revascularisation for chronic stable angina Health Technology Assessment
Invited to speak on behalf of MENARINI at British Cardiovascular Society on angina epidemiology 2009 - waived honorarium

Pecuniary Interest on grants from Wellcome Trust and NIHR using electronic records to investigate causes and prognosis of chest pain angina and MI

DOI dated 20-10-07
None
DOI dated 19/12/08
Grant application: Hemingway H, Feder G, Timmis AD ++ et al. NIHR Programme Grant RP-

PG-0407-10314. Improving the quality of care of patients with angina and heart attack. 2008-2012

Grant application: Hemingway H, Hingorani A, Smeeth L, Kivimaki M, Kalra D, Timmis A. Welcome. Insights into CVD from linking datasets 2008-2012

4. Personal non-pecuniary interest:

DOI dated 20/02/09
Invited to talk at British Cardiovascular Society, June 2009 by marketer of anti-anginal valoazine. Honorarium - Charity.

DOI dated 20-10-07
None

Declaration last renewed: 20/02/2009

Cathryn James

Clinical Pathways Advisor/Emergency Care Practitioner

1. Personal specific pecuniary or personal family interest:

DOI dated 24/11/08
None

DOI dated 20-10-07
None

2. Personal family interest:

DOI dated 24/11/08

	None
	DOI dated 20-10-07
	None
3. Non-personal pecuniary interest:	DOI dated 24/11/08
	None
	DOI dated 20-10-07
	None
4. Personal non-pecuniary interest:	DOI dated 24/11/08
	None
	DOI dated 20-10-07
	None

Declaration last renewed: **24/11/2008**

Heather Jarman

Consultant Nurse in Emergency Care

1. Personal specific pecuniary or personal family interest:	DOI dated 01/04/09
	None
	DOI dated 27/03/09
	None
	DOI dated 21/11/08
	None
	DOI dated 20-10-07
	/one
2. Personal family interest:	DOI dated 01/04/09
	None
	DOI dated 27/03/09
	None
	DOI dated 21/11/08
	None
	DOI dated 20-10-07
	None

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3. Non-personal pecuniary interest:	DOI dated 01/04/09 None DOI dated 01/04/09 None DOI dated 21/11/08 None DOI dated 20-10-07 None
4. Personal non-pecuniary interest:	DOI dated 01/04/09 Vice-chair Royal College of Nursing Emergency Care Association DOI dated 27/03/09 None DOI dated 21/11/08 None DOI dated 20-10-07 None

Jason Kendall

Consultant in Emergency Medicine

1. Personal specific pecuniary or personal family interest:	DOI dated 22-11-08 No additions DOI dated 13-12-07 Previous membership of advisory board for Boehringer Ingelheim (pharmaceutical company that manufactures thrombolytic agents) . No longer member of this advisory board; non-specific interest ' different patient group (i.e. post-diagnosis) . Have received hospitality and honoraria from pharmaceutical companies for speaking at national and international meetings on the subject of reperfusion in acute coronary syndromes; non-specific interest ' different patient group (i.e. post-diagnosis) . DOI dated 18-09-07
2. Personal family interest:	DOI dated 21-11-08 None

Appendix B - GDG Declaration of Interests - Acute Chest Pain

3. Non-personal pecuniary interest:	DOI dated 21-11-08 No additions DOI dated 13-12-07 As a principle investigator for the RATPAC study (a research project evaluating cardiac markers in patients with chest pain) I have received funding for my institution to employ two research nurses for this study; specific non-personal pecuniary interest. DOI dated 18-09-07
4. Personal non-pecuniary interest:	DOI dated on 31-03-09 Co-applicant on National Institute for Health Research application for funding for research project entitled "Development and evaluation of out-of-hospital management of suspected acute coronary syndrome" (Lead NHS organisation Sheffield Teaching Hospitals NHS Foundation Trust) . Also Co-applicant on National Institute for Health Research application for funding for research project entitled "Cost-effectiveness of diagnostic strategies for suspected acute coronary syndrome" (Lead NHS organisation Sheffield Teaching Hospitals NHS Foundation Trust) . DOI dated 21-11-08 No additions DOI dated 13-12-07 Member of the steering group of the ESCAPE Trial evaluating chest pain units in the UK ' project nearing completion, results in public domain; specific ' same patient group. Member of the steering group of the RATPAC Trial evaluating cardiac markers in patients with chest pain ' trail currently recruiting; specific ' same patient group. Member of the executive UK subcommittee of the STREAM Trial evaluating reperfusion strategies for STEMI in the UK; non-specific ' different patient group. National Section Lead (Cardiovascular Emergencies) for ENLIGHTENme (DoH, BMJ, College of Emergency Medicine e-learning project) , authoring modules on diagnosis / management of patients with chest pain / STEMI / NSTEMI / ACS, etc.

Peter Lewis

Chief Clinical Physiologist

1. Personal specific pecuniary or personal family interest:	DOI dated 09-01-09 None DOI dated 20-10-07 None
2. Personal family interest:	DOI dated 09-01-09 None

	DOI dated 20-10-07 None
3. Non-personal pecuniary interest:	DOI dated 09-01-09 None
	DOI dated 20-10-07 None
4. Personal non-pecuniary interest:	DOI dated 09-01-09 None
	DOI dated 20-10-07 None
Declaration last renewed:	09/01/2009

Kiran Patel

Consultant Cardiologist and Hon Senior Lecturer in Cardiovascular Medicine

1. Personal specific pecuniary or personal family interest:	DOI dated 12/02/09 Pfizer Fee received for participation in roundtable consensus discussion on cardiovascular risk at Royal Society of Medicine-January 2008 Pfizer, Astra Zeneca, MSD, Solvay- Speaker fees received for lecturing at a sponsored educational meetings for PCT GP Education- 2005-8 The Lancet Journal, Medtronic- Sponsorship to attend international academic meetings (travel grants) - 2005-7 NICE- Bursary to attend NICE national conference in Bham as NGO member group representative- 2006 DOI dated 23/11/08 Sanofi - Aventis: Advisory Board for diabetes management: No access to confidential papers (Sept 2007) Pfizer: Advisory Board on atorvastatin: No access to confidential papers (Sept 2007) Boston Scientific: Advisory Board for device therapy in heart failure (July 2007)

	Pfizer, Takeda, MSD, Sanofi: Speaker fees received for lecturing at a sponsored educational meetings (2005-7) Menarin: Speaker fees received for lecturing at a sponsored educational meeting for PCT GP Education (Sept 2007) The Lancet Journal, Medtronic:Sponsorship to attend international academic meetings (travel grants) (2005-7) NICE: Bursary to attend NICE national conference in Bham as NGO member group representative (2006) DOI dated 01-02-08 Sanofi - Aventis: Advisory Board for diabetes management: No access to confidential papers (Sept 2007) Pfizer: Advisory Board on atorvastatin: No access to confidential papers (Sept 2007) Boston Scientific: Advisory Board for device therapy in heart failure (July 2007) Pfizer, Takeda, MSD, Sanofi: Speaker fees received for lecturing at a sponsored educational meetings (2005-7) Menarin: Speaker fees received for lecturing at a sponsored educational meeting for PCT GP Education (Sept 2007) The Lancet Journal, Medtronic:Sponsorship to attend international academic meetings (travel grants) (2005-7) NICE: Bursary to attend NICE national conference in Bham as NGO member group representative (2006) DOI dated 20-10-07 Pfizer: Advisory Board on Torcetrapib/atrovastatin: No access to confidential papers (Nov 2006) Pfizer, Takeda, MSD: Speaker fees received for lecturing at a sponsored educational meetings (April 2006-7) Medtronic: Sponsorship to attend international academic meetings (travel grants, May 2007) Takeda: Sponsorship to attend international academic meetings (travel grants, May 2007) Bursary to attend NICE national conference in Bham as NGO member group representative (Dec 2006)
2. Personal family interest:	DOI dated 12/02/09 Noe to declare
3. Non-personal pecuniary interest:	DOI dated 12/02/09 Non personal interests British Heart Foundation Funds heart failure nurses within the Department of Cardiology at Sandwell Hospital where I work. Current

Industry funded Cardiology Departmental meetings where lunch is provided courtesy of a variety of pharmaceutical industries on a weekly basis at Sandwell Hospital
Current

Industry funded: Medtronic
The University Dept of Cardiovascular medicine has an ongoing research study for which I am an investigator funded by Medtronic. Current.

DOI dated 23/11/08
South Asian Health Foundation: Co-signatory to consensus statements relating to statins, metabolic syndrome and cardiovascular risk prediction. Each submission submitted to relevant NICE process as expert documents (2005-6)

South Asian Health Foundation:
I am Chairman of Trustees for this charity which has members appointed to many NICE GDGs and appraisal committees, though I do not influence their contributions after nomination (2003-6)

South Asian Health Foundation and Dept of Health: I participated in a roundtable discussion on Health Inequalities at the Kings Fund with the Secretary of State for Health (Nov 2005)

South Asian Health Foundation: Has strong links with several other organisations e.g. British Heart Foundation, National Heart Forum, Dept of Health, NICE (Current)

South Asian Health Foundation: Has received unrestricted grants from industry, Dept of Health, BHF and National Heart Forum for educational meetings in which the content has not been influenced by the sponsor.

I am a member of the British Cardiovascular Society, SAHF and British Society of Heart Failure. These organisations receive funding from a variety of donors (pharmaceutical and non pharmaceutical) .

DOI dated 01-02-08
South Asian Health Foundation: Co-signatory to consensus statements relating to statins, metabolic syndrome and cardiovascular risk prediction. Each submission submitted to relevant NICE process as expert documents (2005-6)

South Asian Health Foundation:
I am Chairman of Trustees for this charity which has members appointed to many NICE GDGs and appraisal committees, though I do not influence their contributions after nomination (2003-6)

South Asian Health Foundation and Dept of Health: I participated in a roundtable discussion on Health Inequalities at the Kings Fund with the Secretary of Sate for health (Nov 2005)

	South Asian Health Foundation: Has strong links with several other organisations e.g. British Heart Foundation, National Heart Forum, Dept of Health, NICE (Current) South Asian Health Foundation: Has received unrestricted grants from industry, Dept of health, BHF and National Heart Forum for educational meetings in which the content has not been influenced by the sponsor. I am a member of the British Cardiovascular Society, SAHF and British Society of Heart Failure. These organisations receive funding from a variety of donors (pharmaceutical and non pharmaceutical) . DOI dated 20-10-07 BHF: Currently Funds heart failure nurses within the Department of Cardiology at Sandwell Hospital where I work. Industry: Cardiology Departmental meetings where lunch is provided courtesy of a variety of pharmaceutical industries on a weekly basis at Sandwell Hospital
4. Personal non-pecuniary interest:	DOI dated 12/02/09 Non pecuniary personal specific interest National Heart Forum, Cardiovascular coalition - I am trustee to the NHF and member of the CVC steering group, both of which produces consultation papers and strategic documents on CVD Prevention 2006-current Food Standards Agency - I have participated in meetings aimed at promoting food labelling with the FSA, BHF, NHF and SAHF 2006-current South Asian Health Foundation - Co-signatory to consensus statements relating to statins, metabolic syndrome and cardiovascular risk prediction. Each submission submitted to relevant NICE process as expert documents 2005-6 South Asian Health Foundation - I am Chairman of Trustees for this charity which has members appointed to many NICE GDGs and appraisal committees, though I do not influence their contributions after nomination. 2003-current South Asian Health Foundation and Dept of Health- I participated in a roundtable discussion on Health Inequalities at the Kings Fund with the Secretary of Sate for health. Nov 2005 South Asian Health Foundation - Has strong links with several other organisations e.g. British Heart Foundation, National Heart Forum, Dept of health, NICE. Current

South Asian Health Foundation - Has received unrestricted grants from industry, Dept of health, BHF and National Heart Forum for educational meetings in which the content has not been influenced by the sponsor.
I am a member of the British Cardiovascular Society, SAHF and British Society of Heart Failure
These organisations receive funding from a variety of donors (pharmaceutical and non pharmaceutical) .

DOI dated 23/11/08
South Asian Health Foundation Chair of trustees,: Co-signatory to consensus statements relating to statins, metabolic syndrome and cardiovascular risk prediction. Each submission submitted to relevant NICE process as expert documents

I am Chairman of Trustees for this charity which has members appointed to many NICE GDGs and appraisal committees, though I do not influence their contributions after nomination. SAHF has strong links with several other organisations e.g. British Heart Foundation, National Heart Forum, Dept of Health, NICE
SAHF has received unrestricted grants from industry, Dept of health, BHF and National Heart Forum for educational meetings in which the content has not been influenced by the sponsor.

DOI dated 20-10-07
South Asian Health Foundation Chair of trustees,: Co-signatory to consensus statements relating to statins, metabolic syndrome and cardiovascular risk prediction. Each submission submitted to relevant NICE process as expert documents

I am Chairman of Trustees for this charity which has members appointed to many NICE GDGs and appraisal committees, though I do not influence their contributions after nomination. SAHF has strong links with several other organisations e.g. British Heart Foundation, National Heart Forum, Dept of Health, NICE
SAHF has received unrestricted grants from industry, Dept of Health, BHF and National Heart Forum for educational meetings in which the content has not been influenced by the sponsor.

Declaration last renewed: **12/02/2009**

Liam Smeeth

Professor of Clinical Epidemiology

1. Personal specific pecuniary or personal family interest:

DOI dated 28/11/08
Pecuniary Interest on grants from Wellcome Trust and NIHR using electronic records to investigate causes and prognosis of chest pain angina and MI

DOI dated 20-10-07
None

2. Personal family interest:	
4. Personal non-pecuniary interest:	DOI dated 20-10-07 None
Declaration last renewed:	28/11/2008

John Taylor

Patient Rep

1. Personal specific pecuniary or personal family interest:	DOI dated on 03/04/09 Appointed member North West Steering Group for summary care records (S.C.R ˛ s) . Expenses + attendance/LOE payment DOI dated 20/01/09 None DOI dated 21/11/08 None DOI dated 30-08-07 None
2. Personal family interest:	DOI dated 20/01/09 None DOI dated 21/11/08 None
3. Non-personal pecuniary interest:	DOI dated on 03/04/09 Elected Governor Royal Bolton Hospital NHS Foundation Trust. No honorarium. Expenses only. Invitation to present patient view of S.C.R ˛ s for Thames Valley Assist at Oxford John Radcliffe Hospital. Expenses only at this time. DOI dated 20/01/09 None DOI dated 21/11/08 None

	DOI dated 30-08-07 None
4. Personal non-pecuniary interest:	DOI dated 20/01/09 None
	DOI dated 21/11/08 None
	DOI dated 04-07-08 I was sponsored by Connecting for Health "anonymously" (I.e. I was not listed as a CfH Delegate to preserve my status as an Independent Patient) to give a presentation on Summary Care Records at the British Computer Society Primary Care Specialist Group Summer Conference last Tuesday and Wednesday, there was no fee involved and the presentation was non vetted by CfH. CfH paid my travel and accommodation expenses on a cost only basis as a non employee.
Declaration last renewed:	03/04/2009

Staff

Neill Calvert

Health Economist

1. Personal specific pecuniary or personal family interest:	DOI dated 01-04-2008 None
	DOI dated 07-11-07 None current Non-current I was sub-contracted by the University of Sheffield to undertake a review of the evidence for cost-effectiveness of third line treatments for breast cancer for Bristol Myers Squibb. This work was undertaken in July and August of 2007
2. Personal family interest:	DOI dated 01-04-2008 None
3. Non-personal pecuniary	DOI dated 01-04-2008

interest:	None
	DOI dated 07-11-07
	None
4. Personal non-pecuniary interest:	DOI dated 01-04-2008
	None
	DOI dated 07-11-07
	None

Declaration last renewed: 01/04/2008

Angela Cooper

Senior Health Services Research Fellow

1. Personal specific pecuniary or personal family interest:	DOI dated 01-04-2008
	None
	DOI dated 06-05-07
	None
2. Personal family interest:	DOI dated 01-04-2008
	None
3. Non-personal pecuniary interest:	DOI dated 01-04-2008
	BKJ Publication2008 £250.00 Author
	DOI dated 06-05-07
	None
4. Personal non-pecuniary interest:	DOI dated 01-04-2008
	None

Declaration last renewed: 01/04/2008

David Hill

Project Manager

1. Personal specific pecuniary or personal family interest:	DOI dated 01-04-2008
	None
2. Personal family interest:	DOI dated 01-04-2008
	None

Appendix B - GDG Declaration of Interests - Acute Chest Pain

3. Non-personal pecuniary interest:	DOI dated 01-04-2008 None
4. Personal non-pecuniary interest:	DOI dated 01-04-2008 None
Declaration last renewed:	01/04/2008

Nancy Turnbull

Chief Executive

1. Personal specific pecuniary or personal family interest:	DOI dated 01-04-2008 None
	DOI dated 07-03-07 Husband has a small number of shares in Alizyme Company
2. Personal family interest:	DOI dated 01-04-2008 Alizyme Shares
3. Non-personal pecuniary interest:	DOI dated 01-04-2008 None
	DOI dated 07-03-07 None
4. Personal non-pecuniary interest:	DOI dated 01-04-2008 None
	DOI dated 17-05-04 Involvement with La Leche League
Declaration last renewed:	01/04/2008

Appendix C Chest Pain – Guideline Question

PICO Questions

	Questions	Population	Interventions	Comparisons	Outcomes
1	What are the education and information needs in adults presenting with chest pain to optimise their understanding of the diagnostic process and their participation in decisions about their investigations?	Adults presenting with chest pain/discomfort of suspected cardiac origin pending investigation/diagnosis	Education and information	No structured information and education	Optimal understanding and shared decision making
2	What is the incremental benefit and cost effectiveness of a clinical history, risk factors and physical examination in evaluation of individuals with acute chest pain of suspected cardiac origin?	Adults presenting with acute chest pain/discomfort of suspected cardiac origin	Clinical history (descriptors of chest pain and associated symptoms) of people with acute chest pain	None	Discrimination or aid in discrimination between chest pain of cardiac origin (ACS and Angina) and non-cardiac origin for diagnosis
3	What is the diagnostic utility of pain relief with nitrates in the identification of patients with acute chest pain of cardiac origin?	Adults presenting with acute chest pain/discomfort of suspected cardiac origin	Nitrates	None	Diagnosis of angina
4	Are the symptoms and description of the symptoms different in women presenting with acute chest pain of suspected cardiac origin compared with men?	Subgroups presenting with acute chest pain/discomfort of suspected cardiac origin	Clinical history (descriptors of chest pain and associated symptoms) of people with acute chest pain; women versus men	None	Discrimination or aid in discrimination between chest pain of cardiac origin (ACS0) and non-cardiac origin for diagnosis
5	Are the symptoms and description of the symptoms different in Black and Ethnic Minorities presenting with acute chest pain of suspected cardiac	Subgroups presenting with acute chest pain/discomfort of suspected cardiac origin	Clinical history (descriptors of chest pain and associated symptoms) of people with acute chest pain; Black and Ethnic Minorities	None	

Appendix C Chest Pain – Guideline Question

	Questions	Population	Interventions	Comparisons	Outcomes
	origin compared with Caucasians?				
6	What is the utility (incremental value) and cost effectiveness of the resting ECG in evaluation of individuals with acute chest pain of suspected cardiac origin?	Adults presenting with acute chest pain/discomfort of suspected cardiac origin.	Resting ECG	Not applicable	Refine the diagnostic likelihood of cardiac chest pain? or discrimination between chest pain of cardiac origin and non-cardiac origin for diagnosis?
7	What is the utility (incremental value) and cost effectiveness of a chest X ray in evaluation of individuals with chest pain of suspected cardiac origin?	Adults presenting with acute chest pain/discomfort of suspected cardiac origin	Chest X ray	Not applicable	Refine the diagnostic likelihood of cardiac chest pain? or discrimination between chest pain of cardiac origin and non-cardiac origin for diagnosis?
8	Are the symptoms and description of the symptoms different in women presenting with acute chest pain of suspected cardiac origin compared with men?	Adults presenting with acute chest pain/discomfort of suspected cardiac origin	Chest X ray	Not applicable	Refine the diagnostic likelihood of cardiac chest pain? or discrimination between chest pain of cardiac origin and non-cardiac origin for diagnosis?
9	In adults presenting with acute chest pain/discomfort of suspected cardiac origin, what is the clinical and cost effectiveness of giving oxygen compared with a placebo?	Adults presenting with acute chest pain/discomfort of suspected cardiac origin	Oxygen	Placebo, no oxygen and other relevant comparators	Proposed outcomes: Adverse events Mortality Cardiovascular events (including vascular death, non fatal MI, non fatal stroke, recurrent ischaemia) symptoms
10	In adults presenting with acute chest pain, what is the clinical and cost effectiveness of pain management (e.g. sublingual and buccal nitrates, diamorphine, morphine with anti-emetic)	Adults presenting with acute chest pain/discomfort of suspected cardiac origin	Pain management (eg sublingual and buccal nitrates diamorphine, morphine with anti-emetic, tramindol)	Placebo and other relevant comparators, control, usual care, oxygen	Pain relief, adverse events, diagnosis of chest pain

Appendix C Chest Pain – Guideline Question

	Questions	Population	Interventions	Comparisons	Outcomes
	compared with active comparators?				
11	In adults presenting with acute chest pain/discomfort of acute suspected cardiac origin, what is the clinical and cost effectiveness of anti-platelet therapy (aspirin, clopidogrel alone or in combination) compared with a placebo?	Adults presenting with acute chest pain/discomfort of suspected cardiac origin	Anti-platelet therapy: Aspirin, clopidogrel, aspirin and clopidogrel combination	Placebo and other relevant comparators (including comparison to nothing, control, or alternative anti-platelet therapy)	Proposed outcomes: Adverse events Mortality Cardiovascular events (including vascular death, non fatal MI, non fatal stroke, recurrent ischaemia)
12	What is the utility and cost effectiveness of cardiac biomarkers in evaluation of individuals with acute chest pain of suspected cardiac origin?	Adults presenting with acute chest pain/discomfort of suspected cardiac origin	Biomarkers	None	Discrimination between chest pain of cardiac origin and non-cardiac origin for diagnosis
13	What is the diagnostic utility MSCT coronary angiography in the diagnosis of patients with acute chest pain of suspected cardiac origin?	Adults presenting with acute chest pain/discomfort of suspected cardiac origin	MSCT	Coronary angiography	
14	What is the incremental benefit and cost effectiveness of a clinical history, risk factors and physical examination in evaluation of individuals with stable chest pain of suspected cardiac origin?	Adults presenting with stable chest pain/discomfort of suspected cardiac origin	Clinical history (descriptors of chest pain and associated symptoms) of people whose pain is not acute (stable chest pain)	Not applicable	Discrimination or aid in discrimination between chest pain of cardiac origin (Angina) and non-cardiac origin for diagnosis
15	Are the symptoms and description of the symptoms different in women presenting with stable chest pain of suspected cardiac origin compared with men?	Subgroups presenting with stable chest pain/discomfort of suspected cardiac origin	Clinical history (descriptors of chest pain and associated symptoms) of people with stable chest pain; women versus men	Not applicable	
16	Are the symptoms and description of the symptoms	Subgroups presenting with stable chest pain/discomfort	Clinical history (descriptors of chest pain and associated symptoms) of	Not applicable	

Appendix C Chest Pain – Guideline Question

	Questions	Population	Interventions	Comparisons	Outcomes
	different in Black and Ethnic Minorities presenting with stable chest pain of suspected cardiac origin compared with Caucasians?	of suspected cardiac origin	people with stable chest pain; Black and Ethnic Minorities		
17	What is the utility (incremental value) and cost effectiveness of the resting ECG in evaluation of individuals with stable chest pain of suspected cardiac origin?	Adults presenting with stable chest pain/discomfort of suspected cardiac origin	Resting ECG	None	
18	What is the utility (incremental value) and cost effectiveness of a chest X ray in evaluation of individuals with stable chest pain of suspected cardiac origin?	Adults presenting with stable chest pain/discomfort of suspected cardiac origin	Chest X ray	Not applicable	Refine the diagnostic likelihood of cardiac chest pain? or discrimination between chest pain of cardiac origin and non-cardiac origin for diagnosis?
19	What is the diagnostic utility of calcium scoring for the evaluation of patients with stable chest pain of cardiac origin?	Adults presenting with stable chest pain/discomfort of suspected cardiac origin	Calcium scoring	Not applicable	
20	What is the diagnostic utility of non-invasive and invasive tests for the evaluation of patients with stable chest pain of suspected cardiac origin?	Adults presenting with stable chest pain/discomfort of suspected cardiac origin	Stress ECG, stress echocardiography, stress ECG versus myocardial perfusion scintigraphy using single photon emission computed tomography, stress magnetic resonance imaging, stress magnetic resonance perfusion imaging, MSCT	Coronary angiography	Diagnosis of angina

Chest pain search strategies

The strategies were developed for use on the Dialog DataStar and OVID web interfaces. For clarification, access to Dialog DataStar was discontinued during the time the guideline was in production, hence the change to OVID. The following databases were searched: Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), MEDLINE, EMBASE, CENTRAL, and CINAHL. Where appropriate to the question AMED and PsycINFO were also searched. All searches were rerun during March 2009.

The Economic literature was searched using an adapted economic filter developed by the Centre for Reviews and Dissemination (CRD) for Medline and EMBASE. The following were searched: NHS Economic Evaluations Database (NHSEED), MEDLINE, and EMBASE.

The strategies shown are those for MEDLINE using either the Dialog DataStar or OVID interfaces unless otherwise stated. These were then adapted for use on other databases as necessary. Copies of all the search strategies are available on request from the National Clinical Guideline Centre.

Devising a strategy to encompass the wide population included in this guideline proved challenging. A balance had to be achieved in formulating a strategy precise enough to capture the relevant papers amongst a very large literature base, but also sensitive enough to ensure relevant papers were not missed. As a consequence, the strategy was adapted during the development process of the guideline. Due to time constraints it was not possible to go back to earlier searches and rerun them using the new population strategy but checks were made when rerunning all the searches before submission of the guideline to ensure relevant papers had not been missed. Changes to the population strategies are annotated below.

Subsequent to the searching, many of the questions were divided in two - ‘Acute Chest Pain’ and ‘Stable Chest Pain’ and papers allocated to each by the reviewer. In addition, some questions were consolidated, for example those for investigations. The questions and evidence are presented in the guideline in the order of the guideline which does not correspond to the number originally allocated and referred to in this document. The table below links the original number with the final number.

Questions		
Final Question Number:	**Original Question number**	**Questions**
1	20	What are the education and information needs in adults presenting with chest pain to optimise their understanding of the diagnostic process and their participation in decisions about their investigations?
2	1	What is the incremental benefit and cost effectiveness of a clinical history, risk factors and physical examination in evaluation of individuals with acute chest pain of suspected cardiac origin?
3	32	What is the diagnostic utility of pain relief with nitrates in the identification of patients with acute chest pain of cardiac origin.
4	24	Are the symptoms and description of the symptoms different in women presenting with acute chest pain of suspected cardiac origin compared with men
5	35	Are the symptoms and description of the symptoms different in Black and Ethnic Minorities presenting with acute chest pain of suspected cardiac origin compared with Caucasians
6	3	What is the utility (incremental value) and cost effectiveness of the resting ECG in evaluation of individuals with acute chest pain of suspected cardiac origin?
7	4	Are the symptoms and description of the symptoms different in women presenting with acute chest pain of suspected cardiac origin compared with men
8	16	In adults presenting with acute chest pain/discomfort of suspected cardiac origin, what is the clinical and cost effectiveness of giving oxygen compared with a placebo?
9	17	In adults presenting with chest pain, what is the clinical and cost effectiveness of pain management (e.g. sublingual and buccal nitrates, diamorphine, morphine with anti-emetic) compared with active comparators?
10	15	In adults presenting with chest pain/discomfort of acute suspected cardiac origin, what is the clinical and cost effectiveness of anti-platelet therapy (aspirin, clopidogrel alone or in combination) compared with a placebo?
11	11	What is the utility and cost effectiveness of cardiac biomarkers in evaluation of individuals with acute chest pain of suspected cardiac origin?
12	34	What is the diagnostic utility MSCT coronary angiography in the diagnosis of patients with acute chest pain of suspected cardiac origin
13	26	What is the incremental benefit and cost effectiveness of a clinical history, risk factors and physical examination in evaluation of individuals with stable chest pain of suspected cardiac origin?
14	37	Are the symptoms and description of the symptoms different in women presenting with stable chest pain

Questions		
Final Question Number:	**Original Question number**	**Questions**
		of suspected cardiac origin compared with men
15	38	Are the symptoms and description of the symptoms different in Black and Ethnic Minorities presenting with stable chest pain of suspected cardiac origin compared with Caucasians
16	36	What is the utility (incremental value) and cost effectiveness of the resting ECG in evaluation of individuals with stable chest pain of suspected cardiac origin?
17	33	What is the diagnostic utility of calcium scoring for the evaulation of patients with stable chest pain of cardiac origin.
18	31	What is the diagnostic utility of non-invasive and invasive tests for the evaluation of patients with stable chest pain of suspected cardiac origin.
	10	MERGED TO ORIGINAL QUESTION NUMBER 33 What is the utility and cost effectiveness of cardiac MRI (including MRA and stress CMR) in evaluation of individuals with chest pain of suspected cardiac origin
	9	MERGED TO ORIGINAL QUESTION NUMBER 33 What is the utility and cost effectiveness of cardiac CT (including angiography and ? EBCT) in evaluation of individuals with chest pain of suspected cardiac origin?
	8	MERGED TO ORIGINAL QUESTION NUMBER 33 What is the utility and cost effectiveness of myocardial perfusion scintigraphy with and without SPECT in evaluation of individuals with chest pain of suspected cardiac origin?
	7	MERGED TO ORIGINAL QUESTION NUMBER 33 What is the utility and cost effectiveness of stress echocardiography in evaluation of individuals with chest pain of suspected cardiac origin?
	5	MERGED TO ORIGINAL QUESTION NUMBER 33 What is the utility (incremental value) and cost effectiveness of echocardiography in evaluation of individuals with chest pain of suspected cardiac origin?
	2	MOVE TO ORIGINAL QUESTION NUMBER 1 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?
	6	MERGED TO ORIGINAL QUESTION NUMBER 33 What is the utility and cost effectiveness of the exercise ECG in evaluation of individuals with chest pain

Questions		
Final Question Number:	**Original Question number**	**Questions**
		of suspected cardiac origin?
	12	IN ORIGINAL QUESTION NUMBER 11 What is the optimum timing for utility of cardiac biomarkers in evaluation of individuals with chest pain of suspected cardiac origin?
	13	MERGED TO ORIGINAL QUESTION NUMBER 33 What is the utility and cost effectiveness of coronary angiography in evaluation of individuals with chest pain of suspected cardiac origin?
	14	NOT USED What is the utility and cost effectiveness of conducting an algorithm based on computerising relevant information in evaluation of individuals with chest pain of suspected cardiac origin?
	21	Are the presenting symptoms and description of the symptoms different in different groups (based on age, gender, socioeconomic status and ethnicity)?
	22	(MOVED TO ORIGINAL QUESTION NUMBER Q1 What is the incremental benefit and cost effectiveness of a physical examination in evaluation of individuals with acute chest pain of suspected cardiac origin?
	23	What is the accuracy of a computer assisted ECG interpretation
	25	Are the presenting symptoms and description of the symptoms different in women presenting with stable chest pain of cardiac origin compared with men
	27	(QUESTION NOW REDUNDANT MOVE ALL TO Q26 What is the incremental benefit and cost effectiveness of assessment of cardiovascular risk factors in evaluation of individuals with stable chest pain of suspected cardiac origin?
	28	(QUESTION NOW REDUNDANT MOVE ALL TO Q26 What is the incremental benefit and cost effectiveness of a physical examination in evaluation of individuals with stable chest pain of suspected cardiac origin?
	19	MERGED TO ORIGINAL QUESTION NUMBER 2 What are the education and information needs in adults presenting with acute chest pain to encourage early recognition of suspected ACS?

For each question searches were carried out for systematic reviews (SR) and RCTs, (unless otherwise indicated) along with health economic (HE) literature. The MEDLINE filters used for systematic reviews , RCTs and the health economic literature are listed below:

Medline Systematic review filter. adapted from filter developed by Centre of Reviews and Dissemination (CRD)

1. SEARCH: (SYSTEMATIC$ ADJ REVIEW$).AB.
2. SEARCH: REVIEW.PT.
3. SEARCH: META-ANALYSIS OR METAANALYSIS OR (META ADJ ANALYSIS).AB.
4. SEARCH: META-ANALYSIS OR METAANALYSIS OR (META ADJ ANALYSIS).PT.
5. SEARCH: META-ANALYSIS OR METAANALYSIS OR (META ADJ ANALYSIS).TI.
6. SEARCH: 1 OR 2 OR 3 OR 4 OR 5
7. SEARCH: PT=COMMENT OR PT=EDITORIAL OR PT=LETTER OR PT=ENGLISH-ABSTRACT OR PT=CONGRESSES
8. SEARCH: 6 NOT 7

MEDLINE RCT filter developed by the Cochrane Collaboration

(RANDOMIZED ADJ CONTROLLED ADJ TRIAL).PT.
(CONTROLLED ADJ CLINICAL ADJ TRIAL).PT.
(RANDOMIZED ADJ CONTROLLED ADJ TRIALS).SH.
(RANDOM ADJ ALLOCATION).SH.
(DOUBLE ADJ BLIND ADJ METHOD).SH.
(SINGLE ADJ BLIND ADJ METHOD).SH.

MEDLINE HE filter adapted from filter developed by the Centre for Reviews and Dissemination (CRD).

1. ECONOMICS.DE.
2. COSTS-AND-COST-ANALYSIS#.DE.
3. ECONOMICS-DENTAL.DE.
4. ECONOMICS-HOSPITAL#.DE.
5. ECONOMICS-MEDICAL.DE.
6. ECONOMICS-NURSING.DE.
7. ECONOMICS-PHARMACEUTICAL.DE.
8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
9. (COST$ ADJ (EFFECTIVE$ OR UTILIT$ OR BENEFIT$ OR MINIMI$)).AB.
10. (ECONOMIC$ OR COST OR COSTS OR COSTLY OR COSTING OR PRICE OR PRICES OR PRICING OR PHARMACOECONOMIC$).TI,AB.
11. EXPENDITURE$.TI,AB. NOT ENERGY.TI,AB.
12. (VALUE WITH MONEY).TI,AB.
13. BUDGET$.TI,AB.
14. 9 OR 10 OR 11 OR 12 OR 13
15. 8 AND 14
16. Relevant sets for Population & Intervention AND 15
17. (METABOLIC ADJ COST).TI,AB.
18. ((ENERGY OR OXYGEN) ADJ COST).TI,AB.
19. 17 AND 18
20. 16 NOT (17 AND 18)

Question 1 – 14 relating to assessment and investigation

Question 1: What is the utility and cost effectiveness of a clinical history and examination in evaluation of individuals with chest pain of suspected cardiac origin?

Question 2: What is the utility and cost effectiveness of assessment of cardiovascular risk factors in evaluation of individuals with chest pain of suspected cardiac origin?

CP AND RISK, HISTORY & PHYSICAL EXAM MEDLINE SEARCH STRATEGY

1. SEARCH: Risk-Assessment.MJ.
2. SEARCH: Medical-History-Taking.MJ.
3. SEARCH: Physical-Examination.MJ.
4. SEARCH: Risk.W..MJ.
5. SEARCH: (pretest ADJ (probability OR likelihood)).TI,AB.
6. SEARCH: (history NEAR (take OR takes OR taking)).TI,AB.
7. SEARCH: (risk ADJ assess$5).TI,AB.
8. SEARCH: ((physical OR clinical) ADJ exam$8).TI,AB.
9. SEARCH: ((medical OR family OR patient OR clinical) ADJ history).TI,AB.
10. SEARCH: (probability ADJ disease).TI,AB.
11. SEARCH: Framingham.TI,AB.
12. SEARCH: 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11
13. SEARCH: Chest-Pain#.DE.
14. SEARCH: angina.TI,AB.
15. SEARCH: Angina-Pectoris#.DE.
16. SEARCH: (acute ADJ coronary ADJ syndrome$2).TI,AB.
17. SEARCH: Myocardial-Infarction#.DE.
18. SEARCH: 13 OR 14 OR 15 OR 16 OR 17
19. SEARCH: 12 AND 18

Question 3: What is the utility and cost effectiveness of the resting ECG in evaluation of individuals with chest pain of suspected cardiac origin?

CHEST PAIN AND ECG MEDLINE SEARCH STRATEGY

1. SEARCH: CHEST-PAIN#.DE.
2. SEARCH: ANGINA.TI,AB.
3. SEARCH: ANGINA-PECTORIS#.DE.
4. SEARCH: (ACUTE ADJ CORONARY ADJ SYNDROME$2).TI,AB.
5. SEARCH: MYOCARDIAL-INFARCTION#.DE.

6. SEARCH: 1 OR 2 OR 3 OR 4 OR 5
7. SEARCH: ELECTROCARDIOGRAPHY#.W..DE.
8. SEARCH: ECG OR EKG.TI,AB.
9. SEARCH: ELECTROCARDIOGRA$ OR ELECTROKARDIOGRA$.TI,AB.
10. SEARCH: 12-LEAD OR TWELVE-LEAD OR '12' ADJ LEAD OR (TWELVE ADJ LEAD).TI,AB.
11. SEARCH: 7 OR 8 OR 9 OR 10
12. SEARCH: 6 AND 11

CHEST PAIN AND ECG MEDLINE SEARCH STRATEGY

Question 4: What is the utility and cost effectiveness of a chest X-ray in evaluation of individuals with chest pain of suspected cardiac origin?

This strategy was revised to include the original five terms plus two new terms in the population: CORONARY-DISEASE#.MJ. and (CORONARY ADJ HEART ADJ DISEASE).TI,AB. After April 2008, this population was used for the majority of the remaining searches. Any variations to this are noted at the relevant point.

Searches for this question were conducted for **systematic reviews and diagnostic accuracy (filter included below).**

CHEST PAIN & XRAY MEDLINE SEARCH STRATEGY

1. SEARCH: (CHEST NEAR RADIOGRAPH$).TI,AB.
2. SEARCH: RADIOGRAPHY#.W..DE.
3. SEARCH: (XRAY OR X-RAY OR X ADJ RAY).TI,AB.
4. SEARCH: (CHEST NEAR (XRAY OR X-RAY OR X ADJ RAY)).TI,AB.
5. SEARCH: (ROENTOGRA$4 OR ROENTENOGRA$4 OR ROENTNOGRA$4).TI,AB.
6. SEARCH: 1 OR 2 OR 3 OR 4 OR 5
7. SEARCH: CHEST-PAIN#.MJ.
8. SEARCH: ANGINA.TI,AB.
9. SEARCH: ANGINA-PECTORIS#.MJ.
10. SEARCH: (ACUTE ADJ CORONARY ADJ SYNDROME$2).TI,AB.

11. SEARCH: MYOCARDIAL-INFARCTION#.MJ.
12. SEARCH: CORONARY-DISEASE#.MJ.
13. SEARCH: (CORONARY ADJ HEART ADJ DISEASE).TI,AB.
14. SEARCH: 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13
15. SEARCH: 6 AND 14
16. SEARCH: SENSITIVITY-AND-SPECIFICITY.DE.
17. SEARCH: (SENSITIVITY OR SPECIFICITY OR ACCURACY).TI,AB.
18. SEARCH: (PREDICTIVE ADJ VALUE$1).TI,AB.
19. SEARCH: (ROC ADJ CURVE$1).TI,AB.
20. SEARCH: (FALSE ADJ (POSITIV$2 OR NEGATIV$2)).TI,AB.
21. SEARCH: (OBSERVER ADJ VARIATION$).TI,AB.
22. SEARCH: (LIKELIHOOD ADJ RATIO$).TI,AB.
23. SEARCH: DIAGNOSIS-DIFFERENTIAL.DE.
24. SEARCH: LIKELIHOOD-FUNCTIONS.DE.
25. SEARCH: DIAGNOSTIC-ERRORS#.DE.
26. SEARCH: PREDICTIVE-VALUE-OF-TESTS.DE.
27. SEARCH: 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26
28. SEARCH: 15 AND 27
29. SEARCH: 14 AND 27 AND 28
30. SEARCH: ANIMAL=YES
31. SEARCH: HUMAN=YES
32. SEARCH: 30 NOT (30 AND 31)
33. SEARCH: 29 NOT 32
34. SEARCH: (COMMENT OR EDITORIAL OR LETTER OR ENGLISH-ABSTRACT OR CONGRESSES).PT.
35. SEARCH: 33 NOT 34
36. SEARCH: LG=EN
37. SEARCH: 35 AND 36

Question 5: What is the utility and cost effectiveness of echocardiography in evaluation of individuals with chest pain of suspected cardiac origin?

Question 6: What is the utility and cost effectiveness of the exercise ECG in evaluation of individuals with chest pain of suspected cardiac origin?

Question 7: What is the utility and cost effectiveness of stress echocardiography in evaluation of individuals with chest pain of suspected cardiac origin?

Searches were conducted for systematic reviews and diagnostic accuracy (filter included below)

CHEST PAIN & ECG MEDLINE SEARCH STRATEGY

1. SEARCH: CHEST-PAIN#.MJ.
2. SEARCH: ANGINA.TI,AB.
3. SEARCH: ANGINA-PECTORIS#.MJ.
4. SEARCH: (ACUTE ADJ CORONARY ADJ SYNDROME$2).TI,AB.
5. SEARCH: MYOCARDIAL-INFARCTION#.MJ.
6. SEARCH: CORONARY-DISEASE#.MJ.
7. SEARCH: (CORONARY ADJ HEART ADJ DISEASE).TI,AB.
8. SEARCH: 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
9. SEARCH: ELECTROCARDIOGRAPHY.W..MJ.
10. SEARCH: ECG OR EKG.TI,AB.
11. SEARCH: ELECTROCARDIOGRA$ OR ELECTROKARDIOGRA$.TI,AB.
12. SEARCH: 12-LEAD OR TWELVE-LEAD OR '12' ADJ LEAD OR (TWELVE ADJ LEAD).TI,AB.
13. SEARCH: 9 OR 10 OR 11 OR 12
14. SEARCH: 8 AND 13
15. SEARCH: SENSITIVITY-AND-SPECIFICITY.DE.
16. SEARCH: (SENSITIVITY OR SPECIFICITY OR ACCURACY).TI,AB.
17. SEARCH: (PREDICTIVE ADJ VALUE$1).TI,AB.
18. SEARCH: (ROC ADJ CURVE$1).TI,AB.
19. SEARCH: (FALSE ADJ (POSITIV$2 OR NEGATIV$2)).TI,AB.
20. SEARCH: (OBSERVER ADJ VARIATION$).TI,AB.
21. SEARCH: (LIKELIHOOD ADJ RATIO$1).TI,AB.
22. SEARCH: DIAGNOSIS-DIFFERENTIAL.DE.
23. SEARCH: LIKELIHOOD-FUNCTIONS.DE.
24. SEARCH: DIAGNOSTIC-ERRORS#.DE.

25. SEARCH: PREDICTIVE-VALUE-OF-TESTS.DE.
26. SEARCH: 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25
27. SEARCH: 14 AND 26
28. SEARCH: 8 AND 26 AND 27
29. SEARCH: PT=COMMENT OR PT=EDITORIAL OR PT=LETTER OR PT=ENGLISH-ABSTRACT OR PT=CONGRESSES
30. SEARCH: 28 NOT 29
31. SEARCH: ANIMAL=YES
32. SEARCH: HUMAN=YES
33. SEARCH: 31 NOT (31 AND 32)
34. SEARCH: 30 NOT 33
35. SEARCH: LG=EN
36. SEARCH: 34 AND 35

Question 8: What is the utility and cost effectiveness of myocardial perfusion scintigraphy with and without SPECT in evaluation of individuals with chest pain of suspected cardiac origin?

Question 9: What is the utility and cost effectiveness of cardiac CT (including angiography and ? EBCT) in evaluation of individuals with chest pain of suspected cardiac origin?

Question 10: What is the utility and cost effectiveness of cardiac MRI (including MRA and stress CMR) in evaluation of individuals with chest pain of suspected cardiac origin?

Question 13: What is the utility and cost effectiveness of coronary angiography in evaluation of individuals with chest pain of suspected cardiac origin?

Chest Pain and diagnostic accuracy MEDLINE search strategy

1. exp "Sensitivity and Specificity"/
2. (sensitivity or specificity or accuracy).ti,ab.
3. (predictive and value*).ti,ab.
4. (roc and curve*).ti,ab.

5. (false and (positiv* or negative*)).ti,ab.
6. (observer and variation*).ti,ab.
7. (likelihood and ratio*).ti,ab.
8. Likelihood Functions/
9. Diagnosis, Differential/
10. exp Diagnostic Errors/
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp *Chest Pain/
13. exp *Angina Pectoris/
14. angina.ti,ab.
15. (acute and coronary and syndrome*).ti,ab.
16. exp *Myocardial Infarction/
17. exp *Coronary Disease/
18. (coronary and heart and disease).ti,ab.
19. 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 11 and 19
21. limit 20 to (english language and humans)

Question 11: What is the utility and cost effectiveness of cardiac biomarkers in evaluation of individuals with chest pain of suspected cardiac origin?

Question 12: What is the optimum timing for utility of cardiac biomarkers in evaluation of individuals with chest pain of suspected cardiac origin?

CHEST PAIN AND BIOMARKERS MEDLINE SEARCH STRATEGY

1. SEARCH: (CARDIAC ADJ BIOMARKERS).TI,AB.
2. SEARCH: BIOMARKERS-PHARMACOLOGICAL#.DE.
3. SEARCH: (CARDIAC NEAR BIOLOGICAL ADJ MARKERS).TI,AB.
4. SEARCH: (TROPONIN ADJ (I OR 'T')).TI,AB.
5. SEARCH: TROPONIN-I#.DE.
6. SEARCH: TROPONIN-T#.DE.

7. SEARCH: MYOGLOBIN.TI,AB.
8. SEARCH: (CK-MB OR CK ADJ MB OR CKMB).TI,AB.
9. SEARCH: (CPK-MB OR CPK ADJ MB OR CPKMB).TI,AB.
10. SEARCH: (CREATINE ADJ KINASE ADJ MB).TI,AB.
11. SEARCH: (TNI OR TNT OR CTNI OR CTNT).TI,AB.
12. SEARCH: TROPONIN.TI,AB.
13. SEARCH: 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12
14. SEARCH: CHEST-PAIN#.MJ.
15. SEARCH: ANGINA.TI,AB.
16. SEARCH: ANGINA-PECTORIS#.MJ.
17. SEARCH: (ACUTE ADJ CORONARY ADJ SYNDROME$2).TI,AB.
18. SEARCH: MYOCARDIAL-INFARCTION#.MJ.
19. SEARCH: CORONARY-DISEASE#.MJ.
20. SEARCH: (CORONARY ADJ HEART ADJ DISEASE).TI,AB.
21. SEARCH: 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20
22. SEARCH: 13 AND 21

Question 14: What is the utility and cost effectiveness of conducting an algorithm based on computerising relevant information in evaluation of individuals with chest pain of suspected cardiac origin?

CP and algorithms MEDLINE search strategy

1. exp Algorithms/
2. algorithm*.ti,ab.
3. (risk adj scor*).ti,ab.
4. 1 or 3 or 2
5. exp Chest Pain/
6. exp Angina Pectoris/
7. angina.ti,ab.
8. exp Acute Coronary Syndrome/
9. acute coronary syndrome.ti,ab.
10. exp Myocardial Infarction/
11. exp Coronary Disease/
12. coronary heart disease.ti,ab.

13. 8 or 6 or 11 or 7 or 10 or 9 or 12 or 5
14. 4 and 13

Questions 15 to 17 relating to treatment

The searches for questions 15 and 16, carried out in November 2007, were some of the first to be carried out for this guideline before the final population strategy had been agreed upon.

Question 15: 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?

CP AND ANTI-PLATELET THERAPY MEDLINE SEARCH STRATEGY

1. SEARCH: CHEST-PAIN#.DE.
2. SEARCH: (CHEST NEAR (PAIN OR DISCOMFORT OR TIGHT$4 OR PRESSURE)).TI,AB.
3. SEARCH: (CARDIAC ADJ PAIN).TI,AB.
4. SEARCH: (THORA$3 NEAR PAIN).TI,AB.
5. SEARCH: (SUSPECT$2 NEAR CARDIAC NEAR PAIN).TI,AB.
6. SEARCH: (SUSPECT$2 NEAR ACUTE ADJ CORONARY NEAR SYNDROME$2).TI,AB.
7. SEARCH: (UNSTABLE NEAR ANGINA).TI,AB.
8. SEARCH: MYOCARDIAL.TI,AB.
9. SEARCH: INFARCT$3.TI,AB.
10. SEARCH: (MYOCARDIAL ADJ INFARCTION).TI,AB.
11. SEARCH: (PREINFARCTION OR PRE-INFARCTION OR PRE ADJ INFARCTION).TI,AB.
12. SEARCH: (HEART NEAR (ARREST$2 OR ATTACK$2)).TI,AB.
13. SEARCH: 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12
14. SEARCH: PLATELET-AGGREGATION-INHIBITORS#.DE.
15. SEARCH: ((ANTIPLATELET OR ANTI ADJ PLATELET OR ANTI-

PLATELET) NEAR THERAP$3).TI,AB.

16. SEARCH: ASPIRIN#.W..DE.
17. SEARCH: ASPIRIN.TI,AB.
18. SEARCH: CLOPIDOGREL.TI,AB.
19. SEARCH: PLAVIX.TI,AB.
20. SEARCH: 14 OR 15 OR 16 OR 17 OR 18 OR 19
21. SEARCH: 13 AND 20

Question 16: In adults presenting with chest pain/discomfort of suspected cardiac origin, what is the clinical and cost effectiveness of giving oxygen compared with a placebo?

CP AND OXYGEN MEDLINE SEARCH STRATEGY

1. SEARCH: CHEST-PAIN#.DE.
2. SEARCH: (CHEST NEAR (PAIN OR DISCOMFORT OR TIGHT$4 OR PRESSURE)).TI,AB.
3. SEARCH: (CARDIAC ADJ PAIN).TI,AB.
4. SEARCH: (THORA$3 NEAR PAIN).TI,AB.
5. SEARCH: (SUSPECT$2 NEAR CARDIAC NEAR PAIN).TI,AB.
6. SEARCH: (SUSPECT$2 NEAR ACUTE ADJ CORONARY NEAR SYNDROME$2).TI,AB.
7. SEARCH: (UNSTABLE NEAR ANGINA).TI,AB.
8. SEARCH: MYOCARDIAL.TI,AB.
9. SEARCH: INFARCT$3.TI,AB.
10. SEARCH: (MYOCARDIAL ADJ INFARCTION).TI,AB.
11. SEARCH: (PREINFARCTION OR PRE-INFARCTION OR PRE ADJ INFARCTION).TI,AB.
12. SEARCH: (HEART NEAR (ARREST$2 OR ATTACK$2)).TI,AB.
13. SEARCH: 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12
14. SEARCH: OXYGEN.W..MJ.
15. SEARCH: OXYGEN-INHALATION-THERAPY#.DE.
16. SEARCH: OXYGEN.TI,AB.
17. SEARCH: 14 OR 15 OR 16
18. SEARCH: 13 AND 17

Question 17: In adults presenting with chest pain, what is the clinical and cost effectiveness of pain management (e.g. sublingual and buccal nitrates, diamorphine, morphine with anti-emetic) compared with active comparators?

CP and nitrates MEDLINE earch strategy

1. exp NITRATES/
2. nitrate*.ti,ab.
3. (glycerin and trinitrate*).ti,ab.
4. GTN.ti,ab.
5. exp NITROGLYCERIN/
6. (isosorbide and dinitrate).ti,ab.
7. exp ISOSORBIDE DINITRATE/
8. ISDN.ti,ab.
9. (isosorbide and mononitrate).ti,ab.
10. ISMN.ti,ab.
11. nitroglycerin.ti,ab.
12. 6 or 11 or 3 or 7 or 9 or 2 or 8 or 1 or 4 or 10 or 5
13. exp Chest Pain/
14. exp Angina Pectoris/
15. angina.ti,ab.
16. exp Acute Coronary Syndrome/
17. acute coronary syndrome.ti,ab.
18. exp Myocardial Infarction/
19. exp Coronary Disease/
20. coronary heart disease.ti,ab.
21. 17 or 20 or 15 or 14 or 18 or 13 or 16 or 19
22. 21 and 12

Questions 18 to 21 – relating to other questions

Question 18: What are the indicators for referral from primary care to secondary care in adults presenting with chest pain?
Question 19: What are the education and information needs in adults presenting with chest pain to encourage early recognition of suspected ACS?
Question 20: What are the education and information needs in adults presenting with chest pain to optimise their understanding of the diagnostic process and their participation in decisions about their investigations?

CP AND EDUCATION & INFORMATION NEEDS MEDLINE SEARCH STRATEGY

1. psychoeducation.ti,ab.
2. ((panic or anxiety) adj manag*).ti,ab.
3. ((behavioural or behavioral) adj activation).ti,ab.
4. ((behavioural or behavioral) adj motivation).ti,ab.
5. Patient Education as Topic/
6. "Early Intervention (Education)"/
7. (early adj intervention).ti,ab.
8. ((treatment or health) adj seeking adj (behavior or behaviour)).ti,ab.
9. Health Behavior/
10. (health adj behaviour).ti,ab.
11. Decision Making/
12. (decision adj making adj process*).ti,ab.
13. collaborat*.ti,ab.
14. empower*.ti,ab.
15. (illness adj (representation* or perception*)).ti,ab.
16. (control or (perceiv* adj control)).ti,ab.
17. ((education or information) adj need*).ti,ab.
18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. exp Chest Pain/
20. exp Angina Pectoris/
21. angina.ti,ab.
22. exp Acute Coronary Syndrome/
23. (acute adj coronary adj syndrome).ti,ab.
24. exp Myocardial Infarction/
25. exp Coronary Disease/
26. (coronary adj heart adj disease).ti,ab.
27. 25 or 21 or 26 or 20 or 22 or 24 or 19 or 23
28. 27 and 18

Question 21: Are the presenting symptoms and description of the symptoms different in different groups (based on age, gender, diabetes, socioeconomic status and ethnicity)?

CP signs symptoms MEDLINE search strategy

1. exp "SIGNS AND SYMPTOMS"/
2. exp *CHEST PAIN/

3. exp *ANGINA PECTORIS/
4. angina.ti,ab.
5. exp *ACUTE CORONARY SYNDROME/
6. (acute and coronary and syndrome*).ti,ab.
7. exp *MYOCARDIAL INFARCTION/
8. exp *CORONARY DISEASE/
9. (coronary and heart and disease).ti,ab.
10. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. 1 and 10

Appendix D - Clinical Evidence Extractions

Question: 1 What are the education and information needs in adults presenting with chest pain to optimise their understanding of the diagnostic process and their participation in decisions about their investigations?

Grading: 1- Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Arnold J;Goodacre S;Bath P;Price J;

Information sheets for patients with acute chest pain: randomised controlled trial

Ref ID 25415 Brit Med J pgs: b541 to b546 2009

Study Type Randomised Controlled Trial **Funding** Health Foundation Leadership Practice Award

Number of participants Intervention group, n=349; Control group n=351. Total n=700.

Inclusion/Exclusion Criteria Subjects were patients who were investigated for chest pain of possible cardiac origin, were aged over 25, had no changes for acute coronary syndrome on a diagnostic electrocardiogram, had no suspected life threatening non-cardiac disease and did not have known coronary heart disease 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.

Patient Characteristics The study population had a mean age of 48.6 years, and 61.6% were men. Information sheets were deemed suitable for 19 patients with a diagnosis of angina (mean age 69,58% men) 162 with a diagnosis of definite benign non-cardiac pain (mean age 43, 65% men), 61 with a diagnosis of uncertain cause requiring further cardiology investigation (mean age 52, 49% men), and 458 with a diagnosis of uncertain cause suitable for expectant management (mean age 49, 62% men).

Recruitment The aim was to recruit 700 consecutive patients who had been investigated for suspected acute coronary syndrome. The chest pain nurses identified eligible patients.

Setting Chest pain unit, emergency centre, Sheffield

Interventions/ Test/ Factor being investigated The objective was to determine whether providing an information sheet to patients with acute hest pain reduces anxiety, improves health related quality of life, improves satisfaction with care or alters subsequent symptoms or actions. Four separate information sheets were developed: definite angina, definite benign non-cardiac chest pain, uncertain cause requiring further cardiology investigation and uncertain cause suitable for expectant management.

Comparisons This study compared those receiving standard verbal advice with those receiving advice and an information sheet.

Length of Study/ Follow-up One month after recruitment all patients were sent a questionnaire by post. Questionnaires were resent to non-responders at six and eight weeks.

Outcome measures studied The primary outcome was scores on the anxiety subscale of the hospital anxiety and depression scale. Secondary outcomes included the depression and SF-36 scores;satisfaction;further symptoms; life style changes

Results 494 of 700 (70.6%) responses. Compared with those receiving standard verbal advice those 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 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.

Safety and adverse effects None reported

Does the study answer the question?	Provision of an information sheet to patients with acute chest pain can reduce anxiety and depression and improve mental health and perception of general health but does not alter satisfaction with care or other outcomes. The authors of the study conclude that as the information sheets are simple to administer and outcomes were on balance positive, the use of these sheets should be recommended in patients receiving diagnostic assessment for acute chest pain.
Effect due to factor in study?	There are some limitations which may bias the outcome of this study: it is 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.
Consistency of results with other studies?	There are no other studies in this field.
Directly applicable to guideline population?	This study population excluded all patients who could not read English. Thus it may not be generalisable to all individuals with chest pain.
Internal Validity	Subjects are not blinded; 29% non response

Question 2: What is the incremental benefit and cost effectiveness of a clinical history, risk factors and physical examination in evaluation of individuals with acute chest pain of suspected cardiac origin?

Grading: 1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Bruyninckx R;Aertgeerts B;Bruyninckx P;Buntinx F;

Signs and symptoms in diagnosing acute myocardial infarction and acute coronary syndrome: a diagnostic meta-analysis

Ref ID 10251 Br J Gen Pract pgs: e1 to e8 2008

Study Type Systematic Review **Funding** Not reported

Number of participants	28 prospective and retrospective observational studies
Inclusion/Exclusion Criteria	Studies had to describe at least 1 of the 10 signs and symptoms for diagnosing ACS or AMI, and based on original data
Patient Characteristics	Patients with signs and symptoms for the diagnosis of acute MI, unstable angina or ACS.
Recruitment	
Setting	Secondary and primary care
Interventions/ Test/ Factor being investigated	The signs and symptoms considered were 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 or absence of chest wall tenderness
Comparisons	Signs and symptoms to diagnose chest pain
Length of Study/ Follow-up	
Outcome measures studied	
Results	The results of the meta-analysis showed that absence of chest wall tenderness was highly sensitive for AMI and ACS (92 % and 94% respectively). It was seen that when the patient presented with pain on palpation the chance of an AMI or ACS was greatly reduced (LR- 0.23 and 0.17 respectively). The analysis showed that oppressive pain had a sensitivity of 60% and specificity of 58% and had almost no influence on the likelihood of the patient having an AMI. The other signs and symptoms considered in the study had lower sensitivity and specificity and therefore could not be used to exclude an AMI or ACS. The sensitivity of absence of tenderness was high, namely 92% (95% CI = 85.5 to 96.4) for acute myocardial infarction and 94% (95% CI = 91.4 to 96.1) for acute coronary syndrome. Oppressive pain followed with a sensitivity of 60% (95% CI = 53.7 to 66.0 for acute myocardial infarction). Sweating had the highest LR+, namely 2.92 (95% CI = 1.97 to 4.32 for acute myocardial infarction). The LR+ of right arm or shoulder pain was 2.89 (95% CI = 1.40 to 5.98) for acute myocardial infarction (one study). The other LR+ fluctuated between 1.05 and 1.49 for acute coronary syndrome. Absence of tenderness had a LR- of 0.23 (95% CI = 0.18 to 0.29) for acute myocardial infarction and 0.17 (95% CI = 0.11 to 0.26) for acute coronary syndrome. Other LR– varied between 0.69 (oppressive pain and sweating for acute myocardial infarction) and 0.98 (epigastric pain) for acute coronary syndrome.
Safety and adverse effects	None reported

Does the study answer the question?

5606 papers were initially identified of these 28 papers met the inclusion criteria for the use of 10 signs and symptoms, the studies included were prospective and retrospective observational studies, more than half of the studies were published since Mant et al's selection for the HTA published in 2004. A total of 46,908 patients were included in the review. The signs and symptoms considered were 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 or absence of chest wall tenderness. Of the 28 papers, 11 were set in the emergency department, 10 were set in coronary care unit or the patients had been admitted to hospital, 3 were on the paramedics in an ambulance, 2 were set in GPs, 1 was carried out by a cardiologist and 1 was in a chest pain observational unit. 16 of the studies had non-selected patients, 11 had selected patients and 1 was from a chest pain observation unit. Selected patients were those who were recruited by coronary care units and cardiologists. All studies included patients had chest pain, in two studies patients also had pulmonary oedema. The mean age of the participants in all the studies was 53-71 years old, and the % of males was from 40-71%.

The results of the meta-analysis showed that absence of chest wall tenderness was highly sensitive for AMI and ACS (92 % and 94% respectively). It was seen that when the patient presented with pain on palpation the chance of an AMI or ACS was greatly reduced (LR- 0.23 and 0.17 respectively). The analysis showed that oppressive pain had a sensitivity of 60% and specificity of 58% and had almost no influence on the likelihood of the patient having an AMI. The other signs and symptoms considered in the study had lower sensitivity and specificity and therefore could not be used to exclude an AMI or ACS.

The sensitivity of absence of tenderness was high, namely 92% (95% CI = 85.5 to 96.4) for acute myocardial infarction and 94% (95% CI = 91.4 to 96.1) for acute coronary syndrome. Oppressive pain followed with a sensitivity of 60% (95% CI = 53.7 to 66.0 for acute myocardial infarction). Sweating had the highest LR+, namely 2.92 (95% CI = 1.97 to 4.32 for acute myocardial infarction). The LR+ of right arm or shoulder pain was 2.89 (95% CI = 1.40 to 5.98) for acute myocardial infarction (one study). The other LR+ fluctuated between 1.05 and 1.49 for acute coronary syndrome. Absence of tenderness had a LR- of 0.23 (95% CI = 0.18 to 0.29) for acute myocardial infarction and 0.17 (95% CI = 0.11 to 0.26) for acute coronary syndrome. Other LR– varied between 0.69 (oppressive pain and sweating for acute myocardial infarction) and 0.98 (epigastric pain) for acute coronary syndrome.

The authors concluded that it was not possible to define an important role for signs and symptoms in the diagnosis of AMI or ACS. Only chest wall tenderness on palpation largely ruled out AMI or ACS.

See tables in guideline for detailed results.
(NB pleuritic pain not considered).

Effect due to factor in study?

Yes

Consistency of results with other studies?

Consistent

Directly applicable to guideline population?

Correct population

Internal Validity

Mant J;McManus RJ;Oakes RL;Delaney BC;Barton PM;Deeks JJ;Hammersley L;Davies RC;Davies MK;Hobbs FR;

Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care

Ref ID 728 Health technology assessment pgs: 1 to 158 2004

Study Type Systematic Review

Funding NHS R&D Health Technology Assessment Programme

Number of participants	21 observational studies
Inclusion/Exclusion Criteria	Papers used at least one of the signs and symptoms in the diagnosis of chest pain
Patient Characteristics	
Recruitment	
Setting	8 secondary care, 10 A&E, 3 primary secondary care
Interventions/ Test/ Factor being investigated	The signs and symptoms considered were pluritic 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 or a third heart sound
Comparisons	Signs and symptoms to diagnose chest pain
Length of Study/ Follow-up	
Outcome measures studied	
Results	None of the signs and symptoms in isolation were found to be particularly useful: no sign or symptom achieved an LR of <0.1 or >10.22 Indeed, only one of the upper limits of the 95% CIs exceeded 10 – for right-sided radiation of pain in diagnosis of ACS – which was based on only one study. Similarly, only one of the lower limits (for pain on palpation) was <0.1. The results for presence of a sign or symptom (LR+) were more informative than those for the absence of a symptom or sign (LR–) which were non-contributory to making a diagnosis in every case. Systolic hypotension, the presence of a third heart sound and right-sided radiation of chest pain, achieved the highest positive LRs (LR+ 3.21–2.59) for diagnosis of MI. Where the reference standard was MI or unstable angina, right-sided radiation was associated with a higher positive LR (6.68). Clinical features most helpful in ruling out the diagnosis were the presence of pleuritic, sharp or positional pain, and pain produced by palpation (LR+ 0.19–0.32). It should be noted that there was considerable heterogeneity in the results, particularly (although not exclusively) for the negative LRs. This makes the summary statistics difficult to interpret. 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.
Safety and adverse effects	None reported
Does the study answer the question?	10862 papers were initially identified of these 21 papers met the inclusion criteria for the use of 16 difference clinical signs and symptoms. A total of 38638 patients were included in the review. The signs and symptoms considered 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 or a third heart sound. Of the 21 papers, 8 were set in secondary care, 10 in A&E, and 3 in primary and secondary care. The mean age of the participants in all the studies was 50-73 years old, and the % of males was from 50-71%. None of these in isolation were found to be particularly useful: no sign or symptom achieved an LR of <0.1 or >10.22 Indeed, only one of the upper limits of the 95% CIs exceeded 10 – for right-sided radiation of pain in diagnosis of ACS – which was based on only one study. Similarly, only one of the lower limits (for pain on palpation) was <0.1. The results for presence of a sign or symptom (LR+) were more informative than those for the absence of a symptom or sign (LR–) which were non-contributory to making a diagnosis in every case. Systolic hypotension, the presence of a third heart sound and right-sided radiation of chest pain, achieved the highest positive LRs (LR+ 3.21–2.59) for diagnosis of MI. Where the reference standard was MI or unstable angina, right-sided radiation was associated with a higher positive LR (6.68). Clinical features most helpful in ruling out the diagnosis were the presence of pleuritic, sharp or positional pain, and pain produced by palpation (LR+ 0.19–0.32). It

	should be noted that there was considerable heterogeneity in the results, particularly (although not exclusively) for the negative LRs. This makes the summary statistics difficult to interpret. 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.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Correct population
Internal Validity	

Mant J;McManus RJ;Oakes RL;Delaney BC;Barton PM;Deeks JJ;Hammersley L;Davies RC;Davies MK;Hobbs FR;

Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care

Ref ID 728 Health technology assessment pgs: 1 to 158 2004

Study Type	Systematic Review	**Funding**	NHS R&D Health Technology Assessment Programme

Number of participants	21 Cohort studies studies
Inclusion/Exclusion Criteria	papers used at least one of the signs and symptoms in the diagnosis of chest pain
Patient Characteristics	
Recruitment	
Setting	8 secondary care, 10 A&E, 3 primary&secondary care
Interventions/ Test/ Factor being investigated	The signs and symptoms considered were pluritic 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 or a third heart sound
Comparisons	Signs and symptoms to diagnose chest pain
Length of Study/ Follow-up	
Outcome measures studied	
Results	None of the signs and symptoms in isolation were found to be particularly useful: no sign or symptom achieved an LR of <0.1 or >10.22 Indeed, only one of the upper limits of the 95% CIs exceeded 10 – for right-sided radiation of pain in diagnosis of ACS – which was based on only one study. Similarly, only one of the lower limits (for pain on palpation) was <0.1. The results for presence of a sign or symptom (LR+) were more informative than those for the absence of a symptom or sign (LR–) which were non-contributory to making a diagnosis in every case. Systolic hypotension, the presence of a third heart sound and right-sided radiation of chest pain, achieved the highest positive LRs (LR+ 3.21–2.59) for diagnosis of MI. Where the reference standard was MI or unstable angina, right-sided radiation was associated with a higher positive LR (6.68). Clinical features most helpful in ruling out the diagnosis were the presence of pleuritic, sharp or positional pain, and pain produced by palpation (LR+ 0.19–0.32). It should be noted that there was considerable heterogeneity in the results, particularly (although not exclusively) for the negative LRs. This makes the summary statistics difficult to interpret. 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.
Safety and adverse effects	None reported
Does the study answer the question?	10862 papers were initially identified of these 21 papers met the inclusion criteria for the use of 16 difference clinical signs and symptoms. A total of 38638 patients were included in the review. The signs and symptoms considered were pluritic 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 or a third heart sound. Of the 21 papers, 8 were set in secondary care, 10 in A&E, and 3 in primary and secondary care. The mean age of the participants in all the studies was 50-73 years old, and the % of males was from 50-71%. None of these in isolation were found to be particularly useful: no sign or symptom achieved an LR of <0.1 or >10.22 Indeed, only one of the upper limits of the 95% CIs exceeded 10 – for right-sided radiation of pain in diagnosis of ACS – which was based on only one study. Similarly, only one of the lower limits (for pain on palpation) was <0.1. The results for presence of a sign or symptom (LR+) were more informative than those for the absence of a symptom or sign (LR–) which were non-contributory to making a diagnosis in every case. Systolic hypotension, the presence of a third heart sound and right-sided radiation of chest pain, achieved the highest positive LRs (LR+ 3.21–2.59) for diagnosis of MI. Where the reference standard was MI or unstable angina, right-sided radiation was associated with a higher positive LR (6.68). Clinical features most helpful in ruling out the diagnosis were the presence of pleuritic, sharp or positional pain, and pain produced by palpation (LR+ 0.19–0.32). It should be noted that there was considerable heterogeneity in the results, particularly (although not exclusively) for the negative LRs. This makes the summary statistics difficult to interpret. 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.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Correct population
Internal Validity	

Swap CJ;Nagurney JT;

Value and limitations of chest pain history in the evaluation of patients with suspected acute coronary syndromes

Ref ID	381	JAMA : the journal of the American Medical Association	pgs:	2623	to	2629	2005

Study Type	Systematic Review	**Funding**	Not reported

Number of participants	28 prospective and retrospective observational studies and systematic reviews
Inclusion/Exclusion Criteria	Studies needed to be observational studies including at least 80 patients. Studies needed to include at least 1 chest pain characteristic and make a diagnosis of ACS or AMI with appropriate diagnostic tests
Patient Characteristics	Patients described at least on chest pain characteristic which was diagnosed as ACS or AMI.
Recruitment	
Setting	

Interventions/ Test/ Factor being investigated	The studies considered the following chest pain characteristics: quality, location, radiation, size of area or distribution, severity, time of onset and is it continuing, duration, first occurrence frequency, similar to previous cardiac ischemic episodes and the following precipitating or aggravating factors: pleuritic, positional, palpable, exercise, emotional stress, relieving factors, associated symptoms
Comparisons	Chest pain characteristics for diagnosing chest pain
Length of Study/ Follow-up	
Outcome measures studied	
Results	Certain chest pain characteristics decrease the likelihood of ACS or AMI, namely, pain that is stabbing, pleuritic, positional, or reproducible by palpation (likelihood ratios [LRs] 0.2 to 0.3). Conversely, chest pain that radiates to one shoulder or both shoulders or arms or is precipitated by exertion is associated with LRs (2.3 to 4.7) that increase the likelihood of ACS. The chest pain history itself has not proven to be a powerful enough predictive tool to obviate the need for at least some diagnostic testing. Combinations of elements of the chest pain history with other initially available information, such as a history of CAD, have identified certain groups that may be safe for discharge without further evaluation, but further study is needed before such a recommendation can be considered reasonable.
Safety and adverse effects	None reported
Does the study answer the question?	28 papers were initially identified that were relevant to the evaluation of chest pain using signs and symptoms, the studies included were prospective and retrospective observational studies and systematic reviews, considering both predictors of AMI and ACS. The studies considered the following chest pain characteristics: quality, location, radiation, size of area or distribution, severity, time of onset and is it continuing, duration, first occurrence frequency, similar to previous cardiac ischemic episodes and the following precipitating or aggravating factors: pleuritic, positional, palpable, exercise, emotional stress, relieving factors, associated symptoms. Risk stratification for ACS according to components of chest pain history: Low risk: pain that is pleuritic, positional, or reproducible with palpation or is described as stabbing Probable low risk: pain not related to exertion or that occurs in a small inframammary area of the chest wall Probable high risk: pain described as pressure, is similar to that of prior MI or worse than prior anginal pain or is accompanied by nausea, vomiting or diaphoresis High risk: pain that radiates to one or both shoulders or arms or is relate to exertion Certain chest pain characteristics decrease the likelihood of ACS or AMI, namely, pain that is stabbing, pleuritic, positional, or reproducible by palpation (likelihood ratios [LRs] 0.2 to 0.3). Conversely, chest pain that radiates to one shoulder or both shoulders or arms or is precipitated by exertion is associated with LRs (2.3 to 4.7) that increase the likelihood of ACS. The chest pain history itself has not proven to be a powerful enough predictive tool to obviate the need for at least some diagnostic testing. Combinations of elements of the chest pain history with other initially available information, such as a history of CAD, have identified certain groups that may be safe for discharge without further evaluation, but further study is needed before such a recommendation can be considered reasonable. The authors concluded that although certain elements of the chest pain history are associated with increased (LR = 2.3 to 4.7) or decreased (LR = 0.2 to 0.3) likelihoods of a diagnosis of ACS or AMI, none of them alone or in combination identify a group of patients that can be safely discharged without further diagnostic testing (see table in guideline for detailed results).
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent

Directly applicable to guideline population?	Correct population

Internal Validity

Grading: 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

Conti A;Paladini B;Toccafondi S;Magazzini S;Olivotto I;Galassi F;Pieroni C;Santoro G;Antoniucci D;Berni G;

Effectiveness of a multidisciplinary chest pain unit for the assessment of coronary syndromes and risk stratification in the Florence area

Ref ID 926 American heart journal pgs: 630 to 635 2002

Study Type Cohort

Funding Italian Ministry for Scientific and Technological Research

Number of participants	13 762 patients
Inclusion/Exclusion Criteria	Inclusion: over 18 years old, 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
Patient Characteristics	The mean age was 65±18 years and 43% were women Those who were categorised as being at high risk (21%) had a mean age of 63±10 years, 33% were female, 35% smoked, 25% had diabetes, 38% had hypertension, 13.4 % died during the follow up. Those who were categorised as being at intermediate risk (47%) had a mean age of 64±11 years, 38% were female, 33% smoked, 28% had diabetes, 41% had hypertension, 2.2 % died during the follow up. Those who were categorised as being at low risk (32%) had a mean age of 38±15 years, 66% were female, 12% smoked, 8% had diabetes, 22% had hypertension, 0.2 % died during the follow up.
Recruitment	Admitted to emergency department with chest pain as described above
Setting	ED. Careggi General Hospital, Florence, Italy
Interventions/ Test/ Factor being investigated	Diagnosing chest pain
Comparisons	The chest pain score was based on: location of pain, radiation of pain, character of pain, history of angina
Length of Study/ Follow-up	6 months
Outcome measures studied	Effectiveness of chest pain score in diagnosing chest pain
Results	The chest pain score was based on the following elements each of which was given a value: 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 sticking, pleuritic or pinprick = -1; associated symptoms: dyspnea, nausea or diaphoresis = +2; history of angina = +3. The mean age was 65±18 years. Patients were classified into 1 of 4 groups. 1) Patients at low risk with obvious noncardiac causes of chest pain, chest pain score <4, normal ECG, and normal serum markers of cardiac injury obtained at least 6 hours from symptoms, were sent home and followed up. (2672 patients) 2) Patients at low risk with chest pain score ≥ 4, normal ECG, normal serum cardiac markers, independent of age or coexisting coronary risk factors, were not admitted and underwent a second-line evaluation and short-term observation in the CPU area, including chest radiography, serial 12-lead ECG, serial troponins and cardiac enzymes, echocardiography and arterial blood gas analysis. When at least one of these tests or procedure results was found to be suggestive of AMI, unstable angina or CAD or left ventricular failure was detected these patients were considered for angiography with no additional testing. After an observation period up to 6 hours

	patients without ongoing cardiovascular events underwent exercise tolerance test or SPECT or stress echocardiography. (1755 patients) 3) Patients at intermediate risk with clinical score ≥ 4 and abnormal ECG (ST-segment elevation <1mm or ST-segment depression <1mm at 60ms from J point) were admitted and managed in the CPU area. 4) Patients at high risk with ECG suggestive for AMI (defined as ST elevation ≥1 mm at 60ms from J point, ≥2 contiguous leads) were directly transferred to the coronary care unit and patients with suspected major cardiovascular disease, such as aortic arch dissection, pulmonary embolism, pneumothorax and acute pericarditis, were admitted and managed with arterial blood gas analysis, chest radiography, echocardiography, and thorax computed tomography if required by clinical assessment. At six month follow up 0.2% of these patients were recognised as having nonfatal coronary artery disease, hence, the negative predictive value of a chest pain score of < 4 and normal ECG was > 99% Of the patients with a chest pain score ≥ 4 and normal or non diagnostic electrocardiogram results (1755 patients, 40%), 20% of the low risk group with chest pain score < 4 (group 1) (885 patients) had documented coronary artery disease, 18% of which were by recurrent angina, delayed ECG changes, late rise in markers, the other 2% was by positive stress test. There were 9335 intermediate and high risk patients, of which 2420 patients (26%) had an MI, 3764 patients (40%) had unstable angina, 129 (1.4%) had aortic dissection and 408 (4%) had pulmonary embolism, other major cardiovascular conditions were diagnosed, including aortic arch dissection, pulmonary embolism, pneumothorax, and acute pericarditis. 2256 patients had atypical chest pain diagnosed as multi-organ disease including chronic and stable ischemic heart disease, defined as known stable angina, previous myocardial infarction, or angiographically documented CAD
Safety and adverse effects	None reported
Does the study answer the question?	Of the patients with a chest pain score > 4 and normal electrocardiogram results, 20% (885 patients) had documented coronary artery disease. There were 9335 intermediate and high risk patients, of which 2420 patients (26%) had an MI, 3764 patients (40%) had unstable angina, 129 (1.4%) had aortic dissection and 408 (4%) had pulmonary embolism. Other multi-organ disease was found in 2256 patients. The authors concluded that the chest pain score screening programme was effective and could significantly reduce admissions and optimise the care of those with an intermediate or high risk score. The authors also concluded that the screening programme could aid the diagnosis of alternative causes of chest pain in patients who do not have evidence of coronary artery disease
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Correct population
Internal Validity	Well covered

Grading: 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

Schillinger M;Sodeck G;Meron G;Janata K;Nikfardjam M;Rauscha F;Laggner AN;Domanovits H;

Acute chest pain--identification of patients at low risk for coronary events. The impact of symptoms, medical history and risk factors

Ref ID 735 Wiener klinische Wochenschrift pgs: 83 to 89 2004

Study Type Cohort **Funding** Not reported

Number of participants	1288 patients
Inclusion/Exclusion Criteria	Inclusion criteria: all patients presenting with acute chest pain, onset in previous 24 hours, at a non-trauma emergency department
Patient Characteristics	The mean age of the population was 49±17 years, 41% were women, 29% had hypertension, 9% had diabetes mellitus, 35% had hyperlipidaemia, 32% were current smokers, 26% were obese (BMI>28), 20% had a family history of MI, 15% had a history of prior MI, 23% had a history of coronary artery disease, 2% had a history of congestive heart failure, 3% had valvular heart disease
Recruitment	Patients presenting with chest pain at a non-trauma emergency department
Setting	University hospital in Helsinki, Finland
Interventions/ Test/ Factor being investigated	Diagnosing chest pain
Comparisons	Seven pre-defined criteria are evaluated and were assigned as either typical or atypical
Length of Study/ Follow-up	6 months
Outcome measures studied	Prediction or exclusion of acute MI and major adverse coronary events (MACE) at six months
Results	Seven pre-defined criteria are evaluated and were assigned as either typical or atypical; namely, 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 dyspnea / nausea / diaphoreis atypical: absence of vegetative signs), history of coronary artery disease (typical: MI / PTCA / CABD, atypical: none) and risk factors for coronary artery disease namely; smoking, obesity, hypertension, diabetes, hyperlipidemia, and family history all typical, atypical was defined as absence or only one risk factor. The positive predictive value (PPV) and LR of typical and atypical criteria were evaluated for prediction or exclusion of acute MI and major adverse coronary events (MACE) at six months. Thirteen percent (168 patients) of patients had an acute MI and 19% (240 patients) had a MACE (CVD, percutaneous coronary interventions, bypass surgery or MI) at six months follow up. From the typical symptoms or history the likelihood ratios (LR) to predict an MI were: 1 typical symptom or history LR = 1.15; 2 typical symptoms and/or history LR = 1.32; 3 typical symptoms and/or history LR = 1.48; 4 typical symptoms and/or history LR = 1.77; 5 typical symptoms and/or history LR = 1.88; 6 typical symptoms and/or history LR = 1.85

From the typical symptoms or history the LR to predict a cardiac adverse event in the following 6 months were:
1 typical symptom or history LR = 1.15; 2 typical symptoms and/or history LR = 1.34; 3 typical symptoms and/or history LR = 1.58; 4 typical symptoms and/or history LR = 1.87; 5 typical symptoms and/or history LR = 2.11; 6 typical symptoms and/or history LR = 1.54

From the atypical symptoms or history the LR to exclude an MI were:
1 atypical symptom or history LR = 1.05; 2 atypical symptoms and/or history LR = 1.25; 3 atypical symptoms and/or history LR = 1.76; 4 atypical symptoms and/or history LR = 2.22; 5 atypical symptoms and/or history LR = 3.19; 6 atypical symptoms and/or history LR = 3.00
From the atypical symptoms or history the LR to exclude a cardiac adverse event in the following 6 months were:
1 atypical symptom or history LR = 1.04; 2 atypical symptoms and/or history LR = 1.29; 3 atypical symptoms and/or history LR = 1.85; 4 atypical symptoms and/or history LR = 3.02; 5 atypical symptoms and/or history LR = 4.87; 6 atypical symptoms and/or history LR = 4.58

The presence of four or more typical criteria was associated with a PPV of 0.21 (95%CI 0.17 to 0.25) to predict acute MI and 0.30 (95% CI 0.25 to 0.35) for 6 month MACE. Increasing numbers of atypical chest pain criteria was associated with increasing PPVs for excluding acute MI and 6 month MACE. The presence of four or more typical criteria was associated with a PPV of 0.94 (95%CI 0.92 to 0.96) to exclude acute MI and 0.93 (95% CI 0.90 to 0.96) for 6 month absence of MACE. The authors concluded that the evaluation of criteria atypical for MI may identify patients suitable for early discharge; however criteria typical of MI have little diagnostic value

Safety and adverse effects None reported

Does the study answer the question? The presence of four or more typical criteria was associated with a PPV of 0.21 (95%CI 0.17 to 0.25) to predict acute MI and 0.30 (95% CI 0.25 to 0.35) for 6 month MACE. Increasing numbers of atypical chest pain criteria was associated with increasing PPVs for excluding acute MI and 6 month MACE. The presence of four or more typical criteria was associated with a PPV of 0.94 (95%CI 0.92 to 0.96) to exclude acute MI and 0.93 (95% CI 0.90 to 0.96) for 6 month absence of MACE. The authors concluded that the evaluation of criteria atypical for MI may identify patients suitable for early discharge; however criteria typical of MI have little diagnostic value

Effect due to factor in study? Yes

Consistency of results with other studies? Consistent

Directly applicable to guideline population? Correct population

Internal Validity Well covered

Schillinger M;Sodeck G;Meron G;Janata K;Nikfardjam M;Rauscha F;Laggner AN;Domanovits H;

Acute chest pain--identification of patients at low risk for coronary events. The impact of symptoms, medical history and risk factors

Ref ID 735 Wiener klinische Wochenschrift pgs: 83 to 89 2004

Study Type Cohort **Funding** Not reported

Number of participants 1288 patients

Inclusion/Exclusion Criteria Inclusion criteria: all patients presenting with acute chest pain, onset in previous 24 hours, at a non-trauma emergency department

Patient Characteristics	The mean age of the population was 49±17 years, 41% were women, 29% had hypertension, 9% had diabetes mellitus, 35% had hyperlipidaemia, 32% were current smokers, 26% were obese (BMI>28), 20% had a family history of MI, 15% had a history of prior MI, 23% had a history of coronary artery disease, 2% had a history of congestive heart failure, 3% had valvular heart disease
Recruitment	Patients presenting with chest pain at a non-trauma emergency department
Setting	University hospital in Helsinki, Finland
Interventions/ Test/ Factor being investigated	Diagnosing chest pain
Comparisons	Seven pre-defined criteria are evaluated and were assigned as either typical or atypical
Length of Study/ Follow-up	6 months
Outcome measures studied	Prediction or exclusion of acute MI and major adverse coronary events (MACE) at six months
Results	Seven pre-defined criteria are evaluated and were assigned as either typical or atypical; namely, 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 dyspnea / nausea / diaphoreis atypical: absence of vegetative signs), history of coronary artery disease (typical: MI / PTCA / CABD, atypical: none) and risk factors for coronary artery disease namely; smoking, obesity, hypertension, diabetes, hyperlipidemia, and family history all typical, atypical was defined as absence or only one risk factor. The positive predictive value (PPV) and LR of typical and atypical criteria were evaluated for prediction or exclusion of acute MI and major adverse coronary events (MACE) at six months. Thirteen percent (168 patients) of patients had an acute MI and 19% (240 patients) had a MACE (CVD, percutaneous coronary interventions, bypass surgery or MI) at six months follow up. From the typical symptoms or history the likelihood ratios (LR) to predict an MI were: 1 typical symptom or history LR = 1.15; 2 typical symptoms and/or history LR = 1.32; 3 typical symptoms and/or history LR = 1.48; 4 typical symptoms and/or history LR = 1.77; 5 typical symptoms and/or history LR = 1.88; 6 typical symptoms and/or history LR = 1.85 From the typical symptoms or history the LR to predict a cardiac adverse event in the following 6 months were: 1 typical symptom or history LR = 1.15; 2 typical symptoms and/or history LR = 1.34; 3 typical symptoms and/or history LR = 1.58; 4 typical symptoms and/or history LR = 1.87; 5 typical symptoms and/or history LR = 2.11; 6 typical symptoms and/or history LR = 1.54 From the atypical symptoms or history the LR to exclude an MI were: 1 atypical symptom or history LR = 1.05; 2 atypical symptoms and/or history LR = 1.25; 3 atypical symptoms and/or history LR = 1.76; 4 atypical symptoms and/or history LR = 2.22; 5 atypical symptoms and/or history LR = 3.19; 6 atypical symptoms and/or history LR = 3.00 From the atypical symptoms or history the LR to exclude a cardiac adverse event in the following 6 months were: 1 atypical symptom or history LR = 1.04; 2 atypical symptoms and/or history LR = 1.29; 3 atypical symptoms and/or history LR = 1.85; 4 atypical symptoms and/or history LR = 3.02; 5 atypical symptoms and/or history LR = 4.87; 6 atypical symptoms and/or history LR = 4.58 The presence of four or more typical criteria was associated with a PPV of 0.21 (95%CI 0.17 to 0.25) to predict acute MI and 0.30 (95% CI 0.25 to 0.35) for 6 month MACE. Increasing numbers of atypical chest pain criteria was associated with

	increasing PPVs for excluding acute MI and 6 month MACE. The presence of four or more typical criteria was associated with a PPV of 0.94 (95%CI 0.92 to 0.96) to exclude acute MI and 0.93 (95% CI 0.90 to 0.96) for 6 month absence of MACE. The authors concluded that the evaluation of criteria atypical for MI may identify patients suitable for early discharge; however criteria typical of MI have little diagnostic value
Safety and adverse effects	None reported
Does the study answer the question?	The presence of four or more typical criteria was associated with a PPV of 0.21 (95%CI 0.17 to 0.25) to predict acute MI and 0.30 (95% CI 0.25 to 0.35) for 6 month MACE. Increasing numbers of atypical chest pain criteria was associated with increasing PPVs for excluding acute MI and 6 month MACE. The presence of four or more typical criteria was associated with a PPV of 0.94 (95%CI 0.92 to 0.96) to exclude acute MI and 0.93 (95% CI 0.90 to 0.96) for 6 month absence of MACE. The authors concluded that the evaluation of criteria atypical for MI may identify patients suitable for early discharge; however criteria typical of MI have little diagnostic value
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Correct population
Internal Validity	Well covered

Question 3: What is the diagnostic utility of pain relief with nitrates in the identification of patients with acute chest pain of cardiac origin.

Grading: 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

Steele R;McNaughton T;McConahy M;Lam J;

Chest pain in emergency department patients: if the pain is relieved by nitroglycerin, is it more likely to be cardiac chest pain?

Ref ID 7099 CJEM: The Journal of the Canadian Association of Emergency Physicians pgs: 164 to 170 2006

Study Type Diagnostic **Funding** Not stated

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question? The study directly addresses the question of the diagnostic value of nitroglycerin pain relief.
The sensitivity of nitroglycerin as a diagnostic test was 72% (95% CI 64% to 80%). The specificity was 37% (95% CI 34% to 41%). The positive likelihood was 1.1 (95% CI 0.96 to 1.34). Nitroglycerin as a diagnostic tool was not found to be statistically significant in differentiating between patients with and without cardiac chest pain (using Pearson statistic, P = 0.12)

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population? Patient population directly applicable, patients with chest pain of suspected cardiac origin.

Internal Validity

Grading: 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

Diercks DB;Boghos E;Guzman H;Amsterdam EA;Kirk JD;

Changes in the numeric descriptive scale for pain after sublingual nitroglycerin do not predict cardiac etiology of chest pain

Ref ID 983 Annals of Emergency Medicine 45(6):581-5, pgs: to 2005

Study Type Diagnostic

Funding Stated that the authors did not receive any outside funding or support.

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

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 equal to or less than 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%).

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 coronary artery disease in any of these 4 subgroups (using Pearson statistic = 1.0, P = 0.76). The study shows that nitroglycerin pain relief is not a useful diagnostic tool for identifying cardiac-related chest pain.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population? Patient population directly applicable, patients with chest pain of suspected cardiac origin.

Internal Validity

Henrikson CA;Howell EE;Bush DE;Miles JS;Meininger GR;Friedlander T;Bushnell AC;Chandra-Strobos N;

Chest pain relief by nitroglycerin does not predict active coronary artery disease

Ref ID 7172 Ann Intern Med pgs: 979 to NaN 2003

Study Type Diagnostic

Funding National Heart, Lung and Blood Institute Training grant for CA Henrikson, USA.

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question? The study is directly applicable to the question of the utility of nitroglycerin pain relief in the diagnosis of chest pain of cardiac origin.
The sensitivity and specificity of chest pain relief with nitroglycerin for the presence of active coronary artery disease were 35% and 58%, respectively. The positive and negative likelihood ratios 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 coronary artery disease. For troponin negative patients the sensitivity, specificity, positive likelihood ratio and negative likelihood ratio were 39%, 58%, 0.88 and 1.1, respectively. For patients with a history of coronary artery disease the sensitivity, specificity, positive likelihood ratio and negative likelihood ratio were 30%, 63%, 0.84 and 1.3, respectively. For patients with no history of coronary artery disease, the sensitivity, specificity, positive likelihood ratio and negative likelihoods were 40%, 56%, 0.87 and 1.1, respectively. ROC curves were constructed for chest pain relief by nitroglycerin and active coronary artery disease. 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 with nitroglycerin has no value in determining the presence or absence of coronary artery disease.

Effect due to factor in study?

Consistency of results with other studies?	
Directly applicable to guideline population?	Patient population directly applicable, patients with chest pain of suspected cardiac origin.
Internal Validity	

Grading: 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*

Shry EA;Dacus J;Van De GE;Hjelkrem M;Stajduhar KC;Steinhubl SR;

Usefulness of the response to sublingual nitroglycerin as a predictor of ischemic chest pain in the emergency department

Ref ID 7214 Am J Cardiol pgs: 1264 to 1267 2002

Study Type Diagnostic **Funding** Not stated.

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

The study was conducted retrospectively, hence, it is open to selection bias. With this caveat, it provides information on the diagnostic utility of nitrogyicerin in diagnosing chest pain of cardiac origin.

Ninety percent, 199 out of 223 patients responded to nitroglycerin (at least a 2 unit reduction in chest pain based on the 10 point scale). Of the patients diagnosed with chest pain attributable to coronary artery disease, 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).

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Patient population directly applicable, patients with chest pain of suspected cardiac origin.

Question: 4 Are the symptoms and description of the symptoms different in women presenting with acute chest pain of suspected cardiac origin compared with men

Grading: 1- Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Shaw LJ;Bairey Merz CN;Pepine CJ;Reis SE;Bittner V;Kelsey SF;Olson M;Johnson BD;Mankad S;Sharaf BL;Rogers WJ;Wessel TR;Arant CB;Pohost GM;Lerman A;Quyyumi AA;Sopko G;

Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies

Ref ID 10303 J Am Coll Cardiol pgs: S4 to S20 2006

Study Type Systematic Review

Funding National Heart, Lung and Blood institute; National Centre for Research Resources; Gustavus and Louis Pfeiffer Research Foundation; Womens Gulid of Cedars-Sinai Medical Centre; Ladies Hospital Aid Society of Western Pennsylvania

Number of participants 195 Studies,

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

The study reviews papers on the presenting symptoms and links to MI and obstructive coronary disease. The review suggests, despite there being differences in the symptoms women present with; symptoms evaluation in women had not been fully evaluated due to studies often applying typical angina definitions which were defined through male populations to females. These differences are seen in the frequency, type and quality of symptoms. The study reviews evidence which shows that initial symptoms in women often include fatigue, sleep disturbance, and shortness of breath.
The review states that a recent study reported no differences in the accuracy of typical symptoms, defined as chest pain or discomfort, dyspnea, diaphoresis, and arm or shoulder pain between men and women when diagnosing ACS. However chest pain/discomfort and diaphoresis were the most commonly presented symptoms in women who had a confirmed diagnosis of ACS. Women were also more likely to

report acute initial symptoms but up to half of the women had no prior chest pain symptoms when diagnosed with AMI. The review reports that women are less likely to present with exertional chest pain (typical angina) than men but were more likely to be admitted to hospital for chest pain than men (4 million visits for women vs. 2.4 million for men). The review suggests from this evidence that when assessing chest pain in women the effect exertion has on symptoms should be taken into account for defining typical angina. The review states that the Yale group's definition of angina (which includes chest pain or discomfort, dyspnea, diaphoresis, and arm or shoulder pain) gives an accurate method of identifying unstable angina, however other studies have included exertional components to the symptoms which leads to more accurate diagnosis.

The review states that older women are more likely to present with symptoms similar to men compared with younger women, which could be explained by the fact that older women have more typical angina. There are no differences in the rate of diagnosis of ACS in older men and women; however women aged under 65 are more likely to be discharged without a diagnosis of unstable angina, who are also less likely to have ST-segment elevation MI, the review suggests that this can protract their time to diagnosis and the intensity of management and can lead to poorer outcomes.

The review went on to analyse the presenting symptoms which are suggestive of MI, women were less likely to have obstructive CAD than men on angiography, which was first highlighted by Diamond and Forrester in the 1980's. This study showed that women with typical and atypical chest pain symptoms have been used to calculate the probably of a women having obstructive CAD being considerably less than that for a man. The review gives the example of "typical exertional angina in a 55 year old man has a probability of obstructive CAD of approximately 90% as compared with a wide range from 55-90% for a 55 year old woman". The review reports that this leads the conclusion that the use of chest pain symptoms to diagnose obstructive CAD in a woman is not as accurate as for a man. This conclusion and trend of symptoms being inaccurate at diagnosing obstructive CAD by Diamond and Forrester has been reported in later studies with other female populations, especially in women with a history of diabetes. The review states that this could be due to the descriptors of symptoms used by women, as those who report stable or intermittent chest pain, the description of the chest pain is a doctor's most important diagnostic tool which may lead to less intensive management.

The review highlights 2 questions to be answered which current evidence is unable to do: "can current symptom evaluation tolls be improved for more accurate detection of obstructive CAD in women? Do symptom differences suggest s gender-specific pathophysiology such that gender-specific new tools should be developed for the assessment of IHD in women?"

The review stated that the most women who had a coronary angiography which did not show obstructive CAD continued to have symptoms which lead to a poor quality of life and who continued to require repeated health investigations. The study reported that this required many doctors to use cardiac imaging to differentiate cardiac and noncardiac symptoms. The review concludes that this method does not give a technique to identify and manage myocardial ischemia in women who do not have significant obstructive CAD.

The review continued to assess postmenopausal women to show that they are likely to have a cluster of risk factors including hypertension, obesity and dyslipidemia. The study suggests this could be related to gender-specific differences in metabolic rate which is increased due the hormonal imbalances caused by the menopause. This shows a cluster of risk conditions which include insulin resistance (with or without glucose intolerance), dyslipidemia (elevated triglycerides, small LDL particles, or low HDL cholesterol), hypertension, and obesity. The study refers to the National Cholesterol Education Program Adult Treatment Panel-III which has a simplified the definition of clustering risk factors to the presence of 3 or more of "1) waist circumference >35 inches; 2) fasting triglycerides >150 mg/dl; 3) HDL cholesterol <50 mg/dl; 4) hypertension (systolic blood pressure ≥130mmHg, diastolic blood pressure ≥85 mmHg, or use of antihypertensive drug therapy); or 5) a fasting glucose measurement ≥110mg/dl". The authors state the evidence has shown that obesity is not an independent predictor of cardiovascular disease but the metabolic syndrome leads to a link between cardiovascular disease and obesity.

Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	
Internal Validity	

Grading: 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

Pryor DB;Harrell FE;Lee KL;Califf RM;Rosati RA;

Estimating the likelihood of significant coronary artery disease

Ref ID 10283 The American journal of medicine pgs: 771 to 780 1983

Study Type	Cohort	**Funding**	Not reported

Number of participants	3627 in training population, 1811 in test population
Inclusion/Exclusion Criteria	Patients had progressive chest pain in the frequency, severity or duration had increased in the 6 weeks prior to catherisation or preinfarctional chest oan which had a very unstable pain pattern that resulted in admission to the coronary care unit for evaluation of the possible MI
Patient Characteristics	Patient characteristics which were collected were: History: age, sex, chest pain history (pain type, severity, frequency, nocturnal, pregressive, preinfarctional), duration of CAD, preevious history of MI, congestive heart failure, history of vascular disease Risk factors: smoking, hyperlipidaemia, hypertension, diabetes, family history Physical examination: ventricular gallop, systolic blood pressure ECG: ST-T wave changes, electrocardiographic premature ventricular contractions, Electrocardiographic Q waves Chest X-Ray: cardiomegaly
Recruitment	Patients admitted for cardiac catherisation between 1969 and 1982.
Setting	Secondary care, USA
Interventions/ Test/ Factor being investigated	Diagnosis of chest pain.
Comparisons	Patient characteristics which give a probability of disease
Length of Study/ Follow-up	
Outcome measures studied	Probability of disease
Results	The study had a training population of 3627 patients who were seen between 1969 and January 1979, from these patients a stepwise logistic regression analysis was used to develop a model for predicting the probability of significant CAD. A test population of 1811 patients seen between January 1969 and January 1982, in this population the model developed in the test population was used to predict the probability of CAD for each patient. The authors then tested the model in other populations (from CASS study) to estimate the prevalence of disease in subgroups of the patients in the literature (external validation) Results from training population: Clinically Important Characteristics and the Chi-squared: Pain type (typical, atypical or nonanginal) – 1091 Previous MI – 511 Sex – 187 Age – 119 Smoking – 79 Hyperlipidaemia – 26 ST-T wave changes – 28 Diabetes – 12

Interactions
age X sex
age X smoking
age X hyperlipidaemia
sex X smoking

Poor Clinical Predictors of Significant CAD and the Chi-squared:
Chest pain severity – 0.96
Chest pain frequency – 8.57
Nocturnal chest pain – 2.22
Progressive chest pain – 2.54
Preinfarction angina – 9.70
Vascular disease – 0.40
Duration of CAD – 9.16
Congestive heart failure – 0.59
Hypertension – 5.19
Family history – 6.39
Ventricular gallop – 1.06
Cardiomegaly – 1.41
Electrocardiographic premature ventricular contractions – 0.46

The results from the training group are shown under “Clinically Important Characteristics and the Chi-squared” in the order of their importance (chi-squared added to the model by the parameter, adjusting for the characteristics that precede it). The type of chest pain (typical, atypical or nonanginal) was the most important characteristic followed by previous MI, sex, age, smoking, hyperlipidaemia, ST-T wave changes on ECG, diabetes. The table shows the 4 significant interactions which were found.
The study also showed that in men the effect of an increasing age was more important than in women, smoking was more important for women than men, and that smoking and hyperlipidaemia were more important at younger ages. The results for the other characteristics which were found to have small or nonsignificat effects on the prevalence of disease are shown under “Poor Clinical Predictors of Significant CAD and the Chi-squared”

The authors then validated the model in the test population which showed that the predicted probability of disease is nearly identical to the observed prevalence. This was with the exception of the group with predicted estimates of 0.475 to 0.525 (this group 8 out of 34 patients, with significant disease). The median prediction for patients with disease was 94% compared with a median prediction of 33% for patients without disease. A predicted probability of significant disease > 0.83 was found in 75% of patients with disease and in less than 10% of patients with disease. A probability of significant disease < 0.33 was found in nearly 50% of patients without disease and in less than 5% of patients with disease.

The authors then externally validated using the population from the CASS study. There was disagreement on patients classified as having nonanginal chest pain (where the greatest difference in predicted disease compared to observed disease was seen), but the predicted estimates from the model were nearly equal to the observed prevalence of disease. The predicted estimates from the model of the probability of significant disease were nearly identical to the observed prevalence for subgroups based on “age, sex and history of MI” or “age, sex and pain type”.

Safety and adverse effects

None

Does the study answer the question?

The results from the training population showed the type of chest pain (typical, atypical or nonanginal) was the most important characteristic followed by previous MI, sex, age, smoking, hyperlipidaemia, ST-T wave changes on ECG, diabetes. The study also showed that in men the effect of an increasing age was more important than in women, smoking was more important for women than men, and that smoking and hyperlipidaemia were more important at younger ages. The study also found some characteristics to have small or nonsignificat effects on the prevalence of disease.

The authors then validated the model in the test population which showed that the predicted probability of disease is nearly identical to the observed prevalence. When comparing the model to an external population the study showed that the predicted estimates from the model were nearly equal to the observed prevalence of disease.

	The predicted estimates from the model of the probability of significant disease were nearly identical to the observed prevalence for subgroups based on “age, sex and history of MI” or “age, sex and pain type”. However the greatest difference in predicted disease compared to observed disease was seen in patients with nonanginal chest pain.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Patients had chest pain, directly applicable to guideline.
Internal Validity	Well covered

Grading: 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

Griffiths DH;Pokorny ME;Bowman JM;

Differences in African American and white women with myocardial infarction: history, presentation, diagnostic methods, and infarction type

Ref ID 1293 American journal of critical care : an official publication American Association of Critical pgs: 101 to 104 1999

Study Type	Cohort	**Funding**	Not reported

Number of participants	46, of which 18 were african-american, 28 were white
Inclusion/Exclusion Criteria	women diagnosed with MI between January and June 1995
Patient Characteristics	The average age for african-american women was 66.6±14.3 years and for white women 69.1±14.2 years, the age range for all patients was 39-94 years.
Recruitment	Patients who presented with chest pain to a tertiary care facility in North Carolina, USA
Setting	tertiary care facility in North Carolina, USA
Interventions/ Test/ Factor being investigated	differences in african-american and white women with MI
Comparisons	differences in african-american and white women with MI
Length of Study/ Follow-up	Not reported
Outcome measures studied	Risk factors and ECG changes
Results	Patients were initally diagnosed with a 12-lead ECG, if the initial ECG was non-diagnositc other methods included subsequent ECG, echocardiography, coronary angiography, measurement of serum levels of cardiac enzymes and other methods. Admitting diagnosis of: MI – 33% African American, 36% White, 35% total Rule out MI – 11% African American, 32% White, 24% total Angina – 17% African American, 11% White, 13% total Other 39% African American, 21% White, 28% total Types of MI and diagnostic methods: Initial 12-lead ECG – Q wave 6 African American, 13 White, non-Q wave 12 African American, 15 White Subsequent ECG – Q wave 1 African American, 1 White, non-Q wave 0 African American, 2 White Echocardiography – Q wave 1 African American, 1 White, non-Q wave 0 African American, 0 White Coronary angiography – Q wave 0 African American, 0 White, non-Q wave 1 African American, 0 White Measurement of cardiac enzyme levels – Q wave 1 African American, 1 White, non-Q wave 10 African American, 11 White Other – Q wave 0 African American, 1 White (sudden ventricular fibrillation), non-Q wave 0 African American, 1 White (history and physical examination) Medical history variables: Previous MI – 28% African American, 29% White, (P=1.000) Angina – 11% African American, 29% White, (P=0.300)

Congestive heart failure – 28% African American, 29% White, (P=1.000)
Percutaneous transluminal coronary angioplasty – 11% African American, 0% White, (P=0.287)
Coronary artery bypass graft – 11% African American, 7% White, (P=1.000)
Stroke – 28% African American, 4% White, (P=0.027)
Diabetes – 56% African American, 29% White, (P=0.128)
Hypertension – 100% African American, 54% White, (P=0.002)
Current smoker – 17% African American, 21% White, (P=0.986)
Family history of coronary artery disease – 17% African American, 29% White, (P=0.568)
Hypercholesterolemia – 28% African American,18% White, (P=0.667)

Safety and adverse effects

None

Does the study answer the question?

24 patients presented with chest pain (52%), 9 of the 18 African American women (50%) and 15 of 28 white women (54%), this difference was not significant. The results for the diagnosis on admission to hospital were MI in 16 patients, rule out MI in 11 patients, angina in 6 patients and other 13 patients. The other diagnosis included 1 patients with congestive heart failure 1 with a hip fracture, 1 with decreased level of consciousness and 10 with unspecified n=10. There were no significant differences were found between African American and white women in the diagnosis on admission.

In the whole sample population those with a history of MI were more likely to have a non-Q wave than Q wave MI (n=13). In white women those with a history of MI or a history of congestive heart failure had a higher occurrence of non-Q wave then Q wave MI (both n=8). In African American women those with a history of angina had a higher occurrence of Q wave than non-Q wave MI (n=2).

At the time of admission 2 of the medical history variables were shown to be significantly different: stroke (P=0.027) and hypertension (P=0.002).

Effect due to factor in study?

Yes

Consistency of results with other studies?

Consistent

Directly applicable to guideline population?

52% presented with chest pain. On admission, 16 patients had AMI, 11 to rule out AMI, 6 angina, 1 congestive heart failure, 1 hip fracture, 1 decreased level of consciousness, 10 other diagnosis

Internal Validity

Well covered

McSweeney JC;Cody M;Sullivan P;Elberson K;Moser DK;Garvin BJ;

Women's early warning symptoms of acute myocardial infarction

Ref ID 10299 Circulation pgs: 2619 to 2623 2003

Study Type Cohort

Funding National Institute of Nursing Research

Number of participants

515 women

Inclusion/Exclusion Criteria

Women who were diagnosed with AMI and discharged in the previous 4-6 months from 5 sites in Arkansas, North Carolina and Ohio, Patients needed to be cognitively intact, speak english, and have telephone access

Patient Characteristics

The study included 515 women with an average age of 66.4±12 years. Of the 515 women 93% were white, 6.2% black, 2% Native American. For 72% of the women had no prior history of MI, the other 28% gave details of their most recent AMI.

Recruitment

Patients were those diagnosed with AMI and discharged in the previous 4-6 months from 5 sites in Arkansas, North Carolina and Ohio

Setting

Secondary care, USA

Interventions/ Test/ Factor being investigated	symptoms and risk factors for those with AMI
Comparisons	symptoms and risk factors
Length of Study/ Follow-up	Not reported
Outcome measures studied	symptoms and risk factors
Results	See table 1 and 2 in McSweeney, 2003 doccument
Safety and adverse effects	None
Does the study answer the question?	The study included 515 women with an average age of 66.4±12 years. Of the 515 women 93% were white, 6.2% black, 2% Native American. For 72% of the women had no prior history of MI, the other 28% gave details of their most recent AMI. The study considered both initial (prodromal) symptoms and acute symptoms. The average number of initial symptoms experienced was 5.71±4.36, with the most common being unusual fatigue, sleep disturbance, shortness of breath, indigestion, and anxiety. 44% of those reporting sleep disturbances and 42% of those reporting fatigue described them as severe. 29.7% of women reported chest pain/discomfort (aching, tightness, pressure, burning, sharpness fullness or tingling), with the location and descriptors used not being mutually exclusive. 78% of women reported having had at least one of their initial symptoms daily or several times a week for more than 1 month. The average number of acute symptoms experienced was 7.3±4.8, with the most common being shortness of breath, weakness, unusual fatigue, cold sweat, and dizziness. The women reported discomfort in their back and high chest as the most common locations of pain. Again chest pain/discomfort was reported by women (pressure, ache, and tightness), mostly being described as severe pain/discomfort. Over all 43% of women reported no chest pain/discomfort. The study also considered the risk factors; most women had a family history of cardiovascular disease, a history of cardiovascular disease and had diabetes. The average BMI was 28.6±6.5 and less than half of the women did regular exercise before having their AMI. The study carried out multiple regression analysis to assess if the acute score could be predicted from the prodromal score. “The prodromal score accounted for an additional 33.2% of the variance in acute symptom scores after control for risk factors which accounted for only 9.9% of the variance”. The study also carried out a T test to determine the association of symptoms with risk factors. The T test showed that there was significant association between initial symptoms and all risk factors except age >50 years, hypertension and hyperlipidemia. The T test also showed that there was significant association between acute symptoms and all risk factors except hypertension, hyperlipidemia and second hand smoke.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Patients had AMI
Internal Validity	Well covered

Meischke H;Larsen MP;Eisenberg MS;

Gender differences in reported symptoms for acute myocardial infarction: impact on prehospital delay time interval

Ref ID 5613 Am J Emerg Med pgs: 363 to 366 1998

Study Type Cohort **Funding** Not reported

Number of participants	4,497, 2970 men and 1527 women
Inclusion/Exclusion Criteria	Patients with a confirmed MI, admitted between January 1991 and February 1993 to the coronary care units of 16 King County hospitals. Those who had cardiac arrest, coma, and shock were excluded
Patient Characteristics	Gender – 66% men, 34% women Median age – 64 years men, 73 years women (P=<0.001) White – 91% men, 93% women Black – 4% men, 4% women Asian/Pacific Islander – 5% men, 3% women
Recruitment	Consecutive patients admitted between January 1991 and February 1993 to the coronary care units of 16 King County hospitals with AMI were assessed for inclusion.
Setting	Secondary Care, USA
Interventions/ Test/ Factor being investigated	risk factors and medical history of men and women with AMI
Comparisons	risk factors and medical history of men and women with AMI
Length of Study/ Follow-up	Not reported
Outcome measures studied	risk factors (gender, age, race, history of AMI, history of diabetes) medical history (chest pain symptoms, diaphoresis, dyspnea, epigastic pain, nausea/vomiting, syncope)
Results	Univariate comparison of medical history and symptoms: Gender – 66% men, 34% women Median age – 64 years men, 73 years women (P=<0.001) White – 91% men, 93% women Black – 4% men, 4% women Asian/Pacific Islander – 5% men, 3% women History of AMI – 30% men, 26% women (P=0.021) History of diabetes – 19% men, 25% women (P=<0.001) Chest pain symptoms – 92% men, 89% women (P=<0.001) Diaphoresis – 54% men, 44% women (P=<0.001) Dyspnea – 46% men, 52% women (P=<0.001) Epigastric pain – 11% men, 11% women, Not significant Nausea/vomiting – 35% men, 44% women (P=<0.001) Syncope – 3% men, 3% women, Not significant Beta and P value regression for medical history and symptoms: Age – β 0.096, P=<0.001 Gender – β 0.053, P=0.002 History of AMI – β -0.064, P=<0.001 History of diabetes – β 0.048, P=0.004 Diaphoresis – β -0.147, P=<0.001 Chest pain – β -0.059, P=<0.001 Syncope – β -0.039, P=0.02 Dyspnea – β -0.024, Not significant Epigastric pain – β 0.03, Not significant Nausea/vomiting – β 0.014, Not significant
Safety and adverse effects	None
Does the study answer the question?	This study showed that women were significantly older than men and were more likely to have a history of diabetes. Women were also more likely to report sweating and nausea, this difference persisted after adjustment for age and history of diabetes. Women were also more likely to report shortness of breath, especially

	younger women and those who had a history of diabetes. Men were more likely to have a history of AMI than women. There was no difference between men and women in presentation of chest pain, this similarity persisted after adjustment for age and history of diabetes.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Patients had a confirmed AMI
Internal Validity	Well covered

Milner KA;Funk M;Arnold A;Vaccarino V;

Typical symptoms are predictive of acute coronary syndromes in women

Ref ID 10301 Am Heart J pgs: 283 to 288 2002

Study Type Cohort

Funding Part funded by Ethel F. Donoghue Women's Health Investigation Program at Yale

Number of participants	522 in total, 246 women and 276 men
Inclusion/Exclusion Criteria	aged 45 years or older, reportd at least one prespecified set of typical or a typical symptoms suggestive of ACS
Patient Characteristics	The mean age for women with ACS was 69 ± 15 years , the mean age for women without ACS was 64 ± 15 years,
Recruitment	Patietns who were seen in the emergency department with suspected ACS
Setting	Secondary Care, USA
Interventions/ Test/ Factor being investigated	risk factors and symptoms of women and men presenting with suspected ACS
Comparisons	risk factors and symptoms of women and men presenting with suspected ACS
Length of Study/ Follow-up	Not reported
Outcome measures studied	Risk factors and clinical history of patients
Results	Baseline characteristics: White race – 36% women with ACS, 46% men with ACS History of coronary heart disease – 44% women with ACS, 48% men with ACS Systemic hypertension – 38% women with ACS, 49% men with ACS Obesity – 38% women with ACS, 46% men with ACS History of MI – 49% women with ACS, 51% men with ACS Diabetes – 47% women with ACS, 46% men with ACS Hypercholesterolemia – 41% women with ACS, 50% men with ACS Other cardiac problems – 39% women with ACS, 35% men with ACS History of heart failure – 40% women with ACS, 45% men with ACS Current smoker – 26% women with ACS, 42% men with ACS Relationship between typical symptoms and ACS: Chest pain/discomfort present in – 36% women with ACS, 49% men with ACS Dyspnea present in – 44% women with ACS, 41% with ACS

Arm or shoulder pain present in – 38% women with ACS, 47% with ACS
Diaphoresis present in – 53% women with ACS, 44% with ACS
Neck or jaw pain present in – 41% women with ACS, 53% with ACS

Relationship between atypical symptoms and ACS:
Nausea or vomiting present in – 39% women with ACS, 48% men with ACS
Dizziness present in – 36% women with ACS, 32% men with ACS
Indigestion present in – 38% women with ACS, 45% men with ACS
Fatigue present in – 36% women with ACS, 41% men with ACS
Chest fullness, stabbing, numbness,
burning or right chest pain present in – 34% women with ACS, 50% men with ACS
Midback pain present in – 50% women with ACS, 17% men with ACS
Palpitations present in – 35% women with ACS, 29% men with ACS
Upper-extremity numbness present in – 29% women with ACS, 33% men with ACS
Unable to take a deep breath present in – 9% women with ACS, 29% men with ACS
Cough present in – 25% women with ACS, 40% men with ACS

Symptom predictors of ACS in women and men by logistic regression analysis:
(relative risk – RR)
Women
Chest pain or discomfort – RR – 1.81, 95% CI 0.95 to 3.42, P=0.069
Neck or jaw pain – RR – 1.60, 95% CI 0.83 to 3.10, P=0.163
Diaphoresis – RR – 2.53, 95% CI 1.17 to 5.48, P=0.019
Men
Chest pain or discomfort – RR – 1.56, 95% CI 0.86 to 2.82, P=0.142
Neck or jaw pain – RR – 0.69, 95% CI 0.40 to 1.19, P=0.182
Diaphoresis – RR – 0.49, 95% CI 0.26 to 0.93, P=0.028

Relative risk of ACS for typical symptoms in women relative to men:
Chest pain or discomfort – RR – 0.83, 95% CI 0.66 to 1.06, P=0.129
Neck or jaw pain – RR – 0.69, 95% CI 0.40 to 1.15, P=0.141
Diaphoresis – RR – 1.18, 95% CI 0.87 to 1.59, P=0.384
Arm or shoulder pain – RR – 0.91, 95% CI 0.64 to 1.30, P=0.612
Dyspnea – RR – 1.00, 95% CI 0.74 to 1.35, P=0.993

Safety and adverse effects

None

Does the study answer the question?

The study showed that older women and men were both significantly more likely to be diagnosed with ACS than younger men and women. Women with a history of coronary heart disease, MI or diabetes were also significantly more likely to be diagnosed with ACS compared to those without the risk factors. Men without a history other cardiac problems were more likely to be diagnosed with ACS. Women who were diagnosed with ACS had a higher number of symptoms than those without (3.36±1.74 compared to 2.78±1.46 P=0.006), however there was no difference in the number of symptoms for men with ACS compared to men without ACS. Typical symptoms in men were not significantly related to a diagnosis of ACS, however those with dizziness or fainting were less likely to be diagnosed with ACS. Women with typical symptoms (chest pain or discomfort, diaphoresis, dyspnea and arm or shoulder pain) were significantly more likely to be diagnosed with an ACS. A multivariate analysis of independent predictors of ACS showed that diaphoresis was strongest in predicting ACS in women, followed by chest pain or discomfort (81% higher risk for ACS) and arm or should pain had a (60% higher risk for ACS). The model for male patients was a poor fit, the authors suggested that this meant that a patients symptoms were not a useful predictor of ACS.

The study went on to compared men and women, which showed that there was no difference in the typical symptoms for men and women. The study showed that there were no sex differences through comparing the adjusted the relative risks for ACS in women with typical symptoms and in with men with typical symptoms which was both close to 1.

Effect due to factor in study?

Yes

Consistency of results with other studies?

Consistent

Directly applicable to guideline population?	Patients had symptoms suggestive of ACS
Internal Validity	Well covered

Penque S;Halm M;Smith M;Deutsch J;Van RM;McLaughlin L;Dzubay S;Doll N;Beahrs M;

Women and coronary disease: relationship between descriptors of signs and symptoms and diagnostic and treatment course

Ref ID								
10292	American journal of critical care : an official publication American Association of Critical	pgs:	175	to	182		1998

Study Type	Cohort	**Funding**	Not reported

Number of participants	98 patients, of which 51 were women and 47 were men
Inclusion/Exclusion Criteria	Included: primary medical diagnosis of MI, at least 21 years old, english speaking, admission via emergency department, directly from physician's office or by transfer from rural hospital within 6 hours of MI. Exclusion: patients who had sudden cardiac death events. A history of coronary artery disease was not a reason for exclusion and so the population is mixed
Patient Characteristics	The mean age for all patients was 59 years. For the women the mean age was 61 years (range 41-89 years), for the men the mean age was 56 years (range 37-79 years). 3% of all patients were uninsured (measure of socio economic status)
Recruitment	admitted to the hospital during a period of 12 months, with a primary diagnosis of MI
Setting	secondary care, USA
Interventions/ Test/ Factor being investigated	differences between men and women in signs and symptoms of MI
Comparisons	Mena and women
Length of Study/ Follow-up	Not reported
Outcome measures studied	risk factors, signs and symptoms
Results	Cardiovascular risk factor profile Family history of heart disease – women 56%, men 51% Past or current history of smoking – women 57%, men 81% Hypertension – women 41%, men 46% Hyperlipidaemia – women 49%, men 55% Diabetes – women 20%, men 17% Precipitating factors for chest pain Rest – women 53%, men 55% (P=0.89) Exertion – women 63%, men 40% (P=0.09) Sex – women 10%, men 6% (P=0.40) Stress – women 51%, men 34% (P=0.10) Time elapsed after cardiac-related signs or symptoms were first experienced before treatment was sort Less than 24 hours – women 15%, men 22% 1-2 days – women 6%, men 9% 3-7 days – women 15%, men 17% 8-30 days – women 15%, men 15% 2-6 months – women 6%, men 13% 6-12 months – women 6%, men 0% More than 1 year – women 38%, men 24% Descriptors of associated signs and symptoms Fatigue – women 71%, men 70% (P=0.90) Rest pain – women 71%, men 72% (P=0.80)

	Weakness – women 68%, men 62% (P=0.60) Shortness of breath – women 66%, men 66% (P=0.70) Dizziness – women 56%, men 43% (P=0.10) Arm pain – women 53%, men 55% (P=0.70) Nausea – women 51%, men 35% (P=0.10) Back pain – women 52%, men 20% (P=0.005) Loss of appetite – women 43%, men 19% (P=0.03) Neck pain – women 41%, men 35% (P=0.10) Sweating – women 48%, men 42% (P=0.60) Heartburn – women 28%, men 33% (P0.50=) Paroxysmal nocturnal dyspnea – women, 30% men 11% (P=0.05) Palpitations – women 25%, men 26% (P=0.80) Jaw pain – women 10%, men 13% (P=0.90) Throat pain – women 8%, men 22% (P=0.10) Toothache – women 5%, men 2% (P=0.40)
Safety and adverse effects	None
Does the study answer the question?	The study considered the descriptors of signs and symptoms. The study showed that chest discomfort was the most common initial symptom reported by both men (51% as an initial symptom, 99% at some point) and women (49% as an initial symptom, 94% at some point). The 4 most reported symptoms for men and women were fatigue, rest pain, weakness, and shortness of breath, however women reported dizziness and men reported arm pain as the next common symptom. Women were more likely to suffer loss of appetite, paroxysmal nocturnal dyspnea and back pain than men. These differences were significant: loss of appetite (chi-squared=4.48), paroxysmal nocturnal dyspnea (chi-squared=3.80), and back pain (chi-squared=7.60). The study considered the length of time from initial symptoms to seeking medical help. There was no significant difference between men (5.3 hours) and women (4.2 hours), with the majority of men and women first having symptoms in the preceding 24 hours, the previous 3 days to 1 month or more than 1 year before. The study also considered the mean number of words used to describe signs, there was no significant difference between men (58) and women (55). The study concluded that “chest pain was the first sign or symptom of MI reported by both men and women”. Women were more likely to report back pain, loss of appetite, and paroxysmal nocturnal dyspnea as symptoms than men and were less likely than men to have diagnostic angiography and to receive IV nitroglycerin, heparin, and thrombolytics as part of their management.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Patients had a primary diagnosis of MI
Internal Validity	Well covered

Grading: 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*

De S;Searles G;Haddad H;

The prevalence of cardiac risk factors in women 45 years of age or younger undergoing angiography for evaluation of undiagnosed chest pain

Ref ID 923 The Canadian journal of cardiology pgs: 945 to 948 2002

Study Type Cohort	**Funding** Not reported
Number of participants	187 in total, 55 in group A (those with significant CAD) 132 in group B (those without significant CAD)
Inclusion/Exclusion Criteria	Women aged under 45 years, who were referred for coronary angiography due to chest pain and who had no known history of CAD
Patient Characteristics	Not reported. Patients were women aged under 45 who did not have a known history of CAD
Recruitment	Patients referred for coronary angiography due to chest pain during a 4 year period (february 1997-December 2000) at Queen Elizabeth II Health Sciences Centre in Halifax, Nova Scotia
Setting	Secondary care, Nova Scotia, Canada
Interventions/ Test/ Factor being investigated	Risk factors in women with and wothout signficant CAD
Comparisons	Risk factors - obesity, dyslipidemia, diabetes, hypertension, premature family history of CAD, current smoker, past smoker
Length of Study/ Follow-up	Not reported
Outcome measures studied	Diagnosis of CAD
Results	Risk factors: Obesity – 45% group A, 46% group B, P=0.92 Dyslipidemia – 72% group A, 47% group B, P=0.002 Diabetes – 29% group A, 9% group B, P=<0.001 Hypertension – 40% group A, 28% group B, P=0.13 Family history of premature CAD – 65% group A, 67% group B, P=0.79 Current smoker – 55% group A, 35% group B, P=0.03 Past smoker – 13% group A, 15% group B, P=0.03
Safety and adverse effects	None
Does the study answer the question?	The women included were aged <45 years that were referred for coronary angiography due to chest pain but had not been diagnosed and had no history of CAD, the patients were subsequently divided into two groups; dependant upon the presence of CAD or absence. Group A had significant CAD, and group B were without significant CAD. Group B (those without significant CAD) was subdivided into those with noncritial CAD (8%) and those with normal coronary arteries (92%). Group A were significantly more likely to have dyslipidemia (72% group A, 47% group B, P=0.002), diabetes (29% group A, 9% group B, P=0.001), and to smoke (67% group A, 50% group B, P=0.03). There was no significant difference between group A and B in the rates of obesity, hypertension, and family history of premature CAD. The study concluded that women with CAD were more likely to have dyslipidemia, diabetes and smoking. However for women with and without CAD the commonest

	risk factor was a family history of CAD (67%), followed by smoking (55%) and dyslipidemia (55%).
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Patients had chest pain
Internal Validity	Well covered

Question: Are the symptoms and description of the symptoms different in Black and Ethnic Minorities presenting with acute chest pain of suspected cardiac origin compared with Caucasians

Grading: 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

Johnson PA;Lee TH;Cook EF;Rouan GW;Goldman L;

Effect of race on the presentation and management of patients with acute chest pain.[see comment]

Ref ID 25397 Ann Intern Med pgs: 593 to 601 1993

Study Type Cohort **Funding** Not reported

Number of participants	Final study population was 3031 after exclusions
Inclusion/Exclusion Criteria	Inclusion: patients presenting to the emergency department with a chief complaint of anterior, percordial, or left lateral chest pain that could not be explained by obvious local trauma or abnormalities on a chest X ray. 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).
Patient Characteristics	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; coronary artery disease (30% versus 47%, respectively, P < 0.0001), cardiac catheterisation (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 is consistent given the prior history findings of African American patients versus Caucasian patients.
Recruitment	patients presenting to the emergency department with a chief complaint of anterior, percordial, or left lateral chest pain that could not be explained by obvious local trauma or abnormalities on a chest X ray.
Setting	Emergency department USA, Dec 1983 to Oct 1988
Interventions/ Test/ Factor being investigated	History, risk factors and signs and symptoms
Comparisons	African Americans versus Caucasians with suspected acute MI
Length of Study/ Follow-up	Not applicable
Outcome measures studied	History, risk factors and signs and symptoms
Results	African American patients with a final diagnosis of acute Ml had similar presenting signs and symptoms compared with the Caucasian patients. Comparing the two racial groups clinical characteristics of acute M I, the odds ratios were all greater than 1.0 for chest pain greater than or equal to 30 min, pressure type chest pain, radiation of pain to left arm, left shoulder, neck or jaw, diaphoresis and rales on physical examination for both racial groups but these were not statistically different between the groups. 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 for 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).

Safety and adverse effects	Not applicable
Does the study answer the question?	Yes, African Americans had a similar clinical presentation of acute MI compared with Caucasians
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Acute chest pain population therefore directly applicable
Internal Validity	Adequately addressed

Klingler D;Green WR;Nerenz D;Havstad S;Rosman HS;Cetner L;Shah S;Wimbush F;Borzak S;

Perceptions of chest pain differ by race

Ref ID 10300 Am Heart J pgs: 51 to 59 2002

Study Type Cohort

Funding National Institute of Aging, the National Institute of Nursing Research and the Office of Minority Health of the NIH

Number of participants	215 in total, 157 African American, 58 white
Inclusion/Exclusion Criteria	Patients admitted with suspected acute MI. 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.
Patient Characteristics	Mean age - 59±14 years African American, 62±15 years white (P=0.13) Male – 46% African American, 57% white (P=0.15)
Recruitment	Patients who were admitted with acute MI between April 1999 and August 1999 to the ED chest pain unit
Setting	Secondary care, USA
Interventions/ Test/ Factor being investigated	Comparison of Medical history and risk factors between African American and white patients with acute MI
Comparisons	Medical history and risk factors of African American and white patients
Length of Study/ Follow-up	Not reported
Outcome measures studied	Medical history and risk factors
Results	Characteristics: Mean age - 59±14 years African American, 62±15 years white (P=0.13) Male – 46% African American, 57% white (P=0.15) Diabetes – 28% African American, 16% white (P=0.05) Hypertension – 67% African American, 55% white (P=0.12) Hypercholesterolemia – 28% African American, 34% white (P=0.5) Angina – 8% African American, 3% white (P=0.37) Heart attack – 27% African American, 16% white (P=0.06) Congestive heart failure – 12% African American, 12% white (P=0.99)

Coronary angiography – 15% African American, 10% white (P=0.4)
Coronary artery bypass graph – 8% African American, 21% white (P=0.01)
Smoker – 29% African American, 31% white (P=0.74)
Prior stomach complaints – 16% African American, 29% white (P=0.03)

Symptoms:
Cardiac
Chest pain – 78% African American, 79% white (P=0.88)
Chest pressure – 62% African American, 76% white (P=0.06)
Chest tightness – 51% African American, 58% white (P=0.37)
Chest discomfort – 64% African American, 59% white (P=0.5)
Palpitations – 40% African American, 26% white (P=0.07)
Any of the above – 97% African American, 93% white (P=0.16)
Gastrointestinal
Stomach pain – 22% African American, 17% white (P=0.47)
Heartburn – 26% African American, 21% white (P=0.41)
Indigestion – 26% African American, 22% white (P=0.58)
Gas pain – 33% African American, 28% white (P=0.49)
Stomach problem – 22% African American, 19% white (P=0.59)
Any of the above – 57% African American, 59% white (P=0.86)
Associated symptoms
Nausea/vomiting – 44% African American, 41% white (P=0.74)
Arm/shoulder pain – 41% African American, 38% white (P=0.68)
Back pain – 30% African American, 33% white (P=0.69)
Jaw pain – 12% African American, 12% white (P=0.9)
Headache – 37% African American, 29% white (P=0.29)
Neck pain – 29% African American, 28% white (P=0.86)
Numbness/tingling – 33% African American, 32% white (P=0.96)
Shortness of breath – 62% African American, 60% white (P=0.85)
Cough – 38% African American, 26% white (P=0.09)
Dizziness – 54% African American, 48% white (P=0.5)
Sweating – 50% African American, 53% white (P=0.68)
Weakness/fatigue – 68% African American, 60% white (P=0.29)

There was no significant difference in the one worst reported symptom (respiratory, cardiac, gastrointestinal, other, unable to identify) between African American and white 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 white patients.

Safety and adverse effects

Not applicable

Does the study answer the question?

Patients were interviewed from April 1999 to August 1999. Patients were identified 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. 215 met the inclusion criteria out of 588 who were approached.
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.

Demographics and medical history:
27% were white and 73% were African American, there were no significant differences between the two groups' age, sex and insurance status (suggestive of socioeconomic status).
African Americans were significantly more likely to have diabetes (P=0.05) and to be taking calcium-channel blockers (P=0.005), however white 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).

Symptoms at presentation:
Those who were diagnosis as not having an MI were more likely to have had stomach pain (P=0.03) and sweating (P=0.05) at presentation. No significant differences were found between African American and white patients in the objective symptoms. There was no significant difference in the one worst reported symptom (respiratory, cardiac, gastrointestinal, other, unable to identify) between African American and white 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 white 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 Caucasian patients, 11 patients were diagnosed as having had an 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.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Acute chest pain population therefore directly applicable
Internal Validity	Not addressed

Maynard C;Beshansky JR;Griffith JL;Selker HP;

Causes of chest pain and symptoms suggestive of acute cardiac ischemia in African-American patients presenting to the emergency department: a multicenter study

Ref ID 1424 Journal of the National Medical Association pgs: 665 to 671 1997

Study Type	Cohort	**Funding**	Agency for Health Care Policy and Research

Number of participants	10001, of which 3401 (34%) were African Americans,, 6600 were white
Inclusion/Exclusion Criteria	Included: aged greater or equal to 30 years presenting with chest or left arm pain, shortness of breath, or other symptoms suggestive of acute cardiac ischemia from 10 participating hospitals in east and midwest USA. Excluded: patients with chest pain/ discomfort related to trauma, surgical emergencies, those with a clear non-cardiac cause, patients transferred from other hospitals
Patient Characteristics	In the male group, the average age for African American patients was 52±14 years and 60±15 year for white patients (P<0.0001). The average time from symptom onset to emergency department arrival was 3 hours for African American patients and 2 hours for white patients (P=0.0006). 33% of African American men and 15% of white men were uninsured, 23% of African American men and 6% of white men had Medicaid, 28% of African Americans men and 44% of white men had Medicare; for all P <0.0001 (measure of socio economic status). In the female group, the average age for African American patients was 55±15 years and 65±16 year for white patients (P <0.0001). The average time from symptom onset to emergency department arrival was 3.3 hours for African American patients and 3 hours for white patients (P=0.045). 26% of African Americans women and 12% of white women were uninsured, 24% of African Americans and 8% of white women had Medicaid, 33% of African Americans women and 56% of white women had Medicare; for all P <0.0001 (measure of socio economic status).
Recruitment	Patients admitted to 10 hospitals in east and midwest USA
Setting	Secondary care, USA
Interventions/ Test/ Factor being investigated	If race is determinant in diagnosing acute MI or angina
Comparisons	African Americans and white patients

Length of Study/ Follow-up	Not reported
Outcome measures studied	Signs and symptoms and risk factors to diagnose acute MI or angina
Results	Medical History and Clinical Characteristics Men Ulcer – 16% African American, 16% white (P=0.74) Hypertension – 57% African American, 44% white (P=<0.0001) Angina – 29% African American, 42% white (P=<0.0001) MI – 20% African American, 35% white (P=<0.0001) Stroke – 9% African American, 8% white (P=0.47) Diabetes – 20% African American, 20% white (P=0.88) Current smoker – 56% African American, 30% white (P=<0.0001) Cardiac medications – 47% African American, 59% white (P=<0.0001) Chest pain – 77% African American, 75% white (P=0.20) Chest pain as primary symptom – 69% African American, 70% white (P=0.49) Shortness of breath – 62% African American, 51% white (P=<0.0001) Abdominal pain – 20% African American, 12% white (P=<0.0001) Nausea – 28% African American, 24% white (P=0.01) Vomiting – 13% African American, 7% white (P=<0.0001) Dizziness – 35% African American, 26% white (P=<0.0001) Fainting – 6% African American, 7% white (P=0.32) Rales – 19% African American, 20% white (P=0.14) S3 sound – 4% African American, 3% white (P=0.013) Congestive heart failure – 16% African American, 16% white (P=0.65) Systolic blood pressure >160 – 21% African American, 23% white (P=0.29) Diastolic blood pressure >90 – 36% African American, 28% white (P=<0.0001) Women Ulcer – 14% African American, 14% white (P=0.73) Hypertension – 64% African American, 51% white (P=<0.0001) Angina – 32% African American, 39% white (P=<0.0001) MI – 18% African American, 26% white (P=<0.0001) Stroke – 9% African American, 9% white (P=0.85) Diabetes – 32% African American, 23% white (P=<0.0001) Current smoker – 34% African American, 24% white (P=<0.0001) Cardiac medications – 60% African American, 64% white (P=0.01) Chest pain – 79% African American, 72% white (P=<0.0001) Chest pain as primary symptom – 69% African American, 64% white (P=0.0002) Shortness of breath – 61% African American, 55% white (P=<0.0001) Abdominal pain – 17% African American, 13% white (P=<0.0001) Nausea – 35% African American, 29% white (P=<0.0001) Vomiting – 14% African American, 10% white (P=<0.0001) Dizziness – 33% African American, 26% white (P=<0.0001) Fainting – 5% African American, 7% white (P=0.001) Rales – 19% African American, 25% white (P=<0.0001) S3 sound – 3% African American, 3% white (P=0.74) Congestive heart failure – 15% African American, 18% white (P=0.019) Systolic blood pressure >160 – 28% African American, 28% white (P=0.45) Diastolic blood pressure >90 – 34% African American, 23% white (P=<0.0001)
Safety and adverse effects	Not applicable
Does the study answer the question?	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, and the authors stated that this is consistent with the finding of more previous systemic hypertension in African Americans.

	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% in 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. 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 less likely to develop acute MI (odds ratio 0.54, 95% CI 0.41 to 0.68).
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Patients with chest pain, left arm pain, shortness of breath or symptoms suggestive of acute cardiac ischeamia, directly applicable.
Internal Validity	Not addressed

Teoh M;Lalondrelle S;Roughton M;Grocott-Mason R;Dubrey SW;

Acute coronary syndromes and their presentation in Asian and Caucasian patients in Britain

Ref ID 25394 Heart pgs: 183 to 188 2007

Study Type	Cohort	**Funding**	Listed as none
Number of participants	2905 patients, 604 (21%) were Asian and 2301 (79%) were Caucasian		
Inclusion/Exclusion Criteria	Consecutive patients requiring hospital admission for ACS recruited by a senior cardiac nurse. Patients of races other than Asian or Caucasian were excluded		
Patient Characteristics	Asians mean age 60.6 (SD 12.7) years, Caucasians 68.9 (SD 13.9) years (P < 0.001), Asians 66% male, Caucasians 62%		
Recruitment	Consecutive by nurse in emergency department		
Setting	Emergency department UK		
Interventions/ Test/ Factor being investigated	Signs and symptoms, risk factors		
Comparisons	Asians versus Caucasian		
Length of Study/ Follow-up	Not applicable		
Outcome measures studied	Signs and symptoms, risk factors		
Results	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). 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%).		

	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 (odds ratio 1.61, 95% CI 1.08 to 1.10) were also more likely to feel no discomfort compared with Asian patients. Analysis with age as a continuous variable was also associated with silent episode.
Safety and adverse effects	Not applicable
Does the study answer the question?	Yes. 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 than Caucasian patients.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Acute chest pain population therefore directly applicable
Internal Validity	Not addressed

Grading: 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*

Barakat K;Wells Z;Ramdhany S;Mills PG;Timmis AD;

Bangladeshi patients present with non-classic features of acute myocardial infarction and are treated less aggressively in east London, UK

Ref ID 10302 Heart pgs: 276 to 279 2003

Study Type Cohort

Funding K.Barakat wass supported by an MRC Clinical Training Fellowship

Number of participants	371 patients, of which 108 were Bangladeshi and 263 were white
Inclusion/Exclusion Criteria	Patients who were white or Bangladeshi with acute MI. 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).
Patient Characteristics	The mean age was 63±12 years in the Bangladeshi group and 68 ±19years in the white group (P<0.0001). 87% of the Bangladeshi group were male compared to 70% of the white group (P0.002). 1/3 of the Bangladeshi patients were fluent in English
Recruitment	Patients admitted to Royal London Hospital, UK, acute MI between May 1998 and April 2001
Setting	Royal London Hospital, UK
Interventions/ Test/ Factor being investigated	Bangladeshi patients compared to white patients with acute MI
Comparisons	Bangladeshi patients compared to white patients
Length of Study/ Follow-up	Not reported
Outcome measures studied	Risk factors, symptoms
Results	Baseline characteristics: Age (years) – Bangladeshi 63±12; Whites 68±19 (P<0.0001) Male sex – 87% Bangladeshi; 70% Whites (P=0.002) Smoking – 71.3% Bangladeshi; 70.3% Whites (P=0.85) Hypertension – 43.5% Bangladeshi; 38.4% Whites (P=0.36) Diabetes – 50% Bangladeshi; 15.2% Whites (P<0.0001) Family history of IHD – 13% Bangladeshi; 29.3% Whites (P=0.0005) Previous acute MI – 28.7% Bangladeshi; 48% Whites (P=0.0014) Nature of chest pain and interpretation of symptoms by racial group: (Bangladeshi n-32, Whites n=31) Central pain – 40.6% Bangladeshi, 87.1% White (P=0.0006) Left sided pain – 34.4% Bangladeshi, 3.2% White (P=0.0006) Other pain – 25% Bangladeshi, 97% White (P=0.0006) Typical character of pain – 25% Bangladeshi, 58.1% White (P=0.0132) Non-classical character of pain – 75% Bangladeshi, 41.9% White (P=0.0132) Interpreted as acute MI– 46.9% Bangladeshi, 45.2% White (P=0.99) Interpreted as other– 53.1% Bangladeshi, 54.8% White (P=0.99) Initial response of sought health care advice – 46.9% Bangladeshi, 25.8% White (P=0.20) Initial response of sought family advice – 37.5% Bangladeshi, 61.3 White (P=0.20) Initial response of other – 15.6% Bangladeshi, 12.9% White (P=0.20)

	(typical character is: heaviness, tightness, weight, pressure, band-like, gripping; non-classical character is: sharp, stabbing, pinching, burning) Multivariate analysis of the likelihood of Bangladeshi patients to present with typical central chest pain compared with white patients: Crude – (OR 0.11; 95% CI 0.03 to 0.38; P=0.0006) Adjustment for age and sex – (OR 0.10; 95% CI 0.03 to 0.39; P=0.0007) Adjustment for age, sex and diabetes – (OR 0.12; 95% CI 0.03 to 0.49; P=0.0031) Adjustment for age, sex, diabetes, hypertension, smoking, family history of IHD and hypercholesterolemia – (OR 0.11; 95% CI 0.02 to 0.58; P=0.0094) Adjustment for age, sex, diabetes, hypertension, smoking, family history of IHD, hypercholesterolemia and proficiency in English – (OR 0.10; 95% CI 0.01 to 0.79; P=0.0285) Multivariate analysis of the likelihood of Bangladeshi patients to present with typical cardiac chest pain compared with white patients: Crude – (OR 0.25; 95% CI 0.09 to 0.74; P=0.0118) Adjustment for age and sex – (OR 0.25; 95% CI 0.08 to 0.77; P=0.0154) Adjustment for age, sex and diabetes – (OR 0.19; 95% CI 0.05 to 0.70; P=0.0124) Adjustment for age, sex, diabetes, hypertension, smoking, family history of IHD and hypercholesterolemia – (OR 0.13; 95% CI 0.03 to 0.63; P=0.0116) Adjustment for age, sex, diabetes, hypertension, smoking, family history of IHD, hypercholesterolemia and proficiency in English – (OR 0.05; 95% CI 0.004 to 0.46; P=0.0091)
Safety and adverse effects	Not applicable
Does the study answer the question?	The baseline characteristics of the study showed that Bangladeshis were younger, more often male and diabetic, and more likely to report a previous acute MI than Whites. However Bangladeshis were less likely to report a family history of ischaemic heart disease than whites. 1/3 of the Bangladeshi patients were assessed to be fluent in English. Bangladeshis were significantly less likely to report central chest pain (OR 0.11; 95% CI 0.03 to 0.38; P=0.0006) than whites. This significant difference remained after adjustment for difference in age, sex, risk factor profiles and fluency in English. Bangladeshis were also were more likely to offer non-classic descriptions (sharp, stabbing, pinching, burning) and less likely to report classic descriptions of the character of pain (heaviness, tightness, weight, pressure, band-like, gripping) (OR 0.25; 95% CI 0.09 to 0.74; P=0.0118). These differences persisted after adjustment for difference in age, sex, risk factor profiles and fluency in English. The study concluded that Bangladeshi patients with an acute MI were more likely to present with atypical symptoms compared to white patients. The Authors stated that this may lead to slower triage in the emergency department and delay in treatment, this factor needs recognition by emergency department staff in order to reduce mortality rates in this high risk group.
Effect due to factor in study?	Not certain- selected patients with chest pain, hence directness to question may be inappropriate as in that patients with atypical symptoms not necessary included
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Selected patients with chest pain, hence directness to question may be inappropriate as in that patients with atypical symptoms not necessary included
Internal Validity	Not addressed

Question 6: What is the utility (incremental value) and cost effectiveness of the resting ECG in evaluation of individuals with acute chest pain of suspected cardiac origin?

Grading: 1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Mant J;McManus RJ;Oakes RL;Delaney BC;Barton PM;Deeks JJ;Hammersley L;Davies RC;Davies MK;Hobbs FR;

Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care

Ref ID 728 Health technology assessment pgs: 1 to 158 2004

Study Type Systematic Review

Funding NHS R&D Health Technology Assessment Programme

Number of participants In total fifty three cohorts

Inclusion/Exclusion Criteria Papers with patients with acute and stable chest pain of suspected cardiac origin

Patient Characteristics Patients with acute and stable chest pain of suspected cardiac origin

Recruitment

Setting Primary and secondary care

Interventions/ Test/ Factor being investigated Resting ECG. Diagnosis of acute MI and ACS.

Comparisons

Length of Study/ Follow-up

Outcome measures studied Diagnosis of acute MI, ACS and angina.

Results The presence of ST 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 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). A completely normal ECG was reasonably useful at ruling out a MI (LR+ 0.14, 95%CI 0.11 to 0.20, P = 0.007) in patients with acute chest pain. The two next best changes were the presence of Q waves (LR + 5.01, 95% 3.56 to 7.06) and ST depression (LR + 3.13, 95% 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 waves (LR + 5.30 95%CI 3.66 to 7.70). A completely normal ECG was reasonably useful at ruling out a MI (LR+ 0.14, 95%CI 0.11 to 0.20). It was stated that the summary results were difficult to interpret because of significant heterogeneity in the studies but that a single ECG was an important for diagnostic information in the evaluation of acute chest pain. A further number of studies were identified that examined 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 diagnosis for MI and acute coronary syndrome, and A&E decisions to admit for MI and acute coronary syndromes. Clinical interpretation of admission ECG studies showed that there was a very high LR+ (145 in the best quality paper) for ruling in an MI, however the sensitivity was low (LR- 0.58). The one study that examined the exclusive use of signs and symptoms in diagnosis found that clinical evaluation was not helpful. For the studies evaluating A&E initial diagnosis for MI gave a LR+ of 4.48 (95% CI 2.82 to 7.12) and a LR- of 0.29 (95% CI 0.18 to 0.49). For the category of A&E decisions to

	admit for MI the LR+ was 2.55 (95% CI 1.87 to 3.47) with an LR–. Of 0.08 (95% CI 0.05 to 0.18). ECG was not found to be particularly useful in ruling in a diagnosis of angina in patients with stable chest pain. Thirteen studies were identified and the presence of Q wave changes was found to be the most frequently evaluated ECG change. The LR+ was 2.56, however the 95% CI interval was wide (0.86 to 7.30). ST segment plus or minus T wave changes were not found to be useful. The absence of any ECG changes was not helpful.
Safety and adverse effects	None reported
Does the study answer the question?	
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Correct population
Internal Validity	

Grading: 1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Ioannidis JP;Salem D;Chew PW;Lau J;

Accuracy and clinical effect of out-of-hospital electrocardiography in the diagnosis of acute cardiac ischemia: a meta-analysis

Ref ID 198 Ann Emerg Med pgs: 461 to 470 2001

Study Type Systematic Review **Funding** Not reported

Number of participants 8 prospective and retrospective cohort studies

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

The review considered prospective and retrospective English language papers published between 1966 and December 1998 on the diagnostic accuracy of out-of-hospital ECG. 8 of the studies considered the diagnostic accuracy for AMI and 5 of the studies considered the diagnostic accuracy of acute cardiac ischemia (ACI).

See table in guideline.
The studies identified found that out-of hospital ECGs for AMI have a diagnostic odds ratio (OR) of 104 and 95% CI 48 to 224 and for ACI OR of 23 and 95% CI 6.3 to 85. The review reported that there was significant heterogeneity in the sensitivity and specificity results between the 8 studies which was possibly due to the difference in definition of an abnormal ECG. The review identified one study which compared computer interpreted ECG with physician interpreted ECG and showed the computer interpreted ECG had a better specificity (98% versus 95%) but a worse sensitivity (52% versus 66%) when compared to physician interpreted ECG. The review states that the diagnostic accuracy may be affected by the expertise interpreting the ECG but states that even experienced clinicians can miss a diagnosis.

The review concluded there was substantial data to show that out-of-hospital ECGs have similar diagnostic accuracy as standard ECGs for AMI and ACI. The authors suggest that an out-of-hospital ECG should be considered by paramedics in all chest pain patients.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Morrison LJ;Brooks S;Sawadsky B;McDonald A;Verbeek PR;

Prehospital 12-lead electrocardiography impact on acute myocardial infarction treatment times and mortality: a systematic review

Ref ID 555 Acad Emerg Med pgs: 84 to 89 2006

Study Type Systematic Review **Funding** Not stated

Number of participants	Cohort studies best available evidence
Inclusion/Exclusion Criteria	Included studies: advanced notification pre-hosital ECG comparisons with emergency room ECG as comparison.
Patient Characteristics	Suspected acute MI.
Recruitment	Systematic review: 5 studies cohort studies identified.
Setting	Ambulance and emergency department.
Interventions/ Test/ Factor being investigated	ECG
Comparisons	Pre hospital ECG versus emergency department ECG.
Length of Study/ Follow-up	One study reported mortality but this was not significant for pre hospital ECG versus emergency department ECG.
Outcome measures studied	Door to treatment time.
Results	The pre-hospital on scene time for acute MI was not significantly different when comparing these studies (total patient number of 519) (pooled weighted mean difference of 1.19 (95% CI –0.84 to 3.21). The door to treatment interval was compared for 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 considered heterogeneity was found in these studies (Q statistic 10.9, P < 0.01). Only one study examined all cause mortality. There was no difference all cause mortality when PHECG was compared with no advanced notification for patients with acute MI (PHECG: 8.4% versus control: 15.5%, P < 0.22)
Safety and adverse effects	
Does the study answer the question?	Examines pre-hospital ECG recordings for accuracy with subsequent ECG in emergency department. Determines the accuracy of prehospital ECG in final diagnosis. Although not completely relevant to the ECG sensitivity / specificity in the diagnosis of coronary artery disease, informs on the setting of ECG.
Effect due to factor in study?	

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Grading: 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

Aufderheide TP;Xue Q;Dhala AA;Reddy S;Kuhn EM;

The added diagnostic value of automated QT-dispersion measurements and automated ST-segment deviations in the electrocardiographic diagnosis of acute cardiac ischemia

Ref ID 1711 J Electrocardiol pgs: 329 to 339 2000

Study Type Cohort **Funding** Not reported

Number of participants 1568 ECGs

Inclusion/Exclusion Criteria The patients were aged over 18, who sought paramedic evaluation for chest pain which was non-traumatic or equivalent syndrome of presumed cardiac origin and who were 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, and if the ECG showed QRS duration, heart rate, atrial fibrillation or flutter, heat block, or fully paced rhythms.

Patient Characteristics The median age was 62 years and 45.3% were women

Recruitment patients who had a prehospital ECG by paramedics

Setting ambulance, USA

Interventions/ Test/ Factor being investigated ECG diagnosis

Comparisons ST segment, QT-end and QT-peak dispersion, physician and computer interpretation

Length of Study/ Follow-up

Outcome measures studied sensitivity, specificity, PPV and NPV of ECG

Results

The study assessed the sensitivity and specificity of diagnosing AMI by assessment by both physicians of ST segment deviation, QT-end dispersion and QT-peak dispersion measurements independent of each other. The study showed the average sensitivity was 50.5% and specificity was 98%. The study went on to assess the sensitivity and specificity of diagnosing AMI by a computer through independent assessment of ST segment deviation, which showed a higher sensitivity of 90% but lower specificity of 56%. For independent assessment of QT-end and QT-peak dispersion the computer interpretation did not have a significant difference compared to the physicians' interpretation. The study went on to assess the sensitivity and specificity of diagnosing AMI when combining the information of QT-end and QT peak dispersions which showed that the physicians' significantly increased in sensitivity by 88% (90% versus 48%, P=<0.001), but decreased in specificity by 44% (55% vs. 99% P=<0.001) and PPV by 58% (40% vs. 95%, P=<0.001). The sensitivity and specificity were also assessed when ST segment deviation was included in the analysis, which showed this lead to the physicians' highest sensitivity 65% (compared to 48%, P=<0.001) and maintained specificity 97% (compared to 99%, P=<0.001).

The study continued to assess the sensitivity and specificity of diagnosing ACI; the physicians' had a lower sensitivity (38-40%). The study assessed the sensitivity and specificity by assessment by both physicians and the computer of ST segment deviation, QT-end dispersion and QT-peak dispersion measurements independent of each other. For ST segment deviation the computer had a higher sensitivity (75%)

but a lower specificity (66%). The study showed that for independent assessment of QT-end dispersion and QT-peak dispersion the computer had a higher sensitivity compared to the physicians (50-53% compared to 38-40%, P=<0.001), but the specificity, PPV and NPV were all comparable. The study went on to assess the sensitivity and specificity of diagnosing ACI when combining the information of QT-end and QT peak dispersions which showed that the physicians' significantly increased in sensitivity by 70% (65-68% versus %, P=<0.001) and NPV by 19% (68%-69% versus 58%, P=<0.001), but decreased in specificity (80-81% vs. 92% P=<0.001) and PPV (79% vs. 85%, P=<0.001). The sensitivity and specificity were also assessed when ST segment deviation was combined with QT-end dispersion, which showed this lead to the physicians' highest sensitivity 62% (compared to 40%, P=<0.001) and NPV to 68% (compared to 58%, P=<0.001) and maintained specificity 90% (compared to 92%, P=<0.001) and PPV 87% (compared to 85%, P=<0.05).

Safety and adverse effects

None reported

Does the study answer the question?

The study assessed the sensitivity and specificity of diagnosing AMI by assessment of ST segment deviation, QT-end dispersion and QT-peak dispersion measurements independent of each other. The study showed the computer interpretation had a higher sensitivity but lower specificity compared to physician interpretation. The study showed that when combining QT-end and QT-peak dispersion the physicians sensitivity increased but specificity and PPV decreased, when combining ST segment deviation as well the physicians' reached its maximum sensitivity and maintained specificity.

The study assessed the sensitivity and specificity of diagnosing ACI by assessment of ST segment deviation, QT-end dispersion and QT-peak dispersion measurements independent of each other. The study showed the computer interpretation had a higher sensitivity but lower specificity compared to physician interpretation for ST segment deviation, and higher sensitivity but comparable specificity, PPV and NPV for QT-end and QT-peak. The study showed that when combining QT-end and QT-peak dispersion the physicians sensitivity and NPV increased but specificity and PPV decreased, when combining ST segment deviation and QT-end dispersion the physicians' reached its maximum sensitivity and NPV and maintained specificity and PPV.

Effect due to factor in study?

Yes

Consistency of results with other studies?

Consistent

Directly applicable to guideline population?

Patients had chest pain

Internal Validity

Well covered

Conti A;Paladini B;Toccafondi S;Magazzini S;Olivotto I;Galassi F;Pieroni C;Santoro G;Antoniucci D;Berni G;

Effectiveness of a multidisciplinary chest pain unit for the assessment of coronary syndromes and risk stratification in the Florence area

Ref ID 926 American heart journal pgs: 630 to 635 2002

Study Type Cohort

Funding Italian Ministry for Scientific and Technological Research

Number of participants

13 762 patients

Inclusion/Exclusion Criteria

Inclusion: over 18 years old, 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

Patient Characteristics

The mean age was 65±18 years and 43% were women
Those who were categorised as being at high risk (21%) had a mean age of 63±10 years, 33% were female, 35% smoked, 25% had diabetes, 38% had hypertension,

	13.4 % died during the follow up. Those who were categorised as being at intermediate risk (47%) had a mean age of 64±11 years, 38% were female, 33% smoked, 28% had diabetes, 41% had hypertension, 2.2 % died during the follow up. Those who were categorised as being at low risk (32%) had a mean age of 38±15 years, 66% were female, 12% smoked, 8% had diabetes, 22% had hypertension, 0.2 % died during the follow up.
Recruitment	Admitted to emergency department with chest pain as described above
Setting	ED. Careggi General Hospital, Florence, Italy
Interventions/ Test/ Factor being investigated	Diagnosing chest pain
Comparisons	The chest pain score was based on: location of pain, radiation of pain, character of pain, history of angina
Length of Study/ Follow-up	6 months
Outcome measures studied	Effectiveness of chest pain score in diagnosing chest pain
Results	The chest pain score was based on the following elements each of which was given a value: 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 sticking, pleuritic or pinprick = -1; associated symptoms: dyspnea, nausea or diaphoresis = +2; history of angina = +3. The mean age was 65±18 years. Patients were classified into 1 of 4 groups. 1) Patients at low risk with obvious noncardiac causes of chest pain, chest pain score <4, normal ECG, and normal serum markers of cardiac injury obtained at least 6 hours from symptoms, were sent home and followed up. (2672 patients) 2) Patients at low risk with chest pain score ≥ 4, normal ECG, normal serum cardiac markers, independent of age or coexisting coronary risk factors, were not admitted and underwent a second-line evaluation and short-term observation in the CPU area, including chest radiography, serial 12-lead ECG, serial troponins and cardiac enzymes, echocardiography and arterial blood gas analysis. When at least one of these tests or procedure results was found to be suggestive of AMI, unstable angina or CAD or left ventricular failure was detected these patients were considered for angiography with no additional testing. After an observation period up to 6 hours patients without ongoing cardiovascular events underwent exercise tolerance test or SPECT or stress echocardiography. (1755 patients) 3) Patients at intermediate risk with clinical score ≥ 4 and abnormal ECG (ST-segment elevation <1mm or ST-segment depression <1mm at 60ms from J point) were admitted and managed in the CPU area. 4) Patients at high risk with ECG suggestive for AMI (defined as ST elevation ≥1 mm at 60ms from J point, ≥2 contiguous leads) were directly transferred to the coronary care unit and patients with suspected major cardiovascular disease, such as aortic arch dissection, pulmonary embolism, pneumothorax and acute pericarditis, were admitted and managed with arterial blood gas analysis, chest radiography, echocardiography, and thorax computed tomography if required by clinical assessment. At six month follow up 0.2% of these patients were recognised as having nonfatal coronary artery disease, hence, the negative predictive value of a chest pain score of < 4 and normal ECG was > 99% Of the patients with a chest pain score ≥ 4 and normal or non diagnostic electrocardiogram results (1755 patients, 40%), 20% of the low risk group with chest pain score < 4 (group 1) (885 patients) had documented coronary artery disease, 18% of which were by recurrent angina, delayed ECG changes, late rise in markers, the other 2% was by positive stress test. There were 9335 intermediate and high risk patients, of which 2420 patients (26%) had an MI, 3764 patients (40%) had unstable angina, 129 (1.4%) had aortic dissection and 408 (4%) had pulmonary embolism, other major cardiovascular conditions were diagnosed, including aortic arch dissection, pulmonary embolism, pneumothorax, and acute pericarditis. 2256 patients had atypical chest pain

	diagnosed as multi-organ disease including chronic and stable ischemic heart disease, defined as known stable angina, previous myocardial infarction, or angiographically documented CAD.
Safety and adverse effects	None reported
Does the study answer the question?	Of the patients with a chest pain score > 4 and normal electrocardiogram results, 20% (885 patients) had documented coronary artery disease. There were 9335 intermediate and high risk patients, of which 2420 patients (26%) had an MI, 3764 patients (40%) had unstable angina, 129 (1.4%) had aortic dissection and 408 (4%) had pulmonary embolism. Other multi-organ disease was found in 2256 patients. The authors concluded that the chest pain score screening programme was effective and could significantly reduce admissions and optimise the care of those with an intermediate or high risk score. The authors also concluded that the screening programme could aid the diagnosis of alternative causes of chest pain in patients who do not have evidence of coronary artery disease
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Correct population
Internal Validity	Well covered

Fesmire FM;

Which chest pain patients potentially benefit from continuous 12-lead ST-segment monitoring with automated serial ECG?

Ref ID 6025 Am J Emerg Med pgs: 773 to 778 2000

Study Type	Cohort	**Funding**	Not reported
Number of participants	706 patients		
Inclusion/Exclusion Criteria	included: chest pain with suspected ACS		
Patient Characteristics	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 previous MI, 52.3% had previous 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 previous MI, 25.2% had previous 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 previous MI, 15.4% had previous PTCA/CABG		
Recruitment	Patients presented with chest pain of suspected ACS to the emergency department between August 1995 and August 1998		
Setting	Emergency department, USA		
Interventions/ Test/ Factor being investigated	Continuous ST segment monitoring		
Comparisons	Sensitivity and specificity of serial ECG		
Length of Study/ Follow-up			

Outcome measures studied	Sensitivity and specificity of serial ECG
Results	Patients had an initial history, physical examination and ECG, and were subsequently classed in four different categories. Category I were patients with ACS with clinical and ECG criteria for emergency reperfusion therapy, category II were patients with probable ACS but without clinical and ECG criteria for emergency reperfusion therapy, category III were patients with possible ACS, category IV were patients with probable non-ACS chest pain but presence of pre-existing disease or significant risk factors for CAD. Category I were excluded from the study. The serial ECG was obtained at least every 10 minutes until the patient was taken for PTCA or for 2 hours See tables in guideline. 28 patients were placed in category I, 137 patients were placed in category II, 333 patients were placed in category III and 208 patients were placed in category IV.. Serial ECG for new injury or new/evolving ischemia had a sensitivity and specificity of 41.7% (95% CI 27.6 to 58.6) and 98.1% (95% CI 96.7 to 99) respectively for AMI and 15.5% (95% CI 10.6 to 21.5) and 94.4% (95% CI 98.2 to 99.9) for ACS. For AMI the serial ECG had a positive likelihood ratio (LR+) of 21.9 and negative likelihood (LR-) of 0.59 and for ACS a LR+ of 25.4 and LR- of 0.85. As a result of the serial ECG 26 patients had their treatment changed.
Safety and adverse effects	None reported
Does the study answer the question?	Serial ECG for new injury or new/evolving ischemia had a sensitivity and specificity of 41.7% (95% CI 27.6 to 58.6) and 98.1% (95% CI 96.7 to 99) respectively for AMI and 15.5% (95% CI 10.6 to 21.5) and 94.4% (95% CI 98.2 to 99.9) for ACS. For AMI the serial ECG had a positive likelihood ratio (LR+) of 21.9 and negative likelihood (LR-) of 0.59 and for ACS a LR+ of 25.4 and LR- of 0.85. As a result of the serial ECG 26 patients had their treatment changed.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Patients had chest pain with suspected ACS
Internal Validity	Well covered

Ohlsson M;Ohlin H;Wallerstedt SM;Edenbrandt L;

Usefulness of serial electrocardiograms for diagnosis of acute myocardial infarction

Ref ID 1582 The American journal of cardiology pgs: 478 to 481 2001

Study Type	Cohort	**Funding**	Swedish Medical Research Council, Swedish Heart Lung Foundation, Medical Faculty at Lund University, Swedish Foundation for Strategic Research

Number of participants	902 ECGs were reviewed, each ECG was also reviewed with a previous ECG for the same patient
Inclusion/Exclusion Criteria	ECG had to show an AMI, previous ECG had to be available from the clinical electrocardiographic database
Patient Characteristics	The average age of the patients was 74±11 years, with 605% being men
Recruitment	Patients with AMI who presented to emergency department between January 1990 and June 1997

Setting	Emergency department, Sweden
Interventions/ Test/ Factor being investigated	Usefulness of serial ECG
Comparisons	serial ECG versus single ECG, by a cardiologist, intern and computer
Length of Study/ Follow-up	
Outcome measures studied	accuracy of reading ECG
Results	The study recorded a 12 lead ECG by the use of 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 ECGs were interpreted for diagnosis AMI by artificial neutral network which used standard feed forward, multilayer, perceptron architecture, which consisted 1 input layer, 1 hidden layer and 1 output layer with 16 or 32 nodes, the ECGs were then interpreted independently by two physicians (one cardiologist and one intern), on two occasions, the first occasion only the new ECG was shown and the second occasion both ECGs were shown. The study used ROC curves to evaluate the difference in interpretation and diagnosis of AMI when both ECGs were present compared to only the current ECG. The ROC curve showed that the neutral network performance was improved when both ECGs were present (area under ROC with current ECG = 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 diagnosed more AMI with both ECGs. The cardiologist performance did not have a statistically significant improve with both ECGs (area under ROC with current ECG = 0.79, area under ROC with both ECGs = 0.81; P = 0.36).
Safety and adverse effects	None reported
Does the study answer the question?	The study used ROC curves to evaluate the difference in interpretation and diagnosis of AMI when both ECGs were present compared to only the current ECG. The ROC curve showed that the neutral network performance was improved when both ECGs were present, the intern performed better when both ECGs were present and diagnosed more AMI with both ECGs. The cardiologist performance did not have a statistically significant improve with both ECGs.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Patients had AMI
Internal Validity	Well covered

Sanchis J;BodÝ V;Llßcer A;N·±ez J;Consuegra L;Bosch MJ;Bertomeu V;Ruiz V;Chorro FJ;

Risk stratification of patients with acute chest pain and normal troponin concentrations

Ref ID 459 Heart (British Cardiac Society) pgs: 1013 to 1018 2005

Study Type Cohort **Funding** Not reported

Number of participants 609 patients

Inclusion/Exclusion Criteria	Inclusion: Patients with chest pain of suspected cardiac origin as determined by a cardiologist on call with a negative troponin I concentration (measured at baseline, at 6, 8 and 12 hours). Exclusion: ST elevation, Left Bundle Branch Block, and heart failure, killip > 1
Patient Characteristics	The mean age was 64±12 years, 33% were women, 20% were current smokers, 59% had hypertension, 53% had hypercholesterolemia, 25% had diabetes, 44% had a history of IHD, 13% had a family history of IHD, 7% had had coronary surgery, 12% had ST depression, 9% had T wave inversion
Recruitment	Patients admitted to the emergency department in a teaching hospital in Spain
Setting	ED, teaching hospital in Spain
Interventions/ Test/ Factor being investigated	Diagnosing chest pain
Comparisons	The chest pain score was based on: location, radiation, character, severity, what influenced the pain, associated symptoms, history of exertional angina. A clinical history, ECG and for those in the low risk group an early (<24 hours) exercise test
Length of Study/ Follow-up	6 months
Outcome measures studied	Effectiveness of chest pain score in diagnosing chest pain
Results	An ECG was recorded in the emergency room and evaluated for ST segment depression (>1mm) and T wave inversion (peak inversion >1mm) Troponin I concentrations were taken at arrival, 6 hours (is patient arrived within 2 hours of onset of pain), 8 hours and 12 hours after pain onset. All patients had normal troponin concentrations at each measurement. Patients underwent a chest pain score assessment, an ECG, and for those in the low risk group an early (<24 hours) exercise test. The chest pain score was based on: location, radiation, character, severity, influenced by glyceryl trinitrate, stature, breathing, associated symptoms and history of exertional angina = +3. A clinical history was also taken. 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 (AMI or cardiac death). Those who could had a negative exercise test had a very good prognosis compared to those who did not have a negative exercise test or those who could not exercise and do and exercise test. For predictors of AMI the univariate and multivariate analysis showed: ST segment depression (univariate P = 0.004, multivariate P = 0.02, odds ratio (OR) 2.9, 95%CI 1.2 to 6.8), T-wave inversion (univariate P = 0.5, multivariate analysis could not be applied to T-wave inversion). For predictors of a major event (AMI or cardiac death) the univariate and multivariate analysis showed: ST segment depression (univariate P = 0.003, multivariate P = 0.01, OR 2.8, 95%CI 1.3 to 6.3), T-wave inversion (univariate P = 0.7, multivariate analysis could not be applied to T-wave inversion). The patients were stratifies according to the four independent risk factors associated with a major event (AMI or cardiac death), these were chest pain score, diabetes, previous coronary surgery and ST-segment depression. The event rate increased with the number of risk factors: no risk factors 2.5% event rate, 1 risk factor 2.9% event rate, 2 risk factors 10.2% event rate, 3 or 4 risk factors 29.2% event rate. Three risk categories were defined: low risk: no or 1 risk factor 2.7% event rate, intermediate risk: 2 risk factors 10.2% event rate, high risk: 3 or 4 risk factors 29.2% event rate. The differences between the 3 categories were all significant: high and intermediate (P = 0.001), high and low (P = 0.0001), intermediate and low (P = 0.008).
Safety and adverse effects	None reported

Does the study answer the question?	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 (AMI or cardiac death). Multivariate analysis found that ST segment depression was an independent factors in predicting an acute MI (univariate P = 0.004, multivariate P = 0.02, OR 2.9, 95%CI 1.2 to 6.8), and major events (AMI or cardiac death) (univariate P = 0.003, multivariate P = 0.01, OR 2.8, 95%CI 1.3 to 6.3). Further analysis found that the event rate increased progressively with the progression of the number of independent risk factors, with the event rate increasing with the number of risk factors: no risk factors 2.5% event rate, 1 risk factor 2.9% event rate, 2 risk factors 10.2% event rate, 3 or 4 risk factors 29.2% event rate. From this 3 risk categories, low intermediate and high, were formed with the difference between each being significant. NB there is overlap of patients included in this study and the study Sanchis et al 2005, JACC (New Risk Score for Patients with Acute Chest Pain, Non-ST-Segment Deviation, and Normal Troponin Concentrations).
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Correct population
Internal Validity	Well covered

Sanchis J;BodÝ V;N·±ez J;Bertomeu G;G¾mez C;Bosch MJ;Consuegra L;Bosch X;Chorro FJ;LlÓcer A;

New risk score for patients with acute chest pain, non-ST-segment deviation, and normal troponin concentrations: a comparison with the TIMI risk score

Ref ID 447 Journal of the American College of Cardiology pgs: 443 to 449 2005

Study Type	Cohort	**Funding**	RECAVA-FIS

Number of participants	646 patients
Inclusion/Exclusion Criteria	Inclusion criteria: acute chest pain of possible cardiac origin Exclusion: if the initial ECG showed ST-segment deviation (≥1mm elevation or depression) or if they had troponin I elevation
Patient Characteristics	The mean age was 64±12 years and 32% were women. 20% were smokers, 59% had hypertension, 53% had hypercholesterolemia, 26% had diabetes mellitus, 7% insulin dependant diabetes mellitus, 12% had a family history of IHD, 13% had at least 3 risk factors, 24% had prior coronary stenosis ≥ 50%, 43% had used aspirin in the previous 7 days, 25% had a prior MI, 9% had prior PTCA, 8% had prior CABG, 2% had a history of heart failure. On ECG 100% had T-wave inversion,9% had confounding ECG
Recruitment	Patients admitted with acute chest pain to the emergency department in a teaching hospital in Spain during a 34 month period between 15th January 2001 and 30th November 2003
Setting	ED in a teaching hospital in Spain
Interventions/ Test/ Factor being investigated	Diagnosing chest pain
Comparisons	The chest pain score and other variables, described in results
Length of Study/ Follow-up	1 year

Outcome measures studied	The primary end point was all cause mortality or nonfatal myocardial infarction, the secondary end point was all cause mortality, nonfatal myocardial infarction or urgent revascularisation at 14 day follow up.
Results	Patients were excluded if they had ST-segment deviation (≥1mm elevation or depression) on the initial ECG or if they had troponin I elevation. All patients had T-wave inversion and 9% had confounding ECG (left branch bundle block of paced rhythm). An ECG was recorded in the emergency room. Troponin I concentrations were taken at arrival, 6 hours (is patient arrived within 2 hours of onset of pain), 8 hours and 12 hours after pain onset. All patients had normal troponin concentrations at each measurement. Patients underwent a chest pain score assessment based on: location, radiation, character, severity, influenced by glyceryl trinitrate, stature, breathing, associated symptoms and history of exertional angina. A clinical history and risk factor analysis was also taken. At 1 year follow up, the primary end point (all-cause mortality or non-fatal MI) occurred in forty three patients (6.3%). At a 14 day follow up, the secondary end point (all-cause mortality or nonfatal myocardial infarction or urgent revascularisation) occurred in 35 patients (5.4%). The univariate analysis showed that for: T-wave inversion (P = 0.4), confounding ECG (P = 0.09). The multivariate analysis showed that for: confounding ECG (P = 0.3). The multivariate analysis did not give results for T-wave inversion or full results for confounding ECG. The study showed from multivariate analysis ECG changes (T-wave inversion and confounding ECG) were not independent predictors of the primary end point.
Safety and adverse effects	None reported
Does the study answer the question?	Univariate analysis found that the following were independent factors in predicting all cause mortality or nonfatal myocardial infarction; t-wave inversion (P = 0.4), and confounding ECG (P= 0.09). Multivariate analysis found that ECG changes were not independent factors in predicting all cause mortality or nonfatal myocardial infarction. Confounding ECG on multivariate analysis (P=0.3). NB there is overlap of patients included in this study and the study Sanchis et al 2005, Heart J (Risk Stratification of Patients with Acute Chest Pain and Normal Troponin Concentrations).
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Correct population
Internal Validity	Well covered

Grading: 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

Diercks DB;Kontos MC;Chen AY;Pollack CV;Wiviott SD;Rumsfeld JS;Magid DJ;Gibler WB;Cannon CP;Peterson ED;Roe MT;

Utilization and impact of pre-hospital electrocardiograms for patients with acute ST-segment elevation myocardial infarction:data from the NCDR (National Cardiovascular Data Registry) ACTION (Acute Coronary Treatment and Intervention Outcomes Network) Reg

Ref ID 25413 J Am Coll Cardiol pgs: 161 to 166 2009

Study Type Cohort **Funding** Not stated

Number of participants	Final population of 7098
Inclusion/Exclusion Criteria	Acute chest pain suspected to be acute MI and attending an ACTION participating hospital
Patient Characteristics	he 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
Recruitment	consecutive
Setting	Ambulance and hospital
Interventions/ Test/ Factor being investigated	Use of out of hospital ECG to in-hospital ECG
Comparisons	Use of out of hospital ECG to in-hospital ECG
Length of Study/ Follow-up	At 1 month
Outcome measures studied	Mortality, door to needle time, door to treatment time.

Results

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.

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).

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).
Safety and adverse effects	No
Does the study answer the question?	Yes it details the usefulnes of obtaining an ECG prior to arrival at hospital
Effect due to factor in study?	Yes
Consistency of results with other studies?	Study not directly applicable as it is examinge setting of ECG recording, ambulance versus hospital
Directly applicable to guideline population?	Directly applicable, acute chest pain population.
Internal Validity	Not applicable

Question: 7 Are the symptoms and description of the symptoms different in women presenting with acute chest pain of suspected cardiac origin compared with men

Grading: 1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Canto JG;Goldberg RJ;Hand MM;Bonow RO;Sopko G;Pepine CJ;Long T;

Symptom presentation of women with acute coronary syndromes: myth vs reality

Ref ID 25372 Arch Intern Med pgs: 2405 to 2413 2007

Study Type	Systematic Review	**Funding**	Not reported

Number of participants	Cohort, Surveys, Registries.
Inclusion/Exclusion Criteria	Cohort, Surveys, Registries identified between 1970 to 2005
Patient Characteristics	Patients with ACS
Recruitment	Systematic review identified nine large cohort studies, and twenty smaller cohort or personal interview studies that provided information on ACS presentation with and without chest pain or discomfort according to sex
Setting	Emergency departments
Interventions/ Test/ Factor being investigated	Not applicable
Comparisons	Signs and symptoms, men versus women
Length of Study/ Follow-up	Not applicable
Outcome measures studied	
Results	Compared with men, 8 identified 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 five 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 two studies each. Paroxysmal nocturnal dyspnea, indigestion and dizziness were reported as more common in women versus men in one study each. One study found that women appear to have a greater number of associated symptoms as part of their ACS presentation compared with men.
Safety and adverse effects	Not applicable
Does the study answer the question?	Yes. Women are significantly less likely to report chest pain or discomfort at presentation for ACS compared with men from accumulated data from 29 identified studies. The authors identified the following limitations of the review and other related studies; there is a lack of standardisation on data collection and reporting on women's principal or associated ACS symptoms thus formal meta-analyses was not possible due to heterogeneity, a number of studies exclude patients that have ACS and no chest pain or discomfort, chest pain or discomfort is often lumped together with pain localised to other areas of the upper body in the absence of chest pain symptoms, hospital records are often very imprecise in characterising the presence of chest pain, as well as other associated symptoms, physician bias based on the patients pre-test probability in recording symptoms, survey bias when patients recollect symptoms retrospectively, the sensitivity of a particular symptom may be ascertained but the specificity of a symptom may not be considered, and the impact of potential association of co-morbid conditions (such as diabetes), with symptom

	presentation has not been examined in the review due to the lack of currently available data although this is likely to be important.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Directly applicable to the guideline
Internal Validity	Well covered

Patel H;Rosengren A;Ekman I;

Symptoms in acute coronary syndromes: Does sex make a difference?

Ref ID 2613 Am Heart J pgs: 27 to 33 2004

Study Type	Systematic Review	**Funding**	In part: Vardal institute research platform

Number of participants	Systematic review- 15 cohort studies identified
Inclusion/Exclusion Criteria	Studies from a search between 1980 to 2002
Patient Characteristics	Fifteen studies were identified, four cohorts were in patients with all types of ACS and eleven cohorts were in patients with MI. The systematic review did not however provide a definition of ACS that was detailed in the selected studies.
Recruitment	Not applicable
Setting	Emergency departments
Interventions/ Test/ Factor being investigated	Signs and symptoms
Comparisons	Signs and symptoms; men versus women
Length of Study/ Follow-up	Not applicable
Outcome measures studied	Signs and symptoms in ACS patients
Results	Yes. Analysis of the 4 studies identified in patients presenting with ACS found that women are more likely to experience back and jaw pain, nausea and / or vomiting, dyspnea, indigestion and palpitations compared with men. In the 4 ACS cohort studies no gender difference was found for the following symptoms; presence of chest pain (2 studies), arm and shoulder pain (2 studies), neck pain (2 studies), dizziness (3 studies). Analysis of the eleven cohort studies identified in patients with MI found that women are more likely to have back, jaw, and neck pain, and nausea and / or vomiting, dyspnea, palpitations, indigestion, dizziness, fatigue, loss of appetites and syncope. The following symptoms were not associated with gender differences in the presentation of acute MI; arm and shoulder pain (4 studies), epigastric discomfort, heartburn or abdominal pain (7 studies), throat pain (2 studies)
Safety and adverse effects	Not applicable
Does the study answer the question?	Cohort studies suggest that women exhibit different symptoms of ACS versus men, however, here 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 authors

	stated that sex differences may disappear after controlling for variables such as age or co-morbid conditions. Some studies evaluated only a small number of symptoms, and may have missed other statistically significant symptoms.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Directly relevant to guideline population
Internal Validity	Adequately addressed

Grading: 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

Chrysohoou C;Panagiotakos DB;Pitsavos C;Kokkinos P;Marinakis N;Stefanadis C;Toutouzas PK;

Gender differences on the risk evaluation of acute coronary syndromes: The CARDIO2000 study

Ref ID 3520 Preventive Cardiology pgs: 71 to 77 2003

Study Type	Cohort	**Funding**	Not reported

Number of participants	848 patients (701 men, 147 women) and 1078 in the control group (862 men, 216 women)
Inclusion/Exclusion Criteria	Inclusion: first event of acute MI as diagnosed by 2 or more of following; ECG, compatible clinical symptoms, enzyme elevations, or first diagnosis of unstable angina as described by class III of the Braunwald classification
Patient Characteristics	Seven hundred and one (82%) of the cardiac patients were men with a mean age 59 SD 10 years, and 147 (18%) of cardiac patients were women with a mean age of 65.3 SD 8 years. For controls 80% were men and 20% were women with mean ages of 58.8 SD 10 years and 64.8 SD 10 years, respectively
Recruitment	Random selection of patients admitted between January 2000 and August 2001 who met the inclusion criteria. The control group were selected from patients who attended the hospital for routine outpatient appointments who were cardiovascular disease free.
Setting	Secondary Care, Greece
Interventions/ Test/ Factor being investigated	Risk factors for diagnosis ACS
Comparisons	Smoking, hypertension, hypercholesterolemia, diabetes, family history of premature CAD, BMI, physical activity, diet, alcohol consumption
Length of Study/ Follow-up	Not applicable
Outcome measures studied	Risk factors for diagnosis ACS
Results	Women experiencing their first cardiac event were significantly older than men (P < 0.01). Univariant 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. When adjusting for age, multivariate analysis found that for women hypertension was associated with a higher risk of coronary artery disease compared with men (odds ratio 4.86 versus 1.66 P < 0.01, respectively). Family history of coronary artery disease and hypercholesterolemia were associated with a higher risk of coronary artery disease 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.
Safety and adverse effects	Not applicable
Does the study answer the question?	Yes. Study found that impact of CAD is different for women versus men.. Men were more likely to have a family history of CAD and hypertension. Women were more likely to have hypertension compared with men.
Effect due to factor in study?	Yes

Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Not unselected chest pain population, however ACS I population is subset of this, therefore cohort is applicable as subset of the chest pain guideline population
Internal Validity	Well covered

Isaksson RM;Holmgren L;Lundblad D;Brulin C;Eliasson M;

Time trends in symptoms and prehospital delay time in women vs. men with myocardial infarction over a 15-year period. The Northern Sweden MONICA Study

Ref ID 25380 EUR J CARDIOVASC NURS pgs: 152 to 158 2008

Study Type Cohort

Funding Norrbotten County Council provided funding for the myocardial registry

Number of participants	6342 patients (5072 men and 1470 women).
Inclusion/Exclusion Criteria	Patients with a diagnosis of MI according to standard WHO definition. Exclusion criteria were patients in the registry with incomplete data
Patient Characteristics	Patients with MI according to standard WHO definition
Recruitment	Not applicable
Setting	Northern Swedish registry survey
Interventions/ Test/ Factor being investigated	Symptom presentation and prehospital delay and risk stratification according to age and gender
Comparisons	Age and gender, with respect to symptoms of MI
Length of Study/ Follow-up	Records over 15 years
Outcome measures studied	Signs and symptoms, hospital delay
Results	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). Symptoms were also analysed with stratification for age and gender. A greater proportion of younger men (age group 25 to 34 years) had typical pain compared with older male age groups, and with increasing age a greater proportion of men experienced typical symptoms. 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%), hence in the oldest age group the frequency of atypical pain is similar in men and women. The study analysed prehospital delay in seeking medial attention according to age and gender (from < 2 h to > 24 h). For the total male population compared with the female population, there was no difference in the proportions in time to hospital delay; < 2 h, 41.2% men versus 41.2% women, < 4 h, 20.2% men versus 19.8% women, < 4 to 24 h, 27.7% men versus 29.8% women, and < 24 h, 10.9% men versus 9.8% women. Analysis of prehospital delay by stratifying according to age and gender found that there was no consistent difference with gender, although for the oldest age group of 65 to 74 years the delay was greater for women compared with men, 25% of older men delayed for more than 4 h compared with 31% for women.

Safety and adverse effects	Not applicable
Does the study answer the question?	Yes. Study found that typical pain was more common in men than in women with MI, hence women were more likely to experience atypical symptoms. Up to age 65 years there was no gender difference in time between onset of symptoms of MI and medical presence, thereafter women sought medical attention later than men.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Not unselected chest pain population, however MI population is subset of this, therefore cohort is applicable as subset of the chest pain guideline population
Internal Validity	Not addressed

Kosuge M;Kimura K;Ishikawa T;Ebina T;Hibi K;Tsukahara K;Kanna M;Iwahashi N;Okuda J;Nozawa N;Ozaki H;Yano H;Nakati T;Kusama I;Umemura S;

Differences between men and women in terms of clinical features of ST-segment elevation acute myocardial infarction

Ref ID 25382 Circulation Journal pgs: 222 to 226 2006

Study Type Cohort **Funding** Not reported

Number of participants	457 patients (106 women and 351 men)
Inclusion/Exclusion Criteria	Inclusion patients with STEMI with symptom onset within 24 h of admission to the coronary care unit and detailed medical history. Acute MI defined as elevation of greater than 2 mmm at least 2 contiguous precordal leads or ST elevation of greater than 1 mm in at least 2 inferior leads (II, III, or a VF), and a typical increase in serum creatine kinase.
Patient Characteristics	Patients with STEMI within 24 h after symptom onset, 457 patients (106 women and 351 men)
Recruitment	Consecutive recruitment from a coronary care unit
Setting	Coronary care unit in Japan
Interventions/ Test/ Factor being investigated	Signs and symptoms, and risk factors
Comparisons	Men versus women, signs and symptoms and risk factors
Length of Study/ Follow-up	Not applicable
Outcome measures studied	Location of pain, nausea, shortness of breath, risk factors
Results	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 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).
Safety and adverse effects	Not applicable
Does the study answer the question?	Yes. Study found that women have atypical presentation of STEMI compared with men, and higher rates of hypertension, diabetes and hyperlipidaemia compared with men.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Not unselected chest pain population, however STEMI population is subset of this, therefore cohort is applicable as subset of the chest pain guideline population
Internal Validity	Adequately addressed

Grading: 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*

Chua TP;Saia F;Bhardwaj V;Wright C;Clarke D;Hennessy M;Fox KM;

Are there gender differences in patients presenting with unstable angina?

Ref ID 1204 International journal of cardiology pgs: 281 to 286 2000

Study Type	Cohort	**Funding**	Not reported

Number of participants	313, 210 (67%) men, 103 (33%) women
Inclusion/Exclusion Criteria	Patients transferred to St Georges Hospital London UK, with a view to coronary angiography and further management, during a 42 month period (January 1994-January 1997)
Patient Characteristics	The mean age for men was 61.6±11 years, for women 63.5±10.5 years (P=0.14). 184 men were Caucasian, 23 were Asian (Indian subcontinent) and 3 had other ethnic origin. 83 women were Caucasian, 15 were Asian (Indian subcontinent) and 5 had other ethnic origin (P=0.4)
Recruitment	Patients transferred to tertiary care unit
Setting	St Georges Hospital, London, UK
Interventions/ Test/ Factor being investigated	Gender differences in patients presenting with unstable angina
Comparisons	Retrospective review of case notes of risk factors for men and women referred for coronary angiography and further care
Length of Study/ Follow-up	Review of case notes
Outcome measures studied	Differences in risk factors for men and women with unstable angina
Results	The mean age was 61.6±11 years for men and 63.5±10.5 for women (P=0.14) 184 men were Caucasian, 23 were Asian (Indian subcontinent) and 3 had other ethnic origin. 83 women were Caucasian, 15 were Asian (Indian subcontinent) and 5 had other ethnic origin (P=0.4) 51% of men and 39% of women had a history of previous MI (P=0.06) 76% of men and 79% of women had angina pectoris (P=0.73) Time to seeking help: < 1 day - 23% men, 28% women; 1-7 days - 38% men, 33% women; > 1 week: 39% men, 39% women 17% of men and 6% of women had had a previous coronary artery bypass graft operation (P=0.013) 56% of men and 64% of women had hypercholesterolemia (P=0.23) The mean total serum cholesterol concentration was 6.4±1.6 mmol/l in men and 6.7±1.5 mmol/l in women, (P=0.4) 42% of men and 49% of women had a family history of ischaemic heart disease (P=0.28) 11% of men and 23% of women had diabetes mellitus (P=0.007) 32% of men and 52% of women had a history of hypertension (P=0.001) 73% of men and 46% of women were current or previous smokers (P=0.00001) 25% of men and 40% of women were current smokers (P=0.06) The study also considered the management of patients, a similar number of men and women underwent coronary artery bypass graft operation and coronary angioplasty.
Safety and adverse effects	Not applicable

Does the study answer the question?	The results found that more men than women with unstable angina were referred for coronary angiography reflecting the higher prevalence of ischaemic heart disease in men. 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. The prevalence of hypercholesterolemia was higher in women but it was not significant. Women were more likely to have diabetes mellitus, a history of hypertension and to currently smoke. Men were more likely to have a history of previous MI, history of previous coronary artery bypass graft operation and a history of smoking. The study also considered the subsequent management of patients, and showed that the subsequent management of patients was not influenced by their gender. A similar proportion of male and female patients underwent coronary artery bypass graft operation and coronary angioplasty.
Effect due to factor in study?	Highly selected population from a tertiary care centre and recruitment not detailed, and also retrospective therefore risk of bias.
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Not unselected chest pain population, however unstable angina population is subset of this, therefore cohort is applicable as subset of the chest pain guideline population
Internal Validity	Not addressed

Question 8: In adults presenting with acute chest pain/discomfort of suspected cardiac origin, what is the clinical and cost effectiveness of giving oxygen compared with a placebo?

Grading: 1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Meme Wijesinghe;Kyle Perrin;Anil Ranchord;Mark Simmonds;Mark Weatherall;Richard Beasley;

The routine use of oxygen in the treatment of myocardial infarction: systematic review

Ref ID 24290 Heart pgs: 1 to 15 2008

Study Type Systematic Review

Funding No specific funding was sought for this study.

Number of participants Two RCTs

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

This review set out to assess the effectiveness of routine oxygen in the treatment of myocardial infarction (MI) in humans (most of the available evidence on the benefits of routine oxygen in MI come from animal studies). The primary outcome variable was in-hospital mortality. Only two studies met the inclusion criteria and only one included mortality as an outcome. The latter study included 200 patients with suspected MI (43 patients in whom MI was not subsequently confirmed were excluded from the analysis). There were 9/80 (11.3%) deaths in the oxygen group and 3/77(3.9%) in the air group, relative risk of death was 2.9 (95% CI 0.8 to 10.3, P=0.08).

The review concludes that there is little evidence by which to determine the efficacy and safety of high flow oxygen therapy in MI. The evidence that does exist suggests that routine oxygen may result in a greater infarct size and possibly increase the risk of mortality.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Nicholson C;

A systematic review of the effectiveness of oxygen in reducing acute myocardial ischaemia

Ref ID 71 Journal of Clinical Nursing pgs: 996 to 1007 2004

Study Type Systematic Review **Funding** not reported

Number of participants 9 Controlled clinical trials (2 randomised and 7 non randomised)

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

A systematic review (SR) on the effectiveness of oxygen in reducing acute myocardial ischaemia identified 9 studies; 2 randomised controlled trials (RCT(s)) and 7 case control studies (Nicholson 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 93 were women and 37 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. The data synthesis of the SR 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..
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, one 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..
Electrocardiogram data were reported in 3 of the 9 studies. Two examined ST-depression, one 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-elevation and the sum of all ST-segment elevation. ST-elevation is usually ascribed to 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 elevated ST-segments and the sum of all the elevation..

None of the studies reported any respiratory side effects, and only one study reported any side effect which was nausea as a reason for withdrawal from oxygen administration (Nicholson 2004).
The author of the SR concluded that there was a lack of strong evidence for using oxygen as a treatment of acute myocardial infarction (MI), although it was recognised that all patients with systemic hypoxaemia should have this corrected by oxygen administration.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Rawles JM;Kenmure AC;

Controlled trial of oxygen in uncomplicated myocardial infarction

Ref ID 2303 Br Med J pgs: 1121 to 1123 1976

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participants 200 patients were included; 105 were randomised to receive oxygen, 95 to receive air

Inclusion/Exclusion Criteria Patients were under 65 who were admitted to the coronary care unit where the admitting medical officer suspected the patient to have had a MI in the previous 24 hours. Patients were excluded if they had clinical evidence of right or left heart failure, chronic bronchitis or emphysema or breathlessness from any other cause or if the has been transferred from other wards for treatment of arrhythmias or had undergone a cardiac arrest before admission or had suffered from cardiogenic shock.

Patient Characteristics

Those without confirmation of an MI:
Air group –
Number of patients 18
Number of men 17
Mean age 50.8 ± 2.4

Oxygen group –
Number of patients 25
Number of men 19
Mean age 51.3 ± 1.7

Those with a confirmed MI:
Air group –
Number of patients 77
Number of men 61
Mean age 56.4 ± 0.8

Oxygen group –
Number of patients 80
Number of men 63
Mean age 55.1 ± 0.9

Recruitment Patients admitted to the coronary care unit at Aberdeen Royal Infirmary which met the inclusion criteria.

Setting Hospital - Coronary Care Unit

Interventions/ Test/ Factor being investigated Oxygen or compressed air as given through an MC mask at a flow rate of 6 L/min for 24 hours.

Comparisons

The comparison is between receiving oxygen and air.

Length of Study/ Follow-up

Patients were followed up for 24 hours.

Outcome measures studied

In all patients: ECG, serum aspartate aminotransferase level, Pao2, stay in hospital, number of patients given diamorphine and the number of doses. Patients with confirmed MI: arrhythmias, heart rate and PEP/LVET.

Results

Those without confirmation of an MI:

	Air group	Oxygen group	
Number of patients	18	25	
Mean Pao2 (kPa)	11.2 ± 0.17	23.7 ± 1.32	(1kPa = 7.5Hg)
Mean stay in hospital (d)	9.9 ± 1.6	11.1 ± 1.3	
No. Pts given diamorphine	3	11	
Mean no. doses of diamorphine	2.7 ± 0.9	1.4 ± 0.2	
Mean serum aspartate aminotransferase Level (IU/ml)	18.3 ± 3.0	15.8 ± 1.1	

Those with a confirmed MI:

	Air group	Oxygen group	
Number of patients	77	80	
Mean Pao2 (kPa)	8.7 ± 0.29	18.2 ± 1.56	(1kPa = 7.5Hg)
Mean stay in hospital (d)	14.9 ± 0.6	16.2 ± 0.6	
No. Pts given diamorphine	52	57	
Mean no. doses of diamorphine	2.0 ± 0.2	2.1 ± 0.2	
Mean serum aspartate aminotransferase Level (IU/ml)	80.7 ± 6.6	99.9 ± 7.1	
Mean heart rate/min	72.7 ± 1.7	77.0 ± 1.7	
Mean PEP/LVET day 1	0.43 ± 0.04	0.35 ± 0.03	
day 2	0.44 ± 0.06	0.37 ± 0.02	

Number of patients with arrhythmias after MI

	Air group	Oxygen group
Atrial ectopics	35	34
Mean frequency/min (when present)	0.44 ± 0.22	0.45 ± 0.16
Atrial tachycardia	2	6
Atrial flutter	2	0
Atrial fibrillation	4	4
Sinus tachycardia	11	23
Sinus bradycardia	36	26
Junctional rhythm	5	2
Accelerated idioventricular rhythm	9	7
Ventricular ectopics	62	72
Mean frequency/min (when present)	0.57 ± 0.12	0.42 ± 0.08
Ventricular tachycardia	5	11
Ventricular fibrillation	1	1
Heart block 1o	6	2
2o	4	1
3o	1	1

Safety and adverse effects

Those who received oxygen had an increase in sinus tachycardia, Pao2, serum aspartate aminotransferase. There were 12 deaths in total, 9 in the oxygen group and 3 in the air group. 3 of the deaths occurred during treatment 1 was receiving oxygen and 2 were receiving air.

Does the study answer the question?

The paper does start to address the key clinical question; it highlights several effects giving oxygen has to patients. The paper shows there is a significant increase in the sinus tachycardia for those who received oxygen compared to those who received air. The paper also showed that the serum aspartate aminotransferase level is significantly higher in the oxygen group than the air group. The paper shows that giving oxygen does not reduce to number arrhythmias, nor does it affect the number of mortalities or give rise to an improvement in left ventricular function.

The paper suggests that giving oxygen may be harmful and does not appear to give a beneficial effect. It suggests that oxygen should not be given routinely but instead should be given to those with obvious hypoxia.

Effect due to factor in study?	Patients were also able to receive diamorphine, which could have affect results, however it is likely that the intervention of oxygen was most likely to have caused the results of the study.
Consistency of results with other studies?	No other comparable studies
Directly applicable to guideline population?	Correct intervention and population
Internal Validity	Patients changed to oxygen were included in result

Wilson AT;Channer KS;

Hypoxaemia and supplemental oxygen therapy in the first 24 hours after myocardial infarction: the role of pulse oximetry

Ref ID 1796 J R Coll Physicians Lond pgs: 657 to 661 1997

Study Type Randomised Controlled Trial **Funding** Unknown

Number of participants	22 in group 1 receiving continuous oxygen post MI at 4 litres per minute by face mask; 20 in group 2 receiving no supplemental oxygen except for central cyanosis or respiratory distress.
Inclusion/Exclusion Criteria	50 consecutive patients with acute MI admitted to the coronary care unit at the Royal Hallamshire Hospital participate within six hours of the onset of thrombolytic therapy. 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 inotrope support were excluded.
Patient Characteristics	There were 25 men and 17 women in the study. The two groups were comparable for the number of smokers (5 and 7 respectively), diabetics (2 and 2) and mean ages (64 and 65 years).
Recruitment	The subjects were consecutive patients with acute MI admitted to the coronary care unit at the Royal Hallamshire Hospital.
Setting	Royal Hallamshire Hospital, England
Interventions/ Test/ Factor being investigated	The incidence and degree of hypoxaemia in patients with acute MI was studied to assess the use of pulse oximetry and supplemental oxygen therapy in the first 24 hours after MI
Comparisons	A comparison is made between the use of continuous oxygen at 4 litres pre minute and no oxygen therapy. All subjects were monitored with pulse oximetry through the first 24 hours post MI.
Length of Study/ Follow-up	24 hours
Outcome measures studied	Oxygen saturation (SpO-2) and arrhythmias and ST segment changes were measured.
Results	Twenty of the 42 (48%) patients 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 were in group 2 ($p<0.05$) which received no supplemental oxygen and were clinically undetected in all but one case (pO-2 71%). There were no significant differences in the prescription of opiates between groups. There were no significant differences between groups in the incidence or type of arrhythmias (11 in each group) or ST segment changes (3 and 4 respectively). The postal survey revealed the following: 105 units (51%) did not use routine oxygen yet 81 (77%) of these had a pulse oximeter. Only 3% said they measured oxygen saturation in all patients although 14% said they measured if blood gases were poor. In 93 units (45%) oxygen therapy was routinely given and pulse oximetry was available in 76 (80%) of these. However, oxygen saturation was routinely measured in only 6% and measured in 8% when indicated by

	poor arterial blood gases.
Safety and adverse effects	None reported
Does the study answer the question?	This study demonstrates that hypoxaemia in the first 24 hours after an acute MI is a frequent and predictable occurrence and that this remains undetected by the medical and nursing staff unless a pulse oximeter is used.
Effect due to factor in study?	This study demonstrated no statistical correlation between hypoxaemic events and adverse cardiac events but the study was too small to assess this outcome effectively. Otherwise, the results of pulse oximetry appear to be accurate.
Consistency of results with other studies?	With regard to adverse cardiac events there is a lack of consistency.
Directly applicable to guideline population?	Yes
Internal Validity	No control arm and no allocation concealment

Question 9: In adults presenting with chest pain, what is the clinical and cost effectiveness of pain management (e.g. sublingual and buccal nitrates, diamorphine, morphine with anti-emetic) compared with active comparators?

Grading: 1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Hayes MJ;Fraser AR;Hampton JR;

Randomised trial comparing buprenorphine and diamorphine for chest pain in suspected myocardial infarction

Ref ID 3472 Br Med J pgs: 300 to 302 1979

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participants study 1: 10 patients, study 2: 43 patients, study 3: 118 patients

Inclusion/Exclusion Criteria inclusion: patients with chest pain due to suspected MI who required analgesia

Patient Characteristics study 3:
Buprenorphine group - male:female ratio = 5.6:1, mean age 55 ± 10 years, mean duration of chest pain 5.5 ± 7.3 hours, previous analgesia (morphine, diamorphine or pethidine) 54%, admission heart rate 78 ± 19 beats per min, systolic blood pressure 129 ± 28 mm Hg, diastolic blood pressure 82 ± 22 mm Hg, mean AST 136 ± 154 IU/l, mean SHBD 567 ± 352 IU/l, ECG changes - anterior infarction 44%, other sites of infarction 36%, no changes of infarction 20%

Diamorphine group - male:female ratio = 3.5:1, mean age 56 ± 10 years, mean duration of chest pain 7.9 ± 11.6 hours, previous analgesia (morphine, diamorphine or pethidine) 54%, admission heart rate 80 ± 23 beats per min, systolic blood pressure 127 ± 31 mm Hg, diastolic blood pressure 79 ± 24 mm Hg, mean AST 97 ± 68 IU/l, mean SHBD 544 ± 375 IU/l, ECG changes - anterior infarction 41%, other sites of infarction 34%, no changes of infarction 25%

Recruitment patients admitted to the CCU with chest pain due to suspected MI

Setting Secondary care, England

Interventions/ Test/ Factor being investigated intravenous buprenorphine, sublingual buprenorphine, diamorphine

Comparisons intravenous buprenorphine, sublingual buprenorphine, diamorphine

Length of Study/ Follow-up 48 hours

Outcome measures studied pain relief, need for further analgesia, systolic blood pressure, heart rate

Results The paper carried out 3 studies

Study 1
Haemodynamic studies were performed on an initial 10 patients with MI proved on ECG. All had received diamorphine previously but then required further analgesia for recurrent pain. The pulmonary artery pressure was recorded continuously before and after an intravenous injection of 0.3 mg buprenorphine, by means of a 3 F gauge polyethylene catheter inserted percutaneously via an antecubital vein. Cuff measurements of the systemic blood pressure were made at defined intervals. The ECG was monitored continuously and measurements of heart rate obtained from the ECG.

This study showed that intravenous buprenorphine had no significant effect on heart rate or systemic diastolic blood pressure. There was a sustained fall in systemic arterial systolic pressure of about 10 mmHg but this was not statistically significant.

Study 2

43 patients who required analgesia in the coronary care unit were given either injections of intravenous buprenorphine or sublingual tablets. 18 received a total of 20 tablets of sublingual buprenorphine 0.4 mg, and 25 received a total of 40 injections of intravenous buprenorphine 0.3 mg as and when they needed analgesia for chest pain. In this group only systemic blood pressure and heart rate were measured and the ECGs were continuously monitored. The degree of pain relief and more particularly the time of onset of pain relief were assessed subjectively by the medical and nursing staff.

In the intravenous buprenorphine group 9 patients had complete relief after 5 minutes, a further 21 patients had complete relief after 15 minutes, a further 3 patients had complete relief after 30 minutes and 6 further patients had complete relief after 45 minutes. 1 patient reported inadequate pain relief. In the sublingual buprenorphine group 2 patients had complete relief after 5 minutes, a further 2 patients had complete relief after 15 minutes, a further 12 patients had complete relief after 30 minutes and 3 further patients had complete relief after 45 minutes. 1 patient reported inadequate pain relief.

The study showed that sublingual buprenorphine had no significant effect on systolic blood pressure and heart rate and provided good pain relief to most patients. Intravenous buprenorphine gave faster pain relief.

Study 3
120 patients who were admitted to the CCU with chest pain due to suspected myocardial infarction and who required analgesia were randomly allocated in a double-blind fashion to receive either buprenorphine 0 3 mg intravenously or diamorphine 5 mg intravenously. There were no medical contraindications for inclusion in this trial. Patients were randomised in blocks of six, the trial ampoules being prepared and issued by the General Hospital pharmacy daily because of the instability of diamorphine when in solution. After entry into the trial records were kept of the time, dose, and frequency of subsequent analgesic administration. The time, degree, and duration of pain relief were monitored using an unmarked visual analogue scale, 3 which was scored by the patient. The scale was subsequently measured and pain relief expressed as a percentage of the original score. If the patients were asleep they were left undisturbed and considered to have complete pain relief. The incidence of nausea, vomiting, and other adverse reactions was also recorded.

In the buprenorphine group 27 (49%) patients did not require further analgesia after initial dose, 12 (22%) required analgesia within 6 hours after initial dose and 16 (29%) required analgesia in 6-48 hours after initial dose.
In the diamorphine group 23 (42%) patients did not require further analgesia after initial dose, 16 (29%) required analgesia within 6 hours after initial dose and 16 (29%) required analgesia in 6-48 hours after initial dose.

Safety and adverse effects

None reported

Does the study answer the question?

This study showed that sublingual buprenorphine had no significant effect on systolic blood pressure and heart rate and provided good pain relief to most patients. However the concluded that intravenous buprenorphine gave faster pain relief. The difference in the visual pain relief during the 6 hour trial was not statistically significant between the buprenorphine and diamorphine groups. The analgesic requirements for the two groups were not significantly different either. At five minutes the percentage pain relief in the buprenorphine group was significantly less than in the diamorphine group ($p<0.01$), but this difference progressively diminished so that both groups were similar at 15 minutes, there was no difference in the two groups at 6 hours.

Overall the study showed that there was no statistically significant difference in the requirement of subsequent analgesia or in the percentage pain relief.

Effect due to factor in study?

Yes

Consistency of results with other studies?

Consistent

Directly applicable to guideline population?	Patients had chest pain due to suspected MI and required analgesia
Internal Validity	No report of concealment methods

Hew E;Haq A;Strauss H;

A randomized controlled trial of nalbuphine vs morphine in the treatment of ischemic chest pain

Ref ID 3362 | Current Therapeutic Research - Clinical and Experimental | pgs: 394 to 402 | 1987

Study Type Randomised Controlled Trial **Funding** not reported

Number of participants	24 patients received nalbuphine, 29 received morphine
Inclusion/Exclusion Criteria	inclusion: moderately severe to severe pain unresponsive to sublingual nitroglycerin and a suspected diagnosis of MI or unstable angina. Exclusion: heart rate less than 50 beats per minute, systolic blood pressure less than 90 mmHg, cardiac shock, acute or chronic renal failure, valvular heart disease, signs of right or left ventricular failure, pulmonary oedema, patient is a or suspected of being a drug user
Patient Characteristics	In the nalbuphine group 3 were female, mean age was 60 years old. The mean pain was 5.5 ± 0.5, the mean systolic blood pressure was 134.5 ± 4.4 mmHg, diastolic blood pressure was 82.2 ± 2.8, the mean respiratory rate was 19.7 ± 0.6 breaths/min, the mean heart rate was 71.3 ± 3.9 beats/min. the concomitant of treatments were 7 patients had nitroglycerin infusion, 1 patient had antiarrhythmic, 1 patient had beta-blocker, 2 patients had calcium-channel blocker. In the morphine group 9 were women, mean age 62.2 years old. The mean pain was 6.3 ± 0.4, the mean systolic blood pressure was 142.6 ± 5.3 mmHg, diastolic blood pressure was 80.1 ± 2.6, the mean respiratory rate was 20.7 ± 0.7 breaths/min, the mean heart rate was 74.1 ± 3.2 beats/min. the concomitant of treatments were 7 patients had nitroglycerin infusion, 2 patients had antiarrhythmic, 0 patients had beta-blocker, 0 patients had calcium-channel blocker.
Recruitment	patients with ischemic chest pain admitted to 2 hospitals in Canada
Setting	Secondary care (2 hospitals), Canada
Interventions/ Test/ Factor being investigated	10 mg morphine or 20mg nalbuphine
Comparisons	10 mg morphine or 20mg nalbuphine
Length of Study/ Follow-up	2 hours
Outcome measures studied	pain relief
Results	Complete pain relief: At 5 minutes – 21% on morphine, 42% on nalbuphine At 15 minutes – 31% on morphine, 54% on nalbuphine At 30 minutes – 34% on morphine, 54% on nalbuphine At 60 minutes – 48% on morphine, 58% on nalbuphine At 120 minutes – 55% on morphine, 67% on nalbuphine The mean pain scores for nalbuphine group were consistently lower than for the morphine group. The difference in scores was greatest after 5 minutes (nalbuphine = 1.88, morphine = 3.48), however the difference was not significant (F = 3.07, P = 0.08). The mean pain relief scores and the sum of the pain relief scores consistently favoured nalbuphine with the greatest difference at 5 minutes but were not significantly different (F = 2.83, P = 0.10). Neither group had a significant change in either systolic or diastolic blood pressure (F = 1.45, P >0.21). The mean heart rate did not change significantly for either group (F = 1.82, P = 0.11).

Safety and adverse effects	There were 81 unpleasant or unusual side effects reported. In the morphine group 62% reported at least 1 side effect, compared to 75% in the nalbuphine group. The mean number of complaints in the morphine group was 1.5 and in the nalbuphine group was 1.6. there was no statistically significant difference in the incidence of any complaint, including drowsiness and dry mouth which was observed. Adverse events: (number of patients) Drowsiness – 4 on morphine, 9 on nalbuphine Dizziness – 8 on morphine, 4 on nalbuphine Nausea – 5 on morphine, 6 on nalbuphine Dry mouth – 6 on morphine, 1 on nalbuphine Headache – 6 on morphine, 1 on nalbuphine Diaphoresis – 2 on morphine, 2 on nalbuphine Nervousness – 2 on morphine, 1 on nalbuphine Hypotension – 1 on morphine, 2 on nalbuphine Burning at injection site – 2 on morphine, 1 on nalbuphine Vomiting – 1 on morphine, 1 on nalbuphine Euphoria – 0 on morphine, 2 on nalbuphine Depressed – 1 on morphine, 1 on nalbuphine Urticaria – 1 on morphine, 1 on nalbuphine Bradycardia – 0 on morphine, 2 on nalbuphine Other – 4 on morphine, 4 on nalbuphine
Does the study answer the question?	None of the differences were statistically significant, the trend favoured nalbuphine. The greatest difference was seen at 5 minutes. The author states the ideal analgesic should provide prompt relief from pain and anxiety without adversely affecting hemodynamic or respiratory function, this study suggests that nalbuphine fulfils this and should be considered as an alternative to morphine.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Patients had moderately severe to severe pain due to suspected MI or unstable angina and unresponsive to sublingual nitroglycerin

Internal Validity

Jamidar HA CSAA;

Nalbuphine versus diamorphine early in the course of suspected myocardial infarction

Ref ID 4222 Eur Heart J pgs: 597 to 602 1987

Study Type Randomised Controlled Trial **Funding** Dr J Beets and Dupont supplied the Nalbuphine

Number of participants 176 in total; 87 received Nalbuphine, 89 received Diamorphine

Inclusion/Exclusion Criteria Inclusion: patients with moderate or severe pain of suspected AMI who have not received previous analgesia

Patient Characteristics

In the Nalbuphine group:
The mean age was 60.5 years, 41 % were women. 43% smoked, 30% were ex-smokers. 2% had diabetes, 21% had previous hypertension. 13% had previous severe angina, 29% had previous moderate angina, 20% had previous mild angina. 8% had more than 2 previous MIs,14% had 2 previous MIs, 29% had 1 previous MI, 49% had had no previous MI.
In the Diamorphine group:
The mean age was 62.2 years, 34 % were women. 35% smoked, 25% were ex-smokers. 9% had diabetes, 25% had previous hypertension. 18% had previous severe angina, 10% had previous moderate angina, 29% had previous mild angina. 8% had more than 2 previous MIs, 6% had 2 previous MIs, 26% had 1 previous MI, 60% had had no previous MI. NOTE one person died before a full history could be taken (smoking and previous MI data missing)

Recruitment	Patients admitted with moderate or severe chest pain of a suspected acute MI
Setting	Royal Victoria Hospital, Belfast, Northern Ireland
Interventions/ Test/ Factor being investigated	≤ 20 mg nalbuphine or ≤ 5 mg diamorphine intravenously with 10 mg metoclopramide
Comparisons	between ≤ 20 mg nalbuphine or ≤ 5 mg diamorphine intravenously with 10 mg metoclopramide
Length of Study/ Follow-up	2 hours
Outcome measures studied	pain relief at set times
Results	The differences in baseline characteristics were not statistically significant (P=>0.05). Pain was recorded at 10 minutes, 30 minutes, 60 minutes and 120 minutes. At 10 minutes 77% of the nalbuphine group and 68% of the diamorphine group had satisfactory pain relief; 44% of the nalbuphine group and 39% of the diamorphine group had complete pain relief. Satisfactory pain relief (grade 0 or 1 pain) was similar for both groups during each time assessment. So there was no significant difference between the two groups for total pain relief. The average pain score at each time interval was similar for both groups. The number of doses of each drug given over the 120 minutes were comparable (n 114 + SD 0-4, d 1-28±SD 0-5). Of those withdrawn from the trial (two doses of the test drug without satisfactory pain relief) 6 patients had received diamorphine and 11 nalbuphine. This difference was not statistically significant. Pain recurred after satisfactory pain relief in 2 patients who had received diamorphine and in 5 who had received nalbuphine. There were no significant differences for heart rate, systolic and diastolic blood pressures between the two groups throughout the 120 minute observation period. Only one patient in the nalbuphine group and 3 in the diamorphine group required atropine and only 2 in the nalbuphine group and 2 in the diamorphine group received beta-blockers intravenously during the trial period. The numbers with cardiac failure initially and at 120 minutes showed no significant differences for the two groups. There were no significant differences between the two groups for mean peak CK, AST and LDH. Seven patients received streptokinase and their enzyme levels were excluded from analysis.
Safety and adverse effects	Dizziness, nausea and vomiting was infrequent but occurred in both groups. In the Nalbuphine group: 16% had dizziness, 14% had nausea and vomiting, 10% had other side effects, 1% died (1 patient). In the Diamorphine group: 17% had dizziness, 16% had nausea and vomiting, 7% had other side effects, 8% died (7 patients).
Does the study answer the question?	The results for pain relief for the nalbuphine group and the diamorphine group were similar with no statistically significant difference. The study showed that Nalbuphine is safe and is as effective as diamorphine, with the speed of pain relief and reoccurrence of pain being similar for both groups. Nalbuphine had no adverse events on infarct size nor deleterious heamodynamic side effects.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	The population was patients with moderate or severe chest pain of suspected MI
Internal Validity	patients were withdrawn for further pain relief

Grading: 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

Everts B;Karlson BW;Herlitz J;Hedner T;

Morphine use and pharmacokinetics in patients with chest pain due to suspected or definite acute myocardial infarction

Ref ID 2966 European Journal of Pain pgs: 115 to 125 1998

Study Type Cohort

Funding Swedish Medical Research Council and Medical Faculty, University of Goteborg and Bohuslandstinget

Number of participants	2988
Inclusion/Exclusion Criteria	Patients had chest pain or symptoms suggestive of AMI, Patients had to have a confirmed or suspected AMI or myocardial ischaemia and were hospitalised and stayed for more than 1 day.
Patient Characteristics	The mean age was 69.3 ± 0.23 years (range 18-101 years), 40.2% were women. 921 patients developed an MI, 357 had a possible MI, 419 had myocardial ischaemia, 1291 had possible myocardial ischaemia.
Recruitment	patients with chest pain or symptoms suggestive of AMI admitted to CCU in Sweden
Setting	Secondary care, Sweden
Interventions/ Test/ Factor being investigated	10mg morphine hydrochloride intravenously over one minute
Comparisons	pain relief after being given 10mg morphine hydrochloride intravenously over one minute
Length of Study/ Follow-up	3 days
Outcome measures studied	pain, morphine requirement
Results	The average pain intensity was 6.6±0.6 on the Numerical Rating Scale (NRS) before the morphine injection. There was rapid pain relief (6.9±11% after 20 minutes) after the morphine injection. After 20 minutes, a nadir was obtained where NRS ranged between 0 and 3 units. 7 out of 10 patients reported being pain free at one or more measurement point during the first 3 hours following morphine injection. However 3 patients needed supplementary analgesic treatment with meperidine and 1 patient was given metoprolol. 5 patients required diuretics but no patients were given thrombolysis or nitrates. The patient characteristics which were associated with higher morphine requirements were: gender (female) P = <0.0455, history of angina pectoris P = <0.0001, previous CHF P = <0.0001, initial degree of suspicion of AMI P = <0.0001, presence of ST elevation on entry ECG P = <0.0001, presence of ST depression on entry ECG P = <0.0004, Q wave on entry ECG P = <0.0015. The mean systolic/diastolic blood pressure at arrival at the CCU was 143±9.9/91±4.6mm Hg. After intravenous morphine administration there was a significant reduction in the diastolic blood pressure but a similar but non-significant trend in systolic blood pressure. Heart rate was 86±5.1 beats/minute on admission and tended to be reduced during the observation period after intravenous morphine. Respiratory frequency remained unchanged in all patients.

Safety and adverse effects	None reported
Does the study answer the question?	The study showed that there was rapid pain relief 20 minutes after the morphine injection with 7 out of 10 patients reporting complete pain relief at 1 or more measurement points during the 3 hours observation. There were certain patient characteristics associated with higher morphine requirement: gender (female), history of angina pectoris, previous CHF, initial degree of suspicion of AMI, presence of ST elevation on entry ECG, presence of ST depression on entry ECG, Q wave on entry ECG. The authors concluded that when intravenous morphine is given it has full effect after 20 minutes. The authors also concluded that the need for morphine administration in patients with confirmed or suspected AMI differed among subgroups, in particular those with a strongly suspected AMI required higher doses of morphine.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Pains had chest pain or symptoms suggestive of AMI
Internal Validity	Well covered

Grading: 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

Bruns BM;Dieckmann R;Shagoury C;Dingerson A;Swartzell C;

Safety of pre-hospital therapy with morphine sulfate

Ref ID 844 The American journal of emergency medicine, pgs: to 1992

Study Type	Cohort	**Funding**	Not reported

Number of participants	84 patients
Inclusion/Exclusion Criteria	patients who received morphine sulphate in a prehospital setting
Patient Characteristics	the mean age was 68 years, 40 patients were male 39 were female and 5 patients did not have their sex documented
Recruitment	patients who the paramedics assessed as having ischaemic chest pain or pulmonary edema, which was agreed by a doctor at the base hospital were given intravenous morphine sulphate in 2mg increments along with other therapies according to treatment protocol
Setting	Paramedics, San Francisco, USA
Interventions/ Test/ Factor being investigated	safety of prehospital morphine sulphate use in an urban emergency medical system
Comparisons	The diagnosis by a paramedic and an emergency department doctor
Length of Study/ Follow-up	6 months
Outcome measures studied	1: Accuracy of paramedics diagnosis 2: Appropriate use of morphine sulphate 3: Side effects of appropriate and inappropriate use of morphine sulphate
Results	All patients who received morphine sulphate were included in the study. Patients who the paramedics assessed as having ischaemic chest pain or pulmonary oedema, paramedics phone through to the base hospital, where a mobile intensive care nurse and/or a doctor concurred the diagnosis. The paramedic then gave the patient intravenous morphine sulphate in 2mg increments along with other therapies according to treatment protocols. 3 private and 1 public paramedic provider agencies were included which took patients to 10 emergency departments. A total of 84 patients were given morphine sulphate. The paramedics' diagnosis was considered accurate in 77% of cases (65 out of 84) Paramedics diagnosed 40 patients with ischaemic chest pain, when patients were diagnosed in the emergency department - 30 had ischaemic chest pain, 4 had ischaemic chest pain and pulmonary oedema, 1 had a pulmonary oedema and 5 had another diagnosis. Paramedics diagnosed 31 patients with pulmonary oedema, when patients were diagnosed in the emergency department - 23 had pulmonary oedema, 4 had ischaemic chest pain and pulmonary oedema and 4 had another diagnosis. Paramedics diagnosed 13 patients with ischaemic chest pain and pulmonary oedema, when patients were diagnosed in the emergency department – 3 had ischaemic chest pain and pulmonary oedema, 9 had a pulmonary oedema and 1 had another diagnosis. (Other diagnosis included atypical chest pain, atypical chest pain and chronic heart failure, acute bronchospasm and pneumonia) In the 9 cases where the paramedics miss diagnosed ischaemic chest pain or pulmonary oedema 5 patients were diagnosed as ischaemic chest pain but missed a

diagnosis of pulmonary oedema and 4 patients were diagnosed as pulmonary oedema but missed a diagnosis of ischaemic chest pain

The appropriateness of morphine sulphate administration was assessed the 9 diagnosis which missed either ischaemic chest pain or pulmonary oedema were still treated correctly with morphine sulphate. The appropriateness use of morphine sulphate was 88%.

The overall side effects rate was 6%, 3 patients had respiratory depression and 2 had hypotension. 2 of the patients who had respiratory depression were correctly diagnosed with pulmonary oedema, which can lead to respiratory depression; therefore it is unclear if the morphine sulphate caused the side effect. The other patient who had respiratory depression was diagnosed wrongly by the paramedic and had an emergency department diagnosis of pneumonia, therefore it is likely the morphine sulphate caused the respiratory depression. The 2 patients who had hypotension were both correctly diagnosed by the paramedic and it is uncertain if the morphine sulphate caused the hypotension.This shows that only 1 patient suffered an adverse event due to inappropriate use of morphine sulphate, the complication rate for this was 10%.

Safety and adverse effects 3 cases of respiratory depression, 2 cases of hypotension

Does the study answer the question? The study showed that the paramedics' diagnosis was considered accurate in 77% of cases (65 out of 84). The appropriateness use of morphine sulphate was 88, and the overall side effects rate was 6%, the complication rate for inappropriate use of morphine sulphate was 10%.
The authors concluded that paramedics functioning with a system of base hospital direction can safely given morphine sulphate, with the inappropriate administration of morphine sulphate and complication rate being low.

Effect due to factor in study? Yes

Consistency of results with other studies? Consistent

Directly applicable to guideline population? This was a mixed population including some patients with pulmonary oedema

Internal Validity Well covered

Herlitz J;Richterova A;Bondestam E;Hjalmarson A;Holmberg S;Hovgren C;

Chest pain in acute myocardial infarction: a descriptive study according to subjective assessment and morphine requirement

Ref ID 1168 Clin Cardiol pgs: 423 to 428 1986

Study Type Cohort

Funding Swedish Medical Research Council, the Swedish National Association against Heart and Chest Disease, the Goteborg Medical Society, AB Hassle subsidiary of Astra Pharmaceuticals

Number of participants 653 patients

Inclusion/Exclusion Criteria Patients admitted to the CCU with suspected acute MI admitted between 1st May 1983 and 31st May 1984.

Patient Characteristics The age range was 33-92 years with the median being 70 years. 38.3% were women, 47.1% were aged over 70 years, 39.2% had had a previous infarction, 59.4% had angina pectoris, 36.2% had hypertension, 21.2% had congestive heart failure. 24.5% had furosemide before admission, 38.6% had beta blockers before admission,

	10.2% had Ca antagonists before admission.
Recruitment	Patients who were admitted to the CCU with suspected AMI were evaluated for inclusion.
Setting	Patients home and hospital
Interventions/ Test/ Factor being investigated	Patients pain and analgesic requirement
Comparisons	Pain at home and in hospital
Length of Study/ Follow-up	3 days
Outcome measures studied	visual pain score, narcotic analgesic requirement
Results	The study recorded patient's pain by a visual scale of 0-10 as reported by the patients (0 being no pain and 10 being worst pain imaginable). The pain scores recorded were the maximum pain at home (recorded once admitted to CCU) and every two hours for 6 hours after admission to CCU. If patients were asleep at the time of recording a score of 0 was reported. Patients were given morphine intravenously for severe pain and nitroglycerine sublingually for less severe pain interpreted as angina pectoris; where patients were given analgesics the pain score was increase by 2. MI was confirmed in 45% of patients and possible MI in 11.9%. Mean maximum score at home Patients with defined MI: 7.5 Patients with possible MI: 6.6 Patients with ischemia: 6.9 Patients with no ischemia: 5.9 Mean pain score during the first 6 hours (h) after arrival at CCU Patients with defined MI: on arrival 2.3, after 2h 1.4, after 4h 1.1, after 6h 0.9 Patients with possible MI: on arrival 1.2, after 2h 0.7, after 4h 0.6, after 6h 0.4 Patients with ischemia: on arrival 1.4, after 2h 0.8, after 4h 0.6, after 6h 0.7 Patients with no ischemia: on arrival 1.6, after 2h 0.9, after 4h 0.6, after 6h 0.7
Safety and adverse effects	None reported
Does the study answer the question?	The study showed that for pain at home there were small differences in the mean pain scores between the groups of patients. For those with an MI the maximum pain score was 7.5±0.2 where as for those without an MI the maximum pain score was 6.6±0.2 (P<0.001). The study showed that for pain in the CCU the maximum mean score had reduced to 1.8 for all patients compared to 7.0 maximum mean score for all patients at home. The study also showed that 98% of patients had chest pain at home, but only 51% had pain on arrival at the CCU. Figure 1 (see narrative for question 17; figure 1: Herlitz et al, 1986) shows the course of pain after arrival at the CCU. The authors commented that narcotic analgesics were given to 10% of patients after the end of recording pain scores and during the 3 day study 27.4% of patients were given nitroglycerine sublingually. The authors of the study concluded that patients generally had worse pain at home than in the CCU. The mean pain score values show a trend of rapid decline in pain after arrival in the CCU, although there was variability in the intensity and duration of chest pain. The authors commented that there was a low difference in the pain scores between those having an MI and those who were not.
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other studies compare at home to hospital pain management

Directly applicable to guideline population?	Patients had suspected MI
Internal Validity	Well covered

Scott ME;Orr R;

Effects of diamorphine, methadone, morphine, and pentazocine in patients with suspected acute myocardial infarction

Ref ID 10272 Lancet pgs: 1065 to 1067 1969

Study Type	Cohort	**Funding**	Not reported

Number of participants	118 patients; 30 in diamorphine group, 31 in methadone group, 29 in morphine group and 25 in pentazocine group
Inclusion/Exclusion Criteria	Included: patients initially assessed to have moderate or severe pain due to suspected acute MI. Excluded: patients who had cardiac shock, cardiac failure, severe nausea, pronounced bradycardia, who have received a potent analgesic or an anti-emetic in previous 4 hours
Patient Characteristics	25% were women, the age range was 30-79 years old, with 79% of patients aged between 50-69 years old. 36% of the patients had acute myocardial ischaemia rather than definite infarction. There was no significant difference in the sex-distribution, age, previous history of MI among the 4 treatment groups.
Recruitment	Patients who were admitted to the cardiac department, Royal Victoria Hospital, Belfast, Northern Ireland, who were initially assessed to have moderate or severe pain due to suspected acute MI
Setting	Secondary care, Northern Ireland
Interventions/ Test/ Factor being investigated	pain relief from analgesics
Comparisons	5 mg diamorphine or 10 mg methadone, 10 mg morphine, 30 mg pentazocine
Length of Study/ Follow-up	2 hours
Outcome measures studied	Pain relief at 10, 30, 60 and 120 minutes
Results	For some degree of pain relief: At 10 minutes - 90% of patients on diamorphine, 90% on methadone, 93% on morphine, 85% on pentazocine. At 30 minutes - 87% of patients on diamorphine, 94% on methadone, 93% on morphine, 96% on pentazocine. At 60 minutes - 87% of patients on diamorphine, 89% on methadone, 90% on morphine, 82% on pentazocine. At 120 minutes - 90% of patients on diamorphine, 86% on methadone, 86% on morphine, 81% on pentazocine. For complete of pain relief: At 10 minutes - 47% of patients on diamorphine,32% on methadone, 17% on morphine, 19% on pentazocine. At 30 minutes - 43% of patients on diamorphine, 39% on methadone, 38% on morphine, 36% on pentazocine. At 60 minutes - 43% of patients on diamorphine, 50% on methadone, 45% on morphine, 27% on pentazocine. At 120 minutes - 34% of patients on diamorphine, 50% on methadone, 52% on morphine, 33% on pentazocine.
Safety and adverse effects	Nausea and vomiting was similar across all groups (not statistically different). Morphine had an unexpected low number of patients with emetic sequelae

Does the study answer the question?	The results show equal pain relief by all 4 drugs. Diamorphine gave complete pain relief in 10 minutes to a higher number of patients, it was significantly higher compare to morphine and petazocine but not significantly higher compared to methadone. At 30 minutes the pain relief is similar across all 4 drugs, however at 60 minutes patients on pentazocine had lower pain relief than the other 3 groups The authors suggest that diamorphine is the drug of choice.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Patients had moderate or severe pain due to suspected acute MI
Internal Validity	Well covered

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

Grading: 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

Barbash IM;Freimark D;Gottlieb S;Hod H;Hasin Y;Battler A;Crystal E;Matetzky S;Boyko V;Mandelzweig L;Behar S;Leor J;

Outcome of myocardial infarction in patients treated with aspirin is enhanced by pre-hospital administration

Ref ID 10246 Cardiology pgs: 141 to 147 2002

Study Type Cohort **Funding** Not reported

Number of participants 922 patients were included in total; 338 received aspirin before admission to hospital, 584 received aspirin after admission to hospital

Inclusion/Exclusion Criteria Included: Patients who were admitted to hospital with acute myocardial infarction, who received aspirin treatment either before or after admission or hospital.
Excluded: Those who had cardiogenic shock were excluded.

Patient Characteristics

Aspirin before admission to hospital

Mean age	60.9 ± 13
Patients	
<59 years	174 (51%)
60-69 years	75 (22%)
>70 years	92 (27%)
Women	57 (17%)
Diabetes	92 (27%)
Hypertension	136 (40%)
Hyperlipidaemia	159 (47%)
Current smokers	158 (47%)
Prior MI	82 (24%)
Prior angina	98 (29%)
Prior heart failure	13 (4%)
Prior PTCA	49 (15%)
Prior CABG	14 (4%)
PVD	24 (7%)
History of stroke	21 (6%)
Gastrointestinal disorder	31 (9%)
Typical chest pain	318 (94%)
MICU transport	230 (68%)
Anterior MI	159 (47%)
Spontaneous reperfusion	20 (5.9%)

Aspirin after admission to hospital

Mean age	64.5 ± 14
Patients	
<59 years	224 (41%)
60-69 years	114 (20%)
>70 years	222 (39%)
Women	157 (27%)
Diabetes	184 (32%)
Hypertension	248 (43%)
Hyperlipidaemia	241 (42%)
Current smokers	222 (39%)
Prior MI	114 (20%)
Prior angina	154 (27%)
Prior heart failure	33 (6%)
Prior PTCA	51 (9%)
Prior CABG	11 (2%)
PVD	48 (8%)
History of stroke	51 (9%)
Gastrointestinal	

	disorder 74 (13%) Typical chest pain 469 (80%) MICU transport 90 (15%) Anterior MI 260 (45%) Spontaneous reperfusion 20 (3.4%)
Recruitment	Patients who were admitted to 26 coronary care units and 82 medicine wards in 26 hospitals
Setting	Hospital, ambulance & community in Israel
Interventions/ Test/ Factor being investigated	Aspirin administration - dose of >200mg chewable aspirin before or after admission to hospital
Comparisons	Aspirin being given before or after admission to hospital
Length of Study/ Follow-up	Follow up at 7 and 30 days
Outcome measures studied	Mortality, in-hospital complications, in-hospital treatments
Results	Aspirin given: before hospital after hospital P value All cause Mortality 7 days 8 (2.4%) 42 (7.3%) 0.002 30 days 16 (4.9%) 64 (11.1%) 0.001 Re-hospitalisation Non-cardio 5 (13%) 23 (22%) 0.22 Cardiovascular 59 (19%) 134 (27%) 0.02 In-hospital complications Asystole 6 (2%) 39 (7%) < 0.001 Resuscitation 12 (4%) 55 (9%) < 0.001 Ventilation 17 (5%) 66 (11%) 0.001 There was no significant difference in the following in-hospital complications recurrent MI, pulmonary oedema, sustained VT, primary VF, free wall rupture, ventricular septal defect, significant MR and cardiogenic shock In-hospital medications Ticlopidine / clopidogrel 84 (25%) 75 (13%) < 0.001 IIb/IIIa antagonists 97 (29%) 120 (21%) 0.005 Heparin 301 (90%) 466 (80%) < 0.001 Primary reperfusion 219 (65%) 299 (51%) < 0.001 There was no significant difference in in-hospital management in the following drug therapies: aspirin, vasopressors, β-blockers, calcium blockers, nitrates, diuretics, ACE inhibitors, angiotensin-II antagonist, lipid lowering drugs and digitalis In-hospital procedures Coronary angiography 195 (58%) 252 (44%) < 0.001 PTCA 136 (41%) 155 (27%) < 0.001 There was no significant difference in in-hospital management in the following procedures: CABG, intra-aortic balloon pump, pulmonary artery catheter

	Patients, n(%)					
	Primary reperfusion (n=518)			no primary reperfusion (n=404)		
	Early	Late	p value	Early	Late	p value
Age, years	59±12	60±12	0.1	65±13	69±14	0.007
Women	30(14%)	64(21%)	0.02	27(23%)	93(33%)	0.05
Prior MI	54(25%)	53(18%)	0.05	28(23%)	61(22%)	0.69

Prior angina	59(27%)	73(24%)	0.53	39(33%)	81(29%)	0.41
Prior heart failure	5(2%)	8(3%)	0.77	8(7%)	25(9%)	0.47
Prior PTCA	36(16%)	35(12%)	0.13	13(11%)	16(6%)	0.07
Prior CABG	7(3%)	6 (2%)	0.39	7(6%)	5(2%)	0.03
Hypertension	86(39%)	108(36%)	0.50	50(42%)	140(50%)	0.16
Diabetes	60(27%)	89(30%)	0.54	32(27%)	95(34%)	0.17
Hypertension	109(50%)	143(48%)	0.64	50(42%)	98(35%)	0.16
Current smokers	111(51%)	129(44%)	0.13	47(40%)	93(33%)	0.19
Anterior MI	106(48%)	138(46%)	0.31	53(46%)	122(44%)	0.70
Thrombolysis	178(81%)	251(84%)	0.43	0(0%)	0(0%)	
Primary PTCA	43(20%)	50(17%)	0.39	0(0%)	0(0%)	
30-day cardiovascular re-hospitalisation	39(19%)	71(26%)	0.07	20(20%)	63(27%)	0.15
Mortality – 7 D	3(1.4%)	17(5.8%)	0.01	5(4.4%)	25(8.9%)	0.13
Mortality 30 D	7(3.3%)	20(6.8%)	0.08	9(8.0%)	44(15.7%)	0.04

Safety and adverse effects

The paper does not state any adverse events caused by the aspirin administration in patients with a MI

Does the study answer the question?

This study addresses the key clinical question of the effect of aspirin administration, however this is on patients who have an acute MI not those with undifferentiated chest pain. The study suggests that giving aspirin early results in lower mortality rates at 7 and 30 days and a lower rate of re-hospitalisation. This benefit was also seen in a sub-group analysis of patients who underwent reperfusion. The study showed that those who received aspirin before admission to hospital were more likely to be treated with heparin, ticlopidine / clopidogrel, IIb/IIIa antagonists. The paper states that the theoretical basis of early aspirin administration is due to the anti-platelet properties and its ability to aid reperfusion.

Effect due to factor in study?

Yes

Consistency of results with other studies?

Limited studies in this area, results appear consistent

Directly applicable to guideline population?

Population have a confirmed diagnosis of MI, intervention correct

Internal Validity

Well covered

Question 11: What is the utility and cost effectiveness of cardiac biomarkers in evaluation of individuals with acute chest pain of suspected cardiac origin?

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Balk EM;Ioannidis JP;Salem D;Chew PW;Lau J;

Accuracy of biomarkers to diagnose acute cardiac ischemia in the emergency department: a meta-analysis

Ref ID 215 Ann Emerg Med pgs: 478 to 494 2001

Study Type Systematic Review **Funding** Agency for Healthcare Research and Quality

Number of participants 73 diagnostic studies searched from 1966 to December 1998

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

The meta-analysis evaluated the accuracy of biomarkers to diagnose acute cardiac ischemia in the emergency department. The analysis searched for papers examining the diagnostic performance of troponin I, troponin T, creatine kinase, CK-MB, myoglobin and CK-MB with myoglobin from 1966 to December 1998. The analysis considered 73 papers which considered the diagnosis of AMI. Where possible the authors only analyse papers which considered patients in emergency departments and the review took study quality into account when analysing the results. The study did not report the timing of the tests.

The analysis identified 7 studies which evaluated the diagnostic performance of single troponin I, the review reported the timing of the tests for two studies, one was at 2 hours from symptom onset and one was at 7 hours from onset of symptoms, but not for the other 5 studies. The prevalence of AMI ranged from 6%-39% in the studies with a total of 1149 patients included in the studies. The sensitivity ranged from 4% to 100% and the specificity ranged from 89% to 98% but 3 papers did not provide data for the specificity. The over all sensitivity was 39% and the specificity was 93%. For serial troponin I testing 2 studies were identified which had 6% and 9% prevalence of AMI and included 1393 patients. The review did not report the timing of the serial troponin I tests. The studies showed a sensitivity of 95% and specificity of 90% (sensitivity range 90%-100% and specificity range 83%-96%).

The analysis identified 8 studies which evaluated the diagnostic performance of single troponin T. The tests were conducted on admission to the emergency

department. The prevalence of AMI ranged from 6%-78% in the studies with a total of 1348 patients included in the studies. The sensitivity ranged from 15% to 53% and the specificity ranged from 89% to 98%. The over all sensitivity was 39% and the specificity was 93%. For serial troponin T testing 4 studies were identified which had 5% to 78% prevalence of AMI and included 904 patients. The review did not report the timing of the serial troponin T tests. The studies showed a sensitivity of 93% and specificity of 85% (sensitivity range 65%-100% and specificity range 86%-93%).

The analysis identified 12 studies which evaluated the diagnostic performance of single CK. The tests were conducted on admission to the emergency department. The prevalence of AMI ranged from 7%-41% in the studies with a total of 3195 patients included in the studies. The sensitivity ranged from 7% to 55% and the specificity ranged from 65% to 96%. The over all sensitivity was 37% and the specificity was 87%. For serial CK testing 2 studies were identified which had 26% and 43% prevalence of AMI and included 786 patients. The review did not report the timing of the serial CK tests. The studies showed a sensitivity of 83% and specificity of 76% (sensitivity range 69%-99% and specificity range 68%-84%).

The analysis identified 19 studies which evaluated the diagnostic performance of single CK-MB. The tests were conducted on admission to the emergency department. The prevalence of AMI ranged from 6%-42% in the studies with a total of 6425 patients included in the studies. The sensitivity ranged from 14% to 100% and the specificity ranged from 86% to 100%. The over all sensitivity was 42% and the specificity was 97%. For serial CK-MB testing 14 studies were identified which had 1% to 43% prevalence of AMI and included 11625 patients. The review did not report the timing of the serial CK-MB tests. The studies showed a sensitivity of 79% and specificity of 96% (sensitivity range 41%-100% and specificity range 92%-100%).

The analysis identified 18 studies which evaluated the diagnostic performance of single myoglobin. The tests were conducted on admission to the emergency department. The prevalence of AMI ranged from 6%-62% in the studies with a total of 4172 patients included in the studies. The sensitivity ranged from 21% to 100% and the specificity ranged from 61% to 100%. The over all sensitivity was 49% and the specificity was 91%. For serial myoglobin testing 14 studies were identified which had 11% to 37% prevalence of AMI and included 1277 patients. The review did not report the timing of the serial myoglobin tests. The studies showed a sensitivity of 89% and specificity of 87% (sensitivity range 57%-100% and specificity range 72%-100%).

The analysis identified 3 studies which evaluated the diagnostic performance of single CK-MB and myoglobin. Two of the studies included conducted the tests at presentation and one was 2 hours from presentation. The prevalence of AMI ranged from 9%-28% in the studies with a total of 2283 patients included in the studies. The sensitivity ranged from 62% to 100% and the specificity ranged from 72% to 80%. The over all sensitivity was 83% and the specificity was 82%. For serial CK-MB and myoglobin testing 2 studies were identified which had 11% and 20% prevalence of AMI and included 291 patients. The review did not report the timing of the serial CK-MB and myoglobin tests. The studies showed a sensitivity of 100% and specificity of 83% (specificity range 75%-91%).

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Ebell MH;Flewelling D;Flynn CA;

A systematic review of troponin T and I for diagnosing acute myocardial infarction

Ref ID 234 J Fam Pract pgs: 550 to 556 2000

Study Type	Systematic Review	**Funding**	American Academy of Family Physicians and its members

Number of participants	19 diagnostic studies search until December 1999
Inclusion/Exclusion Criteria	
Patient Characteristics	
Recruitment	
Setting	
Interventions/ Test/ Factor being investigated	
Comparisons	
Length of Study/ Follow-up	
Outcome measures studied	
Results	
Safety and adverse effects	
Does the study answer the question?	The systematic review evaluated troponin T and I for diagnosing AMI. The review searched for papers examining the diagnostic performance of troponin T and troponin I until December 1999. The review considered 19 papers which considered the diagnosis of AMI in patients with acute chest pain, presenting to an emergency department, that included the sensitivity or specificity for at least one biomarker at a set time. The study identified 6 studies which evaluated the diagnostic value of troponin I in diagnosing AMI. The review did not report the prevalence of AMI in the test population but it did report a meta-analysis of the sensitivity and specificity of troponin I at 1, 2, 3, 4, 5 and 6 hours from onset of pain. The highest sensitivity occurred at 6 hours from onset of pain and was 90% and had a specificity of 95%. The review identified 14 studies which evaluated the diagnostic value of troponin T in diagnosing AMI. Again the review did not report the prevalence of AMI in the test population but did report sensitivity and specificity for troponin T > 0.1 and for troponin T >0.2 at 1, 2, 3, 4, 6, 8 and 10 hours after onset of pain. The highest sensitivity for troponin T > 0.1 occurred at 10 hours from onset of pain and was 93% and had a specificity of 80%, but had the highest specificity at 1 and 2 hours from onset which had a specificity of 87% but sensitivity of 47% and 53% respectively. The highest sensitivity for troponin T > 0.2 occurred at 8 and 10 hours from onset of pain and was 96% and had a specificity of 81% and 80% respectively, but had the highest specificity at 1 and 2 hours from onset which had a specificity of 87% but sensitivity of 14% and 33% respectively.
Effect due to factor in study?	
Consistency of results with other studies?	
Directly applicable to guideline population?	
Internal Validity	

Grading: 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

Guo X;Feng J;Guo H;

The predictive value of the bedside troponin T test for patients with acute chest pain

Ref ID 1321 Experimental and Clinical Cardiology pgs: 298 to 301 2006

Study Type Diagnostic

Funding Science Research Fund of Guangzhou Red Cross Hospital

Number of participants	502 patients. Patients were included if they had chest pain of suspected AMI, patients were admitted to the cardiac department or CCU. 89.1% had AMI (86.9% had TnT+ and 2.2% had TnT-)
Inclusion/Exclusion Criteria	
Patient Characteristics	Diagnosing AMI
Recruitment	
Setting	
Interventions/ Test/ Factor being investigated	Troponin T at admission and 6 and 12 hours after admission
Comparisons	No comparison
Length of Study/ Follow-up	
Outcome measures studied	
Results	See results in guideline.
Safety and adverse effects	
Does the study answer the question?	
Effect due to factor in study?	
Consistency of results with other studies?	
Directly applicable to guideline population?	
Internal Validity	

Kost GJ;Kirk JD;Omand K;

A strategy for the use of cardiac injury markers (troponin I and T, creatine kinase-MB mass and isoforms, and myoglobin) in the diagnosis of acute myocardial infarction

Ref ID 293 Arch Pathol Lab Med pgs: 245 to 251 1998

Study Type Diagnostic

Funding Equipment and reagents were provided by vendors (names not reported)

Number of participants	97 patients Patients were included if they had acute chest pain which was possible AMI, presenting to the emergency department 28% had AMI
Inclusion/Exclusion Criteria	
Patient Characteristics	Diagnosing AMI
Recruitment	
Setting	
Interventions/ Test/ Factor being investigated	Troponin T, troponin I, CK-MB and myoglobin at presentation and 3, 6 and 12 hours after admission
Comparisons	Biomarkers were compared to each other
Length of Study/ Follow-up	
Outcome measures studied	
Results	See results in guideline.
Safety and adverse effects	
Does the study answer the question?	
Effect due to factor in study?	
Consistency of results with other studies?	
Directly applicable to guideline population?	
Internal Validity	

Grading: 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

Alp NJ;Bell JA;Shahi M;

A rapid troponin-I-based protocol for assessing acute chest pain

Ref ID 780 | QJM - Monthly Journal of the Association of Physicians | pgs: 687 to 694 | 2001

Study Type Diagnostic **Funding** Not reported

Number of participants	397 patients Patients were included if they were aged over 18 years old, had acute chest pain of possible cardiac origin admitted to the CCU Patients were excluded if evidence of ST elevation on admission ECG, evidence of MI in previous 2 weeks, inability to provide informed consent 28% had AMI
Inclusion/Exclusion Criteria	
Patient Characteristics	Diagnosing chest pain
Recruitment	
Setting	
Interventions/ Test/ Factor being investigated	Troponin I at 6 hours from onset of worst symptoms or from presentation if timing of symptoms was unclear
Comparisons	Standard management (CK, AST and ECG)
Length of Study/ Follow-up	
Outcome measures studied	
Results	See results in guideline.
Safety and adverse effects	
Does the study answer the question?	
Effect due to factor in study?	
Consistency of results with other studies?	
Directly applicable to guideline population?	
Internal Validity	

Chiu A;Chan WK;Cheng SH;Leung CK;Choi CH;

Troponin-I, myoglobin, and mass concentration of creatine kinase-MB in acute myocardial infarction

Ref ID 10340 | QJM - Monthly Journal of the Association of Physicians | pgs: 711 to 718 | 1999

Study Type Diagnostic

Funding Not reported

Number of participants

87 patients
Patients were included if they had an initial diagnosis of AMI, patients presented to the emergency department or cardiac ward

86.2% had transmural infarction, 13.8% had non-Q wave myocardial infarction

Inclusion/Exclusion Criteria

Patient Characteristics

Confirming a diagnosis of AMI

Recruitment

Setting

Interventions/ Test/ Factor being investigated

CK-MB, troponin I, myoglobin, triple test (troponin I, myoglobin and CK-MB) at a mean of 4.89 hours over 72 hours from onset of pain

Comparisons

Each biomarker is compared to each other and a confirmed diagnosis of AMI is based on the WHO definition

Length of Study/ Follow-up

Outcome measures studied

Results

See table in guideline.

Safety and adverse effects

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Eggers KM;Oldgren J;Nordenskj÷ld A;Lindahl B;

Diagnostic value of serial measurement of cardiac markers in patients with chest pain: limited value of adding myoglobin to troponin I for exclusion of myocardial infarction

Ref ID 608 | Am Heart J | pgs: to 81 | 2004

Study Type Diagnostic

Funding Dade Behring Inc. and Cardiological Decision Support Uppsala AB,

Uppsala, Sweden

Number of participants	197 consecutive patients with chest pain and a non diagnostic ECG Patients were included if they had had chest pain for longer than 15 minutes within the last 24 hours which was suspected to be unstable angina or AMI and admitted to the CCU Patients were excluded if they had pathological ST-segment elevation on the admission ECG leading to immediate reperfusion 22% had AMI
Inclusion/Exclusion Criteria	
Patient Characteristics	Excluding an AMI diagnosis
Recruitment	
Setting	
Interventions/ Test/ Factor being investigated	Myoglobin with troponin I, CK-MB at presentation at 6 and 12 hours after presentation
Comparisons	Troponin I
Length of Study/ Follow-up	
Outcome measures studied	
Results	See results in guideline.
Safety and adverse effects	
Does the study answer the question?	
Effect due to factor in study?	
Consistency of results with other studies?	
Directly applicable to guideline population?	
Internal Validity	

Falahati A;Sharkey SW;Christensen D;McCoy M;Miller EA;Murakami MA;

Implementation of serum cardiac troponin I as marker for detection of acute myocardial infarction

Ref ID 1983 Am Heart J pgs: 332 to 337 1999

Study Type Diagnostic **Funding** Dade International Inc.

Number of participants	327 consecutive patients over a 3 month period were evaluated for AMI. Patients were excluded if less than 2 blood samples were taken. The study was conducted at the Hennepin county Medical centre, Minneapolis, USA 19% had a final diagnosis of AMI (of which 79% had a diagnostic ECG and 21% had a non diagnostic ECG)

Inclusion/Exclusion Criteria	
Patient Characteristics	The diagnosis of AMI
Recruitment	
Setting	
Interventions/ Test/ Factor being investigated	All patients had CK, CK-MB and CTnI tested every 6-8 hours from admission for 24-48 hours
Comparisons	The tests were compared to each other and the AMI diagnosis was based on the WHO diminution
Length of Study/ Follow-up	
Outcome measures studied	
Results	See results in guideline.
Safety and adverse effects	
Does the study answer the question?	
Effect due to factor in study?	
Consistency of results with other studies?	
Directly applicable to guideline population?	
Internal Validity	

Fesmire FM;Christenson RH;Fody EP;Feintuch TA;

Delta creatine kinase-MB outperforms myoglobin at two hours during the emergency department identification and exclusion of troponin positive non-ST-segment elevation acute coronary syndromes

Ref ID 629 Ann Emerg Med pgs: 12 to 19 2004

Study Type	Diagnostic	**Funding**	Phillips Medical Systems, Millennium Pharmaceuticals Inc, Bristol-Myers Squibb Medical Imaging and EmCare Inc.
Number of participants	975 patients Patients were included if they had a baseline troponin level of 1.0 ng/ml or less and an initial non-diagnostic ECG , presenting to a University hospital, USA 4.5% had AMI		
Inclusion/Exclusion Criteria			
Patient Characteristics	Diagnosing AMI		

Recruitment

Setting

Interventions/ Test/ Factor being investigated CK-MB, myoglobin at 2 hours from presentation

Comparisons no comparison

Length of Study/ Follow-up

Outcome measures studied

Results See results in guideline.

Safety and adverse effects

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Gust R;Gust A;B÷ttiger BW;B÷hrer H;Martin E;

Bedside troponin T testing is not useful for early out-of-hospital diagnosis of myocardial infarction

Ref ID 2014 Acta Anaesthesiol Scand pgs: 414 to 417 1998

Study Type Diagnostic **Funding** Not reported

Number of participants 68 patients
Patients were included if they had chest pain strongly suspected of AMI, (pain radiated to neck or one or both shoulders which was not relieved by rest or sublingual glyceryl trinitrate), presenting to the emergency department

24% had AMI

Inclusion/Exclusion Criteria

Patient Characteristics Diagnosing AMI

Recruitment

Setting

Interventions/ Test/ Factor being investigated Troponin T

Comparisons no comparison

Length of Study/ Follow-up

Outcome measures studied

Results See results in guideline.

Safety and adverse effects

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Planer D;Leibowitz D;Paltiel O;Boukhobza R;Lotan C;Weiss TA;

The diagnostic value of troponin T testing in the community setting

Ref ID 513 Int J Cardiol pgs: 369 to 375 2006

Study Type Diagnostic

Funding Kits were provided by DYN Diagnostics, Israel

Number of participants 349 patients
Patients were included if they were aged over 30 years, with at least 20 consecutive minutes of chest pain beginning at least 8 hours before presentation and occurring within the last 6 days
Patients were excluded if the had renal failure, ST elevation on ECG, had a diagnosis of ACS or had undergone revascularization
Patients were recruited from 44 community clinics in Jerusalem, Israel
1.7% had AMI

Inclusion/Exclusion Criteria

Patient Characteristics Diagnosing AMI

Recruitment

Setting

Interventions/ Test/ Factor being investigated Troponin T

Comparisons No comparison

Length of Study/ Follow-up

Outcome measures studied

Results See results in guideline.

Safety and adverse effects

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Zarich SW;Qamar AU;Werdmann MJ;Lizak LS;McPherson CA;Bernstein LH;

Value of a single troponin T at the time of presentation as compared to serial CK-MB determinations in patients with suspected myocardial ischemia

Ref ID 731 Clin Chim Acta pgs: 185 to 192 2002

Study Type Diagnostic **Funding** Not reported

Number of participants
267 patients
Patients were included if they had a complete evaluation including biomarkers, presenting to the emergency department
Patients were excluded if they had a history of chest trauma or renal failure

32% had AMI or unstable angina

Inclusion/Exclusion Criteria

Patient Characteristics Diagnosing AMI

Recruitment

Setting

Interventions/ Test/ Factor being investigated Single troponin T, CK-MB at presentation and serial CK-MB at presentation, 4, 8 and 16 hours after presentation

Comparisons Compared to each other

Length of Study/ Follow-up

Outcome measures studied

Results See results in guideline.

Safety and adverse effects

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Grading: 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*

al Harbi K;Suresh CG;Zubaid M;Akanji AO;

Establishing a gradient of risk in patients with acute coronary syndromes using troponin I measurements

Ref ID 748 Medical Principles and Practice pgs: 18 to 22 2002

Study Type Diagnostic **Funding** Not reported

Number of participants	124 patients (group 1 = 86 patients, group 2 = 38 patients) Patients were included in group 1if they had a diagnosis of ACS, group 2 were 38 healthy age-matched patients with no history of cardiovascular disease or any other chronic disease Group 1 patients were admitted to the CCU 59% had AMI, 41% had unstable angina
Inclusion/Exclusion Criteria	
Patient Characteristics	Diagnosing AMI and unstable angina
Recruitment	
Setting	
Interventions/ Test/ Factor being investigated	Troponin I at presentation and 8 and 16 hours from presentation
Comparisons	no comparison
Length of Study/ Follow-up	
Outcome measures studied	
Results	See results in guideline.
Safety and adverse effects	
Does the study answer the question?	
Effect due to factor in study?	
Consistency of results with other studies?	
Directly applicable to guideline population?	
Internal Validity	

Vatansever S;Akkaya V;Erk O;Ozt³rk S;Karan MA;Salmayenli N;Tasþioglu C;G³ler K;

The diagnostic value of troponin T and myoglobin levels in acute myocardial infarction: a study in Turkish patients

Ref ID 699 J Int Med Res pgs: 76 to 83 2003

Study Type Diagnostic **Funding** Not reported

Number of participants 60 patients
Patients were included for the study group if they had a confirmed AMI, and for the control group if they were members of the health profession who matched the study group for age and gender but did not have AMI
the study group presented to the emergency department
55% had AMI

Inclusion/Exclusion Criteria

Patient Characteristics Diagnosing AMI

Recruitment

Setting

Interventions/ Test/ Factor being investigated TroponinT and myoglobin at 2 hours from presentation

Comparisons CK

Length of Study/ Follow-up

Outcome measures studied

Results See results in guideline.

Safety and adverse effects

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Zimmerman J;Fromm R;Meyer D;Boudreaux A;Wun CC;Smalling R;Davis B;Habib G;Roberts R;

Diagnostic marker cooperative study for the diagnosis of myocardial infarction

Ref ID 897 Circulation pgs: 1671 to 1677 1999

Study Type Diagnostic **Funding** Boehringer Mannheim Corporation, Dade International, Helena Laboratories, Spectral Diagnostics, Inc, and NHLBI

(grant P50-HL-54313-01)

Number of participants	955 patients Patients were included if aged over 21 years old with chest pain lasting for 15 minutes or longer suspected to be myocardial in origin and occurring within 24 hours of presentation Patients presented to hospitals in Texas, USA 100% had AMI
Inclusion/Exclusion Criteria	
Patient Characteristics	Diagnosing AMI
Recruitment	
Setting	
Interventions/ Test/ Factor being investigated	CK-MB, troponin I, troponin T, myoglobin at 2, 4, 6, 8, 10, 18 and 22 hours after presentation
Comparisons	Biomarkers were compared with each other
Length of Study/ Follow-up	
Outcome measures studied	
Results	See results in guideline.
Safety and adverse effects	
Does the study answer the question?	
Effect due to factor in study?	
Consistency of results with other studies?	
Directly applicable to guideline population?	
Internal Validity	

Question 13: What is the incremental benefit and cost effectiveness of a clinical history, risk factors and physical examination in evaluation of individuals with stable chest pain of suspected cardiac origin?

Grading: 1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Chun AA;McGee SR;

Bedside diagnosis of coronary artery disease: a systematic review

Ref ID 10275 The American journal of medicine pgs: 334 to 343 2004

Study Type Systematic Review **Funding** Not reported

Number of participants 64 studies

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

Most of the papers reviewed were of patients presenting with stable intermittent chest pain who were then referred for coronary angiography. Most of the studies had excluded patients with valvular heart disease or nonischemic cardiomyopathy. The studies used either >50% stenosis or 70-75% stenosis off any epicardial vessel as the diagnostic standard.
The study showed that for diagnosing CAD over all the physical examination gave little additional diagnostic information. The presence of an ear lobe crease gave a small increase to the probability of CAD (likelihood ratio (LR)=2.3). Arcus senilis and an ankle-brachial index <0.9 had no statistical significance, and the presence of chest wall tenderness was also diagnostically unhelpful.
The review calculated the LR by pooling the date from the included studies which used 2 diagnostic criteria for CAD (>50% stenosis and >70% to 75% stenosis). The study also analysed the data separately (>50% stenosis and >70-75% stenosis) which showed the pooled LRs remained the same. In studies which used > 50% stenosis the pooled LRs were 5.6 for typical angina, 1.1 for atypical angina, and 0.1 for nonanginal chest pain. The review calculated LRs including data from studies that combined patients with a history of MI with those without; the LRs were the same if only those studies excluding prior MI were analysed. In studies of patients without a history of MI the pooled likelihood ratios were 5.8 for typical angina, 1.3 for atypical angina and 0.1 for nonanginal chest pain.

The study showed that for the diagnosing MI, the ECG was more useful in diagnosing MI, however systolic blood pressure <100 mmHg (LR=3.6), diaphoresis

on examination (LR=2.9), diastolic blood pressure <60 mmHg (LR=2.5), and presence of jugular venous distention (LR=2.4) were also helpful in diagnosing MI. a normal ECG was most useful in ruling out a diagnosis of MI but the patient having chest wall tenderness was also helpful for ruling out the diagnosis.

Effect due to factor in study? Yes

Consistency of results with other studies? Consistent

Directly applicable to guideline population? Correct population

Internal Validity

Chun AA;McGee SR;

Bedside diagnosis of coronary artery disease: a systematic review

Ref ID 10275 The American journal of medicine pgs: 334 to 343 2004

Study Type Systematic Review **Funding** Not reported

Number of participants 64 studies

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question? Most of the papers reviewed were of patients presenting with stable intermittent chest pain who were then referred for coronary angiography. Most of the studies had excluded patients with valvular heart disease or nonischemic cardiomyopathy. The studies used either >50% stenosis or 70-75% stenosis off any epicardial vessel as the diagnostic standard.
The study showed that for diagnosing CAD over all the physical examination gave little additional diagnostic information (guideline table). The presence of an ear lobe crease gave a small increase to the probability of CAD (likelihood ratio (LR)=2.3). Arcus senilis and an ankle-brachial index <0.9 had no statistical significance, and the presence of chest wall tenderness was also diagnostically unhelpful.
The review calculated the LR by pooling the date from the included studies which used 2 diagnostic criteria for CAD (>50% stenosis and >70% to 75% stenosis). The study also analysed the data separately (>50% stenosis and >70-75% stenosis)

which showed the pooled LRs remained the same. In studies which used > 50% stenosis the pooled LRs were 5.6 for typical angina, 1.1 for atypical angina, and 0.1 for nonanginal chest pain. The review calculated LRs including data from studies that combined patients with a history of MI with those without; the LRs were the same if only those studies excluding prior MI were analysed. In studies of patients without a history of MI the pooled likelihood ratios were 5.8 for typical angina, 1.3 for atypical angina and 0.1 for nonanginal chest pain.

The study showed that for the diagnosing MI, the ECG was more useful in diagnosing MI, however systolic blood pressure <100 mmHg (LR=3.6), diaphoresis on examination (LR=2.9), diastolic blood pressure <60 mmHg (LR=2.5), and presence of jugular venous distention (LR=2.4) were also helpful in diagnosing MI. a normal ECG was most useful in ruling out a diagnosis of MI but the patient having chest wall tenderness was also helpful for ruling out the diagnosis.

Effect due to factor in study? Yes

Consistency of results with other studies? Consistent

Directly applicable to guideline population? Correct population

Internal Validity

Chun AA;McGee SR;

Bedside diagnosis of coronary artery disease: a systematic review

Ref ID 10275 The American journal of medicine pgs: 334 to 343 2004

Study Type Systematic Review **Funding** Not reported

Number of participants 64 studies

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?	Most of the papers reviewed were of patients presenting with stable intermittent chest pain who were then referred for coronary angiography. Most of the studies had excluded patients with valvular heart disease or nonischemic cardiomyopathy. The studies used either >50% stenosis or 70-75% stenosis off any epicardial vessel as the diagnostic standard. The study showed that for diagnosing CAD over all the physical examination gave little additional diagnostic information (See table in guideline). The presence of an ear lobe crease gave a small increase to the probability of CAD (likelihood ratio (LR)=2.3). Arcus senilis and an ankle-brachial index <0.9 had no statistical significance, and the presence of chest wall tenderness was also diagnostically unhelpful. The review calculated the LR by pooling the date from the included studies which used 2 diagnostic criteria for CAD (>50% stenosis and >70% to 75% stenosis). The study also analysed the data separately (>50% stenosis and >70-75% stenosis) which showed the pooled LRs remained the same. In studies which used > 50% stenosis the pooled LRs were 5.6 for typical angina, 1.1 for atypical angina, and 0.1 for nonanginal chest pain. The review calculated LRs including data from studies that combined patients with a history of MI with those without; the LRs were the same if only those studies excluding prior MI were analysed. In studies of patients without a history of MI the pooled likelihood ratios were 5.8 for typical angina, 1.3 for atypical angina and 0.1 for nonanginal chest pain. The study showed that for the diagnosing MI, the ECG was more useful in diagnosing MI, however systolic blood pressure <100 mmHg (LR=3.6), diaphoresis on examination (LR=2.9), diastolic blood pressure <60 mmHg (LR=2.5), and presence of jugular venous distention (LR=2.4) were also helpful in diagnosing MI. a normal ECG was most useful in ruling out a diagnosis of MI but the patient having chest wall tenderness was also helpful for ruling out the diagnosis.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Correct population
Internal Validity	

Grading: 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

Diamond GA;Forrester JS;

Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease

Ref ID 2196 The New England journal of medicine pgs: 1350 to 1358 1979

Study Type	Cohort	**Funding**	Not reported

Number of participants	4952 had coronary angiography, 23 996 autopsy (autopsy patients had died from other causes e.g. trauma and non-cardiac related diseases)
Inclusion/Exclusion Criteria	Not applicable
Patient Characteristics	Not applicable Patients were considered to have typical angina if they had substernal discomfort brought on by physical exertion and was relieved within 10 minutes through rest or nitroglycerin. Patients were considered to have atypical angina if they had discomfort which was either not substernal or was not bought on by exertion or not relieved after 10 minutes by rest or nitroglycerin. Patients were considered to have non-anginal discomfort if they did not have 1 or more of the above characteristics.
Recruitment	Not applicable
Setting	Secondary care, USA
Interventions/ Test/ Factor being investigated	Prevalence of CAD based on age, sex and symptoms
Comparisons	Coronary angiography in symptomatic patients and autopsy
Length of Study/ Follow-up	Not applicable
Outcome measures studied	Prevalence of CAD based on age, sex and symptoms
Results	In 4953 patients with stable chest pain referred for angiogram; the prevalence of disease in patients with typical angina symptoms was about 90%, whereas for atypical angina patients was a 50% prevalence ($P < 0.001$) and non-cardiac chest pain patients was 16% ($P < 0.001$). The prevalence of CAD observed at autopsy is similar to that in asymptomatic patients confirmed by coronary angiography. Significant differences in disease prevalence occurred when patients were classified according to age and sex. For women the differences range from 0.3% for women aged 30 years to 39 years of age, to 7% for women aged 60 years to 69 years. Women in all age ranges had a lower prevalence compared with the respective age ranges in men The pre-test likelihood of disease for any patients (according to any combination of age, sex and symptoms) was determined by conditional-probability analysis. There are a wide range of pre-test likelihoods according to sex, gender and symptoms. For example a women with atypical symptoms and aged 35% has a pre-test likelihoods of 4% compared with 92% for a man aged 55 years with typical symptoms. The authors noted that the approach used in the study was a mathematical formalisation of the intuition of the physicians reviewing the literature, or the use of past experience to assess a patients' pre-test likelihoods. Both of these approaches

	relied upon the use of data from specific populations, but that they do provide reliable estimates of the probability of coronary artery disease based on the patients age, symptoms and gender.
Safety and adverse effects	None
Does the study answer the question?	The study reviewed the literature to estimate the pre-test likelihood of disease (defined by age, sex and symptoms), the results were analysed through Bayes' theorem of conditional probability. The studied described how the probability of CAD can be determined in a patient before testing from information readily obtained from clinical evaluation. The study showed that combining data of the estimate of disease likelihood when the patient's age and sex are known and a second estimate when the presence or absence of symptoms are known. The pre-test likelihood of disease for any patients based on any combination of age, sex and symptoms can be determined by conditional-probability analysis. The results of this analysis can be seen in the tables in the guideline which show the results of all combinations of age, sex and symptoms, which shows a wide range of pre-test likelihoods.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Patients had chest pain
Internal Validity	Well covered

Diamond,G.A.; Staniloff,H.M.; Forrester,J.S.; Pollock,B.H.; Swan,H.J.

Computer-assisted diagnosis in the noninvasive evaluation of patients with suspected coronary

Ref ID 10281 Journal of the American College of Cardiology pgs: 444 to 455 1983

Study Type	Cohort	**Funding**	Not reported

Number of participants	1097, 70% men, 30% women
Inclusion/Exclusion Criteria	Inclusion: referred for non invasive testing for suspected CAD without previous MI or coronary bypass surgery
Patient Characteristics	Mean age 56±11 years Patients were considered to have typical angina if they had substernal discomfort brought on by physical exertion and was relieved within 10 minutes through rest or nitroglycerin. Patients were considered to have atypical angina if they had discomfort which was either not substernal or was not bought on by exertion or not relieved after 10 minutes by rest or nitroglycerin. Patients were considered to have non-anginal discomfort if they did not have 1 or more of the above characteristics.
Recruitment	Patients who were referred for noninvasive testing for suspected CAD at the Cedars-Sinai Medical Center Cardiac Stress Laboratories, USA, between 1st January1979 and 15th November 1980
Setting	Secondary care, USA
Interventions/ Test/ Factor being investigated	Risk factors for diagnosing CAD
Comparisons	Risk factors for diagnosing CAD

Length of Study/ Follow-up	Not reported
Outcome measures studied	Diagnosis of CAD
Results	46 patients had 0 diseased vessels, 21 patients had 1 diseased vessel, 46 patients had 2 diseased vessels, 57 patients had 3 diseased vessels, and 124 patients had 1 + 2 + 3 diseased vessels. CAD probability and angiography (diseased vessels = d.v.) Estimates before testing. Mean probability: 0.291 d.v.=0, 0.595 d.v=1, 0.623 d.v=2, 0.660 d.v=3, 0.635 d.v.=1+2+3 Standard deviation: 0.259 d.v.=0, 0.342 d.v=1, 0.334 d.v=2, 0.327 d.v=3, 0.332 d.v.=1+2+3. Estimates before angiography Mean probability: 0.253 d.v.=0, 0.745 d.v=1, 0.772 d.v=2, 0.843 d.v=3, 0.800 d.v.=1+2+3 Standard deviation: 0.322 d.v.=0, 0.387 d.v=1, 0.321 d.v=2, 0.284 d.v=3, 0.315 d.v.=1+2+3. All estimates Test combinations: 500 d.v.=0, 316 d.v=1, 640 d.v=2, 724 d.v=3, 1680 d.v.=1+2+3 Mean probability: 0.304 d.v.=0, 0.557 d.v=1, 0.730 d.v=2, 0.746 d.v=3, 0.704 d.v.=1+2+3 Standard deviation: 0.321 d.v.=0, 0.377 d.v=1, 0.323 d.v=2, 0.331 d.v=3, 0.322 d.v.=1+2+3.
Safety and adverse effects	None
Does the study answer the question?	The study considered the probability of CAD and the disease prevalence. This showed that there was no significant difference between the predicted probability and the probability shown on angiography if probability was based on the age and sex of the patient, within the difference symptom classes. This, the authors states, shows the importance of clinical history as a diagnostic test. The study stated that the probability of CAD in each symptom class was consistently slightly higher in the patients with CAD compared to those without CAD, which the authors suggest shows that the Framingham risk factors were “modest discriminators for CAD independent of symptom classification”. The data the study gained was assessed based on the age, sex, symptoms and risk factors before diagnostic testing, and based on all the data gained before catheterization and again with all the data after every test had been carried out. For each assessment the probability of disease increased in proportion to the number of diseased vessels, however there were large standard deviations. The study showed that the mean probability for CAD increased from 30% for the patients in the normal group to 56% for the patients with 1 vessel disease, and increased to 75% for patients with 3 vessel disease. There was overlap between data sets especially for those with 2 and 3 vessel disease, which showed no significant difference. This, the study stated, led to 8% of the probability estimates for the normal patients being in excess of 90%, and for 9.7% of the probability estimates for the patients with disease shown on angiography to be 10% under. There was a 3.4% difference between predicted probability and actually probability of CAD from the estimate based on sex, age ,symptoms and risk factors. The study used graphs to determine relationships between the variables and disease prevalence, and showed that the calculated probability of CAD accurately reflected the actual angiographic disease prevalence. The study also assessed the probability of CAD and extent of disease. This showed that when the patient had a probability of below “25% when disease was present single vessel disease was slightly more prevalent than multi-vessel disease, while above a probability of 75% multi-vessel disease predominated. At a probability of 100% multi-vessel disease accounted for 89% of all angiographic disease”. The significance of these differences varied, however it shows that it does indicate that disease probability also acted as a quantitative measure of anatomic severity.

Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Patients had suspected CAD
Internal Validity	Well covered

Pryor DB;Harrell FE;Lee KL;Califf RM;Rosati RA;

Estimating the likelihood of significant coronary artery disease

Ref ID 10283 The American journal of medicine pgs: 771 to 780 1983

Study Type	Cohort	**Funding**	Not reported

Number of participants	3627 in training population, 1811 in test population
Inclusion/Exclusion Criteria	Patients with chest pain who were referred for cardiac catheterization at the Duke University Medical Center between November 1969 and January 1982
Patient Characteristics	Patient characteristics which were collected were: History: age, sex, chest pain history (pain type, severity, frequency, nocturnal, progressive, preinfarctional), duration of CAD, previous history of MI, congestive heart failure, history of vascular disease (Progressive chest pain - the frequency, severity or duration had increased in the 6 weeks prior to catherisation; Preinfarctional chest pain - a very unstable pain pattern that resulted in admission to the coronary care unit for evaluation of the possible MI) Risk factors: smoking, hyperlipidaemia, hypertension, diabetes, family history Physical examination: ventricular gallop, systolic blood pressure ECG: ST-T wave changes, electrocardiographic premature ventricular contractions, Electrocardiographic Q waves Chest X-Ray: cardiomegaly
Recruitment	Patients admitted for cardiac catheterisation between November 1969 and January 1982
Setting	Secondary care, USA
Interventions/ Test/ Factor being investigated	Chest pain diagnosis
Comparisons	Patient characteristics which give a probability of disease
Length of Study/ Follow-up	
Outcome measures studied	Probability of disease
Results	The study had a training population of 3627 patients who were seen between 1969 and January 1979, from these patients a stepwise logistic regression analysis was used to develop a model for predicting the probability of significant CAD. A test population of 1811 patients seen between January 1969 and January 1982, in this population the model developed in the test population was used to predict the probability of CAD for each patient. The authors then tested the model in other populations (from CASS study) to estimate the prevalence of disease in subgroups of the patients in the literature (external validation)

Results from training population:
Clinically Important Characteristics and the Chi-squared:
Pain type (typical, atypical or nonanginal): 1091
Previous MI: 511
Sex: 187
Age: 119
Smoking: 79
Hyperlipidaemia: 26
ST-T wave changes: 28
Diabetes: 12

Interactions
age X sex
age X smoking
age X hyperlipidaemia
sex X smoking

Poor Clinical Predictors of Significant CAD and the Chi-squared:
Chest pain severity: 0.96
Chest pain frequency: 8.57
Nocturnal chest pain: 2.22
Progressive chest pain: 2.54
Preinfarction angina: 9.70
Vascular disease: 0.40
Duration of CAD: 9.16
Congestive heart failure: 0.59
Hypertension: 5.19
Family history: 6.39
Ventricular gallop: 1.06
Cardiomegaly: 1.41
Electrocardiographic premature ventricular contractions: 0.46

The results from the training group are shown under “Clinically Important Characteristics and the Chi-squared” in the order of their importance (chi-squared added to the model by the parameter, adjusting for the characteristics that precede it). The type of chest pain (typical, atypical or nonanginal) was the most important characteristic followed by previous MI, sex, age, smoking, hyperlipidaemia, ST-T wave changes on ECG, diabetes. The results above show the 4 significant interactions which were found.
The study also showed that in men the effect of an increasing age was more important than in women, smoking was more important for women than men, and that smoking and hyperlipidaemia were more important at younger ages. The results for the other characteristics which were found to have small or nonsignificant effects on the prevalence of disease are shown under “Poor Clinical Predictors of Significant CAD and the Chi-squared”

The authors then validated the model in the test population which showed that the predicted probability of disease is nearly identical to the observed prevalence. This was with the exception of the group with predicted estimates of 0.475 to 0.525 (this group 8 out of 34 patients, with significant disease). The median prediction for patients with disease was 94% compared with a median prediction of 33% for patients without disease. A predicted probability of significant disease > 0.83 was found in 75% of patients with disease and in less than 10% of patients with disease. A probability of significant disease < 0.33 was found in nearly 50% of patients without disease and in less than 5% of patients with disease.

The authors then externally validated using the population from the CASS study. There was disagreement on patients classified as having nonanginal chest pain (where the greatest difference in predicted disease compared to observed disease was seen), but the predicted estimates from the model were nearly equal to the observed prevalence of disease. The predicted estimates from the model of the probability of significant disease were nearly identical to the observed prevalence for subgroups based on “age, sex and history of MI” or “age, sex and pain type”.

Safety and adverse effects

None

Does the study answer the question?	Progressive chest pain was described as being chest pain when the frequency, severity or duration had increased in the 6 weeks prior to catherisation. Preinfarctional chest pain was described as chest pain with a very unstable pain pattern that resulted in admission to the coronary care unit for evaluation of the possible MI. The results from the training population showed the type of chest pain (typical, atypical or nonanginal) was the most important characteristic followed by previous MI, sex, age, smoking, hyperlipidaemia, ST-T wave changes on ECG, diabetes. The study also showed that in men the effect of increasing age was more important than in women, smoking was more important for women than men, and that smoking and hyperlipidaemia were more important at younger ages. The study also found some characteristics to have small or nonsignificat effects on the prevalence of disease. The authors then validated the model in the test population which showed that the predicted probability of disease is nearly identical to the observed prevalence. When comparing the model to an external population the study showed that the predicted estimates from the model were nearly equal to the observed prevalence of disease. The predicted estimates from the model of the probability of significant disease were nearly identical to the observed prevalence for subgroups based on “age, sex and history of MI” or “age, sex and pain type”. However the greatest difference in predicted disease compared to observed disease was seen in patients with nonanginal chest pain.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Patients had chest pain
Internal Validity	Well covered

Pryor DB;Harrell FE;Lee KL;Califf RM;Rosati RA;

Estimating the likelihood of significant coronary artery disease

Ref ID 10283 The American journal of medicine pgs: 771 to 780 1983

Study Type Cohort **Funding** Not reported

Number of participants	3627 in training population, 1811 in test population
Inclusion/Exclusion Criteria	Patients with chest pain who were referred for cardiac catheterization at the Duke University Medical Center between November 1969 and January 1982
Patient Characteristics	Patient characteristics which were collected were: History: age, sex, chest pain history (pain type, severity, frequency, nocturnal, progressive, preinfarctional), duration of CAD, previous history of MI, congestive heart failure, history of vascular disease (Progressive chest pain - the frequency, severity or duration had increased in the 6 weeks prior to catherisation; Preinfarctional chest pain - a very unstable pain pattern that resulted in admission to the coronary care unit for evaluation of the possible MI). Risk factors: smoking, hyperlipidaemia, hypertension, diabetes, family history Physical examination: ventricular gallop, systolic blood pressure ECG: ST-T wave changes, electrocardiographic premature ventricular contractions, Electrocardiographic Q waves Chest X-Ray: cardiomegaly
Recruitment	Patients admitted for cardiac catheterisation between November 1969 and January 1982

Setting	Secondary care, USA
Interventions/ Test/ Factor being investigated	Chest pain diagnosis
Comparisons	Patient characteristics which give a probability of disease
Length of Study/ Follow-up	
Outcome measures studied	Probability of disease
Results	The study had a training population of 3627 patients who were seen between 1969 and January 1979, from these patients a stepwise logistic regression analysis was used to develop a model for predicting the probability of significant CAD. A test population of 1811 patients seen between January 1969 and January 1982, in this population the model developed in the test population was used to predict the probability of CAD for each patient. The authors then tested the model in other populations (from CASS study) to estimate the prevalence of disease in subgroups of the patients in the literature (external validation. Clinically Important Characteristics and the Chi-squared: Pain type (typical, atypical or nonanginal): 1091 Previous MI: 511 Sex: 187 Age: 119 Smoking: 79 Hyperlipidaemia: 26 ST-T wave changes: 28 Diabetes: 12 Interactions age X sex age X smoking age X hyperlipidaemia sex X smoking Poor Clinical Predictors of Significant CAD and the Chi-squared: Chest pain severity: 0.96 Chest pain frequency: 8.57 Nocturnal chest pain: 2.22 Progressive chest pain: 2.54 Preinfarction angina: 9.70 Vascular disease: 0.40 Duration of CAD: 9.16 Congestive heart failure: 0.59 Hypertension: 5.19 Family history: 6.39 Ventricular gallop: 1.06 Cardiomegaly: 1.41 Electrocardiographic premature ventricular contractions: 0.46 The results from the training group are shown under “Clinically Important Characteristics and the Chi-squared” in the order of their importance (chi-squared added to the model by the parameter, adjusting for the characteristics that precede it). The type of chest pain (typical, atypical or nonanginal) was the most important characteristic followed by previous MI, sex, age, smoking, hyperlipidaemia, ST-T wave changes on ECG, diabetes. The results above show the 4 significant interactions which were found. The study also showed that in men the effect of an increasing age was more important than in women, smoking was more important for women than men, and that smoking and hyperlipidaemia were more important at younger ages. The results for the other characteristics which were found to have small or nonsignificat effects on the prevalence of disease are shown under “Poor Clinical Predictors of Significant CAD and the Chi-squared” .

The authors then validated the model in the test population which showed that the predicted probability of disease is nearly identical to the observed prevalence. This was with the exception of the group with predicted estimates of 0.475 to 0.525 (this group 8 out of 34 patients, with significant disease). The median prediction for patients with disease was 94% compared with a median prediction of 33% for patients without disease. A predicted probability of significant disease > 0.83 was found in 75% of patients with disease and in less than 10% of patients with disease. A probability of significant disease < 0.33 was found in nearly 50% of patients without disease and in less than 5% of patients with disease.

The authors then externally validated using the population from the CASS study. There was disagreement on patients classified as having nonanginal chest pain (where the greatest difference in predicted disease compared to observed disease was seen), but the predicted estimates from the model were nearly equal to the observed prevalence of disease. The predicted estimates from the model of the probability of significant disease were nearly identical to the observed prevalence for subgroups based on “age, sex and history of MI” or “age, sex and pain type”.

Safety and adverse effects

None

Does the study answer the question?

Progressive chest pain was described as being chest pain when the frequency, severity or duration had increased in the 6 weeks prior to catherisation. Preinfarctional chest pain was described as chest pain with a very unstable pain pattern that resulted in admission to the coronary care unit for evaluation of the possible MI

The results from the training population showed the type of chest pain (typical, atypical or nonanginal) was the most important characteristic followed by previous MI, sex, age, smoking, hyperlipidaemia, ST-T wave changes on ECG, diabetes. The study also showed that in men the effect of an increasing age was more important than in women, smoking was more important for women than men, and that smoking and hyperlipidaemia were more important at younger ages. The study also found some characteristics to have small or nonsignificat effects on the prevalence of disease.

The authors then validated the model in the test population which showed that the predicted probability of disease is nearly identical to the observed prevalence. When comparing the model to an external population the study showed that the predicted estimates from the model were nearly equal to the observed prevalence of disease. The predicted estimates from the model of the probability of significant disease were nearly identical to the observed prevalence for subgroups based on “age, sex and history of MI” or “age, sex and pain type”. However the greatest difference in predicted disease compared to observed disease was seen in patients with nonanginal chest pain.

Effect due to factor in study?

Yes

Consistency of results with other studies?

Consistent

Directly applicable to guideline population?

Patients had chest pain

Internal Validity

Well covered

Pryor DB;Harrell FE;Lee KL;Califf RM;Rosati RA;

Estimating the likelihood of significant coronary artery disease

Ref ID 10283 The American journal of medicine pgs: 771 to 780 1983

Study Type Cohort **Funding** Not reported

Number of participants	3627 in training population, 1811 in test population
Inclusion/Exclusion Criteria	Patients with chest pain who were referred for cardiac catheterization at the Duke University Medical Center between November 1969 and January 1982
Patient Characteristics	Patient characteristics which were collected were: History: age, sex, chest pain history (pain type, severity, frequency, nocturnal, progressive, preinfarctional), duration of CAD, previous history of MI, congestive heart failure, history of vascular disease (Progressive chest pain - the frequency, severity or duration had increased in the 6 weeks prior to catherisation; Preinfarctional chest pain - a very unstable pain pattern that resulted in admission to the coronary care unit for evaluation of the possible MI). Risk factors: smoking, hyperlipidaemia, hypertension, diabetes, family history Physical examination: ventricular gallop, systolic blood pressure ECG: ST-T wave changes, electrocardiographic premature ventricular contractions, Electrocardiographic Q waves Chest X-Ray: cardiomegaly
Recruitment	Patients admitted for cardiac catheterisation between 1969 and 1982
Setting	Secondary care, USA
Interventions/ Test/ Factor being investigated	Chest pain diagnosis
Comparisons	Patient characteristics which give a probability of disease
Length of Study/ Follow-up	
Outcome measures studied	Probability of disease
Results	The study had a training population of 3627 patients who were seen between 1969 and January 1979, from these patients a stepwise logistic regression analysis was used to develop a model for predicting the probability of significant CAD. A test population of 1811 patients seen between January 1969 and January 1982, in this population the model developed in the test population was used to predict the probability of CAD for each patient. The authors then tested the model in other populations (from CASS study) to estimate the prevalence of disease in subgroups of the patients in the literature (external validation). Results from training population: Clinically Important Characteristics and the Chi-squared: Pain type (typical, atypical or nonanginal): 1091 Previous MI: 511 Sex: 187 Age: 119 Smoking: 79 Hyperlipidaemia: 26 ST-T wave changes: 28 Diabetes: 12 Interactions age X sex age X smoking age X hyperlipidaemia sex X smoking Poor Clinical Predictors of Significant CAD and the Chi-squared: Chest pain severity: 0.96 Chest pain frequency: 8.57 Nocturnal chest pain: 2.22 Progressive chest pain: 2.54

Preinfarction angina: 9.70
Vascular disease: 0.40
Duration of CAD: 9.16
Congestive heart failure: 0.59
Hypertension: 5.19
Family history: 6.39
Ventricular gallop: 1.06
Cardiomegaly: 1.41
Electrocardiographic premature ventricular contractions: 0.46

The results from the training group are shown under “Clinically Important Characteristics and the Chi-squared” in the order of their importance (chi-squared added to the model by the parameter, adjusting for the characteristics that precede it). The type of chest pain (typical, atypical or nonanginal) was the most important characteristic followed by previous MI, sex, age, smoking, hyperlipidaemia, ST-T wave changes on ECG, diabetes. The results above show the 4 significant interactions which were found.
The study also showed that in men the effect of an increasing age was more important than in women, smoking was more important for women than men, and that smoking and hyperlipidaemia were more important at younger ages. The results for the other characteristics which were found to have small or nonsignificat effects on the prevalence of disease are shown under “Poor Clinical Predictors of Significant CAD and the Chi-squared”

The authors then validated the model in the test population which showed that the predicted probability of disease is nearly identical to the observed prevalence. This was with the exception of the group with predicted estimates of 0.475 to 0.525 (this group 8 out of 34 patients, with significant disease). The median prediction for patients with disease was 94% compared with a median prediction of 33% for patients without disease. A predicted probability of significant disease > 0.83 was found in 75% of patients with disease and in less than 10% of patients with disease. A probability of significant disease < 0.33 was found in nearly 50% of patients without disease and in less than 5% of patients with disease.

The authors then externally validated using the population from the CASS study. There was disagreement on patients classified as having nonanginal chest pain (where the greatest difference in predicted disease compared to observed disease was seen), but the predicted estimates from the model were nearly equal to the observed prevalence of disease. The predicted estimates from the model of the probability of significant disease were nearly identical to the observed prevalence for subgroups based on “age, sex and history of MI” or “age, sex and pain type”.

Safety and adverse effects

None

Does the study answer the question?

The results from the training population showed the type of chest pain (typical, atypical or nonanginal) was the most important characteristic followed by previous MI, sex, age, smoking, hyperlipidaemia, ST-T wave changes on ECG, diabetes. The study also showed that in men the effect of an increasing age was more important than in women, smoking was more important for women than men, and that smoking and hyperlipidaemia were more important at younger ages. The study also found some characteristics to have small or nonsignificat effects on the prevalence of disease.

The authors then validated the model in the test population which showed that the predicted probability of disease is nearly identical to the observed prevalence. When comparing the model to an external population the study showed that the predicted estimates from the model were nearly equal to the observed prevalence of disease. The predicted estimates from the model of the probability of significant disease were nearly identical to the observed prevalence for subgroups based on “age, sex and history of MI” or “age, sex and pain type”. However the greatest difference in predicted disease compared to observed disease was seen in patients with nonanginal chest pain.

Effect due to factor in study?

Yes

Consistency of results with other studies?

Consistent

Directly applicable to guideline population?	Patients had chest pain
Internal Validity	Well covered

Grading: 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

Pryor DB;Shaw L;McCants CB;Lee KL;Mark DB;Harrell FE;Muhlbaier LH;Califf RM;

Value of the history and physical in identifying patients at increased risk for coronary artery disease

Ref ID 1751 Annals of internal medicine pgs: 81 to 90 1993

Study Type Cohort

Funding Agency for Health Care Policy and Research, National Heart, Lung and Blood institute, National Library of Medicine

Number of participants	1030 patients, 168 had cardiac catheterization
Inclusion/Exclusion Criteria	Inclusion: Symptomatic patients, referred for non-invasive testing for suspected coronary artery disease Exclusion: previous cardiac catheterization
Patient Characteristics	The mean age was 55, 37% were female, the mean pain frequency was 2 episodes a week, the mean durations of CAD symptoms was 12 months, 28% had typical angina symptoms, 52% atypical angina symptoms, 20% nonanginal pain, 18% progressive angina, 22% nocturnal angina, 44% smoked, 41% had a history of hypertension, 10% had diabetes, 11% had hyperlipidemia, 35% had ST-T wave changes on ECG, 18% had a history of MI, 8% had Q waves on ECG, 14% had a history of congestive heart failure, 0% had class IV congestive heart failure, 1% had ventricular gallop, 3% had peripheral vascular disease, 3% had cerebral vascular disease. Of the patients who went on to have a cardiac catheterization the mean age was 56, 31% were female, the mean pain frequency was 2 episodes a week, the mean durations of CAD symptoms was 7 months, 49% had typical angina symptoms, 47% atypical angina symptoms, 4% nonanginal pain, 24% progressive angina, 24% nocturnal angina, 53% smoked, 42% had a history of hypertension, 10% had diabetes, 13% had hyperlipidemia, 42% had ST-T wave changes on ECG, 33% had a history of MI, 11% had Q waves on ECG, 11% had a history of congestive heart failure, 0% had class IV congestive heart failure, 1% had ventricular gallop, 4% had peripheral vascular disease, 2% had cerebral vascular disease. It can therefore be seen that those having a cardiac catheterization were more likely to be male, smoke, have a history of MI, have ST-T wave changes on ECG and to be suffering typical or progressive angina.
Recruitment	Patients were referred for non-invasive testing for suspected coronary artery disease
Setting	Duke University Medical Centre USA
Interventions/ Test/ Factor being investigated	Physicians initial evaluation of patients with suspected CAD predicts coronary anatomy
Comparisons	The presence of significant coronary disease defined as any disease, severe disease, left main disease
Length of Study/ Follow-up	90 days
Outcome measures studied	Effectiveness of chest pain score to predict coronary artery disease
Results	The three diagnostic outcomes were; the presence of significant coronary artery disease defined as ‘any disease’ (≥ 75% luminal diameter narrowing of at least one major coronary artery), presence of severe coronary artery disease defined as ‘severe disease’ (significant obstruction of all 3 main coronary arteries or the left main coronary artery) and the presence of significant left main artery obstruction defined as ‘left main disease’ (168 patients referred for cardiac catheterization). The prognostic

outcome was survival at 3 years.
In the multivariable regression model used, the following variables were significant predictors for any disease; age, gender, chest pain (type), diabetes, smoking, hyperlipidaemia, previous history of myocardial infarction, and significant Q waves and ST-T wave changes. For severe disease, the following variables were significant predictors; age, gender, chest pain (type, frequency, course, nocturnal, length of time present), diabetes, smoking, hyperlipidaemia, hypertension, peripheral or cerebral artery disease, carotid bruit, previous history of myocardial infarction, and significant Q waves and ST-T wave changes. For left main disease, the following variables were significant predictors; age, gender, chest pain (type), diabetes, peripheral or cerebral artery disease and carotid bruit. For survival at 3 years the following variables were significant predictors; age, gender, chest pain (frequency, course, nocturnal), peripheral or cerebral artery disease, carotid bruit, ventricular gallop, previous history of myocardial infarction, significant Q waves and ST-T wave changes, conduction abnormalities, premature ventricular contractions and cardiomegaly. The likelihood of any disease, severe coronary disease, left main disease and survival was predicted from the initial history, physical examination, electrocardiogram and chest X ray (these tests were defined as the 'initial evaluation').
Predicted coronary artery endpoints and survival based on the initial evaluation closely corresponded to actual findings. Predictions using the initial evaluation were then compared with predictions based on the treadmill exercise test. The initial evaluation was slightly better at distinguishing patients with and without coronary artery disease compared with the treadmill exercise test. The initial evaluation and the treadmill exercise test had similar discriminatory performances for patients with and without severe disease and risk of death at 3 years, while for left main disease, the treadmill exercise test was slightly better for identify patients with left main disease.

Safety and adverse effects

None reported

Does the study answer the question?

In the multivariable regression model used, the following variables were significant predictors for any disease; age, gender, chest pain (type), diabetes, smoking, hyperlipidaemia, previous history of MI, and significant Q waves and ST-T wave changes. For severe disease, the following variables were significant predictors; age, gender, chest pain (type, frequency, course, nocturnal, length of time present), diabetes, smoking, hyperlipidaemia, hypertension, peripheral or cerebral artery disease, carotid bruit, previous history of MI, and significant Q waves and ST-T wave changes. For left main disease, the following variables were significant predictors; age, gender, chest pain (type), diabetes, peripheral or cerebral artery disease and carotid bruit. For survival at 3 years the following variables were significant predictors; age, gender, chest pain (frequency, course, nocturnal, peripheral or cerebral artery disease, carotid bruit, ventricular gallop, previous history of MI, significant Q waves and ST-T wave changes, conduction abnormalities, premature ventricular contractions and cardiomegaly. The likelihood of any disease, severe coronary disease, left main disease and survival was predicted from the initial history, physical examination, electrocardiogram and chest X ray (these tests were defined as the 'initial evaluation').

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During the study a chest X-ray was also performed, the results did not help in predicting coronary disease, however they could be used to predict survival.

Effect due to factor in study?

Yes

Consistency of results with other studies?

Consistent

Directly applicable to guideline population?	Correct population
Internal Validity	Well covered

Pryor DB;Shaw L;McCants CB;Lee KL;Mark DB;Harrell FE;Muhlbaier LH;Califf RM;

Value of the history and physical in identifying patients at increased risk for coronary artery disease

Ref ID 1751 Annals of internal medicine pgs: 81 to 90 1993

Study Type	Cohort	**Funding**	Agency for Health Care Policy and Research, National Heart, Lung and Blood institute, National Library of Medicine

Number of participants	1030 patients, 168 had cardiac catheterization
Inclusion/Exclusion Criteria	Inclusion: Symptomatic patients, referred for non-invasive testing for suspected coronary artery disease Exclusion: previous cardiac catheterization
Patient Characteristics	The mean age was 55, 37% were female, the mean pain frequency was 2 episodes a week, the mean durations of CAD symptoms was 12 months, 28% had typical angina symptoms, 52% atypical angina symptoms, 20% nonanginal pain, 18% progressive angina, 22% nocturnal angina, 44% smoked, 41% had a history of hypertension, 10% had diabetes, 11% had hyperlipidemia, 35% had ST-T wave changes on ECG, 18% had a history of MI, 8% had Q waves on ECG, 14% had a history of congestive heart failure, 0% had class IV congestive heart failure, 1% had ventricular gallop, 3% had peripheral vascular disease, 3% had cerebral vascular disease Of the patients who went on to have a cardiac catheterization the mean age was 56, 31% were female, the mean pain frequency was 2 episodes a week, the mean durations of CAD symptoms was 7 months, 49% had typical angina symptoms, 47% atypical angina symptoms, 4% nonanginal pain, 24% progressive angina, 24% nocturnal angina, 53% smoked, 42% had a history of hypertension, 10% had diabetes, 13% had hyperlipidemia, 42% had ST-T wave changes on ECG, 33% had a history of MI, 11% had Q waves on ECG, 11% had a history of congestive heart failure, 0% had class IV congestive heart failure, 1% had ventricular gallop, 4% had peripheral vascular disease, 2% had cerebral vascular disease. It can therefore be seen that those having a cardiac catheterization were more likely to be male, smoke, have a history of MI, have ST-T wave changes on ECG and to be suffering typical or progressive angina
Recruitment	Patients were referred for non-invasive testing for suspected coronary artery disease
Setting	Duke University Medical Centre USA
Interventions/ Test/ Factor being investigated	Physicians initial evaluation of patients with suspected CAD predicts coronary anatomy
Comparisons	The presence of significant coronary disease defined as any disease, severe disease, left main disease
Length of Study/ Follow-up	90 days
Outcome measures studied	Effectiveness of chest pain score to predict coronary artery disease
Results	The three diagnostic outcomes were; the presence of significant coronary artery disease defined as ‘any disease’ (≥ 75% luminal diameter narrowing of at least one major coronary artery), presence of severe coronary artery disease defined as ‘severe disease’ (significant obstruction of all 3 main coronary arteries or the left main coronary artery) and the presence of significant left main artery obstruction defined as ‘left main disease’ (168 patients referred for cardiac catheterization). The prognostic outcome was survival at 3 years.

In the multivariable regression model used, the following variables were significant predictors for any disease; age, gender, chest pain (type), diabetes, smoking, hyperlipidaemia, previous history of myocardial infarction, and significant Q waves and ST-T wave changes. For severe disease, the following variables were significant predictors; age, gender, chest pain (type, frequency, course, nocturnal, length of time present), diabetes, smoking, hyperlipidaemia, hypertension, peripheral or cerebral artery disease, carotid bruit, previous history of myocardial infarction, and significant Q waves and ST-T wave changes. For left main disease, the following variables were significant predictors; age, gender, chest pain (type), diabetes, peripheral or cerebral artery disease and carotid bruit. For survival at 3 years the following variables were significant predictors; age, gender, chest pain (frequency, course, nocturnal), peripheral or cerebral artery disease, carotid bruit, ventricular gallop, previous history of myocardial infarction, significant Q waves and ST-T wave changes, conduction abnormalities, premature ventricular contractions and cardiomegaly. The likelihood of any disease, severe coronary disease, left main disease and survival was predicted from the initial history, physical examination, electrocardiogram and chest X ray (these tests were defined as the 'initial evaluation'). The models which were used were based on mathematical models in a previous study (Pryor, 1983 – see extraction).
Predicted coronary artery endpoints and survival based on the initial evaluation closely corresponded to actual findings. Predictions using the initial evaluation were then compared with predictions based on the treadmill exercise test. The initial evaluation was slightly better at distinguishing patients with and without coronary artery disease compared with the treadmill exercise test. The initial evaluation and the treadmill exercise test had similar discriminatory performances for patients with and without severe disease and risk of death at 3 years, while for left main disease, the treadmill exercise test was slightly better for identify patients with left main disease.

Safety and adverse effects

None reported

Does the study answer the question?

In the multivariable regression model used, the following variables were significant predictors for any disease; age, gender, chest pain (type), diabetes, smoking, hyperlipidaemia, previous history of MI, and significant Q waves and ST-T wave changes. For severe disease, the following variables were significant predictors; age, gender, chest pain (type, frequency, course, nocturnal, length of time present), diabetes, smoking, hyperlipidaemia, hypertension, peripheral or cerebral artery disease, carotid bruit, previous history of MI, and significant Q waves and ST-T wave changes. For left main disease, the following variables were significant predictors; age, gender, chest pain (type), diabetes, peripheral or cerebral artery disease and carotid bruit. For survival at 3 years the following variables were significant predictors; age, gender, chest pain (frequency, course, nocturnal, peripheral or cerebral artery disease, carotid bruit, ventricular gallop, previous history of MI, significant Q waves and ST-T wave changes, conduction abnormalities, premature ventricular contractions and cardiomegaly. The likelihood of any disease, severe coronary disease, left main disease and survival was predicted from the initial history, physical examination, electrocardiogram and chest X ray (these tests were defined as the 'initial evaluation').

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During the study a chest X-ray was also performed, the results did not help in predicting coronary disease, however they could be used to predict survival.

Effect due to factor in study?

Yes

Consistency of results with other studies?

Consistent

Directly applicable to guideline population?	Correct population
Internal Validity	Well covered

Sox HC;Hickam DH;Marton K;Moses L;Skeff KM;Sox CH;Neal EA;

Using the patient's history to estimate the probability of coronary artery disease: a comparison of primary care and referral practices

Ref ID 1895 The American journal of medicine pgs: 7 to 14 1990

Study Type Cohort

Funding Veterans Administration Health Services Research and Development Service, Henry J. Kaiser Family Foundation and Henry J. Kaiser Family Foundation General Internal Medicine Fellowship Program

Number of participants	1074 patients
Inclusion/Exclusion Criteria	Inclusion: had at least 2 episodes of chest pain that led to the index visit. Exclusion: patients whose index visit led to a diagnosis of acute MI were excluded.
Patient Characteristics	
Recruitment	Patients admitted to Stanford University Medical Centre, or seen at Palo Alto VA Medical Center and Kaiser-Permanente Medical Center, Santa Medical Centre, USA
Setting	Primary and Secondary care USA
Interventions/ Test/ Factor being investigated	Diagnosing coronary artery disease
Comparisons	Age, men, pain brought on by exertion, having to stop all activities when pain occurs, history of MI, pain relieved within 3 minutes of taking nitroglycerin, and ≥ 20 pack years of smoking.
Length of Study/ Follow-up	Median follow up 11 months
Outcome measures studied	Effectiveness of chest pain score to predict coronary artery disease
Results	Seven clinical characteristics were identified as independent predictors of significant coronary stenosis; age > 60 years, pain brought on by exertion, patient having to stop all activities when pain occurs, history of myocardial infarction, pain relieved within 3 minutes of taking nitroglycerin, at least 20 pack years of smoking, and male gender. The following were not independent predictors of disease status; location and radiation of pain, character of pain, history of hypertension, history of hypercholesterolaemia, history of angina pectoris, pain worsened by cough, deep breathing, movement of torso, or movement of arm. The chest pain score was used to test the probability of coronary artery disease (CAD) in patients from two primary care practices (997 patients) and one angiography referral practice (166 patients). 1980 Arteriography Training Set: Score 0-4: 1 had significant CAD, 9 had insignificant CAD and the prevalence of CAD was 0.10 Score 5-9: 13 had significant CAD, 20 had insignificant CAD and the prevalence of CAD was 0.39 Score 10-14: 33 had significant CAD, 16 had insignificant CAD and the prevalence of CAD was 0.67 Score 15-19: 77 had significant CAD, 8 had insignificant CAD and the prevalence of

CAD was 0.91
Score 20-25: 34 had significant CAD, 0 had insignificant CAD and the prevalence of CAD was 1.00
The total number of patients was: 158 with significant CAD, 53 had insignificant CAD and the prevalence of CAD was 0.76

1982 Arteriography Test Set:
Score 0-4: 1 had significant CAD, 6 had insignificant CAD and the prevalence of CAD was 0.14
Score 5-9: 4 had significant CAD, 13 had insignificant CAD and the prevalence of CAD was 0.24
Score 10-14: 31 had significant CAD, 13 had insignificant CAD and the prevalence of CAD was 0.70
Score 15-19: 49 had significant CAD, 10 had insignificant CAD and the prevalence of CAD was 0.83
Score 20-25: 37 had significant CAD, 6 had insignificant CAD and the prevalence of CAD was 0.86
The total number of patients was: 122 with significant CAD, 48 had insignificant CAD and the prevalence of CAD was 0.72

VA Test Set:
Score 0-4: 0 had significant CAD, 4 had insignificant CAD and the prevalence of CAD was 0.00
Score 5-9: 9 had significant CAD, 139 had insignificant CAD and the prevalence of CAD was 0.06
Score 10-14: 27 had significant CAD, 99 had insignificant CAD and the prevalence of CAD was 0.21
Score 15-19: 64 had significant CAD, 26 had insignificant CAD and the prevalence of CAD was 0.71
Score 20-25: 33 had significant CAD, 3 had insignificant CAD and the prevalence of CAD was 0.92
The total number of patients was: 133 with significant CAD, 271 had insignificant CAD and the prevalence of CAD was 0.33

Kaiser Test Set:
Score 0-4: 0 had significant CAD, 98 had insignificant CAD and the prevalence of CAD was 0.00
Score 5-9: 7 had significant CAD, 118 had insignificant CAD and the prevalence of CAD was 0.06
Score 10-14: 4 had significant CAD, 35 had insignificant CAD and the prevalence of CAD was 0.10
Score 15-19: 6 had significant CAD, 14 had insignificant CAD and the prevalence of CAD was 0.30
Score 20-25: 6 had significant CAD, 1 had insignificant CAD and the prevalence of CAD was 0.86
The total number of patients was: 23 with significant CAD, 266 had insignificant CAD and the prevalence of CAD was 0.08

The prevalence of a coronary artery disease diagnosis in primary care patients is lower than in arteriography patients with similar chest pain histories. With the exception of the highest chest pain score subgroup, analysis on the two primary care population's show there is not perfect agreement.

Although the patients in the primary and secondary settings had similar chest pain scores derived from the clinical history, the prevalence of coronary artery disease in the primary care patients was lower than the angiography patients across the first four scores bands compared with the angiography patients, while the prevalence at the highest score band was similar in both the primary and secondary settings.

The authors concluded that health care professionals should take in to account the clinical setting when using the patient's history to estimate the probability of disease.

Safety and adverse effects

None reported

Does the study answer the question?

The chest pain score was used to test the probability of coronary artery disease in patients from two primary care practices (997 patients) and one angiography referral practice (166 patients). Although the patients in the primary and secondary settings had similar chest pain scores derived from the clinical history, the prevalence of coronary artery disease in the primary care patients was lower than the angiography

	patients across the first four scores bands compared with the angiography patients, while the prevalence at the highest score band was similar in both the primary and secondary settings. The authors concluded that health care professionals should take in to account the clinical setting when using the patient's history to estimate the probability of disease
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Correct population
Internal Validity	Well covered

Sox HC;Hickam DH;Marton K;Moses L;Skeff KM;Sox CH;Neal EA;

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Results	Seven clinical characteristics were identified as independent predictors of significant coronary stenosis; age > 60 years, pain brought on by exertion, patient having to stop all activities when pain occurs, history of myocardial infarction, pain relieved within 3 minutes of taking nitroglycerin, at least 20 pack years of smoking, and male gender. The following were not independent predictors of disease status; location and radiation of pain, character of pain, history of hypertension, history of hypercholesterolaemia, history of angina pectoris, pain worsened by cough, deep

breathing, movement of torso, or movement of arm. The chest pain score was used to test the probability of coronary artery disease (CAD) in patients from two primary care practices (997 patients) and one angiography referral practice (166 patients).

For distribution of patients among Chest Pain Score Subgroups see results in guideline.
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Safety and adverse effects	None reported
Does the study answer the question?	The chest pain score was used to test the probability of coronary artery disease in patients from two primary care practices (997 patients) and one angiography referral practice (166 patients). Although the patients in the primary and secondary settings had similar chest pain scores derived from the clinical history, the prevalence of coronary artery disease in the primary care patients was lower than the angiography patients across the first four scores bands compared with the angiography patients, while the prevalence at the highest score band was similar in both the primary and secondary settings. The authors concluded that health care professionals should take in to account the clinical setting when using the patient's history to estimate the probability of disease.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Correct population
Internal Validity	Well covered

Wu EB;Hodson F;Chambers JB;

A simple score for predicting coronary artery disease in patients with chest pain

Ref ID	394	QJM : monthly journal of the Association of Physicians	pgs:	803	to	811	2005

Study Type	Cohort	**Funding**	Grant from the special Trustee's of Guy's and St Thomas' NHS trust

Number of participants	404 patients recruited from 363 consecutive patients seen as out-patients, and 829 consecutive patients undergoing day-case coronary angiography. 155 of the 404 had an exercise test
Inclusion/Exclusion Criteria	Inclusion: chest pain for > 1 month without a previous history of MI, coronary angiography, angioplasty or coronary artery bypass grafting Exclusion: ECG showed pathological Q waves or regional wall motion abnormalities on echocardiogram
Patient Characteristics	The mean age was 60.6±9.5 years. 66% (268) were males, the mean age for males 60.5±9.1 years; 34% (137) were females, the mean ages for females was 60.8±10.2 years. Of all the patients 60% (244) had significant coronary artery disease; 40% (161) had normal coronary anatomy
Recruitment	Patients who met criteria recruited from out patients at Cardiothoracic Centre, Guy's and St Thomas' Hospital, London, UK
Setting	Guy's and St Thomas' Hospital, London, UK
Interventions/ Test/ Factor being investigated	Diagnosing chest pain
Comparisons	The chest pain score was based on: description of pain, clinical history, medication, clinical examination, stigmata of risk, resting ECG

Length of Study/ Follow-up	Not reported
Outcome measures studied	Diagnosis of coronary artery disease, or exclusion of diagnosis of coronary artery disease
Results	The chest pain score was based on the following: localisation of pain, radiation, quality of pain, duration, length of pain episode, frequency, associated features (breathlessness, digital paraesthesiae, palpation, light-headedness), precipitation (exercise, rest, any time, neck or back movement, carrying, swallowing, lying flat/stooping, emotional stress, particular situations), exacerbating / relieving factors (inspiration, GNT, genuine relief < 5 minutes) relief with (milk/antacids, belching, local massage rest). A medical history was also taken of: hypertension, hypercholesterolemia, diabetes, smoking and number of cigarettes per day, previous MI, alcohol intake per week, medication being used (aspirin, statins, beta blockers, calcium antagonists, nitrates, other), the patients weight, height, heart rhythm, systolic, diastolic, heart rate, apex position and character, intercostal space, heart murmur, heart sounds stigmata of risk (arcus, xanthelasmata, xanthomata, ear lobe crease) and a resting ECG. This chest pain score was based on a modification of the Master Questionnaire with 3 additional questions to define the exercise score, the rest and duration score. 1) if you go up a hill on 10 separate occasions how many do you experience chest pain; 2) if you have chest pain 10 times in a row how many happen when you are sitting or resting; 3) how long does the pain last for. For question 1 10/10 was described as “typical” and 1-9/10 was “atypical”; for question 2 a rest index or 0 or 1 was “typical and 2 or more was “atypical”; for question 3 pain lasting less than 5 minutes was “typical” and pain last more than 5 minutes was “atypical” Multivariant Poisson Regression Analysis showed that gender (P < 0.001), age (P < 001), relief with rest (P=0.046), dizziness (P=0.030), smoking (P=0.006), hypertension (P=0.016), hypercholesterolemia (P=0.214), diabetes (P=0.016) and chest pain score (P = 0.009) were independently differentiated those patients with and without CAD. A secondary analysis was conducted to relate the chest pain score to the Framingham and Duke Scores. The Duke Score is a weighted index based on ST-segment deviation, treadmill time and exercised-induced angina (Duke Treadmill Score = Exercise time – [5xSTdevistion] – [4xtreadmill angina]). The chest pain score was found to have a sensitivity of 91.4% and a specificity of 28%, compared to the Duke score’s sensitivity of 82.4% and specificity of 31%. The study found that the combination of the chest pain score with Framingham and the Duke score had additive predictive value for risk of coronary artery disease.
Safety and adverse effects	None reported
Does the study answer the question?	Multivariant Poisson regression analysis showed that gender (P < 0.001), age (P < 001), relief with rest (P=0.046), dizziness (P=0.030), smoking (P=0.006), hypertension (P=0.016), hypercholesterolemia (P=0.214), diabetes (P=0.016) and chest pain score were (P = 0.009) independently differentiated those patients with and without coronary artery disease. A secondary analysis was conducted to relate the chest pain score to the Framingham and Duke scores. The chest pain score was found to have a sensitivity of 91.4% and a specificity of 28%, compared to the Duke score’s sensitivity of 82.4% and specificity of 31%. The study found that the combination of the chest pain score with Framingham and the Duke score had additive predictive value for risk of coronary artery disease
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Correct population
Internal Validity	Well covered

Wu EB;Hodson F;Chambers JB;

A simple score for predicting coronary artery disease in patients with chest pain

Ref ID 394 QJM : monthly journal of the Association of Physicians pgs: 803 to 811 2005

Study Type Cohort

Funding Grant from the special Trustee's of Guy's and St Thomas' NHS trust

Number of participants	404 patients recruited from 363 consecutive patients seen as out-patients, and 829 consecutive patients undergoing day-case coronary angiography. 155 of the 404 had an exercise test
Inclusion/Exclusion Criteria	Inclusion: chest pain for > 1 month without a previous history of MI, coronary angiography, angioplasty or coronary artery bypass grafting Exclusion: ECG showed pathological Q waves or regional wall motion abnormalities on echocardiogram
Patient Characteristics	The mean age was 60.6±9.5 years. 66% (268) were males, the mean age for males 60.5±9.1 years; 34% (137) were females, the mean ages for females was 60.8±10.2 years. Of all the patients 60% (244) had significant coronary artery disease; 40% (161) had normal coronary anatomy
Recruitment	Patients who met criteria recruited from out patients at Cardiothoracic Centre, Guy's and St Thomas' Hospital, London, UK
Setting	Guy's and St Thomas' Hospital, London, UK
Interventions/ Test/ Factor being investigated	Diagnosing chest pain
Comparisons	The chest pain score was based on: description of pain, clinical history, medication, clinical examination, stigmata of risk, resting ECG
Length of Study/ Follow-up	Not reported
Outcome measures studied	Diagnosis of coronary artery disease, or exclusion of diagnosis of coronary artery disease
Results	The chest pain score was based on the following: localisation of pain, radiation, quality of pain, duration, length of pain episode, frequency, associated features (breathlessness, digital paraesthesiae, palpation, light-headedness), precipitation (exercise, rest, any time, neck or back movement, carrying, swallowing, lying flat/stooping, emotional stress, particular situations), exacerbating / relieving factors (inspiration, GNT, genuine relief < 5 minutes) relief with (milk/antacids, belching, local massage rest). A medical history was also taken of: hypertension, hypercholesterolemia, diabetes, smoking and number of cigarettes per day, previous MI, alcohol intake per week, medication being used (aspirin, statins, beta blockers, calcium antagonists, nitrates, other), the patients weight, height, heart rhythm, systolic, diastolic, heart rate, apex position and character, intercostal space, heart murmur, heart sounds stigmata of risk (arcus, xanthelasmata, xanthomata, ear lobe crease) and a resting ECG. This chest pain score was based on a modification of the Master Questionnaire with 3 additional questions to define the exercise score, the rest and duration score. 1) if you go up a hill on 10 separate occasions how many do you experience chest pain; 2) if you have chest pain 10 times in a row how many happen when you are sitting or resting; 3) how long does the pain last for. For question 1 10/10 was described as “typical” and 1-9/10 was “atypical”; for question 2 a rest index or 0 or 1 was “typical and 2 or more was “atypical”; for question 3 pain lasting less than 5 minutes was “typical” and pain last more than 5 minutes was “atypical” Multivariant Poisson Regression Analysis, showed that gender (P < 0.001), age (P < 001), relief with rest (P=0.046), dizziness (P=0.030), smoking (P=0.006), hypertension (P=0.016), hypercholesterolemia (P=0.214), diabetes (P=0.016) and chest pain score (P = 0.009) were independently differentiated those patients with and without CAD. A secondary analysis was conducted to relate the chest pain score to the Framingham and Duke Scores. The Duke Score is a weighted index based on ST-segment deviation, treadmill time and exercised-induced angina (Duke Treadmill Score = Exercise time – [5xSTdevistion] – [4xtreadmill angina]). The chest pain score

	was found to have a sensitivity of 91.4% and a specificity of 28%, compared to the Duke score's sensitivity of 82.4% and specificity of 31%. The study found that the combination of the chest pain score with Framingham and the Duke score had additive predictive value for risk of coronary artery disease.
Safety and adverse effects	None reported
Does the study answer the question?	Multivariant Poisson regression analysis showed that gender (P < 0.001), age (P < 001), relief with rest (P=0.046), dizziness (P=0.030), smoking (P=0.006), hypertension (P=0.016), hypercholesterolemia (P=0.214), diabetes (P=0.016) and chest pain score were (P = 0.009) independently differentiated those patients with and without coronary artery disease. A secondary analysis was conducted to relate the chest pain score to the Framingham and Duke scores. The chest pain score was found to have a sensitivity of 91.4% and a specificity of 28%, compared to the Duke score's sensitivity of 82.4% and specificity of 31%. The study found that the combination of the chest pain score with Framingham and the Duke score had additive predictive value for risk of coronary artery disease
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Correct population
Internal Validity	Well covered

Wu EB;Hodson F;Chambers JB;

A simple score for predicting coronary artery disease in patients with chest pain

Ref ID	394	QJM : monthly journal of the Association of Physicians	pgs:	803	to	811	2005

Study Type	Cohort	**Funding**	Grant from the special Trustee's of Guy's and St Thomas' NHS trust

Number of participants	404 patients recruited from 363 consecutive patients seen as out-patients, and 829 consecutive patients undergoing day-case coronary angiography. 155 of the 404 had an exercise test.
Inclusion/Exclusion Criteria	Inclusion: chest pain for > 1 month without a previous history of MI, coronary angiography, angioplasty or coronary artery bypass grafting. Exclusion: ECG showed pathological Q waves or regional wall motion abnormalities on echocardiogram.
Patient Characteristics	The mean age was 60.6±9.5 years. 66% (268) were males, the mean age for males 60.5±9.1 years; 34% (137) were females, the mean ages for females was 60.8±10.2 years. Of all the patients 60% (244) had significant coronary artery disease; 40% (161) had normal coronary anatomy.
Recruitment	Patients who met criteria recruited from out patients at Cardiothoracic Centre, Guy's and St Thomas' Hospital, London, UK
Setting	Guy's and St Thomas' Hospital, London, UK
Interventions/ Test/ Factor being investigated	Diagnosing chest pain
Comparisons	The chest pain score was based on: description of pain, clinical history, medication, clinical examination, stigmata of risk, resting ECG.
Length of Study/ Follow-up	Not reported

Outcome measures studied	Diagnosis of coronary artery disease, or exclusion of diagnosis of coronary artery disease
Results	The chest pain score was based on the following: localisation of pain, radiation, quality of pain, duration, length of pain episode, frequency, associated features (breathlessness, digital paraesthesiae, palpation, light-headedness), precipitation (exercise, rest, any time, neck or back movement, carrying, swallowing, lying flat/stooping, emotional stress, particular situations), exacerbating / relieving factors (inspiration, GNT, genuine relief < 5 minutes) relief with (milk/antacids, belching, local massage rest). A medical history was also taken of: hypertension, hypercholesterolemia, diabetes, smoking and number of cigarettes per day, previous MI, alcohol intake per week, medication being used (aspirin, statins, beta blockers, calcium antagonists, nitrates, other), the patients weight, height, heart rhythm, systolic, diastolic, heart rate, apex position and character, intercostal space, heart murmur, heart sounds stigmata of risk (arcus, xanthelasmata, xanthomata, ear lobe crease) and a resting ECG. This chest pain score was based on a modification of the Master Questionnaire with 3 additional questions to define the exercise score, the rest and duration score. 1) if you go up a hill on 10 separate occasions how many do you experience chest pain; 2) if you have chest pain 10 times in a row how many happen when you are sitting or resting; 3) how long does the pain last for. For question 1 10/10 was described as “typical” and 1-9/10 was “atypical”; for question 2 a rest index or 0 or 1 was “typical and 2 or more was “atypical”; for question 3 pain lasting less than 5 minutes was “typical” and pain last more than 5 minutes was “atypical” Multivariant Poisson Regression Analysis showed that gender (P < 0.001), age (P < 001), relief with rest (P=0.046), dizziness (P=0.030), smoking (P=0.006), hypertension (P=0.016), hypercholesterolemia (P=0.214), diabetes (P=0.016) and chest pain score (P = 0.009) were independently differentiated those patients with and without CAD. A secondary analysis was conducted to relate the chest pain score to the Framingham and Duke Scores. The Duke Score is a weighted index based on ST-segment deviation, treadmill time and exercised-induced angina (Duke Treadmill Score = Exercise time – [5xSTdevistion] – [4xtreadmill angina]). The chest pain score was found to have a sensitivity of 91.4% and a specificity of 28%, compared to the Duke score’s sensitivity of 82.4% and specificity of 31%. The study found that the combination of the chest pain score with Framingham and the Duke score had additive predictive value for risk of coronary artery disease.
Safety and adverse effects	None reported
Does the study answer the question?	Multivariant Poisson regression analysis showed that gender (P < 0.001), age (P < 001), relief with rest (P=0.046), dizziness (P=0.030), smoking (P=0.006), hypertension (P=0.016), hypercholesterolemia (P=0.214), diabetes (P=0.016) and chest pain score were (P = 0.009) independently differentiated those patients with and without coronary artery disease. A secondary analysis was conducted to relate the chest pain score to the Framingham and Duke scores. The chest pain score was found to have a sensitivity of 91.4% and a specificity of 28%, compared to the Duke score’s sensitivity of 82.4% and specificity of 31%. The study found that the combination of the chest pain score with Framingham and the Duke score had additive predictive value for risk of coronary artery disease
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Correct population
Internal Validity	Well covered

Grading: 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*

Cook DG;Shaper AG;

Breathlessness, angina pectoris and coronary artery disease

Ref ID 10282 The American journal of cardiology pgs: 921 to 924 1989

Study Type Cohort

Funding Royal Free Hospital, London; British Heart Foundation Research Group; Medical Research Council and Department of Health, London; The Chest Heart and Stroke Association; Scottish Home and Health Department; Greater Glasgow Health Board

Number of participants	7735 men
Inclusion/Exclusion Criteria	Random selection of men from different GP practices, patients were excluded if they had sever mental or physical disability
Patient Characteristics	Not reported
Recruitment	Random selection of men from different GP practices, patients were excluded if they had sever mental or physical disability
Setting	Primary care, UK
Interventions/ Test/ Factor being investigated	Breathlessness affecting Angina
Comparisons	Breathlessness and other risk factors
Length of Study/ Follow-up	5 years
Outcome measures studied	prevalence of Angina after 5 years
Results	Age-standardised prevalence rates of CAD by breathlessness grade: None: 6394 men, 3.5% recall, 6.5% ECG, 7% possible MI, 4.4% angina Mild: 697 men, 8.7% recall, 9.1% ECG, 12.6% possible MI, 15.5% angina Moderate: 358 men, 17.7% recall, 14.6% ECG, 21.6% possible MI, 28.8% angina Severe: 273 men, 27.6% recall, 18.5% ECG, 33.3% possible MI, 40.9% angina All: 7722 men, 5.5% recall, 7.6% ECG, 9.1% possible MI, 7.9% angina. Prevalence of angina by breathlessness grade: None: 89% none, 7% mild, 3% moderate, 1% severe Nonexertional pain: 79% none, 11% mild, 5% moderate, 4% severe Possible angina Grade 1: 51% none, 18% mild, 16% moderate, 15% severe Grade 2: 31% none, 9% mild, 17% moderate, 43% severe Definite angina Grade 1: 45% none, 22% mild, 19% moderate, 14% severe Grade 2: 30% none, 2% mild, 20% moderate, 48% severe. Mean levels of risk factors for CAD by breathlessness grade:

None: 49.9 years old, 39% smokers, 25.4 kg/m2 BMI, 144.9 mmHg systolic blood pressure, 6.30 mmol/l serum total cholesterol
Mild: 51.1 years old, 53% smokers, 26.1 kg/m2 BMI, 146.4 mmHg systolic blood pressure, 6.27 mmol/l serum total cholesterol
Moderate: 52.6 years old, 53% smokers, 26.2 kg/m2 BMI, 145.4 mmHg systolic blood pressure, 6.31 mmol/l serum total cholesterol
Severe: 53.5 years old, 52% smokers, 25.7 kg/m2 BMI, 143.4 mmHg systolic blood pressure, 6.24 mmol/l serum total cholesterol.

Age-standardised prevalence rate of angina in % by breathlessness grade and smoking:
None: 4.5% never smoked, 4.5% ex-smoker, 4.3% current smoker
Mild: 18.5% never smoked, 18.2% ex-smoker, 12.6% current smoker
Moderate: 25.7% never smoked, 26.7% ex-smoker, 30% current smoker
Severe: 25.5% never smoked, 36.5% ex-smoker, 45.9% current smoker
All: 6.2% never smoked, 7.9% ex-smoker, 8.6% current smoker.

Age-standardised prevalence rate of angina in % 5 years after initial screening:
None: 5.8% no angina, 47.1% angina
Mild: 13% no angina, 44.9% angina
Moderate: 24.6% no angina, 58.6% angina
Severe: 28.2% no angina, 74.4% angina.

Relation of breathlessness grade at screening to outcome at 5 years in men with no evidence of CAD:
None: 5228 men, 91.9% alive with no CAD, 4% alive with angina, 1.6% nonfatal MI, 0.9% dead from MI, 1.6% dead from non CAD cause
Mild: 471 men, 82.6% alive with no CAD, 10% alive with angina, 2.3% nonfatal MI, 0.8% dead from MI, 4.3% dead from non CAD cause
Moderate: 177 men, 72.7% alive with no CAD, 20.9% alive with angina, 2.1% nonfatal MI, 0.9% dead from MI, 3.4% dead from non CAD cause
Severe: 100 men, 62.8% alive with no CAD, 25.4% alive with angina, 2.7% nonfatal MI, 2.4% dead from MI, 6.7% dead from non CAD cause.

Safety and adverse effects

None

Does the study answer the question?

This study is a publication from the British Regional Heart Study.
The men in the study were classified into 3 groups based on the smoking status (never smoked, ex-smoker, current smoker), their BMI was also recorded. A modified version of the Medical Research Council Questionnaire on Respiratory Symptoms (1966 version) was also carried out. The patient's lung function was also recorded based on the forced expiratory volume in 1 second measured using a Vitalograph J49-B2 spirometer, based on 2 consecutive readings 15 seconds apart (after an initial "practice"). The men were also split into two groups based on the presence or absence of CAD was also evaluated based on the World Health Organisation questionnaire on chest pain (which cover both CAD and MI), a 3-lead ECG recording and the patient reporting being given a diagnosis of angina or MI by a doctor. The patients were followed up for 5 years with 99% of the population being followed up. At the follow up there had been 166 nonfatal heart attacks, 119 fatal heart attacks or sudden cardiac deaths and 155 deaths from non-ischemic causes.

The study applied logistic models to find the age standardised prevalence and incidence rates of angina with age being the continuous variable. The study considered the relationship between breathlessness and chest pain, with the result of men with breathlessness being more likely to have angina than those with chest pain or with non-exertional chest pain. Breathlessness was also more common in those with grade 2 angina than those with grade 1 angina (however the study states that grade1 angina only had 95 men and was too small to be used in evaluation).
The study also considered the effect of smoking, which showed that smoking was not strongly related to breathlessness in men, with the rate of angina increasing dependant upon the breathlessness grade but not with smokers. This can be seen as men who had smoked had only a 39% higher rate of angina compared to those who had never smoked. The authors concluded that smoking was not an important risk factor for angina. However breathlessness was strongly related to angina (men with grade 2 or 3 breathlessness were 5 times as likely to develop angina after 5 years as those with graded 0 or 1). There was also a strong relationship between breathlessness and the presence of signs and symptoms of CAD.

Effect due to factor in study?	Yes
Consistency of results with other studies?	Yes
Directly applicable to guideline population?	Mixed population, selected from GP practices
Internal Validity	Well covered

Question 14: Are the symptoms and description of the symptoms different in women presenting with stable chest pain of suspected cardiac origin compared with men

Grading: 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

Diamond GA;Forrester JS;

Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease

Ref ID 2196 The New England journal of medicine pgs: 1350 to 1358 1979

Study Type	Cohort	**Funding**	Not reported.

Number of participants	Two separate cohorts assessed: 4952 patients referred for coronary angiography, 23 996 autopsies
Inclusion/Exclusion Criteria	Not applicable
Patient Characteristics	Suspected stable angina in 1 cohort (patients referred for angiogram) Patients were considered to have typical angina if they had substernal discomfort brought on by physical exertion and was relieved within 10 minutes through rest or nitroglycerin. Patients were considered to have atypical angina if they had discomfort which was either not substernal or was not bought on by exertion or not relieved after 10 minutes by rest or nitroglycerin. Patients were considered to have non-anginal discomfort if they did not have 1 or more of the above characteristics. Autopsy: general population
Recruitment	Patients referred for angiography
Setting	Secondary care, USA
Interventions/ Test/ Factor being investigated	Prevalence of coronary artery disease based on age, sex and symptoms.
Comparisons	Coronary angiography in 1 cohort, evidence of stenosis in 2 cohort at autopsy.
Length of Study/ Follow-up	Not applicable
Outcome measures studied	Prevalence of coronary artery disease based on age, sex and symptoms.
Results	In 4953 patients with stable chest pain referred for angiogram; the prevalence of disease in patients with typical angina symptoms was about 90%, whereas for atypical angina patients was a 50% prevalence ($P < 0.001$) and non-cardiac chest pain patients was 16% ($P < 0.001$). The prevalence of CAD observed at autopsy is similar to that in asymptomatic patients confirmed by coronary angiography. Significant differences in disease prevalence occurred when patients were classified according to age and sex. For women the differences range from 0.3% for women aged 30 years to 39 years of age, to 7% for women aged 60 years to 69 years. Women in all age ranges had a lower prevalence compared with the respective age ranges in men The pre-test likelihood of disease for any patients (according to any combination of age, sex and symptoms) was determined by conditional-probability analysis. There are a wide range of pre-test likelihoods according to sex, gender and symptoms. For example a women with atypical symptoms and aged 35% has a pre-test likelihoods of 4% compared with 92% for a man aged 55 years with typical symptoms. The authors noted that the approach used in the study was a mathematical formalisation of the intuition of the physicians reviewing the literature, or the use of

	past experience to assess a patients' pre-test likelihoods. Both of these approaches relied upon the use of data from specific populations, but that they do provide reliable estimates of the probability of coronary artery disease based on the patients age, symptoms and gender.
Safety and adverse effects	Not reported
Does the study answer the question?	Yes. The study reviewed the literature to estimate the pre-test likelihood of disease (defined by age, sex and symptoms), and the results were analysed through Bayes' theorem of conditional probability. The studied described how the probability of CAD can be determined in a patient before testing from information readily obtained from clinical evaluation. The study showed that combining data of the estimate of disease likelihood when the patient's age and sex are known and a second estimate when the presence or absence of symptoms are known provides an estimate of the pre-test likelihood of disease for any patients based on any combination of age, sex and symptoms can be determined by conditional-probability analysis. For example, the likelihood of a woman having CAD at age ranges less than 59 years and with typical angina symptoms will be lower than a man with in the comparable age ranges.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Patients in cohort used to develop theoretical pre-test likelihoods had stable chest pain, directly applicable to the guideline.
Internal Validity	Well covered

Zaman MJ;Junghans C;Sekhri N;Chen R;Feder GS;Timmis AD;Hemingway H;

Presentation of stable angina pectoris among women and South Asian people.[see comment]

Ref ID 25388 CMAJ Canadian Medical Association Journal 179(7):659-67, pgs: 659 to 667 2008

Study Type Cohort

Funding In part, British Heart Foundation for primary author

Number of participants	Of 11 082 patients seen at the rapid chest pain access clinic the following patients where excluded; 579 previous CAD, 246 patients diagnosed with ACS on day of visit, 448 prior visit to the unit during study period, 291 no chest pain, 501 due to missing data, 83 pain not diagnosed with angina, 40 not tracked by the Office for National Statistics, 968 excluded as other ethnic background (not Caucasian or Asian). Thus of the final number of people identified (7794), 2676 were Caucasian women, 2929 were Caucasian men, 980 were South Asian women, and 1209 were South Asian men
Inclusion/Exclusion Criteria	Inclusion: suspected angina, recent onset chest pain
Patient Characteristics	Women South Asian median age 57.6 years (49 to 67 years), Women Caucasian median age 50.6 years (42 to 58 years) ($P < 0.001$), Men South Asian median age 49.8 years (41 to 69 years), Men Caucasian median age 54.7 years (45 to 65 years) ($P < 0.001$). South Asian versus Caucasian women more likely to have diabetes and hypertension, less likely to smoke. South Asian versus Caucasian men more likely to have hypertension, less likely to smoke.
Recruitment	Consecutive recent onset chest pain from 6 rapid access chest pain clinics
Setting	UK rapid access chest pain clinics

Interventions/ Test/ Factor being investigated	Gender and race presentation atypical versus typical pain
Comparisons	Gender and race presentation atypical versus typical pain, outcomes of death from ACS and hospital admission due to ACS (coded according to ICD-10 classification) determined up to 3 years of clinic visit.
Length of Study/ Follow-up	3 years from clinic visit
Outcome measures studied	Outcomes of death from ACS and hospital admission due to ACS (coded according to ICD-10 classification)
Results	More women than men reported atypical chest pain symptoms (56.5% versus 54.5%, respectively P = 0.054). Cardiologists were more likely to describe the symptoms of women as atypical compared with men (73.3% agreement between cardiologist summary and the symptom score, kappa statistic 0.43). With respect to symptoms and diagnosis, sex did not modify the association between exercise echocardiology results and receiving a diagnosis of angina, and after excluding patients with a positive exercise test result, cardiologist and typical symptom scores both remained predictive of a diagnosis of angina. With respect to symptoms and prognosis, using cardiologist summaries typical symptoms in women were more strongly associated with coronary death or ACS (hazard ratio 3.74, 95% CI 2.80 to 5.01) than among men (hazard ratio 1.51, 95% CI 1.16 to 1.97, P < 0.001). This finding was also true for symptom scores (women; hazard ratio 2.30, 95% CI 1.70 to 3.11, men; hazard ratio 1.23, 95% CI 0.96 to 1.57, P < 0.002). According to cardiologist summaries and symptom scores, women with typical symptoms were more likely than men to have coronary outcomes (cardiologist summaries for women hazard ratio 1.49, 95% CI 1.09 to 2.04, and symptom score for women hazard ratio 1.39, 95% CI 1.06 to 1.84). Women with atypical symptoms were less likely than men with atypical symptoms to experience a coronary outcome (unadjusted log rank test P = 0.001), although adjusted Cox regression ratios showed that atypical pain had similar prognostic value for coronary outcomes for women and men. The authors stated that compared to those with atypical chest pain, women with typical symptoms had worse clinical outcomes More South Asians compared with Caucasians reported atypical chest pain symptoms (59.9% versus 52.5%, respectively P < 0.001), and the cardiologist described more South Asians as having atypical presentation compared with Caucasians. South Asians were also more likely to report pain that was not associated with exercise. With respect to symptoms and diagnosis, ethnicity did not modify the association between exercise echocardiology results and receiving a diagnosis of angina, and after excluding patients with a positive exercise test result, cardiologist and typical symptom scores both remained predictive of a diagnosis of angina. According to cardiologist summaries and symptom scores, South Asians with typical symptoms were as likely as Caucasians with typical symptoms to have a coronary outcome for cardiologist summaries (hazard ratio 1.27, 95% CI 0.89 to 1.81), and more likely with symptom scores (hazard ratio 1.41, 95% CI 1.04 to 1.91). Among South Asians with atypical symptoms, the symptom score was associated with coronary outcomes (unadjusted log rank test P = 0.30), although adjusted Cox regression ratios showed that atypical pain had similar prognostic value for coronary outcomes across ethnic background.
Safety and adverse effects	Not applicable
Does the study answer the question?	The authors stated that compared to those with atypical chest pain, women with typical symptoms had worse clinical outcomes, with atypical chest pain, South Asians with typical symptoms had worse clinical outcomes.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Chest pain patients with suspected angina, directly relevant to guideline

Internal Validity	Well covered

Question: 15 Are the symptoms and description of the symptoms different in Black and Ethnic Minorities presenting with stable chest pain of suspected cardiac origin compared with Caucasians

Grading: 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

Zaman MJ;Junghans C;Sekhri N;Chen R;Feder GS;Timmis AD;Hemingway H;

Presentation of stable angina pectoris among women and South Asian people.[see comment]

Ref ID 25388 CMAJ Canadian Medical Association Journal 179(7):659-67, pgs: 659 to 667 2008

Study Type Cohort

Funding

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Question 16: What is the utility (incremental value) and cost effectiveness of the resting ECG in evaluation of individuals with stable chest pain of suspected cardiac origin?

Grading: 1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Chun AA;McGee SR;

Bedside diagnosis of coronary artery disease: a systematic review

Ref ID 10275 The American journal of medicine pgs: 334 to 343 2004

Study Type Systematic Review

Funding Not reported

Number of participants 64 studies

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

The paper reviewed both studies of acute patients and stable patients.
Acute patients
The review considered patients with acute chest pain of suspected cardiac origin, ECG changes were found to the most discriminating criteria for the diagnosis of acute MI compared with signs and symptoms and risk factors. For a normal ECG the sensitivity was 1 to 13%, specificity was 48 to 77%, LR+ 0.20 (95%CI 0.1 to 0.3) and LR- 1.4 (95% CI 1.4 to 1.6). For ST-T wave abnormalities the sensitivity was 5 to 7%, specificity was 47 to 77%, LR+ 0.20 (95%CI 0.1 to 0.6) and LR- 1.5 (95% CI 0.9 to 2.6). For ST elevation the sensitivity was 31 to 49%, specificity was 97 to 100%, LR+ 22 (95%CI 16 to 30) and LR- 0.6 (95% CI 0.6 to 0.6). For ST depression the sensitivity was 20 to 62%, specificity was 88 to 96%, LR+ 4.5 (95%CI 3.6 to 5.6) and LR- 0.8 (95% CI 0.7 to 0.9). Q wave had a sensitivity of 10 to 34% and a specificity of 96 to 100%, LR+ 22 (95% CI 7.6 to 62) and LR- 0.8 (95% CI 0.8 to 0.9). T wave inversion had a sensitivity of 9 to 39%, and a specificity of 84 to 94%, LR+ 2.2 (95%CI 1.8 to 2.6) and LR- 0.9 (95% CI 0.8 to 1.0).

The review found that for diagnosing coronary artery disease in patients with stable chest pain the ECG gave little additional diagnostic information to the history and risk factor findings.

Stable patients:
Most studies, in patients presenting with stable intermittent chest pain were then referred for coronary angiography. The majority of these studies excluded patients

	with valvular heart disease or non-ischaemic cardiomyopathy. The studies used either > 50% stenosis or 70-75% stenosis off any epicardial vessel as the diagnostic standard. Patients presenting with acute MI were hospitalised for further monitoring and testing. The review found that for diagnosing coronary artery disease the ECG gave little additional diagnostic information. A normal ECG gave a sensitivity of 23 to 33%, a specificity of 50-69%, LR+ 0.7 (95%CI 0.3 to 1.6) and a LR- 1.2 (95%CI 0.8 to 1.9). For ST-T wave abnormalities the sensitivity was 14 to 44%, specificity was 73 to 93%, LR+ 1.4 (95%CI 1.0 to 1.9) and LR- 0.9 (95% CI 0.9 to 1.0).
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Correct population
Internal Validity	

Grading: 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

Pryor DB;Shaw L;McCants CB;Lee KL;Mark DB;Harrell FE;Muhlbaier LH;Califf RM;

Value of the history and physical in identifying patients at increased risk for coronary artery disease

Ref ID 1751 Annals of internal medicine pgs: 81 to 90 1993

Study Type Cohort

Funding Agency for Health Care Policy and Research, National Heart, Lung and Blood institute, National Library of Medicine

Number of participants	1030 patients, 168 had cardiac catheterization
Inclusion/Exclusion Criteria	Inclusion: Symptomatic patients, referred for non-invasive testing for suspected coronary artery disease Exclusion: previous cardiac catheterization
Patient Characteristics	The mean age was 55, 37% were female, the mean pain frequency was 2 episodes a week, the mean durations of CAD symptoms was 12 months, 28% had typical angina symptoms, 52% atypical angina symptoms, 20% nonanginal pain, 18% progressive angina, 22% nocturnal angina, 44% smoked, 41% had a history of hypertension, 10% had diabetes, 11% had hyperlipidemia, 35% had ST-T wave changes on ECG, 18% had a history of MI, 8% had Q waves on ECG, 14% had a history of congestive heart failure, 0% had class IV congestive heart failure, 1% had ventricular gallop, 3% had peripheral vascular disease, 3% had cerebral vascular disease Of the patients who went on to have a cardiac catheterization the mean age was 56, 31% were female, the mean pain frequency was 2 episodes a week, the mean durations of CAD symptoms was 7 months, 49% had typical angina symptoms, 47% atypical angina symptoms, 4% nonanginal pain, 24% progressive angina, 24% nocturnal angina, 53% smoked, 42% had a history of hypertension, 10% had diabetes, 13% had hyperlipidemia, 42% had ST-T wave changes on ECG, 33% had a history of MI, 11% had Q waves on ECG, 11% had a history of congestive heart failure, 0% had class IV congestive heart failure, 1% had ventricular gallop, 4% had peripheral vascular disease, 2% had cerebral vascular disease. It can therefore be seen that those having a cardiac catheterization were more likely to be male, smoke, have a history of MI, have ST-T wave changes on ECG and to be suffering typical or progressive angina
Recruitment	Patients were referred for non-invasive testing for suspected coronary artery disease
Setting	Duke University Medical Centre USA
Interventions/ Test/ Factor being investigated	Physicians initial evaluation of patients with suspected CAD predicts coronary anatomy
Comparisons	The presence of significant coronary disease defined as any disease, severe disease, left main disease
Length of Study/ Follow-up	90 days
Outcome measures studied	Effectiveness of chest pain score to predict coronary artery disease
Results	The three diagnostic outcomes were; the presence of significant coronary artery disease defined as ‘any disease’ (≥ 75% luminal diameter narrowing of at least one major coronary artery), presence of severe coronary artery disease defined as ‘severe disease’ (significant obstruction of all 3 main coronary arteries or the left main coronary artery) and the presence of significant left main artery obstruction defined as ‘left main disease’ (168 patients referred for cardiac catheterization). The prognostic

	outcome was survival at 3 years. In the multivariable regression model used, the following variables were significant predictors for any disease; significant Q waves and ST-T wave changes (as well as age, gender, chest pain (type), diabetes, smoking, hyperlipidaemia and previous history of myocardial infarction). For severe disease, the following variables were significant predictors; significant Q waves and ST-T wave changes (as well as age, gender, chest pain (type, frequency, course, nocturnal, length of time present), diabetes, smoking, hyperlipidaemia, hypertension, peripheral or cerebral artery disease, carotid bruit and previous history of myocardial infarction). For left main disease ECG changes were not significant predictors. For survival at 3 years the following variables were significant predictors; significant Q waves and ST-T wave changes, conduction abnormalities, (as well as age, gender, chest pain (frequency, course, nocturnal), peripheral or cerebral artery disease, carotid bruit, ventricular gallop, previous history of myocardial infarction, premature ventricular contractions and cardiomegaly). The likelihood of any disease, severe coronary disease, left main disease and survival was predicted from the initial history, physical examination, electrocardiogram and chest X ray (these tests were defined as the 'initial evaluation'). The models which were used were based on mathematical models in a previous study (Pryor, 1983 – see extraction). Predicted coronary artery endpoints and survival based on the initial evaluation closely corresponded to actual findings. Predictions using the initial evaluation were then compared with predictions based on the treadmill exercise test. The initial evaluation was slightly better at distinguishing patients with and without coronary artery disease compared with the treadmill exercise test. The initial evaluation and the treadmill exercise test had similar discriminatory performances for patients with and without severe disease and risk of death at 3 years, while for left main disease, the treadmill exercise test was slightly better for identify patients with left main disease.
Safety and adverse effects	None reported
Does the study answer the question?	In the multivariable regression model used, the following variables were significant predictors for any disease; significant Q waves and ST-T wave changes. For severe disease, the following variables were significant predictors; significant Q waves and ST-T wave changes. For left main disease ECG results were not significant predictors. For survival at 3 years the following variables were significant predictors; significant Q waves and ST-T wave changes. The likelihood of any disease, severe coronary disease, left main disease and survival was predicted from the initial history, physical examination, electrocardiogram and chest X ray (these tests were defined as the 'initial evaluation'). Predicted coronary artery endpoints and survival based on the initial evaluation closely corresponded to actual findings. Predictions using the initial evaluation were then compared with predictions based on the treadmill exercise test. The initial evaluation was slightly better at distinguishing patients with and without coronary artery disease compared with the treadmill exercise test. The initial evaluation and the treadmill exercise test had similar discriminatory performances for patients with and without severe disease and risk of death at 3 years, while for left main disease, while the treadmill exercise test was slightly better for identify patients with left main disease. The models which were used were based on mathematical models in a previous study (Pryor, 1983 – see extraction).
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent
Directly applicable to guideline population?	Correct population
Internal Validity	Well covered

Grading: 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

Pryor DB;Shaw L;McCants CB;Lee KL;Mark DB;Harrell FE;Muhlbaier LH;Califf RM;

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Recruitment	Patients were referred for non-invasive testing for suspected coronary artery disease
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Comparisons	The presence of significant coronary disease defined as any disease, severe disease, left main disease
Length of Study/ Follow-up	90 days
Outcome measures studied	Effectiveness of chest pain score to predict coronary artery disease
Results	The three diagnostic outcomes were; the presence of significant coronary artery disease defined as ‘any disease’ (≥ 75% luminal diameter narrowing of at least one major coronary artery), presence of severe coronary artery disease defined as ‘severe disease’ (significant obstruction of all 3 main coronary arteries or the left main coronary artery) and the presence of significant left main artery obstruction defined as ‘left main disease’ (168 patients referred for cardiac catheterization). The prognostic

outcome was survival at 3 years.
In the multivariable regression model used, the following variables were significant predictors for any disease; age, gender, chest pain (type), diabetes, smoking, hyperlipidaemia, previous history of myocardial infarction, and significant Q waves and ST-T wave changes. For severe disease, the following variables were significant predictors; age, gender, chest pain (type, frequency, course, nocturnal, length of time present), diabetes, smoking, hyperlipidaemia, hypertension, peripheral or cerebral artery disease, carotid bruit, previous history of myocardial infarction, and significant Q waves and ST-T wave changes. For left main disease, the following variables were significant predictors; age, gender, chest pain (type), diabetes, peripheral or cerebral artery disease and carotid bruit. For survival at 3 years the following variables were significant predictors; age, gender, chest pain (frequency, course, nocturnal), peripheral or cerebral artery disease, carotid bruit, ventricular gallop, previous history of myocardial infarction, significant Q waves and ST-T wave changes, conduction abnormalities, premature ventricular contractions and cardiomegaly. The likelihood of any disease, severe coronary disease, left main disease and survival was predicted from the initial history, physical examination, electrocardiogram and chest X ray (these tests were defined as the 'initial evaluation').
Predicted coronary artery endpoints and survival based on the initial evaluation closely corresponded to actual findings. Predictions using the initial evaluation were then compared with predictions based on the treadmill exercise test. The initial evaluation was slightly better at distinguishing patients with and without coronary artery disease compared with the treadmill exercise test. The initial evaluation and the treadmill exercise test had similar discriminatory performances for patients with and without severe disease and risk of death at 3 years, while for left main disease, the treadmill exercise test was slightly better for identify patients with left main disease.

Safety and adverse effects

None reported

Does the study answer the question?

In the multivariable regression model used, the following variables were significant predictors for any disease; age, gender, chest pain (type), diabetes, smoking, hyperlipidaemia, previous history of MI, and significant Q waves and ST-T wave changes. For severe disease, the following variables were significant predictors; age, gender, chest pain (type, frequency, course, nocturnal, length of time present), diabetes, smoking, hyperlipidaemia, hypertension, peripheral or cerebral artery disease, carotid bruit, previous history of MI, and significant Q waves and ST-T wave changes. For left main disease, the following variables were significant predictors; age, gender, chest pain (type), diabetes, peripheral or cerebral artery disease and carotid bruit. For survival at 3 years the following variables were significant predictors; age, gender, chest pain (frequency, course, nocturnal, peripheral or cerebral artery disease, carotid bruit, ventricular gallop, previous history of MI, significant Q waves and ST-T wave changes, conduction abnormalities, premature ventricular contractions and cardiomegaly. The likelihood of any disease, severe coronary disease, left main disease and survival was predicted from the initial history, physical examination, electrocardiogram and chest X ray (these tests were defined as the 'initial evaluation').

Predicted coronary artery endpoints and survival based on the initial evaluation closely corresponded to actual findings. Predictions using the initial evaluation were then compared with predictions based on the treadmill exercise test. The initial evaluation was slightly better at distinguishing patients with and without coronary artery disease compared with the treadmill exercise test. The initial evaluation and the treadmill exercise test had similar discriminatory performances for patients with and without severe disease and risk of death at 3 years, while for left main disease, while the treadmill exercise test was slightly better for identify patients with left main disease. The models which were used were based on mathematical models in a previous study

During the study a chest X-ray was also performed, the results did not help in predicting coronary disease, however they could be used to predict survival.

Effect due to factor in study?

Yes

Consistency of results with other studies?

Consistent

Directly applicable to guideline population?	Correct population
Internal Validity	Well covered

Question 17: What is the diagnostic utility of calcium scoring for the evaulation of patients with stable chest pain of cardiac origin.

Grading: 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

Becker CR;Knez A;Jakobs TF;Aydemir S;Becker A;Schoepf UJ;Bruening R;Haberl R;Reiser MF;

Detection and quantification of coronary artery calcification with electron-beam and conventional CT

Ref ID 11854 Eur Radiol pgs: 620 to 624 1999

Study Type Diagnostic **Funding** Not reported.

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question? 106 consecutive patients, 81% had positive calcium score. Mean Agatston score and Volume score were 401±382 (range 0 to 6941) and 348±299 (range 0 to 5827). Total calcium scores were higher for men compared with women regardless of angiographic status (P = 0.001). Overall sensitivity and specificity for both scores to predict stenosis was 99% and 37%, respectively, when calcification of > 1 was used as a cut-off. Sensitivity and specificity dependant upon calcium scores threshold. There was a close correlation in diagnostic accuracy of the Agatston score compared with the Volume score (r = 0.99).

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population? The results are directly applicable.

Internal Validity

Budoff MJ;Diamond GA;Raggi P;Arad Y;Guerci AD;Callister TQ;Berman D;

Continuous probabilistic prediction of angiographically significant coronary artery disease using electron beam tomography

Ref ID 9143 Circulation pgs: 1791 to 1796 2002

Study Type Diagnostic **Funding** Not reported.

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question? Of the 1851 patients, 1466 (79%) had a total calcium score of > 0 (range from 1 to 6649). Overall sensitivity prediction of obstructive CAD was 96% and specificity was 40% for calcium scoring. For calcium scores >20, >80 and >100, sensitivity decreased from 90% to 79% to 76%, specificity increased from 58% to 72% to 75%. Of 1851 patients, 938 (53%) had luminal stenosis greater 50% in 1 or more vessels, and their mean total calcium score was 608 (range 0 to 6646). Calcium scores were lower for patients without obstructive disease (838 patients, mean calcium score 123 with range 0 to 3761, P > 0.001) compared with patients with obstructive disease. Calcium scoring considerably alters the post test probability across a wide range of patients. Patients that exhibited the greatest change from pre- to post-test probability were those patients with pre-test probabilities ranging from 20% to 70%.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population? The results are directly applicable.

Internal Validity

Haberl,R.; Becker,A.; Leber,A.; Knez,A.; Becker,C.; Lang,C.; Bruning,R.; Reiser,M.; Steinbeck,G.

Correlation of coronary calcification and angiographically documented stenoses in patients with suspected coronary artery disease: results of 1,764 patients

Ref ID 10437 Journal of the American College of Cardiology pgs: 451 to 457 2001

Study Type Diagnostic **Funding**

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question? Men had higher calcium compared with women, increasing age was associated with higher scores, and calcium scores in patients with coronary artery disease were higher than those patients without coronary artery disease. No calcium was detected in 128 (23.7%) of 540 men and in 116 (40.8%) of 284 women without significant coronary artery disease, as compared with 5 (0.7%) of 685 men and 0 of 255 women with coronary stenoses greater than or equal to 50%. Thus, exclusion of coronary calcification was associated with an extremely low probability of stenoses greater than or equal to 50% in men and women. At various score ranges. The sensitivities for calcium scores were higher than their respective specificities and this was especially marked for a score > 0 (any calcium detected) (sensitivities; 99% in men and 100% in women, specificities; 23% in men and 40% in women).

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population? results are directly applicable.

Internal Validity Well covered

Knez A;Becker A;Leber A;White C;Becker CR;Reiser MF;Steinbeck G;Boekstegers P;

Relation of coronary calcium scores by electron beam tomography to obstructive disease in 2,115 symptomatic patients

Ref ID 6184 Am J Cardiol pgs: 1150 to 1152 2004

Study Type Diagnostic **Funding** Not reported

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

2115 patients referred by primary care physicians with suspected myocardial ischaemia (with no prior CAD), 1789 patients (84%) had positive Ca score (> 0). Patients with CAD versus patients without CAD Agatston score 492±1124 versus 323±842 / Volumetric 486±842 versus 53± 175. No CAD found in 326 symptomatic patients without coronary calcium (7 men and 1 woman had no calcium but had significant luminal stenosis on coronary angiography). Sensitivity and specificity for presence of any coronary calcium being predicative of obstructive angiographic disease were 99% and 28% respectively. For prediction of coronary stenosis a Volume score in the 75th percentile best compromise of a sensitivity 85% and specificity 80%, an Agatston score sensitivity 86% and specificity 75%. ROC curve analysis showed best results for patients age < 40 years.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

The results are directly applicable.

Internal Validity

Konieczynska M;Tracz W;Pasowicz M;Przewlocki T;

Use of coronary calcium score in the assessment of atherosclerotic lesions in coronary arteries

Ref ID 2708 Kardiol Pol pgs: 1073 to 1079 2006

Study Type Diagnostic

Funding Not reported.

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

340 patients had mean calcium score 271±606 (range 0 to 7002). 92 patients had score of 0 / 248 patients > 0. 162 patients (48%) no significant angiographic legions. Mean calcium scores increased with coronary artery disease severity, and the calcium score mean differences were significant comparing patients without coronary stenosis, and patients with vessel disease, respectively (P < 0.001). Patients with > 70% stenosis and three-vessel disease had median score of 3740 (range 2635 to 4716, 3 patients). For calcium score greater or equal to 56 sensitivity 86% and specificity 85%. PPV 86% and NPV 84%. 92 patients (27%) had calcium scores of 0: 44 women and 48 men. In 44 women coronary angiography no stenosis. In 6 men (6.5%) with calcium scores of 0, coronary angiography found stenoses; single vessel disease in 3 men, 2 vessel disease in 2 men, and 3 vessel disease in 1 man.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

The results are directly applicable.

Internal Validity

Pundziute G;Schuijf JD;Jukema JW;Lamb HJ;de RA;van der Wall EE;Bax JJ;

Impact of coronary calcium score on diagnostic accuracy of multislice computed tomography coronary angiography for detection of coronary artery disease

Ref ID 2334 J Nucl Cardiol pgs: 36 to 43 2007

Study Type Diagnostic

Funding European Society of Cardiology and Netherlands Heart Foundation.

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting	
Interventions/ Test/ Factor being investigated	
Comparisons	
Length of Study/ Follow-up	
Outcome measures studied	
Results	
Safety and adverse effects	
Does the study answer the question?	41 patients 16 slice-CT and 60 patients 64-slcie CT. 16-slice MSCT: coronary angiography detected obstructive coronary lesions in 18 (44%) patients, and overall calcium score sensitivity and specificity values 89% and 87%. 64-slice MSCT: coronary angiography detected obstructive coronary lesions in 32 (53%) patients, and the overall sensitivity and specificity values 91% and 96%. There was little difference in the diagnostic accuracy of 16- and 64-slice MSCT between the four Agatston groups (0 to 100, 101 to 400, > 400 and > 100) Patients with > 70% stenosis and only single vessel involvement had a median score of 482 (range 23 to 2450, 12 patients).
Effect due to factor in study?	
Consistency of results with other studies?	
Directly applicable to guideline population?	The results are directly applicable.
Internal Validity	

Grading: 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

Herzog C;Britten M;Balzer JO;Mack MG;Zangos S;Ackermann H;Schaechinger V;Schaller S;Flohr T;Vogl TJ;

Multidetector-row cardiac CT: diagnostic value of calcium scoring and CT coronary angiography in patients with symptomatic, but atypical, chest pain

Ref ID 6464 Eur Radiol pgs: 169 to 177 2004

Study Type Diagnostic **Funding** Not reported.

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question? 38 consecutive patients. For calcium score > 0: sensitivity 94%, specificity 25%, PPV 52%, NPV 80%. For calcium score > 400, sensitivity 67%, specificity 25%, PPV 75%, NPV 72%. Highly significant correlation between calcium score and degree of CAD. Patients with no signs of atherosclerosis from coronary angiography (20 patients) mean total scores of 104 (range 0 to 1459). Patients with > 70% stenosis and only single vessel involvement had a median score of 482 (range 23 to 2450, 12 patients). Patients with > 70% stenosis and three-vessel disease had median score of 3740 (range 2635 to 4716, 3 patients).

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population? The results are directly applicable.

Internal Validity

Kitamura A;Kobayashi T;Ueda K;Okada T;Awata N;Sato S;Shimamoto T;

Evaluation of coronary artery calcification by multi-detector row computed tomography for the detection of coronary artery stenosis in Japanese patients

Ref ID 4238 J Epidemiol pgs: 187 to 193 2005

Study Type Diagnostic **Funding** Not reported.

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question? 38 consecutive patients. For calcium score > 0: sensitivity 94%, specificity 25%, PPV 52%, NPV 80%. For calcium score > 400, sensitivity 67%, specificity 25%, PPV 75%, NPV 72%. Highly significant correlation between calcium score and degree of CAD. Patients with no signs of atherosclerosis from coronary angiography (20 patients) mean total scores of 104 (range 0 to 1459). Patients with > 70% stenosis and only single vessel involvement had a median score of 482 (range 23 to 2450, 12 patients). Patients with > 70% stenosis and three-vessel disease had median score of 3740 (range 2635 to 4716, 3 patients).

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population? The results are directly applicable.

Internal Validity

Lau GT;Ridley LJ;Schieb MC;Brieger DB;Freedman SB;Wong LA;Lo SK;Kritharides L;

Coronary artery stenoses: detection with calcium scoring, CT angiography, and both methods combined

Ref ID 4898 Radiology pgs: 415 to 422 2005

Study Type Diagnostic **Funding** Departments of Cardiology and Radiology, Concord

Hospital, National Heart Foundation of Australia and Pfizer Cardiovascular Lipid Research Grant.

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question? 50 consecutive patients. Coronary stenosis greater 50% present in 30 (60%) of 50 patients. 14 patients had single vessel disease 16 sixteen patients had multivessel disease. Sensitivity and specificity varied according to calcium score thresholds. Mean calcium scores were higher in patients with stenosis compared with patients without stenosis: 700±541 versus 99±140 (P < 0.001). Calcium score to discriminate between the presence or absence of stenosis greater for patients than for individual vessels and segments as demonstrated by ROC curve analysis (area under ROC curve 0.88, 0.84 and 0.74, respectively).

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population? The results are directly applicable.

Internal Validity

Raff GL;Gallagher MJ;O'Neill WW;Goldstein JA;

Diagnostic accuracy of noninvasive coronary angiography using 64-slice spiral computed tomography.

Ref ID 4496 J Am Coll Cardiol pgs: 552 to 557 2005

Study Type Diagnostic

Funding Ministrelli Cardiovascular Research Fund.

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

70 consecutive patients. The mean calcium score in patients was 326±472. 35 patients: scores from 0 to 100 / 17 patients scores of 101 to 400, and 18 out of 70 had scores of 401 to 1804. When a calcium score was low (0 to 100), sensitivity, specificity, and positive and negative predictive values for the presence of significant stenosis (stenosis > 50%) were 94%, 95%, 94% and 95%. Diagnostic accuracy was also good for score 101 to 400, however, with extreme calcification the specificity and negative predictive values were reduced (both 67%).

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

The results are directly applicable.

Internal Validity

Rubinshtein R;Gaspar T;Halon DA;Goldstein J;Peled N;Lewis BS;

Prevalence and extent of obstructive coronary artery disease in patients with zero or low calcium score undergoing 64-slice cardiac multidetector computed tomography for evaluation of a chest pain syndrome

Ref ID 2317 Am J Cardiol pgs: 472 to 475 2007

Study Type Diagnostic

Funding Not reported.

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting	
Interventions/ Test/ Factor being investigated	
Comparisons	
Length of Study/ Follow-up	
Outcome measures studied	
Results	
Safety and adverse effects	
Does the study answer the question?	231 low to intermediate risk CAD based on calcium score calcium score patients. Obstructive CAD (greater than 50%) in 9 patients (7%) with calcium score = 0. In patients with a low calcium score (1 to 100) obstructive CAD in 18 patients. Highly significant correlation between calcium score and degree of CAD. Patients with no signs of atherosclerosis from coronary angiography (20 patients) mean total scores of 104 (range 0 to 1459).
Effect due to factor in study?	
Consistency of results with other studies?	
Directly applicable to guideline population?	The results are directly applicable.
Internal Validity	

Question 18: What is the diagnostic utility of non-invasive and invasive tests for the evaluation of patients with stable chest pain of suspected cardiac origin.

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Sharples L;Hughes V;Crean A;Dyer M;Buxton M;Goldsmith K;Stone D;

Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial. [Review] [207 refs]

Ref ID 527 Health Technol Assess pgs: 1 to 115 2007

Study Type Diagnostic **Funding** HTA NHS R&D programme.

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

The aim of the study was to demonstrate equivalence in exercise time between those randomised to functional tests (SPECT, MRI, stress echo) compared with angiography. The clinical outcome measure was exercise time (Modified Bruce protocol) at 18 months. After initial testing, there were unequivocal results for 98% of angiography, 94% of SPECT (P = 0.05), 78% of MRI (P < 0.001) and 90% of stress echocardiography patients (P < 0.001). Twenty two percent of SPECT patients, 20% of MRI patients and 25% of stress echo patients were not subsequently referred for an angiogram. Positive functional tests were confirmed by positive angiography in 83% of SPECT patients, 89% of MRI patients and 84% of stress echo patients. Negative functional tests were followed by positive angiograms in 31% of SPECT patients, 52% of MRI patients and 48% of stress echo patients tested. Coronary artery bypass graft surgery was performed in 10% of the angiography group, 11% in the MRI group and 13% in both the SPECT and stress echo group. Percutaneous coronary artery intervention was performed in 25% of the angiography group, 18% in the SPECT group and 23% in both the MRI and stress echo group.

At 18 months, there was no clinical difference in total exercise time comparing SPECT and stress echo with angiography. The MRI group had significantly shorter mean total exercise time compared with the angiography group (mean 35 seconds less (P < 0.05) with an upper limit of the CI 1.14 minutes less than in the angiography group). It was concluded that between 20 to 25% patients can avoid invasive testing using functional testing as a gateway to angiography without substantial effects on

	outcome. MRI had the largest number of test failures and in this study had the least practical use in screening patients with suspected CAD, although it had similar outcomes to stress echo.
Effect due to factor in study?	
Consistency of results with other studies?	
Directly applicable to guideline population?	The results are directly applicable to the guideline.
Internal Validity	

Grading: 1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Gianrossi R;Detrano R;Mulvihill D;Lehmann K;Dubach P;Colombo A;McArthur D;Froelicher V;

Exercise-induced ST depression in the diagnosis of coronary artery disease. A meta-analysis. [Review] [171 refs]

Ref ID 17910 Circulation pgs: 87 to 98 1989

Study Type Systematic Review **Funding** Not reported.

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question? The SR reports that there are wide variabilities in the sensitivities and the specificities in the identified 147 diagnostic studies (mean sensitivity, 68%; range, 23-100%; SD, 16%; and mean specificity, 77%; range, 17-100%; SD, 17%). These differences cannot be explained by publication year, but lower sensitivities are reported in studies with consider additional tests in conjunction with exercise ECG.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population? The results of the study are applicable to the guideline.

Internal Validity

Grading: 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

Danias PG;Roussakis A;Ioannidis JP;

Diagnostic performance of coronary magnetic resonance angiography as compared against conventional X-ray angiography: a meta-analysis. [Review] [60 refs]

Ref ID 5534 J Am Coll Cardiol pgs: 1867 to 1876 2004

Study Type Diagnostic **Funding** Not stated.

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question? The SR examined magnetic resonance angiography diagnostic performance at the segment, vessel and patient level, and meta-analysis found that in evaluable segments of native coronary arteries, coronary magnetic resonance angiography has moderately high sensitivity for detecting significant proximal stenosis

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population? The results of the SR are directly applicable to the guideline.

Internal Validity

Heijenbrok-Kal MH;Fleischmann KE;Hunink MG;

Stress echocardiography, stress single-photon-emission computed tomography and electron beam computed tomography for the assessment of coronary artery disease: a meta-analysis of diagnostic performance

Ref ID 1215 Am Heart J pgs: 415 to 423 2007

Study Type Diagnostic

Funding Netherlands Organisation for Scientific Research (program grant 904-66-09) and grant from American Society of Echocardiology

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question? Study identifies the sensitivities and specificities of imaging technologies enabling an assessment of diagnostic performance and hence provides appropriate information for the guideline.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population? The results are directly applicable to the guideline.

Internal Validity

Mowatt G;Cummins E;Waugh N;Walker S;Cook J;Jia X;Hillis GS;Fraser C;

Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease

Ref ID 20845 Health Technol Assess pgs: 1 to 143 2008

Study Type Diagnostic

Funding HTA NHS R&D programme.

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

This SR and meta-analysis aimed to assess the diagnostic value of 64-slice CT in CAD when compared to conventional CA. Methodology was clearly described. Twenty-one diagnostic studies (n=1286 patients) were included. Levels of analysis included patient (n=18), segment (n=17), left main artery (n=5), left anterior descending (LAD) overall (n=7), LAD proximal (n=5), left circumflex overall (n=7), right coronary artery overall (n=7), stents (n=6) and CABGs (n=4). The median prevalence of CAD across the 21 studies was 58%. A separate SROC curve was derived for each level of analysis e.g. one for patient-level and another for segment level. Sensitivity, specificity, PPV and NPV for patient-based evaluation were 99%, 89%, 93%, and 100%, respectively. For segment-based analysis results were 90%, 97%, 76% and 99%, respectively. The studies were heterogeneous in terms of their participants. In some studies the participants were all suspected CAD, in others they were all known CAD or a mixture of both, or with previous CABG or had LBBB.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

The results of the study are broadly applicable to the guideline, although up to 75% of included studies were not on stable chest pain patients.

Internal Validity

Mowatt G;Vale L;Brazzelli M;Hernandez R;Murray A;Scott N;Fraser- C;McKenzie L;Gemmell H;Hillis G;Metcalfe M;

Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction

Ref ID 786 Health Technol Assess pgs: iii to 89 2004

Study Type Diagnostic

Funding HTA NHS R&D programme.

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics	
Recruitment	
Setting	
Interventions/ Test/ Factor being investigated	
Comparisons	
Length of Study/ Follow-up	
Outcome measures studied	
Results	
Safety and adverse effects	
Does the study answer the question?	For diagnostic studies the interventions included were SPECT vs. stress ECG, with CA as the reference standard test. In situations where CA would be inappropriate reference standard, clinical follow-up was accepted as the reference standard. For prognostic studies, strategies involving SPECT were compared with strategies that did not. These included: -Stress ECG-SPECT-CA vs Stress ECG-CA -Stress ECG-SPECT vs stress ECG alone -SPECT-CA vs CA alone Stress ECG vs SPECT vs CA -SPECT vs CA -Stress ECG vs SPECT Sensitivity: For studies excluding patients with previous MI: SPECT (n=4) median range 0.92 (0.76-0.93); Stress ECG (n=4) median range 0.66 (0.42-0.85). For studies including patients with previous MI: SPECT (n=10) median range 0.76 (0.63-0.93); Stress ECG (n=10) median range 0.63 (0.44-0.92). Due to heterogeneity among studies no weighted averages were conducted for either SPECT or stress ECG. Specificity:For studies excluding patients with previous MI: SPECT (n=4) median range 0.74 (0.54-0.90); Stress ECG (n=4) median range 0.77 (0.58-0.88). For studies including patients with previous MI: SPECT (n=10) median range 0.65 (0.10-0.80); Stress ECG (n=10) median range 0.77 (0.41-0.80). Due to heterogeneity among studies no weighted averages were conducted for either SPECT or stress ECG Positive LRs: the range of positive LRs was 0.95-8.99 (median 2.33) for SPECT and 1.14-5.60 (median 2.06) for stress ECG. All positive LRs were <10 in both tests. LRs for both tests were calculated for 12 of the 16 studies. For both tests there was significant heterogeneity among positive LRs ($p<0.001$). Negative LRs: Negative LRs ranged from 0.09 to 1.12 (median 0.29) for SPECT and from 0.18 to 0.91 (median 0.57) for stress ECG. Values varied considerably among studies. Two studies showed negative LR for SPECT <0.1 (0.09) and LRs for SPECT were smaller than those for stress ECG.
Effect due to factor in study?	
Consistency of results with other studies?	
Directly applicable to guideline population?	High quality SR. Heterogeneity of studies was taken into consideration in analysis. Prospective and retrospective primary studies of SPECT MPS.

Internal Validity

Nandalur KR;Dwamena BA;Choudhri AF;Nandalur MR;Carlos RC;

Diagnostic performance of stress cardiac magnetic resonance imaging in the detection of coronary artery disease: a meta-analysis. [Review] [44 refs]

Ref ID 1118 J Am Coll Cardiol pgs: 1343 to 1353 2007

Study Type Diagnostic **Funding** Not stated.

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question? The SR determines the diagnostic utility of cardiac magnetic resonance imaging in the detection of CAD. The SR found that the tests have good sensitivity and specificities, however, the disease prevalence in the identified is studies high, and the performance of the test may not be as sensitive or specific in lower prevalence populations.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population? The included studies were determining the performance of the test to determine CAD hence the population is directly applicable to the guideline.

Internal Validity

Pryor DB;Harrell FE;Lee KL;Califf RM;Rosati RA;

Estimating the likelihood of significant coronary artery disease

Ref ID 10283 The American journal of medicine pgs: 771 to 780 1983

Study Type	Cohort	**Funding**	Not reported

Number of participants	3627 in training population, 1811 in test population
Inclusion/Exclusion Criteria	Patients with chest pain who were referred for cardiac catheterization at the Duke University Medical Center between November 1969 and January 1982
Patient Characteristics	Patient characteristics which were collected were: History: age, sex, chest pain history (pain type, severity, frequency, nocturnal, progressive, preinfarctional), duration of CAD, previous history of MI, congestive heart failure, history of vascular disease (Progressive chest pain - the frequency, severity or duration had increased in the 6 weeks prior to catherisation; Preinfarctional chest pain - a very unstable pain pattern that resulted in admission to the coronary care unit for evaluation of the possible MI) Risk factors: smoking, hyperlipidaemia, hypertension, diabetes, family history Physical examination: ventricular gallop, systolic blood pressure ECG: ST-T wave changes, electrocardiographic premature ventricular contractions, Electrocardiographic Q waves Chest X-Ray: cardiomegaly
Recruitment	Patients admitted for cardiac catheterisation between November 1969 and January 1982
Setting	Secondary care, USA
Interventions/ Test/ Factor being investigated	Chest pain diagnosis
Comparisons	Patient characteristics which give a probability of disease
Length of Study/ Follow-up	
Outcome measures studied	Probability of disease
Results	The study had a training population of 3627 patients who were seen between 1969 and January 1979, from these patients a stepwise logistic regression analysis was used to develop a model for predicting the probability of significant CAD. A test population of 1811 patients seen between January 1969 and January 1982, in this population the model developed in the test population was used to predict the probability of CAD for each patient. The authors then tested the model in other populations (from CASS study) to estimate the prevalence of disease in subgroups of the patients in the literature (external validation) Results from training population: Poor Clinical Predictors of Significant CAD and the Chi-squared: See narrative for question 4; Table 1:Pryor et al, 1983 Cardiomegaly: 1.41 The results from the training group show that cardiomegaly shown on chest x-ray was a poor predictor of significant coronary artery disease The authors then validated the model in the test population which showed that the predicted probability of disease is nearly identical to the observed prevalence.The authors then externally validated using the population from the CASS study. There was disagreement on patients classified as having nonanginal chest pain (where the greatest difference in predicted disease compared to observed disease was seen), but the predicted estimates from the model were nearly equal to the observed prevalence of disease. The predicted estimates from the model of the probability of significant disease were nearly identical to the observed prevalence for subgroups based on “age, sex and history of MI” or “age, sex and pain type”.
Safety and adverse effects	None

Does the study answer the question?	Progressive chest pain was described as being chest pain when the frequency, severity or duration had increased in the 6 weeks prior to catherisation. Preinfarctional chest pain was described as chest pain with a very unstable pain pattern that resulted in admission to the coronary care unit for evaluation of the possible MI The results from the training group show that cardiomegaly shown on chest x-ray was a poor predictor of significant coronary artery disease (chi-square = 1.41). The authors then validated the model in the test population which showed that the predicted probability of disease is nearly identical to the observed prevalence. When comparing the model to an external population the study showed that the predicted estimates from the model were nearly equal to the observed prevalence of disease. The predicted estimates from the model of the probability of significant disease were nearly identical to the observed prevalence for subgroups based on “age, sex and history of MI” or “age, sex and pain type”. However the greatest difference in predicted disease compared to observed disease was seen in patients with nonanginal chest pain.
Effect due to factor in study?	Yes
Consistency of results with other studies?	No similar studies
Directly applicable to guideline population?	Patients had chest pain
Internal Validity	Well covered

Vanhoenacker PK;Heijenbrok-Kal MH;Van HR;Decramer I;Van-Hoe LR;Wijns W;Hunink MM;

Diagnostic performance of multidetector CT angiography for assessment of coronary artery disease: meta-analysis

Ref ID 10274 Radiology pgs: 419 to 428 2007

Study Type Diagnostic **Funding** Not reported

Number of participants Study types not specified.

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?	This review assessed the diagnostic performance of CT angiography using 4,16, and 64-slice detectors. Six studies of 64-slice CT were included. The study concluded that the newer generation scanners significantly reduced the proportion of non-assessable coronary artery segments. Combined with reduction of the heart rate through the use of beta-blockers, practically all coronary artery segments are assessable. Also, as one increases the size of the unit analysed from coronary arterial segments, to vessels, and to patients, the sensitivity increase, the specificity decreases, , and the overall diagnostic performance decreases. Prevalence of CAD was relatively high in the source populations. The results of this study may therefore not be generalizable to low-prevalence populations.
Effect due to factor in study?	
Consistency of results with other studies?	
Directly applicable to guideline population?	The results are directly applicable to the guideline.
Internal Validity	

Grading: 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

Abdulla J;Abildstrom SZ;Gotzsche O;Christensen E;Kober L;Torp-Pedersen C;

64-Multislice detector computed tomography coronary angiography as potential alternative to conventional coronary angiography: A systematic review and meta-analysis

Ref ID 21285 Eur Heart J pgs: 3042 to 3050 2007

Study Type Diagnostic **Funding** Not reported.

Number of participants Type of study not specified.

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question? This meta-analyses found that there were differences in sensitivity and specificity values in per-segment vs. per-patient analysis due to calculated higher prevalence of CAD in per-patient data. Sensitivity in per-patient data was 97.5% vs. 86 in per-segment data, in analysis of native coronary arteries. And specificity was 91% vs. 96%, in per-patient and per-segment, respectively.

In general CT demonstrated high accuracy particularly by its high negative predictive values. The accuracy was highest in assessing CABG (96.5) and lowest in stented segments (92%).

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population? The results are directly applicable.

Internal Validity

Geleijnse ML;Krenning BJ;Soliman OI;Nemes A;Galema TW;Ten Cate FJ;

Dobutamine stress echocardiography for the detection of coronary artery disease in women

Ref ID 1961 Am J Cardiol pgs: 714 to 717 2007

Study Type Diagnostic **Funding** Not reported

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question? The aim of the SR was to examine the diagnostic accuracy of dobutaine stress echocardiography in women. For the detection of coronary artery disease in women, dobutamine stress echocardiography has reasonable sensitivity and good specificity. Similar sensitivities and specificities were found in studies comparing diagnostic performance in men versus women. Dobutamine stress echochardiology is at least as sensitive as SPECT for the detection of coronary artery disease in women.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population? The study is directly applicable to the guideline.

Internal Validity

Kwok Y;Kim C;Grady D;Segal M;Redberg R;

Meta-analysis of exercise testing to detect coronary artery disease in women.[see comment]

Ref ID 12044 Am J Cardiol pgs: 660 to 666 1999

Study Type Diagnostic **Funding** National Institute of Health, Bethesda, Maryland USA. Grant RO1-HL 50772.

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

The study found that the exercise ECG for women had lower accuracy compared with men, sensitivity 61% versus 70% and specificity 70% versus 77%. There was wide variability in the sensitivities for exercise ECG in women (27% to 91%) and also specificity (46% to 86%).The variability was not associated with the exclusion of patients with baseline ECG changes. Sensitivity and specificity were highly correlated suggesting that investigators may have different threshold for the identification for interpreting a test as positive, despite using the same threshold for interpreting a test as positive. Exercise thallium scanning in women had a higher sensitivity but a lower specificity compared with exercise ECG in women, but the differences were not clinically relevant. Although data was limited in this study exercise echocardiography has higher sensitivities and specificities compared with the other 2 tests.

No information was given on heterogeneity.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

The results are directly applicable to the guideline.

Internal Validity

Pryor DB;Shaw L;McCants CB;Lee KL;Mark DB;Harrell FE;Muhlbaier LH;Califf RM;

Value of the history and physical in identifying patients at increased risk for coronary artery disease

Ref ID 1751 Annals of internal medicine pgs: 81 to 90 1993

Study Type Cohort

Funding Agency for Health Care Policy and Research, National Heart, Lung and Blood institute, National Library of Medicine

Number of participants	1030 patients, 168 had cardiac catheterization. At 3 years data for 973 patients (94%) was obtained.
Inclusion/Exclusion Criteria	Inclusion: Symptomatic patients, referred for non-invasive testing for suspected coronary artery disease Exclusion: previous cardiac catheterization
Patient Characteristics	The mean age was 55, 37% were female, the mean pain frequency was 2 episodes a week, the mean durations of CAD symptoms was 12 months, 28% had typical angina symptoms, 52% atypical angina symptoms, 20% nonanginal pain, 18% progressive angina, 22% nocturnal angina, 44% smoked, 41% had a history of hypertension, 10% had diabetes, 11% had hyperlipidemia, 35% had ST-T wave changes on ECG, 18% had a history of MI, 8% had Q waves on ECG, 14% had a history of congestive heart failure, 0% had class IV congestive heart failure, 1% had ventricular gallop, 3% had peripheral vascular disease, 3% had cerebral vascular disease Of the patients who went on to have a cardiac catheterization the mean age was 56, 31% were female, the mean pain frequency was 2 episodes a week, the mean durations of CAD symptoms was 7 months, 49% had typical angina symptoms, 47% atypical angina symptoms, 4% nonanginal pain, 24% progressive angina, 24% nocturnal angina, 53% smoked, 42% had a history of hypertension, 10% had diabetes, 13% had hyperlipidemia, 42% had ST-T wave changes on ECG, 33% had a history of MI, 11% had Q waves on ECG, 11% had a history of congestive heart failure, 0% had class IV congestive heart failure, 1% had ventricular gallop, 4% had peripheral vascular disease, 2% had cerebral vascular disease. It can therefore be seen that those having a cardiac catheterization were more likely to be male, smoke, have a history of MI, have ST-T wave changes on ECG and to be suffering typical or progressive angina At 3 years data for 973 patients (94%) was obtained. At the end of 3 years 844 patients were alive. 30 had died of cardiovascular causes, 19 had died of noncardiac causes, 18 had undergone angioplasty and 62 had had coronary artery bypass graft surgery.
Recruitment	Patients were referred for non-invasive testing for suspected coronary artery disease
Setting	Duke University Medical Centre USA
Interventions/ Test/ Factor being investigated	Physicians initial evaluation of patients with suspected CAD
Comparisons	The presence of significant coronary disease defined as any disease, severe disease, left main disease, predicting survival
Length of Study/ Follow-up	3 years
Outcome measures studied	Effectiveness of chest pain score to predict coronary artery disease and survival
Results	The three diagnostic outcomes were; the presence of significant coronary artery disease defined as ‘any disease’ (≥ 75% luminal diameter narrowing of at least one major coronary artery), presence of severe coronary artery disease defined as ‘severe disease’ (significant obstruction of all 3 main coronary arteries or the left main coronary artery) and the presence of significant left main artery obstruction defined as ‘left main disease’ (168 patients referred for cardiac catheterization). The prognostic outcome was survival at 3 years. In the multivariable regression model used, chest x-ray to show cardiomegaly was not a significant predictor for any disease, severe disease or left main disease. However for cardiomegaly (shown on chest x-ray) was a significant predictor for survival at 3 years.
Safety and adverse effects	None reported
Does the study answer the question?	In the multivariable regression model used, chest x-ray which showed cardiomegaly was shown to be a significant predictor of survival. However it could not be used to predict coronary disease.

Effect due to factor in study?	Yes
Consistency of results with other studies?	No other similar studies
Directly applicable to guideline population?	Correct population
Internal Validity	Well covered

Schuijf JD;Bax JJ;Shaw LJ;de RA;Lamb HJ;van der Wall EE;Wijns W;

Meta-analysis of comparative diagnostic performance of magnetic resonance imaging and multislice computed tomography for noninvasive coronary angiography.[see comment]. [Review] [57 refs]

Ref ID 3788 Am Heart J pgs: 404 to 411 2006

Study Type Diagnostic

Funding Netherlands Heart Foundation (grant 2002B105).

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?	The SR the summary odds ratio for an abnormal multislice CT was elevated 16.9 fols (95% CI 11.0 to 26.1) indicating that an abnormal segment had a 16.9 fold increased odds of significant CAD at cardiac catheterization. In contrast the summary odds ratio was increased 6.4 fold (95% CI 5.0 to 8.3) for MRI. An inverse relationship between diagnostic specificity and CAD prevalence for multislice CT was observed, which remained consistent when controlling for average age and the frequency of men enrolled in each study. No relationship was found for MRI. The authors concluded that MSCT has a significantly better diagnostic accuracy in the detection of CAD compared with MRI.
Effect due to factor in study?	

Consistency of results with other studies?

Directly applicable to guideline population? The results of the SR are directly applicable to the guideline.

Internal Validity

Sun Z;Lin C;Davidson R;Dong C;Liao Y;

Diagnostic value of 64-slice CT angiography in coronary artery disease: A systematic review

Ref ID 20820 Eur J Radiol pgs: 78 to 84 2008

Study Type Diagnostic **Funding** Not reported

Number of participants Type of study not specified. All studies on human subjects were included except case reports and abstracts.

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question? This review answers the question it set out to answer. That is, it provides an estimate of the diagnostic value of 64-slice CT when compared to coronary angiography (CA). It included patients with known CAD and those with suspected CAD (those presenting with chest pain) and as such is useful for our question. However, it would have been even more useful if separate results had been presented for those groups separately.

Very little information on the type of studies included was reported. E.g. number of RCTs, cohort studies etc. And no details of the number of patients included in the sensitivity/specificity calculations were reported. However, sensitivity/specificity was reported at patient, vessel and segment level.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?	The results of this SR are directly applicable to the guideline.

Internal Validity

Grading: 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*

d'Othee Janne B;Siebert U;Cury R;Jadvar H;Dunn EJ;Hoffmann U;

A systematic review on diagnostic accuracy of CT-based detection of significant coronary artery disease. [Review] [60 refs]

Ref ID 177 Eur J Radiol pgs: 449 to 461 2008 Mar

Study Type Diagnostic **Funding** Not stated.

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question? This study assessed the diagnostic accuracy of multislice CT (4- 8- 16- and 64-slice), although only 5 studies were 64 slice and study sizes ranged from 35 to 84 patients. The main conclusion is that with 64 slice scanners, diagnostic accuracy is high on a per segment basis. Per patient however, this accuracy may be lower in patients with multivessel disease, which may limit the utility of CT in populations at high risk for CAD. Apart from selection bias, this study highlights the fact that most of the studies used two independent investigators to read the scans which might differ from routine clinical practice, and which consequently could limit the applicability of the findings.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population? The results of the study may not be applicable to the guideline as it was poorly conducted. Very little information is given on the type of studies included (RCTs, cohorts). No details of the number of patients included in the meta-analysis are given.

Internal Validity

Appendix E - Health Economics Extractions

11

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

No 838 **Study Quality:** The diagnostic value and cost-effectiveness of creatine kinase-MB, myoglobin and cardiac troponin-T for patients with chest pain in emergency department observation ward (Structured abstract)

Author: Choi YF;Wong TW;Lau CC; 2004

Relevance:

Intervention: Standard clinical evaluation including serial ECG and troponin T determinations at presentation and again at 6 to 8 hours post presentation.

Comparison: Standard clinical evaluation including serial ECG and CK-MB determinations at presentation and again at 6 to 8 hours post presentation.

Population: 480 patients presenting to a Hong Kong emergency department, all over age 30 years and had primary complaint of chest pain of suspected cardiac origin with onset within one week.

Perspective: Not stated

Exclusion criteria: Patients whose ECG suggested AMI or who had a clinical diagnosis of ACS or unstable angina or who had had an AMI or cardiac catheterisation within one month.

Study type: Prospective study with cost benefit analysis

Methods: Prospective study

Health valuations: NOT APPLICABLE

Cost components: Costs of cardiac biomarker tests, cost of false positive (estimated as cost of 2-day hospital admission), cost of AMI (estimated as cost of 6-day hospital admission)

Currency: Hong Kong dollars (HK$)

Cost year: 2002

Time horizon: Patients were followed up for 6 months

Discount rate: Not applicable

Results-cost: Costs of each strategy were measured as the cost of the cardiac biomarker tests.

Cost of TnT = HK$25440
Cost of CK-MB = HK$1259

Results-effectiveness: Effectiveness was measured as the cost of resources not used when unnecessary admission was avoided and when future AMIs were prevented through diagnosis with cardiac biomarker.

Effects of TnT = HK$147900 (25 avoided hospital admissions) + HK$53244 (3 prevented AMIs)
Effects of CK-MB = HK$5916 (1 avoided hospital admission) + HK$0 (0 prevented AMIs)

Results-ICER: As this was not a full economic evaluation, no incremental analysis was performed.

Result-Uncertainty: As this was not a full economic evaluation, no sensitivity analysis was undertaken.

Source Funding: Not stated

Comments: Results of the partial economic analysis showed that testing for TnT would yield a cost savings of an estimated HK$171047 compared with testing for CK-MB. This was largely due to the superior sensitivity and specificity of TnT over CK-MB. Although the TnT test was about HK$20 more expensive per unit, the savings generated by avoiding unnecessary hospital admissions (HK$141984) and from correctly diagnosing significant coronary heart disease and thus avoiding future AMI (HK$53244) made it a cost saving option. The study deemed myoglobin to be of no value due to its lack of specificity.

No 837 **Study Quality:** Cost effectiveness of diagnostic strategies for patients with acute, undifferentiated chest pain (Structured abstract)

Author: Goodacre S;Calvert N; 2003

Relevance:

Intervention: 3 enzyme testing strategies compared with a baseline strategy of discharging all patients without additional testing.

Comparison: Enzyme testing at presentation vs. Enzyme testing at presentation and again 6 hrs after onset of pain vs. 24 hr admission and then enzyme testing.

Population: Hypothetical cohort of 1000 patients presenting to hospital with acute undifferentiated chest pain and: no ECG changes diagnostic of AMI or UA; negligible risk of CHD based on clinical features/risk factors; no evidence of other serious abnormality requiring hospital admission; no clinically obvious UA (defined as known CHD with prolonged or recurrent episodes of cardiac type chest pain).

Perspective: NHS

Study type: CUA (QALYs)

Methods: DECISION ANALYSIS Model

Health valuations: 3-year survival data estimated using data from a multicentre chest pain study (Lee t al. 1992)

Cost components: Direct costs of running each strategy estimated by summing constituent elements: unit costs of admission, medical treatment of AMI and UA, cardiac enzyme tests, investigations of false positives and terminal care.

Currency: £

Cost year: 2000/01

Time horizon: Lifetime

Discount rate: 6% per annum for both costs and effects

Results-cost: Strategy 0 (discharge all patients without additional testing): 1,399,700 per 1,000 patients
Strategy 1 (enzyme testing at presentation): 1,499,600 per 1,000 patients
Strategy 2(enzyme testing at presentation then observation until min 6 hrs and repeat enzyme testing): 1,597,100 per 1,000 patients
Strategy 4 (Admit to hospital for 24 hrs and then enzyme test): 1,796,100 per 1,000 patients

Results-effectiveness: Strategy 0: 8853.7 QALYs per 1000 patients
Strategy 1: 8859.4 QALYs per 1000 patients
Strategy 2: 8864.7 QALYs per 1000 patients
Strategy 4: 8870.2 QALYs per 1000 patients

Results-ICER: Strategy 1: £17,432/QALY
Strategy 2: £18,567/QALY
Strategy 4: £36,069/QALY

Result-Uncertainty: Results were insensitive to variation of prevalence of AMI or UA; utilities of AMI or UA; mortality estimates; treatment effect estimates; costs of treatment of 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.

Source Funding: Public

Comments: The results show that a strategy of cardiac enzyme testing at presentation is likely to be cost-effective (£17,432/QALY) compared with a do-nothing strategy. A strategy of enzyme testing at presentation and again 6 hours after the onset of pain is also likely to be cost-effective (£18,567/QALY) compared with testing only at presentation. A strategy of testing after 24 hours of observation is unlikely to be considered cost-effective (£36,069/QALY). The analysis indicates that serial enzyme testing at presentation and again 6 hours after the onset of pain is a cost-effective strategy, and that strategies involving a long period of observation are unlikely to be.

Although the model is not sophisticated, it is one of only two UK studies looking at the economic impact of biomarkers. But,

because it does not compare specific enzyme tests, it does not give definitive information on the most cost-effective approach or whether any other approaches are more cost-effective.

No 836 **Study Quality:** Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care

Author: Mant J;McManus RJ;Oakes RL;Delaney BC;Barton PM;Deeks JJ;Hammersley L;Davies RC;Davies MK;Hobbs FR; 2004

Relevance:

Intervention: 4 testing and treatment strategies

Comparison: Compares testing for troponin T versus not testing for troponin T with and without pre-hospital telemetry ECG.

Population: Patients presenting in primary care with acute chest pain suspicious of ACS.

Perspective: NHS

Study type: CEA using Monte Carlo simulation model with outcomes measured as percent achieving 28-day survival

Methods: DECISION ANALYSIS (sens and spec of POCT indexed w time, values obtained from systematic review)

Health valuations: NOT APPLICABLE

Cost components: Ambulance call-out; telemetry ECG; Reteplase; Streptokinase; A&E died; A&E referred; A&E discharged; treatment of MI; TnT test

Currency: £

Cost year: 2000

Time horizon: 28 days

Discount rate: Not applicable

Results-cost: A&E ECG and POCT: £757 per patient
A&E based on ECG: £916 per patient
Pre-hosp thromb and A&E ECG only £1166 per patient
Pre-hosp thromb and A&E ECG and POCT: £1209 per patient

Results-effectiveness: Percent achieving 28-day survival

A&E ECG and POCT: 96.6%

A&E based on ECG: 96.4%
Pre-hosp thromb and A&E ECG only 96.1%
Pre-hosp thromb and A&E ECG and POCT: 97.3%

Results-ICER: Use of troponin T dominates non-use of troponin T with or without pre-hospital telemetry ECG.

Result-Uncertainty: Sensitivity analysis was performed allowing for first and second order uncertainty. Dominant results were robust to sensitivity analysis of varying the pain to needle time (15 minutes to 180 minutes to 3 hours) and cost of telemetry ECG (£50 - £400).

Source Funding: Public

Comments: A biomarkers analysis was elicited from the full Mant analysis, such that the incremental benefit of using a troponin T test could be isolated from other strategies modelled (e.g. pre-hospital telemetry ECG).

No 768 **Study Quality:** Impact of troponin T determinations on hospital resource utilization and costs in the evaluation of patients with suspected myocardial ischemia

Author: Zarich S;Bradley K;Seymour J;Ghali W;Traboulsi A;Mayall ID;Bernstein L; 2001

Relevance:

Intervention: Standard clinical evaluation including serial ECG and CK-MB determinations with the addition of serial troponin-T determinations measured at presentation, 3 and 12 hours post presentation (n=447).

Comparison: Standard clinical evaluation including serial ECG and CK-MB determinations only (n=409).

Population: 891 patients (aged over 18 years) presenting to the emergency department with chest pain symptoms suspicious for myocardial ischemia of >30 minutes duration that warranted an evaluation for myocardial infarction. 77% of the patients included presented with chest pain and 23% presented with no chest pain. A sub-group analysis of the chest pain patients is presented.

Perspective: THIRD PAYER

Study type: RCT with analysis of resource impact

Methods: RCT

Health valuations: NOT APPLICABLE

Cost components: Total hospital charges (costs estimated at 60% of charges based on hospital accounting methods)

Currency: US$

Cost year: Not stated

Time horizon:

Discount rate: Not applicable

Results-cost: In the sub-group analysis for patients presenting with chest pain, there was a strong trend toward reduced length of stay (1.4 vs 1.9 days; p=0.09) with a significant reduction in total hospital charges ($6993 vs $8753; p=0.05) in TnT compared with control patients.

In patients without ACS, fewer TnT group patients were admitted to hospital compared with controls (31% vs 25%; p=0.04) and there was a significant reduction in length of stay (1.2 vs 1.6 days; p=0.03) with a trend toward reduced total charges ($4487 vs $6187; p=0.17).

TnT determinations appeared particularly useful in patients with falsely elevated CK-MB values.

In patients with ACS both length of stay (3.7 vs 4.6 days; p=0.01) and total charges ($15004 vs $19202; p=0.02) were significantly reduced in TnT patients compared with controls. Significant reductions were also seen in telemetry or cardiac care unit length of stay (3.5 vs 4.6 days; p=0.03).

Patients examined in and discharged from the emergency department had an average stay of 10.5 hours at a charge of $2047. Those admitted to telemetry were admitted for an average length of stay of 4.0 days at a charge of $12636. Patients admitted to the cardiac care unit had an average length of stay of 7.0 days at a charge of $31152. On average, total charges for TnT patients were $1538 less than control patients (representing a potential $923 cost saving). The estimated annual savings to the hospital based on this analysis were $4 million in 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 TnT group.

Results-effectiveness: Cardiac events at 30 days occurred in 18 patients (3.1%) and did not differ between controls and interventions for whole cohort and subgroups.

Results-ICER: As this was not a true cost-effectiveness analysis, there was no incremental analysis undertaken.

Result-Uncertainty: Sensitivity analysis was not applicable to this study, therefore none was performed.

Source Funding: Roche Diagnostics

Comments: The study indicates that the utilisation of TnT in addition to CK-MB led to a 20-25% reduction in length of stay and total charges in high and low risk patients with and without ACS. The evidence indicates that the addition of TnT reduced admissions by 7-11% and that ACS patients were managed more efficiently with a lower length of stay, shorter telemetry or cardiac care unit stay and lower total charges (and costs) despite a similar number of hospital admissions.

The potential savings are substantial and may have been underestimated due to case mix in the TnT and control groups and as many as two-thirds of patients without ACS but with raised CK-MB and despite normal TnT were admitted to hospital (as emergency department physicians became more familiar with TnT determinations).

The use of TnT determinations in addition to CK-MB determinations is likely to be safe, effective and resource saving in the evaluation of high and low risk patients with suspected ACS/AMI presenting to an emergency department. Although the analysis was undertaken in North America, it is likely that these results are generalisable to an NHS A&E setting given the relatively low cost of TnT testing compared to the costs of admitting patients to hospital and cardiac care units.

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What is the diagnostic utility MSCT coronary angiography in the diagnosis of patients with acute chest pain of suspected cardiac origin

No 1156 **Study Quality:** Sixty-four-slice computed tomography of the coronary arteries: cost-effectiveness analysis of patients presenting to the emergency department with low-risk chest pain

Author: Khare RK;Courtney DM;Powell ES;Venkatesh AK;Lee TA; 2008

Relevance:

Intervention: 64 slice MDCTCA

Comparison: Stress Echocardiography, Stress ECG

Population: Patients presenting with low risk chest pain (2% to 10% risk) in an emergency department.

Perspective: US payer perspective

Study type: Cost-Utility analysis i.e. incremental cost per QALY

Methods: Decision analytic model

Health valuations: N/A. Used published estimates

Cost components: Cost of diagnostic tests, observation unity care, MI, death, coronary angiography, PCI, CABG, costs of missed CAD and MI.

Currency: US dollars

Cost year: 2007

Time horizon: lifetime although only first 30 day costs included.

Discount rate: not used.

Results-cost: MDCT mean $2,684 (SD range $1,773 to $4,418); Stress Echo = $3,265 ($2,383 to $4,836); Stress ECG = $3,461 ($2,533 to $4,836).

Results-effectiveness: MDCT mean 24.69 QALYs (SD range 24.54 to 24.76); Stress Echo = 24.63 (24.28 to 24.74); Stress ECG = 24.59 (24.21 to 24. 75).

Results-ICER: MDCT dominates stress Echo and stress ECG. I.e. more effective and less costly for all three levels of risk modelled (2%, 6% and 10%).

Result-Uncertainty: Probabilistic sensitivity analysis demonstrated that for the majority of Monte Carlo runs of the base case, the majority of plots are in the bottom right hand quadrant of the cost-effectiveness plane (i.e. MDCT is dominant). Threshold sensitivity analysis indicate that in order for the cost saving result to become cost-neutral, prevalence of CAD would have to be greater than 70%, sensitivity of MDCT would have to drop to 65%, or there would have to be an MDCT indeterminate rate of 30%. In general the ICER remained below $10,000 per QALY.

Source Funding: Agency for Healthcare Research and Quality

Comments: MDCT was cost-saving despite the exclusion of the ED work up costs from the analysis. The model results were robust to nearly all of the assumptions used in the model. Using a threshold willingness to pay of $50,000 per QALY, MDCT would always be considered cost-effective in the scenarios modelled. Because 64 slice MDCT is a relatively new technology, there is relatively little evidence for test sensitivity a and specificity although this was allowed for in the sensitivity analysis by examining quite wide ranges of uncertainty. Risk of radiation was not incorporated into the model. Any risk of renal failure from a double dye load for patients with a positive MDCT test who then require another immediate catheterization is also not incorporated into the model.

No 1161 **Study Quality:** Cost-effectiveness of coronary MDCT in the triage of patients with acute chest pain

Author: Ladapo JA;Hoffmann U;Bamberg F;Nagurney JT;Cutler DM;Weinstein MC;Gazelle GS; 2001

Relevance:

Intervention: 64-MDCTCA.

Comparison: Standard of Care (SOC) Algorithm based on biomarkers and randomly allocating patients to stress tests using SPECT, Echocardiography, or stress ECG.

Population: hypothetical cohort of 55 year old men and women (separately) with low risk acute chest pain, defined as negative initial troponins, normal or non-diagnostic ECG, and no history of heart disease.

Perspective: Stated as Societal perspective in the context of the US healthcare system but no evidence that patient costs or costs to the economy were included in the analysis.

Study type: Cost-Utility analysis i.e. Incremental costs per QALY.

Methods: A decision analytic model using various published sources for effectiveness/ test characteristics.

Health valuations: N/A used published estimates of health state valuations (quality adjusted life expectancies)

Cost components: Emergency department visits and imaging/testing. Medical treatment for mild heart disease and hospital admissions and Treatment for moderate to severe heart disease.

Currency: US dollars.

Cost year: 2005

Time horizon: lifetime

Discount rate: 3% for both costs and QALYs

Results-cost: 64CTCA Men $10,190; Women $6,630;
SoC Men $9,990; Women $7,010;

Results-effectiveness: 64CTCA Men 15.31 QALYs; Women 16.99 QALYs;
SoC Men 15.27 QALYs; Women 19.98 QALYs;

Results-ICER: Men $6,400 per incremental QALY
Women 64CTCA is cost-saving and dominates SoC

Result-Uncertainty: Sensitivity analysis indicates that the ICER for men remains within generally acceptable levels of cost-effectiveness (e.g. reducing by 25% the ability of 64CT to correctly classify healthy patients increases the ICER to $17,000). Women remain cost-saving of low cost-effectiveness. Using SPECT as the only stress test option results in 64CTCA dominating SoC for both man and women.

Source Funding: Walker Fund of the Harvard PhD programme in Health Policy

Comments: Only modest gains in QALYs because of the assumed low prevalence of ACS in the modelled population. Results were better for women because of the lower prevalence of ACS in 55 year old women compared to men. The authors indicate that the ICER for higher risk patients is uncertain and needs further investigation. They state that their results may not be generalisable to other countries due to demography and resource valuations, although their base case results are relatively stable under a variety of sensitivity analyses. The authors indicate that clinical trials evaluating this technology are underway and that the results "may ultimately illuminate a more efficient and cost-effective management approach to low risk patients with chest pain in an emergency department."

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What is the diagnostic utility of calcium scoring for the evaulation of patients with stable chest pain of cardiac origin.

No 1015 **Study Quality:** Coronary calcification by electron beam computed tomography and obstructive coronary artery disease: a model for costs and effectiveness of diagnosis as compared with conventional cardiac testing methods

Author:	Rumberger JA;Behrenbeck T;Breen JF;Sheedy PF; 1999
Relevance:	
Intervention:	Electron beam computed tomography with calcium scoring - 4 different Agatston calcium score thresholds (>0; =37; =80; =168) were used to define positive diagnosis
Comparison:	Stress ECG, stress thallium scintigraphy, stress echo and coronary angiography
Population:	Hypothetical cohort of 100 patients for each CAD prevalence's tested (10%, 20%, 50%, 70% and 100%).
Perspective:	THIRD PAYER
Study type:	CEA (average cost per correct diagnosis of CAD)
Methods:	DECISION ANALYSIS
Health valuations:	NOT APPLICABLE
Cost components:	Total direct costs: cost of test performed and cost of complications (death, ventricular fibrillation, myocardial infarction, cerebral infarction and vascular surgical repair)
Currency:	US$
Cost year:	Not stated
Time horizon:	Not applicable
Discount rate:	Not applicable
Results-cost:	Total costs for the entire 100 patient cohort at each CAD prevalence: 10% CAD Prevalence: EBCT (=168) = $105112 EBCT (=80) = $126400 EBCT (=37) = $151236 ETT = $166019 Echo = $191295 Thallium = $241083 EBCT (>0) = $247030 CA = $354000 20% CAD Prevalence: EBCT (=168) = $126392 EBCT (=80) = $151232 EBCT (=37) = $171864

ETT = $180210
Echo = $216121
EBCT (>0) = $261212
Thallium = $265914
CA = $354000

50% CAD Prevalence:
EBCT (=168) = $186696
EBCT (=80) = $222180
ETT = $222804
EBCT (=37) = $243450
Echo = $283542
EBCT (>0) = $303792
Thallium = $333315
CA = $354000

70% CAD Prevalence:
EBCT (=168) = $229350
ETT = $247605
EBCT (=80) = $268273
EBCT (=37) = $289548
Echo = $329640
EBCT (>0) = $332119
CA = $354000
Thallium = $377748

100% CAD Prevalence:
ETT = $290175
EBCT (=168) = $293112
EBCT (=80) = $335664
CA = $354000
EBCT (=37) = $356940
EBCT (>0) = $374680
Echo = $397035
Thallium = $446810

Results-effectiveness: Effectiveness was measured as the number of patients out of 100 correctly diagnosed as having obstructive CAD.

10% CAD Prevalence:
EBCT (=168) = 7 True Positive (TP) and 3 False Negative (FN)
EBCT (=80) = 8 TP and 2 FN
EBCT (=37) = 9 TP and 1 FN
ETT = 7 TP and 3 FN
Echo = 9 TP and 1 FN
Thallium = 9 TP and 1 FN
EBCT (>0) = 10 TP and 0 FN

CA = 10 TP and 0 FN

20% CAD Prevalence:
EBCT (=168) = 14 TP and 6 FN
EBCT (=80) = 17 TP and 3 FN
EBCT (=37) = 18 TP and 2 FN
ETT = 15 TP and 5 FN
Echo = 17 TP and 3 FN
EBCT (>0) = 19 TP and 1 FN
Thallium = 18 TP and 2 FN
CA = 20 TP and 0 FN

50% CAD Prevalence:
EBCT (=168) = 36 TP and 14 FN
EBCT (=80) = 42 TP and 8 FN
ETT = 36 TP and 14 FN
EBCT (=37) = 45 TP and 5 FN
Echo = 43 TP and 7 FN
EBCT (>0) = 48 TP and 2 FN
Thallium = 45 TP and 5 FN
CA = 50 TP and 0 FN

70% CAD Prevalence:
EBCT (=168) = 50 TP and 20 FN
ETT = 51 TP and 19 FN
EBCT (=80) = 59 TP and 11 FN
EBCT (=37) = 63 TP and 7 FN
Echo = 60 TP and 10 FN
EBCT (>0) = 67 TP and 3 FN
CA = 70 TP and 0 FN
Thallium = 63 TP and 7 FN

100% CAD Prevalence:
ETT = 73 TP and 27 FN
EBCT (=168) = 72 TP and 28 FN
EBCT (=80) = 84 TP and 16 FN
CA = 100 TP and 0 FN
EBCT (=37) = 90 TP and 10 FN
EBCT (>0) = 95 TP and 5 FN
Echo = 85 TP and 15 FN
Thallium = 91 TP and 9 FN

Results-ICER: The authors presented only average cost-effectiveness of the strategies. However, the presentation of their results allowed for an incremental cost-effectiveness analysis to be performed. ICERs for each strategy compared to the next best strategy are presented here. ICERs are presented as the cost ($) per additional correct CAD diagnosis:

10% CAD Prevalence:
EBCT (=168) =
EBCT (=80) = $21288
EBCT (=37) = $24836
ETT = dominated
Echo = dominated
Thallium = dominated
EBCT (>0) = $95794
CA = dominated

20% CAD Prevalence:
EBCT (=168) = extendedly dominated
EBCT (=80) = $8280
EBCT (=37) = $20632
ETT = dominated
Echo = dominated
EBCT (>0) = $89348
Thallium = dominated
CA = $92788

50% CAD Prevalence:
EBCT (=168) = $5186
EBCT (=80) = $5914
ETT = dominated
EBCT (=37) = $7090
Echo = dominated
EBCT (>0) = $20114
Thallium = dominated
CA = $25104

70% CAD Prevalence:
EBCT (=168) = extendedly dominated
ETT = extendedly dominated
EBCT (=80) = $2584
EBCT (=37) = $5319
Echo = dominated
EBCT (>0) = extendedly dominated
CA = $7290
Thallium = dominated

100% CAD Prevalence:
ETT = extendedly dominated
EBCT (=168) = dominated
EBCT (=80) = extendedly dominated
CA = $1146
EBCT (=37) = dominated

EBCT (>0) = dominated
Echo = dominated
Thallium = dominated

Result-Uncertainty: No sensitivity analysis was undertaken.

Source Funding: Mayo Clinic and Foundation

Comments: The incremental analysis performed on the published findings shows that using EBCT using any calcium score threshold (>0; =37; =80; =168) is cost saving compared with stress echo and stress thallium testing. At low to moderate disease prevalence (10% to 20%), EBCT using thresholds of =37, =80 or =168 are cost saving compared with ETT. Without an explicit cost-effectiveness threshold, it is difficult to determine which is the most cost-effective strategy at 50% CAD prevalence. It is clear that EBCT strategies with higher calcium thresholds are less expensive than an EBCT strategy with a >0 calcium score threshold. However, the lower sensitivity of higher calcium score thresholds means that many true positives are misdiagnosed as negatives. At high CAD prevalence, (70% and 100%), direct to coronary angiography is likely to be the most cost-effective strategy.

18

What is the diagnostic utility of non-invasive and invasive tests for the evaluation of patients with stable chest pain of suspected cardiac origin.

No 879 **Study Quality:** Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease

Author: Mowatt G;Cummins E;Waugh N;Walker S;Cook J;Jia X;Hillis GS;Fraser C; 2008

Relevance:

Intervention: 64-slice MDCT (multidetector computed tomography)

Comparison: ETT (exercise tolerance test), MPS (myocardial perfusion scintigraphy) and invasive CA (coronary angiography)

Population: A hypothetical cohort of male patients coming through from resting ECG. In the first analysis, a short-term diagnostic model, patient age was not reported, although the earlier model on which it is based assumes a starting age of 60 years (Mowatt 2004). In the long-term model the cohort age is 50.

Perspective: NHS

The prevalence of CAD in the population is a modelled variable ranging from 10% to 70%. The cost- effectiveness of the different diagnostic strategies are estimated with CAD prevalence of 10%, 30%, 50% and 70%.

Study type: CUA

Methods: DECISION ANALYSIS

Health valuations: NOT APPLICABLE

Cost components: Short term diagnostic model includes costs of diagnostic tests. Longer term model includes above costs as well as costs of treating CAD including MI.

Currency: £

Cost year: States "current prices". Assume circa 2007/2008.

Time horizon: Short term diagnostic model did not specify time horizon Longer term model = 25 year time horizon.

Discount rate: Not applicable to short term diagnostic model. Longer term model used 3.5% for costs and benefits.

Results-cost: Although 8 short term diagnostic strategies were analysed, only the results of three (five were dominated) are presented here.
The base case assumes CAD prevalence of 10%.
Diagnostic strategy 1 is ETT to CT to CA. Total cost for hypothetical cohort of patients =£21,085.
Diagnostic strategy 2 is ETT to CA. Total cost for hypothetical cohort of patients = £22,695.
Diagnostic strategy 3 is ETT to CT. Total cost for hypothetical cohort of patients = £17,283.

Longer term model result with 10% CAD prevalence.
Strategy 1 total cost = £616,732
Strategy 2 total cost = £618,196
Strategy 3 total cost = £618,629

Results-effectiveness: Strategy 1 true positives = 7.41
Strategy 2 true positives = 7.48
Strategy 3 true positives = 7.42

Longer term model with 10% CAD prevalence. Total number of QALYs are as follows:

Strategy 1 total QALYs = 1060.5
Strategy 2 total QALYs = 1060.0
Strategy 2 total QALYs = 1056.9

Results-ICER: No incremental cost-effectiveness results presented. Cost per true positive results are as follows:

Strategy 1 cost per true positive = £2,845.
Strategy 2 cost per true positive = £3,034.
Strategy 3 cost per true positive = £2,329.

No incremental costs presented for Longer term model. Cost per QALY as follows:

Strategy 1 cost per QALY = £581
Strategy 2 cost per QALY = £583

Strategy 3 cost per QALY = £585

Result-Uncertainty: In the short term diagnostic model, base case CAD prevalence is 10% but is allowed to vary from 10% to 70%. Cost per true positive for each strategy at 70% CAD prevalence is as follows: Strategy 1= £724, strategy 2= £533 and strategy 3= £400.

Cost of CA is uncertain and in base case was £320 although another cost for CA is estimated at £1556. A mid point estimate of £900 was used in sensitivity analysis. This has an effect on strategies where CT replaces CA. To render CT strategies more expensive than CA (CAD prevalence 10%) the additional cost of a false positive would have to be around £7000. For CAD prevalence of 70% cost range would have to be £20,000 to £30,000.

In the longer-term model higher costs for CA increases the anticipated savings from using strategy 3 to around £300 per patient.

Sensitivity analysis used lower values for sensitivity(97% vs. 99% in the base case) and specificity(83% vs. 89% in the base case) for 64-slice CT. This causes CT to perform slightly worse when set against those strategies where patients go straight to CA. For the short term diagnostic model these lower values produced the following results:

Strategy 1 cost per true positive = £3,009
Strategy 2 cost per true positive = £3,034
Strategy 3 cost per true positive = £2,377

In the longer term model these lower values for sensitivity and specificity of 64-slice CT leads to a lower aggregate QALY. But given the tightness of the confidence intervals for sensitivity and specificity bounds, the impact of this is limited.

Source Funding: UK NHS Health Technology Assessment programme.

Comments: The report concludes that the high sensitivity and negative predictive value of 64-slice CT suggest scope for avoiding unnecessary CAs in those referred for investigation but who do not have CAD. Given the small risk of death associated with CA, CT might also confer a small immediate survival advantage. Avoidance of CAs may result in cost savings even if positive results mean confirmation by CA. Also, of note is the suggestion that if CT were available immediately in a emergency department setting it may reduce the need to admit patients. The resulting cost savings have not been included in this analysis.

No 878 **Study Quality:** Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial. [Review] [207 refs]

Author: Sharples L;Hughes V;Crean A;Dyer M;Buxton M;Goldsmith K;Stone D; 2007

Relevance:

Intervention: Coronary angiography

Comparison: SPECT, stress echo, stress MRI

Population: Patients referred for non-urgent coronary angiography

Perspective: NHS and PSS

Inclusion criteria: Established or suspected chronic stable angina referred for angiography and an ETT result which merited referral for angiography

NOTE: Because these are patients who have already undergone an ETT and have been referred for angiography, the prevalence of/pre-test likelihood for CAD within this population is likely to be high.

Study type: CUA (QALYs)

Methods: Economic evaluation conducted alongside RCT

Health valuations: Face-to-face interviews using the Seattle Angina Questionnaire, Short Form-36 and EQ5D

Cost components: Diagnostic tests, revascularisation procedures, admissions, cardiac-related tests (e.g. echo, ETT, CT scan, blood pressure monitoring), outpatient and GP visits, medications (e.g. statins, beta-blockers, nitrates, etc).

Currency: £

Cost year: 2005-06

Time horizon: 18 months

Discount rate: 3.5% per annum

Results-cost: Mean cost per patient per strategy:
Angiography: £3,630 (95%CI: 3,196 to 4,154)
SPECT: £4,045 (95%CI: 3,494 to 4,590)
Stress MRI: £4,056 (95%CI: 3,575 to 4,550)
Stress echo: £ 4,452 (95%CI: 3,817 to 5,223)

Cost comparison:
SPECT cf angiography: £415 (95%CI: -310 to 1,084)
Stress MRI cf angiography: £426 (95%CI: -247 to 1,088)
Stress echo cf angiography: £821 (95%CI: 10 to 1,715)

There is substantial probability around values of zero difference in costs giving little evidence of higher costs associated with functional testing. Extra costs for patients in these groups were largely due to patients who underwent confirmatory angiography following positive test results. The significant difference between stress echo and angiography was caused mainly by a greater number of hospital admissions as a result of adverse events (one patient in particular who had 7 admissions for chest pain plus both PCI and CABG surgery).

Results-effectiveness: Mean effect per patient per strategy:
Angiography: 1.13 QALYs (95%CI: 1.08 to 1.17)
SPECT: 1.17 QALYs (95%CI: 1.13 to 1.20)

Stress MRI: 1.14 QALYs (95%CI: 1.10 to 1.18)
Stress echo: 1.17 QALYs (95%CI: 1.13 to 1.20)

QALY comparison:
SPECT cf angiography: 0.0362 (95%CI: -0.092 to 0.080)
Stress MRI cf angiography: 0.00956 (95%CI: -0.055 to 0.074)
Stress echo cf angiography: 0.0371 (95%CI: -0.024 to 0.095)

Results of the QALY estimates did not show any statistically significant differences between the groups. There was little difference in overall quality-adjusted survival between groups, nor significant differences in EQ-5D utilities up to 18-months post-randomisation.

Results-ICER: Cost (£) per QALY gained:

SPECT cf angiography: 11,463/QALY (95%CI: -99,480 to 120,130)
Stress MRI cf angiography: 44,573/QALY (95%CI: -80,543 to 282,058)
Stress echo cf angiography: 22,157/QALY (95%CI: -253,083 to 213,286)

A strategy of going to angiography is less expensive but only marginally less effective than SPECT, stress MRI and stress echo. Although non-invasive tests are slightly more effective, the benefit is so near to zero in all three cases that the ICERs are unstable. CIs around the ICERs are so wide that they are effectively uninformative.

Result-Uncertainty: Various one-way sensitivity analyses together demonstrate that the rank order of costs and QALYs and the magnitude of differences between options are sensitive to reasonable alternative methods of estimation. However, in no case do the 18-month costs of the 3 non-invasive alternatives fall below those of angiography, and the alternative estimation of QALYs (using SF-6D) makes all three alternatives less effective (in QALY terms) than angiography.

Assumptions tested in sensitivity analysis:
Use of SF-6D utility measure in place of EQ-5D
Unit costs of diagnostic strategies
Potential cost savings if negative functional tests were not followed by confirmatory angiography
Removing outliers
Sub-group analysis by type of referring clinical (interventional vs non-interventional cardiologists)

Source Funding: NA

Comments: In terms of cost-effectiveness, all three non-invasive strategies were slightly more expensive than angiography and with similar QALYs. Overall results suggest that functional testing may have a valuable place in the diagnostic pathway for the assessment of chest pain in an outpatient population because of 'process' advantages to patients, clinicians and hospitals. All three tests can avoid invasive diagnostic tests in a significant proportion of patients.

No 823 **Study Quality:** Cost effectiveness of coronary angiography and calcium scoring using CT and stress MRI for diagnosis of coronary artery disease

Author:	Dewey M;Hamm B; 2007
Relevance:	
Intervention:	ETT, stress echo, coronary angiography
Comparison:	CT angiography, EBT, stress MRI
Population:	Hypothetical cohort of patients with different pre-test likelihoods for CAD.
Perspective:	partial SOCIETAL
Study type:	CEA (outcome measure: average cost per correctly identified patient with CAD)
Methods:	DECISION ANALYSIS (effectiveness data taken from published meta-analyses)
Health valuations:	NOT APPLICABLE
Cost components:	Direct costs (reimbursement rates for the test) and indirect costs (costs of subsequent tests, complications, additional tests and false negative diagnosis)
Currency:	EURO
Cost year:	not stated
Time horizon:	For patients receiving a false negative diagnosis, the model includes follow-up for AMI over 10 years.
Discount rate:	5% per annum
Results-cost:	Results were presented in graphical form, and thus providing specific numerical data is difficult. However, from the graphs, results indicate that the cost per correctly diagnosed CAD patient decreased hyperbolically with increasing pre-test likelihood in all diagnostic tests.
Results-effectiveness:	Results were presented in graphical form, and thus providing specific numerical data is difficult. However, from the graphs, results show that coronary angiography (the gold standard) was 100% accurate and its advantage over other diagnostic tests increased with pre-test likelihood for CAD. CT angiography was second most accurate, followed by EBT, stress MRI and stress echo.
Results-ICER:	The authors presented their results only in terms of average cost-effectiveness and did so only in graphical form. In order to perform an incremental analysis based on the published findings, the results were estimated from the graphs. Although the figures are estimated, some strategies were clearly dominated. Estimated results of the incremental analysis are given below as the cost per additional correct CAD diagnosis. 10% CAD prevalence: MSCT = CA = €86600

20% CAD prevalence:
MSCT =
CA = €35000

30% CAD prevalence:
MSCT =
CA = €20100

40% CAD prevalence:
MSCT =
CA = €10700

50% CAD prevalence:
MSCT =
CA = €3300

Exercise stress testing was ruled out through extended dominance at 10-40% CAD prevalence and was dominated at 50-100%. Stress echo, stress MRI and EBCT were dominated at all CAD prevalence. MSCT was the least cost non-dominated or extendedly dominated strategy from 10-50% CAD prevalence. MSCT was ruled out through extended dominance at 60-70% and was dominated at 80-100%. At 60-70%, coronary angiography was the least cost non-dominated or extendedly dominated strategy, and from 80-100% it is the least cost strategy.

Result-Uncertainty: At a maximally increased and decreased accuracy within the 95% CI, CT angiography remained the most effective and least costly strategy up to 60% and 50% pre-test likelihoods respectively.

If diagnostic accuracy of CT angiography was reduced maximally (within in 95% CI) and increased maximally for EBT, CT angiography remained more effective than EBT.

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

An increase (€750) and decrease (€500) of the reimbursement for coronary angiography meant that invasive coronary angiography was more effective and less expensive than CT angiography for pre-test likelihoods from 80% and 50% on, respectively.

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

Source Funding: Not reported

Comments: The study offers a straightforward analysis of cost for diagnostic accuracy of each test, without looking at the prognostic value any of the technologies might add. The incremental analysis performed is based on estimates derived from the graphical presentation of results. Despite rough estimation, some strategies were clearly dominated.

No 801 **Study Quality:** Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction

Author: Mowatt G;Vale L;Brazzelli M;Hernandez R;Murray A;Scott N;Fraser- C;McKenzie L;Gemmell H;Hillis G;Metcalfe M; 2004

Relevance:

Intervention: SPECT MPS (single photon emission computed tomography myocardial perfusion scintigraphy)

Comparison: Stress ECG (electrocardiography) and CA (coronary angiography)

Population: Hypothetical cohort of male patients aged 60 years. A subgroup analysis was conducted for a hypothetical cohort of women aged 60 years.

Perspective: NHS

Study type: CUA

Methods: DECISION ANALYSIS

Health valuations: NOT APPLICABLE

Cost components: The decision tree model which considered a clinical decision problem included costs of the three interventions: ECG, CA and SPECT MPS. The Markov model estimated costs over the cohort's lifetime: med mgt, myocardial infarction and revascularisation.

Currency: £

Cost year: 2001/02

Time horizon: The decision tree model (DTM) was "static" but in reality the decision may have taken weeks or even months. The time horizon for the Markov model was 25 years.

Discount rate: No discount rate used in the DTM. Markov model used a rate of 6% for costs and 1.5% for benefits.

Results-cost: The model included 4 diagnostic strategies. For the base case of 10.5% prevalence of CAD, the average diagnostic cost as well as the diagnostic + treatment cost combined were respectively:
Strategy 1 = ECG-SPECT-CA £603 and £5190

Strategy 2 = ECG-CA £799 and £5395
Strategy 3 = SPECT-CA £921 and £5529
Strategy 4 = CA £1310 and £5929

Results-effectiveness: In the base case (10.5% CAD prevalence) the percent of true positives (TP) diagnosed and the % of accurate diagnoses respectively, are:
Strategy 1 = ECG-SPECT-CA 6.39 and 95.85
Strategy 2 = ECG-CA 7.56 and 96.99
Strategy 3 = SPECT-CA 8.86 and 98.30
Strategy 4 = CA 10.48 and 99.85

The numbers of QALYs for each of the 4 strategies are respectively: 12.473, 12.481, 12.497 and 12.506

Results-ICER: For the four strategies (10.5% CAD prevalence) incremental cost-effectiveness results (£) are as follows for per TP diagnosed, per accurate diagnosis and per QALY, respectively.

	TP	Acc diag	QALY
ECG-SPECT-CA			
ECG-CA	16761	17267	23468
SPECT-CA	9339	9295	8723
CA	23956	24998	42225

Result-Uncertainty: Sensitivity analysis (SA)
1. SPECT is able to identify 50% (vs. 0% in base case) of positive patients who can be satisfactorily managed medically. Result is improved CE for SPECT strategies. Incremental cost per QALY is reduced compared to base case:

	SA1	Base case
Strategy 1 = ECG-SPECT-CA		
Strategy 2 = ECG-CA	17928	23648
Strategy 3 = SPECT-CA	6495	8723
Strategy 4 = CA	16558	42225

2. Higher rate of indeterminacy for stress ECG (30 vs. 18%) and lower rate of indeterminacy for SPECT (2 vs. 9%). Result is improved CE for SPECT strategies. Incremental cost per QALYs as follows:

	SA2	Base case
Strategy 1 = ECG-SPECT-CA		
Strategy 2 = ECG-CA	Dominated by SPECT-CA	23648
Strategy 3 = SPECT-CA	11422 (relative to strategy 1)	8723 (relative to strategy 1=£14,123)
Strategy 4 = CA	41404	42225

3. Cost of stress ECG varied from £25 to £225, angiogram from £895 to £1724 and SPECT from £128 to £340. Result is no change in rank order of strategies from base case.

4. Changing the time horizon from 25 years. Result is that as the time horizon reduces, the incremental cost per QALY increases as the costs of initial diagnosis and treatment are not offset by survival and QoL gains. Results shown in graph form.

5. Changing the time it takes false negative to be correctly diagnosed. In base case all survivors are correctly diagnosed by

year 10. SA changed this to 2 years and 5 years and never. Result is that it improves the CE of non-invasive strategies compared with CA. Incremental cost per QALY for 5 years compared to base case is as follows:

	SA5	Base case
Strategy 1 = ECG-SPECT-CA		
Strategy 2 = ECG-CA	16931	23648
Strategy 3 = SPECT-CA	7644	8723
Strategy 4 = CA	28868	42225

6. Other sensitivity analysis results CA assumed to give perfect information. If that is not the case then the relative CE of a non-invasive strategy would improve.

Risk of MI for all risk states were allowed to increase. There was no difference in the order of the strategies compared to the base case.

Discount rate for costs and benefits was set at 0% for both and 6% for both. There was one change in the order of the strategies compared to base case. For low values of cost for SPECT and zero discount rates SPECT-CA dominates the stress ECG-CA strategy.

QALY value were allowed to vary due to mortality risk reduction after revascularisation. No changes were observed in the order of strategies compared to base case.

Source Funding: Public

Comments: Subgroup analysis was conducted for women aged 60, using sensitivities and specifities for that group and a lower prevalence rate of CAD, different MI rates and mortality rates for women aged 60. Strategy 1 was less costly whereas stress ECG-CA and CA were dominated by the SPECT-CA strategy (less costly and slightly more effective in the second case).

The model suggests that for low levels of prevalence it is possible that the incremental cost per unit of output (TPs diagnosed, accurate diagnosis, QALY) for the move from stress ECG-SPECT-CA and from stress ECG-CA to SPECT-CA might be considered worthwhile. At high risk of prevalence (e.g. 85% risk of CAD) the stress ECG-SPECTCA strategy is dominated by the stress ECG-CA strategy.

No 790 **Study Quality:** The value of myocardial perfusion scintigraphy in the diagnosis and management of angina and myocardial infarction: a probabilistic economic analysis

Author: Hernandez R;Vale L; 2007

Relevance:

Intervention: MPS SPECT, alone or in combination with other non-invasive tests; stress echocardiography was evaluated in a sensitivity analysis

Comparison: ETT (exercise tolerance test), invasive CA (coronary angiography)

Population: Hypothetical cohort of patients aged 60 years. Prevalence of CAD in the population is a modelled variable ranging from 10.5% to 85%. The cost-effectiveness of the different diagnostic strategies are estimated with CAD prevalence of 10.5%, 30%, 50% and 85%.

Perspective: NHS

Study type: CUA with deterministic and probabilistic results

Methods: Cost and effectiveness data obtained from literature - specifically Mowatt et al. 2004

Health valuations: NA

Cost components: Short term diagnostic model includes costs of diagnostic tests. Longer term model includes additional costs of treating CAD (medical management, MI event management, revascularisation).

Currency: UK pounds sterling

Cost year: 2001/2002

Time horizon: Short term diagnostic model did not specify time horizon. Longer term model has 25 year time horizon.

Discount rate: NA to short term diagnostic model. Longer term model used 6% for costs and 1.5% for outcomes.

Results-cost: Deterministic results of base case at 10.5% CAD prevalence (95% CI from probabilistic SA):
ETT-SPECT-CA = £5192 (£4906 - £5473)
ETT-CA = £5396 (£5081 - £5722)
SPECT-CA = £5529 (£5183 - £5821)
CA = £5929 (£5505 - £6345)

Deterministic results of at 30% CAD prevalence (95% CI from probabilistic SA):
ETT-SPECT-CA = £5787 (£5506 - £6070)
ETT-CA = £5958 (£5647 - £6297)
SPECT-CA = £6155 (£5793 - £6471)
CA = £6484 (£6052 - £6926)

Deterministic results of at 50% CAD prevalence (95% CI from probabilistic SA):
ETT-SPECT-CA = £6397 (£6068 - £6709)
ETT-CA = £6535 (£6167 - £6906)
SPECT-CA = £6797 (£6356 - £7198)
CA = £7053 (£6539 - £7551)

Deterministic results of at 85% CAD prevalence (95% CI from probabilistic SA):
ETT-SPECT-CA = £7464 (£7002 - £7917)
ETT-CA = £7543 (£7034 - £8060)
SPECT-CA = £7921 (£7306 - £8469)

CA = £8049 (£7364 - £8726)

Results-effectiveness: Deterministic results of base case at 10.5% CAD prevalence (95% CI from probabilistic SA):
ETT-SPECT-CA = 12.510 QALYs (11.902-13.501)
ETT-CA = 12.518 QALYs (11.907 - 13.066)
SPECT-CA = 12.532 QALYs (11.930 - 13.084)
CA = 12.541 QALYs (11.926 - 13.089)

Deterministic results of at 30% CAD prevalence (95% CI from probabilistic SA):
ETT-SPECT-CA = 11.727 QALYs (11.235 - 12.173)
ETT-CA = 11.759 QALYs (11.270 - 13.215)
SPECT-CA = 11.798 QALYs (11.310 - 12.264)
CA = 11.840 (11.330 - 12.311)

Deterministic results of at 50% CAD prevalence (95% CI from probabilistic SA):
ETT-SPECT-CA = 10.924 (10.524 - 11.294)
ETT-CA = 10.979 (10.578 - 11.367)
SPECT-CA = 11.045 (10.631 - 11.455)
CA = 11.121 (10.668 - 11.551)

Deterministic results of at 85% CAD prevalence (95% CI from probabilistic SA):
ETT-SPECT-CA = 9.518 (9.146 - 9.862)
ETT-CA = 9.616 (9.219 - 9.994)
SPECT-CA = 9.726 (9.284 - 10.147)
CA = 9.862 (9.330 - 10.337)

Results-ICER: Incremental cost-effectiveness results are as follows for cost per QALY:

	ICER
10.5% CAD Prevalence:	
ETT-SPECT-CA	
ETT-CA	26249
SPECT-CA	9261
CA	48576
30% CAD Prevalence	
ETT-SPECT-CA	
ETT-CA	5454
SPECT-CA	4997
CA	7893
50% CAD Prevalence	
ETT-SPECT-CA	
ETT-CA	2473
SPECT-CA	4032
CA	3372

85% CAD Prevalence
ETT-SPECT-CA
ETT-CA 803
SPECT-CA 3428
CA 948

Result-Uncertainty: Authors presented the results of the probabilistic sensitivity analysis in a series of cost-effectiveness acceptability curves for each level of CAD prevalence modelled. In the base case (10.5% CAD prevalence), ETT-CA is highly unlikely to be optimal. If willingness to pay is £8000 per QALY, the strategy with a higher probability of being optimal is ETT-SPECT-CA. At £9000 per QALY, ETT-SPECT-CA and SPECT-CA strategies have a similar probability of being optimal. At a ceiling ratio of £20000 per QALY, SPECT-CA has a 90% likelihood of being considered the more cost-effective option, but beyond this value, the likelihood falls such that at a WTP over £75000 per QALY, CA is the strategy most likely to be optimal.

At 30% CAD prevalence, strategies that involve SPECT seem to be optimal for a WTP of up to £20000, with CA being the optimal strategy for higher WTP values. For higher levels of CAD prevalence and for thresholds greater than £10000 per QALY, CA is the optimal decision.

The diagnostic accuracy of SPECT was taken to both optimistic and pessimistic extremes, and as expected, when less favourable SPECT figures were used (i.e. lower sensitivity and specificity), the SPECT-CA strategy did not appear on the CEAC frontier of optimal strategies at any level of CAD prevalence. However, in this scenario ETT-SPECT-CA appear optimal at 10.5% CAD prevalence when the WTP threshold his £5000. Using more favourable SPECT parameter values produced similar results to the base case. The authors point out that even for the most optimistic scenario, when CAD prevalence is greater than 60% and the WTP threshold is more than £16000, the CA strategy appears to be optimal.

When the time horizon for the longer term model was reduced, the incremental cost per QALY increases. This is because the costs of initial diagnosis and treatment are not offset by survival and quality-of-life gains.

Increasing the likelihood that misdiagnoses will be rectified reduces the penalty associated with making a false-negative diagnosis (i.e. it improves the cost-effectiveness of non-invasive strategies compared with CA).

Using higher values for ETT indeterminacy and lower values for SPECT indeterminacy, it was found that SPECT strategies were more likely to be considered cost-effective.

Results were relatively insensitive to changes in cost and to changes in the sensitivity and specificity of CA (reduced to 99% CI (98.995 to 99.005)).

When subgroup analysis was restricted to women, results were slightly more favourable to SPECT-based strategies.

When stress echo were added to the model, they were shown to be potentially cost-effective options. At 10.5% CAD prevalence, ECHO-SPECT-CA dominated both ETT-SPECT-CA and ETT-SPECT strategies, whereas ECHO-CA dominated both ETT-CA and SPECT-CA strategies.

At low levels of CAD prevalence, up to 1%, ETT-SPECT-CA strategy dominated all others. For prevalence between 1% and 4%, SPECT-based strategies dominated non-SPECT-based strategies. At 5% CAD prevalence, SPECT-CA strategy dominated CA only strategy.

Source Funding: UK Department of Health on a grant administered by NCCHTA

Comments: Results of the probabilistic analysis show that ETT-CA is unlikely to ever be the optimal strategy. SPECT-CA looks optimal below 30% CAD prevalence, and CA only looks optimal above 30% CAD prevalence. Stress echocardiography has a possible role, although the test data used came from an ad hoc review and included indirect comparator analysis. Thus the results of the analysis which included stress echo should be interpreted with some caution.

1 Economic Models for Stable Chest Pain

1.1 Replicated Mowatt 2008 short-term diagnostic Economic Model with Revised Assumptions and Addition of Calcium Scoring Treatment Arms.

1.1.1 Introduction

The Mowatt et al HTA for 64-slice CT coronary angiography scanning included a short-term diagnostic economic model (Mowatt, G., Cummins, E., Waugh, N. et al, 2008). The model results were very favourable to 64-slice CT coronary angiography. The GDG felt that some of the modelled assumptions were over-optimistic in favour of 64-slice CT coronary angiography. Consequently, the guideline health economist was asked to replicate the model with a view to exploring the clinical and health economic implications of alternative model assumptions. We acknowledge the help of the developers of the HTA models who provided a template of their short-term model. Here we present some results from having replicated and revised the Mowatt et al model. The key revisions are to reduce the test sensitivity of 64-slice CT coronary angiography, and to add additional treatment arms which begin with calcium scoring using a 64-slice CT scanner. The latter was done because of concerns about radiation exposure for patients who might be subjected to repeat MSCT coronary angiography.

1.1.2 Methods and Model Assumptions

Using the model structure used by Mowatt and colleagues in their 2008 HTA (Mowatt, G., Cummins, E., Waugh, N. et al, 2008), their short term diagnostic model was rebuilt using Microsoft Excel™. The excel model was validated by replicating their base case results. The original HTA presented results for assumed CAD prevalence (pre-test likelihood) rates of 10%, 30%, 50% and 70%. In the following analyses model outputs are presented for a cohort of 1000 patients at assumed CAD prevalence of 5%, 20%, 40%, 60% and 80% respectively.

Ten diagnostic strategies have been modeled, the first eight of which represent the sequences presented by Mowatt and colleagues (Mowatt, G., Cummins, E., Waugh, N. et al, 2008). The two additional strategies incorporate calcium scoring as a rule out strategy prior to 64-slice CT coronary angiography.

Test	Strategy 1	Strategy 2	Strategy 3	Strategy 4	Strategy 5	Strategy 6	Strategy 7	Strategy 8	Strategy 9	Strategy 10
1st	ECG	ECG	ECG	MPS	CT	CA	ECG	CT	Ca Score	Ca Score
2nd	MPS	CT	CA	CA	CA	-	CT	-	CT	CT
3rd	CA	CA	-	-	-	-	-	-	-	CA

ECG=exercise ECG; MPS = MPS with SPECT; CA=invasive coronary angiography; CT=64-slice CT coronary angiography; Ca Score=calcium scoring with 64-slice CT scanner.

The treatment protocol assumptions are that patients only move on to subsequent tests if they test positive or indeterminate for the initial test(s). Patients who test negative are not subjected to further testing. For example, in strategy 1, exercise ECG is the first diagnostic test. Patients having an indeterminate or positive exercise test result move on to the second line MPS with SPECT. Patients having a positive or indeterminate MPS with SPECT result then have invasive coronary angiography as a final test. Strategies 6 and 8 assume that patients are sent straight to and only have invasive coronary angiography or 64-slice CT coronary angiography, respectively. In Strategies 1 to 6 and 10, patients testing positive always end up having an invasive coronary angiography as final confirmatory test. Strategies 7, 8 and 9 assume that only those patients who have an indeterminate result after 64-slice CT coronary angiography will go on to invasive coronary angiography in order to ensure that all patients end with a definitive diagnosis. The model assumes that invasive coronary angiography is the ‘gold standard’ and assigns 100% diagnostic sensitivity and specificity to this test.

The input assumptions required by the model for each of the 5 diagnostic technologies are the diagnostic sensitivity and specificity, a small risk of

immediate mortality induced by the test, the probability that the test is indeterminate and the estimated cost of the test. Table 1 summarises the model inputs used in the base case analysis.

Table 1: Base Case Model Parameters

Test	Value	Source
Exercise ECG		
Sensitivity	67%	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Specificity	69%	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Indeterminacy	24%	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Mortality Risk	0.005%	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Cost	£66	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
MPS with SPECT		
Sensitivity	86%	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Specificity	64%	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Indeterminacy	6%	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Mortality Risk	0.005%	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Cost	£293	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Calcium Scoring (>0) with MSCT		
Sensitivity	89%	(Kitamura, A., Kobayashi, T., Ueda, K. et al, 2005)
Specificity	43%	(Kitamura, A., Kobayashi, T., Ueda, K. et al, 2005)
Indeterminacy	2%	(Dewey, M. and Hamm, B., 2007)
Mortality Risk	0.000%	(Dewey, M. and Hamm, B., 2007)
Cost	£103	Expert opinion
64-slice CT coronary angiography		
Sensitivity	80%	Expert opinion

Specificity	89%	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Indeterminacy	2%	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Mortality Risk	0.001%	Expert opinion
Cost CT alone	£206	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Cost after calcium scoring	£103	(Dewey, M. and Hamm, B., 2007); Expert opinion
Invasive coronary angiography		
Sensitivity	100%	Assumption
Specificity	100%	Assumption
Indeterminacy	0%	Assumption
Mortality Risk	0.020%	Expert opinion
Cost	£850	(Department of Health, 2008); (Sculpher, M., Smith, D., Clayton, T. et al, 2002)

1.1.3 Revisions to Mowatt base case assumptions

The base case model inputs used in this analysis include some key revisions from the Mowatt et al 2008 (Mowatt, G., Cummins, E., Waugh, N. et al, 2008) base case. Following discussions at the October 2008 GDG meeting, some GDG members indicated that they considered that the diagnostic sensitivity of 99%, attributed to 64-slice CT coronary angiography, was over-optimistic. This figure was derived from a systematic review, which primarily used a threshold of 50% stenosis to define presence of CAD. GDG members indicated that more recent papers, using a CAD threshold of 70% stenosis, showed 64-slice CT coronary angiography to have a test sensitivity of around 80%. (Expert opinion). The GDG also suggested revised estimates for the risk of immediate mortality from invasive coronary angiography which was subsequently reduced from the 0.15% used by Mowatt and colleagues to 0.02% in the new base case. Also, a 1 in 80,000 risk of mortality from reaction to contrast in patients undergoing 64-slice CT coronary angiography was introduced at the request of the GDG.

In their 2008 HTA, Mowatt and colleagues (Mowatt, G., Cummins, E., Waugh, N. et al, 2008) indicate that the cost of invasive coronary angiography may have been underestimated in their analysis. Indeed their base case estimate of £320 seems low compared with other published estimates. For example, an estimate close to £1,300 was used in the EMPIRE study (Underwood, S. R., Godman, B., Salyani, S. et al, 1999) and in the Mowatt 2004 HTA (Mowatt, G., Vale, L., Brazzelli, M. et al, 2004) evaluating the use of MPS with SPECT. More recent publications and the NHS reference costs suggest that the cost of invasive coronary angiography is £832 (Sculpher, M., Smith, D., Clayton, T. et al, 2002) or higher (2006/07 NHS reference costs (Department of Health, 2008) HRG code EA41z). For the revised model we have assumed a base case invasive coronary angiography cost of £850.

In addition to the above revisions, the Mowatt 2008 model was expanded to include two additional arms to evaluate calcium scoring as a rule out strategy prior to 64-slice CT coronary angiography. The inputs for calcium scoring were taken from two sources: indeterminacy was taken from an analysis by Dewey and Hamm (Dewey, M. and Hamm, B., 2007) and sensitivity and specificity were taken from a study identified in the clinical search, (Kitamura, A., Kobayashi, T., Ueda, K. et al, 2005)\which scored coronary calcification using 4-slice CT coronary angiography. In the base case, an Agatston score threshold of >0 was used to define a positive diagnosis of significant CAD. Dewey and Hamm (Dewey, M. and Hamm, B., 2007) calculate the cost of doing calcium scoring as roughly 54% of the cost of MSCT coronary angiography. This figure was confirmed by the GDG who stated that calcium scoring represents the first 50% of the cost of a complete 64-slice CT coronary angiography. Therefore, the cost of calcium scoring used in the model is £103 (50% of the cost of 64-slice CT coronary angiography as defined by Mowatt et al (Mowatt, G., Cummins, E., Waugh, N. et al, 2008)). The GDG also advised that the cost of doing 64-slice CT coronary angiography following calcium scoring is the remaining 50% of the total cost of 64-slice CT coronary angiography. For strategies where calcium scoring

is not a discrete step in the diagnostic pathway, the full cost of £206 is used for 64-slice CT coronary angiography.

1.1.4 Model Outputs

Like the 2008 HTA (Mowatt, G., Cummins, E., Waugh, N. et al, 2008) on 64-slice CT coronary angiography, this model calculates the short-term diagnostic cost for each of the defined strategies. Our model also presents the full two by two true-false, positive-negative matrix. We also presented an incremental economic analysis using the incremental cost per correctly diagnosed case. There is evidence from the 2004 HTA on MPS with SPECT that this ICER is a close proxy to the value of the longer-term cost per QALY ICER for higher levels of modelled CAD prevalence (Mowatt, G., Vale, L., Brazzelli, M. et al, 2004).

1.1.5 Base Case Results

Table 2 summarises the results of a 1000 patient cohort in the base case analysis at a range of modelled prevalence rates (5%, 20%, 40%, 60% and 80%). As prevalence increases, total costs increase and the proportion of accurate diagnoses decreases.

Table 2: Total costs and outcomes for 1000 patient cohort for each diagnostic strategy at each level of CAD prevalence modelled.

Prevalence	Strategy	Description	Total Cost	% Accurately Diagnosed	FP	FN	Total Deaths	CAD Negative Deaths
5%	9	Ca-CT	£164,211	92.66%	59.3	14.1	0.01	0.01
	7	ECG-CT	£175,104	93.14%	48.7	19.9	0.06	0.05
	8	CT	£223,000	88.78%	102.4	9.8	0.02	0.02
	2	ECG-CT-CA	£241,463	98.00%	0	19.9	0.07	0.06
	10	Ca-CT-CA	£254,407	98.58%	0	14.1	0.03	0.02
	5	CT-CA	£343,367	99.02%	0	9.8	0.04	0.04
	1	ECG-MPS-CA	£389,989	98.24%	0	17.5	0.12	0.11
	3	ECG-CA	£481,867	98.73%	0	12.5	0.15	0.14
	4	MPS-CA	£651,597	99.33%	0	6.6	0.13	0.12
	6	CA	£850,000	99.98%	0	0	0.2	0.19
20%	9	Ca-CT	£169,056	89.36%	49.9	56.5	0.01	0.01
	7	ECG-CT	£184,255	87.94%	41	79.5	0.06	0.05
	8	CT	£223,000	87.45%	86.2	39.2	0.02	0.01
	2	ECG-CT-CA	£318,964	92.04%	0	79.5	0.09	0.05
	10	Ca-CT-CA	£341,282	94.34%	0	56.5	0.05	0.02
	5	CT-CA	£429,581	96.07%	0	39.2	0.07	0.03
	1	ECG-MPS-CA	£460,801	93.00%	0	69.9	0.13	0.09
	3	ECG-CA	£516,749	94.97%	0	50.2	0.16	0.12
	4	MPS-CA	£711,519	97.35%	0	26.3	0.15	0.1
	6	CA	£850,000	99.98%	0	0	0.2	0.16
40%	9	Ca-CT	£175,516	84.95%	37.4	113.1	0.01	0
	7	ECG-CT	£196,457	81.01%	30.8	159	0.06	0.03
	8	CT	£223,000	85.69%	64.7	78.4	0.02	0.01
	2	ECG-CT-CA	£422,297	84.08%	0	159	0.11	0.04
	10	Ca-CT-CA	£457,116	88.69%	0	113.1	0.08	0.01

	5	CT-CA	£544,534	92.15%	0	78.4	0.09	0.02
	1	ECG-MPS-CA	£555,216	86.01%	0	139.7	0.15	0.07
	3	ECG-CA	£563,259	89.95%	0	100.3	0.17	0.09
	4	MPS-CA	£791,415	94.72%	0	52.6	0.17	0.08
	6	CA	£850,000	99.98%	0	0	0.2	0.12
60%	9	Ca-CT	£181,976	80.54%	24.9	169.6	0.01	0
	7	ECG-CT	£208,659	74.09%	20.5	238.6	0.06	0.02
	8	CT	£223,000	83.93%	43.1	117.6	0.02	0.01
	2	ECG-CT-CA	£525,631	76.13%	0	238.6	0.14	0.03
	10	Ca-CT-CA	£572,950	83.03%	0	169.6	0.1	0.01
	3	ECG-CA	£609,769	84.93%	0	150.5	0.18	0.06
	1	ECG-MPS-CA	£649,632	79.02%	0	209.6	0.18	0.04
	5	CT-CA	£659,486	88.23%	0	117.6	0.12	0.02
	6	CA	£850,000	99.98%	0	0	0.2	0.08
	4	MPS-CA	£871,311	92.09%	0	79	0.19	0.05
80%	9	Ca-CT	£188,436	76.14%	12.5	226.1	0.01	0
	7	ECG-CT	£220,861	67.16%	10.3	318.1	0.06	0.01
	8	CT	£223,000	82.16%	21.6	156.8	0.02	0
	2	ECG-CT-CA	£628,965	68.17%	0	318.1	0.16	0.01
	3	ECG-CA	£656,278	79.92%	0	200.6	0.19	0.03
	10	Ca-CT-CA	£688,784	77.37%	0	226.1	0.13	0
	1	ECG-MPS-CA	£744,048	72.03%	0	279.5	0.2	0.02
	5	CT-CA	£774,439	84.31%	0	156.8	0.15	0.01
	6	CA	£850,000	99.98%	0	0	0.2	0.04
	4	MPS-CA	£951,207	89.45%	0	105.3	0.2	0.03

Results of the incremental cost-effectiveness analysis are presented in Table 3. Diagnostic strategies are ranked in order of increasing cost and incremental cost-effectiveness ratios are calculated as the additional cost per additional accurate diagnosis. Table 3 does not include strategies that were excluded through dominance or extended dominance. At all levels of modelled CAD prevalence, MPS with SPECT is excluded through dominance or extended dominance, and therefore does not appear in the table of incremental results.

Table 3: Total costs, outcomes and incremental cost-effectiveness of each non-dominated and non-extendedly dominated diagnostic strategy for hypothetical cohort of 1000 patients

Prevalence	Strategy	Description	Total Cost	% Accurately Diagnosed	FP	FN	ICER (cost per correct diagnosis)
5%	9	Ca-CT	£164,211	92.66%	59.3	14.1	
	2	ECG-CT-CA	£241,463	98.00%	0	19.9	£1,466
	10	Ca-CT-CA	£254,407	98.58%	0	14.1	£2,234
	5	CT-CA	£343,367	99.02%	0	9.8	£20,605
	6	CA	£850,000	99.98%	0	0	£52,530
20%	9	Ca-CT	£169,056	89.36%	49.9	56.5	
	10	Ca-CT-CA	£341,282	94.34%	0	56.5	£3,454
	5	CT-CA	£429,581	96.07%	0	39.2	£5,099
	6	CA	£850,000	99.98%	0	0	£10,732
40%	9	Ca-CT	£175,516	84.95%	37.4	113.1	
	6	CA	£850,000	99.98%	0	0	£4,488
60%	9	Ca-CT	£181,976	80.54%	24.9	169.6	
	8	CT	£223,000	83.93%	43.1	117.6	£1,213
	6	CA	£850,000	99.98%	0	0	£3,906
80%	9	Ca-CT	£188,436	76.14%	12.5	226.1	
	8	CT	£223,000	82.16%	21.6	156.8	£574
	6	CA	£850,000	99.98%	0	0	£3,519

Results indicate that strategy 9 (Ca Score – CT) is the least cost option at all levels of CAD prevalence, but gives rise to a non-negligible number of false positives and false negatives. At 5% CAD prevalence, the move to strategy 2 (exercise ECG – CT – CA) from strategy 9 has a favourable incremental cost-effectiveness, but it is worth highlighting that while the number of false positive diagnoses falls to 0, the number of false negatives increases by 5.8. Strategy 10 (Ca Score – CT – CA) has a favourable incremental cost-effectiveness over

strategy 2. If, due to its increased number of false negatives, strategy 2 is removed from the incremental analysis, the incremental cost per correct diagnosis of strategy 10 compared to strategy 9 is £1,523. Strategies 5 (CT – CA) and 6 (CA only), though more effective, are considerably more expensive, with each additional correct diagnosis costing £20,605 and £52,530, respectively compared to the next most effective strategies.

At 20% CAD prevalence, the move to strategy 10 (Ca Score – CT – CA) from strategy 9 is likely to be considered cost-effective, as is the further move to strategy 5 (CT – CA). Strategy 6 is the most effective and most costly, with additional correct diagnoses costing £10,732 each compared to strategy 5.

At higher levels of prevalence (40%, 60% and 80%) the ICER for the move from strategy 9 (Ca Score – CT) to strategy 6 (CA only) is likely to be considered cost-effective. At 60% and 80%, strategy 8 (CT only) appears to have a favourable incremental cost-effectiveness compared to strategy 9, but it is worth pointing out the increased number of false positives arising from this move. These false positives are more than offset by a substantial decrease in the number of false negatives identified, but the most clinically and cost-effective option in this high prevalence population is likely to be strategy 6 (CA only).

1.1.6 Sensitivity Analysis

The following sensitivity analyses use the above base case assumptions, except that in each case one variable has been altered. The GDG was interested in looking at how further reducing the specificity of 64-slice CT coronary angiography would affect the relative cost-effectiveness of 64-slice CT coronary angiography based strategies. Additionally, there was interest in how increasing the calcium score threshold used to define positive diagnosis might affect calcium scoring based strategies' relative cost-effectiveness.

1.1.6.1 Reduced specificity of 64-slice CT coronary angiography

The following sensitivity analysis uses the above base case assumptions, except that the specificity of 64-slice CT coronary angiography is reduced from 89% to 67%. This reflects the less favourable results emerging from recent multi-centre studies. It is worth pointing out that the base case presented above had already reduced sensitivity of 64-slice CT coronary angiography from 99% in Mowatt 2008 (Mowatt, G., Cummins, E., Waugh, N. et al, 2008) to 80%.

Results of this sensitivity analysis compared with the base case are summarised in table 4. When specificity of 64-slice CT coronary angiography is reduced to 67%, strategy 9 (Ca score – CT) remains the least cost option, but gives rise to a substantial number of false positives. At 5% CAD prevalence, strategy 7 (exercise ECG – CT) was excluded through extended dominance in the base case, but emerges as a potentially cost-effective option in this sensitivity analysis. However, strategy 2 (exercise ECG – CT – CA) is likely to be a better option than strategy 7 given its incremental cost-effectiveness and dramatically reduced number of false positives. Strategy 10 (Ca score – CT – CA) is still likely to be cost-effective, although with a much higher incremental cost-effectiveness ratio at 5% CAD prevalence than in the base case. However, at 20% CAD prevalence, the ICER for strategy 10 over strategy 9 is much lower than in the base case, as the incremental benefit, in terms of correct diagnoses, between the strategies is much larger in the sensitivity analysis than the base case. Strategy 10 would ensure there are no false positive diagnoses and minimise the number of false negatives (14.1 and 56.5 at 5% and 20% CAD prevalence, respectively).

At 40% CAD prevalence and above, the most cost-effective strategy is still sending all patients directly for invasive coronary angiography.

Table 4: Incremental cost per accurate diagnosis and false positive and negative outcomes: reduced specificity value for CT.

Prevalence	Strategy	Description	ICER SA	ICER Base Case	SA		Base Case	
					FP	FN	FP	FN
5%	9	Ca Score - CT			177.8	14.1	59.3	14.1
	7	ECG - CT	£421	ext dom.	146.1	19.9	48.7	19.9
	2	ECG - CT - CA	£1,021	£1,466	0	19.9	0	19.9
	10	Ca Score - CT - CA	£5,335	£2,234	0	14.1	0	14.1
	5	CT-CA	ext dom.	£20,605	0	9.8	0	9.8
	6	CA	£35,383	£52,530	0	0	0	0
20%	9	Ca Score - CT			149.7	56.5	49.9	56.5
	10	Ca Score - CT - CA	£1,718	£3,454	0	56.5	0	56.5
	5	CT-CA	ext dom.	£5,099	0	39.2	0	39.2
	6	CA	£7,515	£10,732	0	0	0	0
40%	9	Ca Score - CT			112.3	113.1	37.4	113.1
	6	CA	£2,996	£4,488	0	0	0	0
60%	9	Ca Score - CT			74.8	169.6	24.9	169.6
	8	CT	dominated	£1,213	129.4	117.6	43.1	117.6
	6	CA	£2,735	£3,906	0	0	0	0
80%	9	Ca Score - CT			37.4	226.1	12.5	226.1
	8	CT	£821	£574	64.7	156.8	21.6	156.8
	6	CA	£2,833	£3,519	0	0	0	0

1.1.6.2 Increasing Calcium Score Threshold

The base case demonstrated that calcium scoring as an initial test in the low risk groups is very likely to be cost-effective. In the base case an Agatston score threshold of >0 was used to define a positive diagnosis warranting further testing with 64-slice CT coronary angiography. This threshold was chosen because diagnostic studies have shown it to have very high sensitivity and negative predictive value which makes it an excellent test for ruling out CAD. However, a

>0 threshold has a poor specificity which means that many people who do not have CAD will receive a false positive diagnosis and go on for further unnecessary testing. By increasing the threshold score for positive diagnosis to >100, the sensitivity of calcium scoring decreases to 72%, but the specificity increases to 81% (Kitamura, A., Kobayashi, T., Ueda, K. et al, 2005).

Table 6 summarises the results of this sensitivity analysis and compares them to those generated in the base case. When the calcification threshold is increased to a minimum score of 100, strategy 9 (Ca Score – CT) remains the least cost option at all levels of CAD prevalence, but strategy 10 (Ca Score – CT – CA) performs less favourably than in the base case. At 5% CAD prevalence, strategy 10 is still likely to be cost-effective, but with an increased ICER of £2,183 over strategy 9. In this scenario, strategy 2 (exercise ECG – CT – CA) is ruled out through extended dominance. At 20% CAD prevalence, strategy 10 is ruled out through extended dominance. Therefore, at 20% CAD prevalence, strategy 5 may be a cost-effective option (ICER = £4,764 compared to strategy 9). At 40% CAD prevalence and greater, a strategy of sending all patients directly to invasive coronary angiography is still likely to be cost-effective.

Table 5: Incremental cost per accurate diagnosis and false positive and negative outcomes: increased Agatston score threshold for coronary calcification (>100).

					SA		Base Case	
Prevalence	**Strategy**	**Description**	**ICER (Ca Score >100)**	**ICER Base Case**	**FP**	**FN**	**FP**	**FN**
5%	9	Ca Score - CT			21.1	20.8	59.3	14.1
	2	ECG-CT-CA	ext. dom	£1,466	0	19.9	0	19.9
	10	Ca Score - CT - CA	£2,183	£2,234	0	20.8	0	14.1
	5	CT-CA	£15,489	£20,605	0	9.8	0	9.8
	6	CA	£52,530	£52,530	0	0	0	0
20%	9	Ca Score - CT			17.8	83.3	49.9	56.5
	10	Ca Score - CT - CA	ext dom.	£3,454	0	83.3	0	56.5
	5	CT-CA	£4,764	£5,099	0	39.2	0	39.2
	6	CA	£10,762	£10,732	0	0	0	0
40%	9	Ca Score - CT			13.3	166.6	37.4	113.1

	8	CT	£2,097	ext dom.	64.7	78.4	64.7	78.4
	6	CA	£4,488	£4,488	0	0	0	0
60%	9	Ca Score - CT			8.9	250	24.9	169.6
	8	CT	£679	£1,213	43.1	117.6	43.1	117.6
	6	CA	£3,906	£3,906	0	0	0	0
80%	9	Ca Score - CT			4.4	333.3	12.5	226.1
	8	CT	£351	£574	21.6	156.8	21.6	156.8
	6	CA	£3,519	£3,519	0	0	0	0

1.1.7 Summary and Discussion

The analysis presented here represents a revision and expansion of the short term diagnostic model built for the Mowatt 2008 HTA (Mowatt, G., Cummins, E., Waugh, N. et al, 2008). Several adjustments were made to Mowatt et al's input assumptions, including a reduced diagnostic accuracy of 64-slice CT coronary angiography and an increased cost of invasive coronary angiography. In addition, two new arms which each include calcium scoring as a discrete step in the diagnostic pathway leading to 64-slice CT coronary angiography have been added and analysed. Finally, two one-way sensitivity analyses have been undertaken to test the sensitivity of results to assumptions made regarding 64-slice CT coronary angiography's specificity, and an alternative calcium score threshold for positive diagnosis.

Essentially this paper has presented a cost-consequence analysis, although an incremental analysis has been conducted with outcomes presented as the additional cost per accurate diagnosis. This is an enhancement on analyses previously presented to the GDG, in that other analyses involving key technologies do not undertake incremental analysis (Mowatt, G., Cummins, E., Waugh, N. et al, 2008) (Dewey, M. and Hamm, B., 2007) (Rumberger, J. A., Behrenbeck, T., Breen, J. F. et al, 1999) at all.

Results of the base case analysis presented here indicate that for lower risk groups (5% and 20%), the use of calcium scoring as a first line testing strategy is

likely to be cost-effective and should be followed by either 64-slice CT coronary angiography alone or with additional invasive coronary angiography as a confirmatory 3rd test. In higher risk populations (CAD prevalence greater than 40%), a strategy of sending all patients directly for invasive coronary angiography is likely to be cost-effective.

The model indicates that MPS with SPECT is excluded through dominance or extended dominance at every level of CAD prevalence. It also indicates that exercise ECG is only cost-effective as a first line investigation strategy at 5% CAD prevalence, but that even in this instance replacing exercise ECG with calcium scoring is likely to improve effectiveness at a reasonable level of additional cost.

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

The current model and results have several limitations worth mentioning. The model has the same structure as the short-term diagnostic model presented in Mowatt 2008 (Mowatt, G., Cummins, E., Waugh, N. et al, 2008) for the diagnosis of CAD, and no attempt has been made to extend the model to account for resource and health implications beyond the diagnosis timeframe. Thus, for example, any adverse health and resource implications of false negative diagnoses have not been accounted for in the current model. Similarly, the current model does not consider the prognostic value of the modelled technologies as these considerations were outside the scope of the guideline.

Although all of the short-term diagnostic costs and healthcare consequence outputs of the model are presented in this paper, the incremental economic evaluation focuses on the cost per correctly diagnosed patient. Although this is

more informative than previously published analyses presented to the GDG, it still has the disadvantage of not having a readily available NHS threshold for cost-effectiveness (e.g. £20,000 per QALY). However, evidence from the Mowatt 2004 HTA (Mowatt, G., Vale, L., Brazzelli, M. et al, 2004) indicated that for levels of modelled prevalence 30% and greater, the incremental cost per correct diagnosis values resulting from the short term model were similar to the incremental cost per QALY values estimated by the longer-term Markov model.

Finally, the GDG considered that the model did not adequately represent patients with an intermediate risk of disease for whom anatomical testing may not be sufficient to appropriately assess the functional significance of the CAD. In other words, it is possible that for some patients presenting with stable chest pain, doubt will remain as to whether the degree of stenosis observed on anatomical investigation is the cause of their chest pain. For this population, the GDG wanted to explore the cost-effectiveness of first line functional testing.

2 Cost-Effectiveness of First Line Functional Testing

2.1 Introduction

The economic model presented above has given support to use of anatomical imaging (64-slice CT coronary angiography preceded by calcium scoring in low risk CAD patients, and invasive coronary angiography in high risk patients) for patients presenting with stable chest pain respectively. The model indicated that functional testing, as represented by exercise ECG and MPS with SPECT, does not appear to cost-effective, (often dominated), for almost the full range of CAD prevalences modelled.

As discussed above, the GDG had reservations about the applicability of the model for patient with an intermediate risk of disease. Furthermore, they anticipated that this group of patients could constitute a relatively large group of patients in the context of the stable chest pain care pathway. The GDG believed

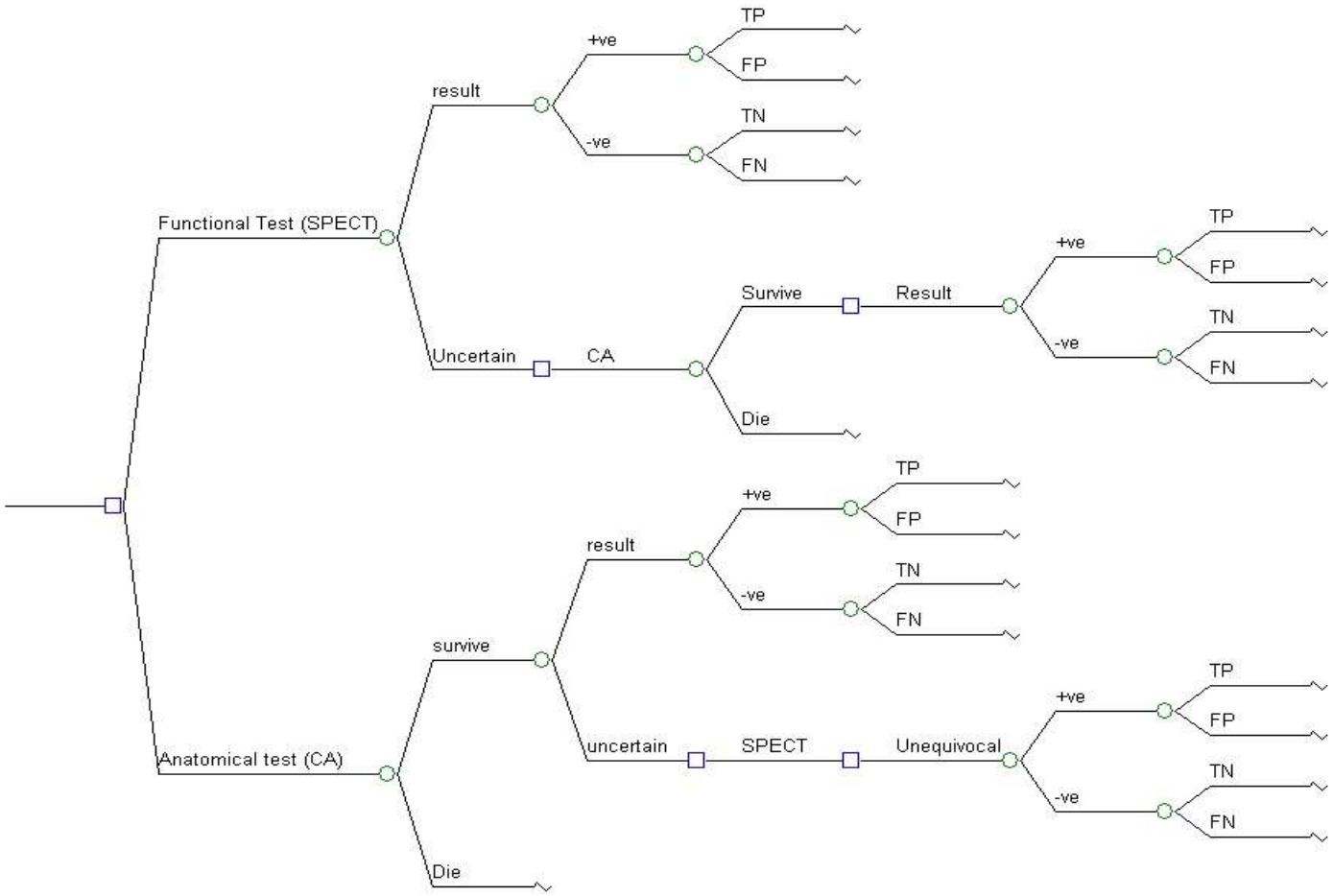
that there was likely to be a role for first line functional testing for this group of patients, and requested an alternative economic model appropriate for this patient group.

The model evaluates the cost-effectiveness of first line functional testing using MPS with SPECT, compared to first line anatomical testing, in patient populations presenting with stable chest pain, and a moderate pre-test likelihood of CAD (20% to 60%).

2.2 Model Structure and Input Assumptions

The model structure is illustrated in the decision tree presented in Figure 2.2.1.below.

Figure 2.2.1. First Line Functional Testing Model Structure



There are two alternative treatment arms in the model:

- First line functional testing using MPS with SPECT
- First line anatomical testing with invasive coronary angiography.

2.2.1 First Line Functional Testing

In line with the models presented in the Mowatt HTA for Angina (Mowatt, G., Vale, L., Brazzelli, M. et al, 2004), and CAD (Mowatt, G., Cummins, E., Waugh, N. et al, 2008), MPS with SPECT is used to represent first line functional testing. The first branch of the decision tree allows for the possibility of an equivocal (indeterminate) functional test result. The Mowatt 2004 (Mowatt, G., Vale, L., Brazzelli, M. et al, 2004) model used a figure of 9% to represent this proportion of uncertain results. Using results from their literature review, and including results from other reviews, Mowatt and colleagues used an uncertain proportion estimate of 6% for SPECT in their 2008 HTA model (Mowatt, G., Vale, L., Brazzelli, M. et al, 2004). The latter is used in the current base case model scenario. Patients with an equivocal first line functional test result, are assumed to go on to have a second line invasive coronary angiography, which is assumed to be 100% sensitive and specific, with no equivocal test results.

For a given prevalence (pre-test likelihood) of CAD in the modelled population, the model then calculates the expected number of true positive (TP), true negative (TN), false positive (FP), and false negative (FN) results based on the assumed test sensitivities and specificities. In the working base case it has been assumed that the sensitivity and specificity results for MPS with SPECT used in the Mowatt and colleagues 2008 (Mowatt, G., Cummins, E., Waugh, N. et al, 2008) model are appropriate (see table below for details of assumed parameter values).

2.2.2 First line Anatomical Testing

The structure of the first line anatomical testing arm is effectively a replica of the first line functional testing arm except that patients in this arm of the model have invasive coronary angiography as first line test (in a sensitivity analysis, invasive coronary angiography is replaced with 64-slice CT coronary angiography). The model allows for the possibility of a small proportion of patients having invasive coronary angiography to die from the procedure, (this risk is very small and has minimal impact on the model outputs). Patients with an equivocal invasive coronary angiography result for diagnosis of angina, are assumed to have a second line functional test (MPS with SPECT). Although the model structure allows for a proportion of second line functional tests producing an equivocal result, the base case assumes all second line test results are unequivocal. Again the model then calculates the outputs of the two by two true-false, positive-negative matrix.

2.2.3 Cost and Assumptions Summary

The cost of MPS with SPECT (£293) in the base case is taken from the Mowatt 2008 HTA(Mowatt, G., Cummins, E., Waugh, N. et al, 2008). Base case cost of invasive coronary angiography is assumed to be £850, based on the same estimates described previously. All base case input parameter values are presented in the table below.

Test characteristics	MPS	CA
Death Rate	0.000%	0.020%
Equivocal/Indeterminate	6.00%	Pt%
Sensitivity	86%	100%
Specificity	64%	100%
Cost	£293	£850

2.3 Analytical Methods

Our literature search did not identify the proportion of stable chest pain patients likely to have an equivocal/indeterminate invasive coronary angiography result for diagnosis of angina. As such, the model has been used to identify a threshold proportion (Pt) of equivocal invasive coronary angiography results. That is, the threshold at which decision makers are likely

to be indifferent between first line functional, and first line anatomical testing. In order to facilitate this, it is necessary to define a threshold willingness to pay (WTP). It is normal convention for NICE guidelines to use an incremental threshold willingness to pay of between £20,000 to £30,000 per QALY. In the absence of a QALY outcome from our diagnostic accuracy based cost-effectiveness model, we use anecdotal evidence from the, the analysis presented in the 2004 HTA for MPS SPECT,(Mowatt, G., Vale, L., Brazzelli, M. et al, 2004) which demonstrates incremental cost per proportion of patients correctly diagnosed values with very similar values to the modelled incremental cost per QALY, (see tables 38 and 39 in Mowatt 2004). That is, in the following analysis, we assumed a willingness to pay threshold of £20,000 per proportion of patients correctly diagnosed.

Having identified a threshold proportion of equivocal invasive coronary angiography results (Pt), if decision makers believe that the likely proportion of equivocal results (p) is higher than the identified threshold value (Pt) estimated by the model, then the model indicates that first line functional testing is cost-effective compared to first line anatomical testing. Conversely, if decision makers believe that the likely proportion of equivocal invasive coronary angiography results is lower than the identified threshold (Pt), the model indicates that first line anatomical testing is cost-effective compared to first line functional testing.

2.4 Results

2.4.1 Base Case

In the base case scenario the pre-test likelihood of CAD in the modelled patient population is assumed to be 50%. The model indicates that first line MPS with SPECT is the least cost of the two modelled options costing £344,000 per 1,000 patients and 76.5% of patients would get a correct diagnosis based on the MPS with SPECT test accuracy input assumptions presented in section 2.2.3. Assuming that coronary angiography is 100% accurate and unequivocal/determinate, the modelled cost of the first line coronary angiography treatment arm is £850,000. The incremental cost per

proportion of patients correctly diagnosed is therefore £21,549. Assuming a WTP threshold of £20,000, and given that we have presented an optimistic scenario for invasive coronary angiography (assumed that it is 100% accurate with no equivocal results), then our model indicates that it looks unlikely that use of first line coronary angiography for the modelled scenario is cost-effective compared with first line functional testing.

2.4.2 Sensitivity on Pre-test likelihood

In the following sensitivity analysis, the CAD prevalence (pre-test likelihood) in the modelled population is varied from 20% to 50%. Again assuming a threshold cost-effectiveness estimate of £20,000 per proportion of patients correctly diagnosed, the table below presents the estimated threshold of indifference values for the proportion of equivocal anatomical stenoses (Pt).

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

As the pre-test likelihood rises from 20% to 40%, the model indicates that the proportion of equivocal invasive coronary angiography results would have to be less than 9.5% (20% pre-test likelihood) and less than 0.6% (40% pre-test likelihood) for first line anatomical testing using invasive coronary angiography to have an ICER below £20,000. So, assuming a 40% population prevalence (pre-test likelihood) of 40%, invasive coronary angiography would have to be 100% sensitive and specific and have an equivocal result rate of less than 0.6%, (6 per 1,000), before it is likely to be considered cost-effective compared with first line functional testing using MPS with SPECT. It is not possible to find a positive Pt value in the 50% prevalence base case population discussed above, because it is not possible for invasive coronary angiography to achieve an ICER below £21,549.

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

From the modelling results presented in section 1.1 above, first line 64-slice CT coronary angiography is the most cost-effective diagnostic testing strategy for low pre-test likelihood populations. A sensitivity analysis using the current model has been run, assuming a pre-test likelihood of 20%, and using the previously used test characteristic assumptions for 64-slice CT coronary angiography (presented in the following table).

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

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

2.4.4 Summary and Discussion

Previously published economic models (Mowatt, G., Vale, L., Brazzelli, M. et al, 2004) (Mowatt, G., Cummins, E., Waugh, N. et al, 2008) have been replicated, with modified assumptions for this guideline (section 1.1 of this Appendix). This was done to help inform recommendations for diagnosis of populations with either low or high pre-test likelihood of CAD and with stable chest pain. Because the guideline group had reservations about the applicability of the existing models for informing the diagnosis of angina in

stable chest pain patients with an intermediate pre-test likelihood, a new model was requested and developed and has been presented here. The model compares first line functional testing using MPS with SPECT with first line anatomical testing using invasive coronary angiography.

For a range of pre-test likelihoods of 30% to 50%, the model indicates that first line functional testing is the least cost of the two modelled testing strategies. Above 30% pre-test likelihood, invasive coronary angiography would have to provide 100% sensitivity and specificity and an equivocal result rate lower than 5.3% for it likely to be considered cost-effective compared to first line functional testing using a £20,000 WTP threshold. In a base case scenario using a pre-test likelihood of 50%, the model demonstrates that the incremental cost per proportion of patients correctly diagnosed from using first line invasive anatomical testing could never have an ICER below £21,500 compared to first line functional testing.

The model lends further to support to the use of 64-slice CT coronary angiography in low risk stable chest pain populations. For a pre-test likelihood of 20%, the model indicates that first line testing using 64-slice CT coronary angiography is more accurate, and costs less, than first line MPS with SPECT testing (dominant).

All models are simplifications of the real world, and our model and analysis has its limitations. Mainly because of the diagnostic focus of this guideline and time constraints, the de novo models developed for this guideline were restricted to assessing short term diagnostic outcomes, (discussed further below). The main drawback of having assessed the short term cost per proportion of patients correctly diagnosed is that there is no recognised WTP threshold for our effectiveness outcome variable. Based on the results of the model presented in the MPS HTA by Mowatt et al 2004, our model assumed that the short term diagnostic ICER is a close proxy to the cost per QALY ICER. This was demonstrated for modelled CAD prevalence at and above 30%, which is consistent with the range that we have modelled above. Admittedly this assumption is based on the results from a single study, and is therefore somewhat anecdotal, and our model, although similar, is not

structurally identical to the Mowatt model. Having said this, our results are not inconsistent with the results of the Mowatt 2004 QALY model, which indicated a role for functional testing in populations with a moderate pre-test likelihood of CAD. Furthermore, our model demonstrated dominance when 64TC angiography was compared to functional testing in a lower pre-test likelihood population, and as such there was no need to consider the size of the ICER.

The model has been subjected only to limited deterministic sensitivity analysis. Having said this, we believe that the model results presented are likely to be relatively insensitive to further analyses. We have used best case possible estimates for the diagnostic performance (sensitivity, specificity, equivocal result rate) of invasive coronary angiography, and as such, the model assumptions are weighted in favour of CA and against MPS). Also, we may have used a relatively conservative estimate for the cost of invasive CA. Finance and coding experts at an NHS hospital have indicated that based on OPCS codes, invasive coronary angiography for adults (>19 years) is likely to fall into HRG EA36Z, which has current estimated costs ranging from £792 to £2,490 depending on whether the procedure is done as a day case, or as an elective inpatient stay (personal communication). These figures are estimates of the mean cost. The inter-quartile ranges presented in the NHS reference costs database show an even wider range of costs, particularly at the upper end. Also, HRG EA36Z covers procedures other than invasive coronary angiography, and so it is not possible to get an accurate cost estimate for invasive coronary angiography from NHS reference costs(Department of Health, 2008). The evidence appears to indicate that our base case estimate of £850 may be at the lower end of the likely cost estimate distribution. Given this and the best case performance assumptions for CA, our ICER estimates may be very much on the low side thereby lending further support to our conclusions regarding the relative cost-effectiveness of functional imaging using MPS SPECT compared with invasive CA in patients with a moderate pre-test CAD likelihood (30% to 60%).

One sensitivity analysis that we did undertake compared 64-slice CT angiography with functional imaging for a pre-test CAD likelihood of 20%. With

relative conservative estimates regarding the performance of 64CT angiography, our model demonstrated dominance, and indicated that 64CT diagnostic performance would have to deteriorate to unrealistically low levels in terms of equivocal result rate to give us considerable confidence in this result.

We have only modelled MPS with SPECT to represent functional testing. The CECaT trial (Sharples, L., Hughes, V., Crean, A. et al, 2007) has indicated that in terms of both resource use and QALYs, MPS with SPECT, stress echocardiography and stress MR perfusion imaging were not significantly different from each other, in a population consistent with the patients modelled above (CAD prevalence greater than 20%). Also, other economic evaluations including these technologies demonstrated similar result, for example, dominance by CT angiography (Rumberger, J. A., Behrenbeck, T., Breen, J. F. et al, 1999). We may therefore have reached similar conclusions to those for MPS SPECT had we modelled stress echocardiography or stress MR perfusion imaging to represent functional testing.

Economic evaluation undertaken for this guideline has proved challenging from a number of respects. Not least, the fact that the technologies used to diagnose chest pain of suspected cardiac origin are numerous and improving rapidly. Ideally, economic evaluation involving NHS resources should take account of both the short-term diagnostic, and also the longer term prognostic implications on resource use and health outcomes. The scope of this guideline is focussed on diagnosis, and as such, the economic evaluation has also focused on the shorter term diagnostic costs and outcomes. Having said this, there is some evidence from previous economic modelling work in this area, longer term more speculative models may be subject to diminishing returns in terms of additional information for decision makers. In the 2008 HTA on 64-slice CT coronary angiography by Mowatt and colleagues (Mowatt, G., Cummins, E., Waugh, N. et al, 2008), their longer-term speculative Markov model, (which required assumptions to be made about the future risk of CAD events and how they would be treated), resulted in QALY differences which differed by less than one quarter of one percent for the testing strategies

assessed. Our additional analysis and revision of their model, also indicates that most treatment strategies (usually those including MPS and stress ECG) can be rejected through dominance, thereby negating the need to consider the ICER values for most strategies modelled. Also, there is a high degree of correlation of dominance between the short term and the longer term models. Comparison of the short and longer-term modelling output of the model presented in the 2004 HTA on MPS with SPECT (Mowatt, G., Vale, L., Brazzelli, M. et al, 2004) indicated that, for all but the lowest CAD prevalence groups, the estimated incremental cost per proportion of patients correctly diagnosed has a similar value to the longer-term incremental cost per QALY. Longer-term economic model evaluations, which have been published since the short term de novo models for this guideline have been developed, lend some support to the results of our modelling (e.g. that use of 64-slice CT coronary angiography is cost-effective or cost-saving in lower risk patients presenting with acute chest pain (Khare, R. K., Courtney, D. M., Powell, E. S. et al, 2008) (Min, J. K., Kang, N., Shaw, L. J. et al, 2008). Because of time constraints and the scoping boundary of this Guideline, further investigation of these issues, and research into the validity of our current assumptions, was not attempted, but could be considered in future work in this area.

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