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Abstract

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

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Objectives: To ascertain the value of a range of methods – including clinical features, resting and exercise electrocardiography, and rapid access chest pain clinics (RACPCs) – used in the diagnosis and early management of acute coronary syndrome (ACS), suspected acute myocardial infarction (MI), and exertional angina.

Data sources: MEDLINE, EMBASE, CINAHL, the Cochrane Library and electronic abstracts of recent cardiological conferences.

Review methods: Searches identified studies that considered patients with acute chest pain with data on the diagnostic value of clinical features or an electrocardiogram (ECG); patients with chronic chest pain with data on the diagnostic value of resting or exercise ECG or the effect of a RACPC. Likelihood ratios (LRs) were calculated for each study, and pooled LRs were generated with 95% confidence intervals. A Monte Carlo simulation was performed evaluating different assessment strategies for suspected ACS, and a discrete event simulation evaluated models for the assessment of suspected exertional angina.

Results: For acute chest pain, no clinical features in isolation were useful in ruling in or excluding an ACS, although the most helpful clinical features were pleuritic pain (LR+ 0.19) and pain on palpation (LR+ 0.23). ST elevation was the most effective ECG feature for determining MI (with LR+ 13.1) and a completely normal ECG was reasonably useful at ruling this out (LR+ 0.14). Results from 'black box' studies of clinical interpretation of ECGs found very high specificity, but low sensitivity. In the simulation exercise of management strategies for suspected ACS, the point of care testing with troponins was cost-effective. Pre-hospital thrombolysis on the basis of ambulance telemetry was more effective but more costly than if performed in hospital. In cases of chronic chest pain, resting ECG features were not found to be very useful (presence of Q-waves had LR+ 2.56). For an exercise ECG, ST depression performed only moderately well (LR+ 2.79 for a 1 mm cutoff), although this did improve for a 2 mm cutoff (LR+ 3.85). Other methods of interpreting the exercise ECG did not result in dramatic improvements in these results. Weak evidence was found to suggest that RACPCs may be associated with reduced admission to hospital of patients with non-cardiac pain, better recognition of ACS, earlier specialist assessment of exertional angina and earlier diagnosis of non-cardiac chest pain. In a simulation exercise of models of care for investigation of suspected exertional angina, RACPCs were predicted to result in earlier diagnosis of both confirmed coronary heart disease (CHD) and non-cardiac chest pain than models of care based around open access exercise tests or routine cardiology outpatients, but they were more expensive. The benefits of RACPCs disappeared if waiting times for further investigation (e.g. angiography) were long (6 months).

Conclusions: Where an ACS is suspected, emergency referral is justified. ECG interpretation in acute chest pain can be highly specific for diagnosing MI. Point of care testing with troponins is cost-effective in the triaging of patients with suspected ACS. Resting ECG and exercise ECG are of only limited value in the diagnosis of CHD. The potential advantages of RACPCs

are lost if there are long waiting times for further investigation. Recommendations for further research include the following: determining the most appropriate model of care to ensure accurate triaging of patients with suspected ACS; establishing the cost-effectiveness of pre-hospital thrombolysis in rural areas; determining the relative cost-effectiveness of rapid access chest pain clinics compared with other innovative models of care; investigating how rapid access chest pain clinics should be managed; and establishing the long-term outcome of patients discharged from RACPCs.

Contents

List of abbreviations

A&E	accident and emergency
ACS	acute coronary syndrome
CABG	coronary artery bypass graft
CASS	coronary artery surgery study
CHD	coronary heart disease
CI	confidence interval
CK	creatinine kinase
CKMB	creatinine kinase MB sub-fraction
CPOU	chest pain observation unit
DES	discrete event simulation
ECG	electrocardiogram
ER	emergency room
ETT	exercise tolerance test
ICER	incremental cost-effectiveness ratio
IU	international unit
LR	likelihood ratio
MI	myocardial infarction
MPI	myocardial perfusion imaging
NSF	National Service Framework
PMH	previous medical history
POCT	point of care test
PTCA	percutaneous transluminal coronary angioplasty
QALY	quality-adjusted life-year
QoL	quality of life
RACPC	rapid access chest pain clinic
RCT	randomised controlled trial
TnT	troponin T
ULN	upper limit normal
WHO	World Health Organization

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Chest pain is a common symptom in primary care, and may reflect coronary heart disease (CHD), as either an acute coronary syndrome (ACS) or exertional angina. Recent national guidance has emphasised the importance of inpatient assessment for the former and rapid specialist assessment for the latter. However, chest pain is a common symptom that is due to CHD in only a minority of cases, and specialist and emergency services would become swamped if everyone with chest pain was referred.

Objectives

Questions the review sought to answer were the following:

- What is the value of individual clinical features in the diagnosis of an acute myocardial infarction (MI)?
- How accurate are electrocardiogram (ECG) changes in the diagnosis of ACS?
- What is the most cost-effective way to manage patients presenting in the community with suspected acute MI?
- What is the value of a resting ECG in the diagnosis of CHD?
- What is the value of an exercise ECG in the diagnosis of CHD?
- How effective are rapid access chest pain clinics in the diagnosis of exertional angina?
- What is the impact of rapid access chest pain clinics (RACPCs) compared with other possible models of care in the investigation of exertional angina?

Methods

Data sources

MEDLINE, EMBASE, CINAHL, the Cochrane Library and electronic abstracts of recent cardiological conferences were searched for articles about the diagnosis of chest pain between 1966 and October 1999. Researchers identified from the National Research Register were surveyed and reference lists of relevant papers were checked.

Study selection (inclusion and exclusion criteria)

Studies were included if they involved

- patients with acute chest pain with data on the diagnostic value of clinical features or an ECG
- patients with chronic chest pain with data on the diagnostic value of resting or exercise ECG
- the effect of a RACPC.

Studies were excluded if they were solely concerned with the prognostic value of the test, if they used a case–control design or if, in the evaluation of chronic chest pain, they included >20% of patients with known CHD.

Data extraction (and assessment of validity)

Eligible papers were reviewed in duplicate. Data were extracted on inclusion criteria, sources of bias, patient demographics and test performance results. A third reviewer checked extracted data.

Data synthesis

Likelihood ratios (LRs) were calculated for each study, and pooled LRs were generated with 95% confidence intervals (CIs).

Simulation exercises

A Monte Carlo simulation was performed evaluating different assessment strategies for suspected ACS, and a discrete event simulation for the evaluation of models for the assessment of suspected exertional angina.

Results (research findings)

Acute chest pain: clinical symptoms and signs

No clinical features in isolation were useful in ruling in or excluding an ACS. The clinical features most helpful were pleuritic pain (LR+ 0.19, 95% CI 0.14 to 0.25) and pain on palpation (LR+ 0.23, 95% CI 0.08 to 0.30).

Acute chest pain: resting ECG

The presence of ST elevation was highly specific for MI, with LR+ 13.1 (95% CI 8.28 to 20.6). A completely normal ECG was reasonably useful at

ruling out a myocardial infarction (LR+ 0.14 (95% CI 0.11 to 0.20). 'Black box' studies of clinical interpretation of ECGs found very high LR+ (145 in the best quality study), but low sensitivity (LR– 0.58).

Simulation exercise of management strategies for suspected ACS

Point of care testing with troponins was cost-effective. Pre-hospital thrombolysis on the basis of ambulance telemetry was more effective but more costly than thrombolysis performed in hospital.

Chronic chest pain: resting ECG

Resting ECG features were not found to be very useful. Presence of Q-waves had LR+ 2.56 (95% CI 0.89 to 7.30). One study reported a high LR+ of 9.96 (95% CI 2.58–38.5) for QRS notching.

Chronic chest pain: exercise ECG

Presence of ST depression had LR+ 2.79 (95% CI 2.53 to 3.07) for a 1 mm cutoff and 3.85 (95% CI 2.49 to 5.98) for a 2 mm cutoff. The LR–s were 0.44 (95% CI 0.40 to 0.47) (1 mm) and 0.72 (95% CI 0.65 to 0.81) (2 mm). Other methods of interpreting the exercise ECG did not result in dramatic improvements in these results. The test performed better in men than women.

RACPCs

No true evaluative studies were identified. Weak evidence was found to suggest that these clinics might be associated with reduced admission to hospital of patients with non-cardiac pain, better recognition of ACS, earlier specialist assessment of exertional angina and earlier diagnosis of non-cardiac chest pain.

Simulation exercise of models of care for investigation of suspected exertional angina

RACPCs were predicted to result in earlier diagnosis of both confirmed CHD and non-cardiac chest pain than models of care based around open access exercise tests or routine cardiology outpatients, but were more expensive. The benefits of RACPCs disappeared if waiting times for further investigation (e.g. angiography) were long (6 months).

Conclusions

Implications for health care

- In patients in whom an ACS is suspected, emergency referral for further assessment in a specialist setting is justified.
- ECG interpretation in acute chest pain can be highly specific for diagnosing MI.
- Point of care testing with troponins is cost-effective in triaging patients with suspected ACS.
- Resting ECG and exercise ECG are of only limited value in the diagnosis of CHD.
- The potential advantages of RACPCs are lost if there are long waiting times for further investigation.

Recommendations for research

Relevant research questions include the following:

- What is the most appropriate model of care to ensure accurate triaging of patients with suspected ACS?
- What is the cost-effectiveness of pre-hospital thrombolysis in rural areas?
- What is the relative cost-effectiveness of RACPCs compared with other innovative models of care such as open access exercise testing?
- How should RACPCs be managed? (e.g. proportion of exercise ECGs performed; skill mix of staff; maximum waiting time from referral).
- What is the long-term outcome of patients discharged from RACPCs?

Chapter 1
Background

Chest pain is a common presenting symptom in primary care, of which there are many possible causes. The most important of these in terms of subsequent morbidity and mortality are the acute coronary syndromes (ACSs) comprising unstable angina and acute myocardial infarction (MI) and the chronic condition of exertional angina.

Morbidity data for MI are notoriously inaccurate, but figures from the British Heart Foundation suggest that the incidence rate for men aged between 30 and 69 years is about 600 per 100,000 and that for women it is about 200 per 100,000 per year. Extrapolating from these figures to the UK population as a whole, there are about 149,000 heart attacks in men of all ages and about 125,000 in women, giving a total of about 274,000 per year. In addition, there are about 174,000 new cases of angina per year in all men living in the UK and about 158,000 in women, giving a total of about 330,000.[1] Morbidity arising from coronary heart disease (CHD) therefore affects over 600,000 new patients per year.

The reduction of deaths from CHD has recently become a major target for governmental intervention. The publication of the White Paper *Saving Lives: Our Healthier Nation* in 1998 set out the aims of the government in detail.[2] The principal aim is to reduce the death rate from CHD and stroke and related diseases in people under 75 years of age by a least two-fifths by 2010.

The National Service Framework (NSF) for Coronary Heart Disease has clarified expectations of the healthcare system in the UK.[3] Standards have been set for the care of patients with both acute and chronic chest pain that aim to ensure systematic and prompt treatment. Patients suffering from acute chest pain that is subsequently diagnosed as being due to an MI should receive thrombolysis within 1 hour of calling for professional assistance. Those presenting with symptoms suggestive of exertional angina should have been reviewed in a rapid access chest pain clinic (RACPC) within a fortnight of referral from their general practitioner (GP).

It is appropriate to divide the strategies for investigation of chest pain into two main pathways: the investigation of an episode of acute chest pain, with the purpose of diagnosing an ACS (acute MI or unstable angina) and the investigation of chronic or recurrent chest pain with the purpose of diagnosing CHD (exertional angina). The focus of this report takes into account the policy directions of the NSF by concentrating on those questions that are of particular current relevance to primary care and the development of services to which GPs will have access. Current recommended practice is for patients with suspected ACS to be transferred to hospital as soon as possible and for patients with suspected angina to be seen in an RACPC.

The evaluation of suspected ACS

Patients experiencing chest pain may currently seek help in a number of ways, including calling an ambulance, calling their GP or attending at an accident and emergency (A&E) unit. In a study in north-east Scotland, it was found that GPs were the first medical contact for 97% of rural patients and 68% of urban patients with suspected MI.[4] However, current national guidance is that patients should dial '999' if experiencing symptoms suggestive of an MI.[3] Similarly, if called to such a patient, a GP should also dial '999' before attending. Therefore, the proportion of patients with suspected ACS seen by their GP is likely to diminish.

If a GP does see a patient, the main question that needs to be answered is whether or not the chest pain is due to an ACS (in which case the patient will be admitted urgently to hospital). If an ACS is suspected, a supplementary question is whether or not a confident diagnosis of MI can be made – in which case the option of pre-hospital thrombolysis might be considered, since most benefit is derived from earlier treatment.[5,6]

Paramedics will transfer people who call on their services to hospital. One model of care is that pre-hospital thrombolysis might be administered in the ambulance if a positive diagnosis of acute MI can be made. The NSF recommends audit of the proportion of people eligible for thrombolysis who receive it within 60 minutes of calling for

professional help.[3] In rural areas in particular, pre-hospital thrombolysis is likely to play an important role if this target is to be achieved.[7] Recent advances in single-bolus administration of thrombolytic agents, suitable for pre-hospital use, such as reteplase, have made such a policy feasible.[8]

If GPs are to be able to decide to keep a patient safely at home, then they will need to have a test with very high sensitivity, since they will not want to keep at home erroneously people who are suffering from an ACS. Conversely, if GPs or the ambulance staff are considering giving thrombolysis, they will require a test with high specificity, since they would not want to give this treatment to people who are not suffering from acute MI. Pre-hospital diagnosis of MI by electrocardiogram (ECG) telemetry and point of care tests (POCTs) using troponin T (TnT) offer possible diagnostic strategies whereby pre-hospital diagnosis might be confirmed.

It can also be argued that high specificity is useful to avoid unnecessary hospital admissions. For example, in the USA, over 3 million patients are admitted with chest pain per annum. The cost of caring for those patients who in hindsight do not have MI has been estimated at over US$3 billion per annum.[9] However, it is unclear to what extent this expenditure could have been avoided, since the standardised mortality ratio of patients admitted to hospital with suspected MI where a final diagnosis of 'no infarction' was made was found to be 4.7 [95% confidence interval (CI) 4.2 to 5.2] in the first year following the admission.[10] Therefore, it is likely that these patients do require investigation and treatment.

Owing to the serious consequences of the diagnostic decisions made for patients with acute chest pain, this review will assess the value of the clinical tools currently widely available in the community. In differentiating between the possible causes of acute chest pain, the GP will initially rely on the history and examination. Therefore, the first topic area covered by this systematic review is the value of specific clinical features used in making a judgement on the likelihood of chest pain being an ACS (i.e. MI or unstable angina). Clinical features such as pleuritic chest pain that raise the possibility of an alternative diagnosis (e.g. pulmonary embolus) are considered to the extent that they change the probability of an ACS, but not in terms of their value in making an alternative diagnosis. The second topic area is the diagnostic value of an ECG, which is the only near patient test currently available to GPs in the surgery.[11,12] The third topic area involves assessing the cost-effectiveness of different strategies for initial assessment of suspected ACS including the use of pre-hospital thrombolysis.

The evaluation of suspected exertional angina

Each year in the UK, more than 300,000 people develop angina.[3] However, the differential diagnosis of chronic and recurrent chest pain is wide, and includes cardiac, gastro-oesophageal, pulmonary, musculo-skeletal and psychogenic causes.[13,14] Age, gender and the patient's description of the chest pain have been established as the most important clinical features for predicting heart disease.[15] Pryor and colleagues found that previous MI, smoking and diabetes were also significant components of the history.[16]

Apart from the clinical details available from interview and examination, a GP is likely to have access to a 12-lead ECG, either within the surgery or on an outpatient basis at the local hospital. It is not clear whether the results of an ECG are informative in this setting, so the fourth topic that the review addresses is the question of whether a resting ECG performed in general practice adds useful information in the diagnosis of CHD.

The gold standard test for the diagnosis of CHD is the coronary angiogram. However, this is both expensive and potentially dangerous and so additional investigations are commonly used in order to choose appropriate subjects for angiogram. The exercise ECG is the most commonly used of these investigations in the UK.[17] Subjects are exercised using either a treadmill or bicycle ergometer to provide increasing levels of work while being continuously monitored using a 12-lead ECG. Results from the test are commonly expressed in terms of changes to the ECG tracing and blood pressure at the various stages of the test. The fifth topic area that this review explores is the diagnostic value of this test.

Setting of investigation of suspected exertional angina

RACPCs

The assessment of new onset symptoms possibly due to CHD has important consequences.[18] Half of patients admitted to hospital with acute chest pain do not have an ACS, but the diagnosis of

CHD is missed in some patients with chronic symptomatic disease in the community.

Two new models of assessment have emerged. In the USA, chest pain observation units (CPOUs) provide short stay inpatient care where chest pain is monitored and investigated prior to either formal admission or discharge. A recent review of CPOUs has concluded that they are safe and reduce costs, at least in the USA.[19] In England, the government's NSF is promoting outpatient RACPCs in which 'people who develop new symptoms that their GP thinks might be due to angina can be assessed by a specialist within 2 weeks of referral'.[3] It was envisaged that 100 such clinics would be in place by April 2002 and subsequently rolled out nation-wide.

The final topic covered by the review concerns the evidence for RACPCs and was undertaken to ascertain whether their provision leads to fewer unnecessary admissions, better recognition of patients with ACS, earlier specialist assessment of patients with stable angina and more rapid and accurate identification of patients with non-cardiac chest pain.

Complexities of the topic areas

Throughout the review a number of complexities within the topic areas have had to be taken into account, in both the review process and in the interpretation of the findings. The first of these is that the performances of the diagnostic tests are critically dependent on their timing. Second, the tests are likely to perform differently in different sub-groups. For example, the more severe the coronary artery disease, the larger the likelihood ratios (LRs) for abnormal exercise ECG.[20] Third, the performances of the tests are likely to depend upon the skills of the people performing them or interpreting them. The ability to diagnose MI on the basis of ECG reading varies.[21] Fourth, most of the evidence available concerning diagnostic tests performance is derived from secondary care settings; the applicability of these results to primary care depends upon patient characteristics, how the test is carried out and the operator/interpreter characteristics.[22]

Chapter 2

Research questions

Aims

The review aimed to answer a group of related research questions pertaining to the diagnosis of (1) suspected ACS and (2) suspected exertional angina in primary care.

The investigation of suspected ACS

For patients presenting with acute chest pain in primary care, the following questions were addressed:

- What is the value of individual clinical features in the diagnosis of an acute MI?
- How accurate are ECG changes (individually and together) in the diagnosis of an acute MI?
- What is the most cost-effective way to manage patients presenting in the community with suspected ACS?

The investigation of chronic and recurrent chest pain

For patients presenting with chronic or recurrent chest pain in primary care, the following questions were addressed:

- What is the value of a resting ECG in the diagnosis of CHD?
- What is the value of an exercise ECG in the diagnosis of CHD?
- How effective are RACPCs in the diagnosis of CHD?
- What is the most effective way to manage patients with suspected exertional angina?

Objectives

1. To conduct a systematic review to establish how useful clinical features are in making (or ruling out) a diagnosis of an acute MI in a patient presenting with acute chest pain.
2. To conduct a systematic review to establish how helpful an ECG is in making (or ruling out) a diagnosis of acute MI in a patient presenting with acute chest pain.
3. To perform modelling of health economic, test performance and epidemiological data to ascertain the most cost-effective approach to the diagnosis of ACS in a patient presenting with acute chest pain in primary care.
4. To conduct a systematic review to establish how helpful a resting ECG is in making (or ruling out) a diagnosis of suspected exertional angina in the evaluation of adult patients presenting with suspected exertional angina.
5. To conduct a systematic review to establish how helpful an exercise ECG is in making (or ruling out) a diagnosis of CHD in the evaluation of adult patients presenting with suspected exertional angina.
6. To conduct a literature search to identify evidence regarding the value of RACPCs in diagnosing suspected exertional angina.
7. To perform modelling of test performance and epidemiological data to ascertain the most effective strategy in the diagnosis of suspected exertional angina in primary care.

Chapter 3
Review methods

Definitions

The following definitions were adopted for use throughout the review.

Primary care
Any medical practice taking place in a community rather than hospital setting and representing the first point of contact with medical care for the patient. It includes GPs (as in UK, Australia, New Zealand and The Netherlands), family practitioners and primary care physicians (as in the USA) and family medicine (as in Canada). For the purposes of the review, paramedics/ambulance crews were classed as primary care.

A&E
Emergency medical setting which accepts both self-referrals and primary care referrals, usually attached to a hospital. Previously called casualty departments in the UK and known as emergency Rooms (ERs) in the USA and Canada.

Secondary care
Any hospital setting other than A&E where patients are either admitted or seen on an outpatient basis. In the UK patients would largely be seen following referral from primary care.

Acute chest pain
Acute chest pain was defined pragmatically as pain thought possibly to be due to an ACS with a history of less than 24 hours.

Chronic chest pain
Chronic chest pain was defined pragmatically as pain thought possibly to be due to CHD (i.e. suspected exertional angina) with a history of over 24 hours.

MI
Definitions of MI varied from study to study and are presented in *Tables 41*, *43* and *45* for each study reviewed. The most widely used definition was that of the World Health Organization (WHO), which are two or more features from the following:[23]

1. evolution of unequivocal findings for MI on serial ECGs in at least two leads of the same territory (i.e. diagnostic Q waves or QS complexes)
2. serial creatinine kinase (CK) and creatinine kinase MB sub-fraction (CKMB) rise and fall with peak $\geq 2 \times$ ULN (upper limit normal)
3. typical prolonged severe chest pain and related symptoms >20 minutes.

ACS
ACS includes both MI and unstable angina. There were no standard diagnostic criteria and again definitions are included in *Tables 41*, *43* and *45* where appropriate. Unstable angina can be defined as ischaemic type-chest pain that is more frequent, severe, or prolonged than the patient's usual angina symptoms, occurs at rest or minimal exertion or is difficult to control with drugs.[24]

Black box studies
A number of studies were evaluated as part of the review where the diagnostic test under examination was a physician's interpretation of a combination of some or all of signs, symptoms and investigations. These combinations of features and diagnostic acumen have been labelled as 'black box' for the purpose of the review.

Systematic review methods

In order to identify appropriate published literature, the following search strategy was utilised.

Electronic database searches
MEDLINE, EMBASE, CINAHL, the Cochrane Library and electronic abstracts of recent cardiological conferences were searched for articles about the diagnosis of both acute and chronic chest pain appearing between 1966 and October 1999. The precise search strategies used are documented in Appendix 1. The papers identified from each database were transferred to a bibliographic database (Reference Manager) prior to merging and removal of duplicates.

Expert survey
Holders of current research grants in the area of chest pain diagnosis as identified from the National Research Register were surveyed requesting information about studies in the area.

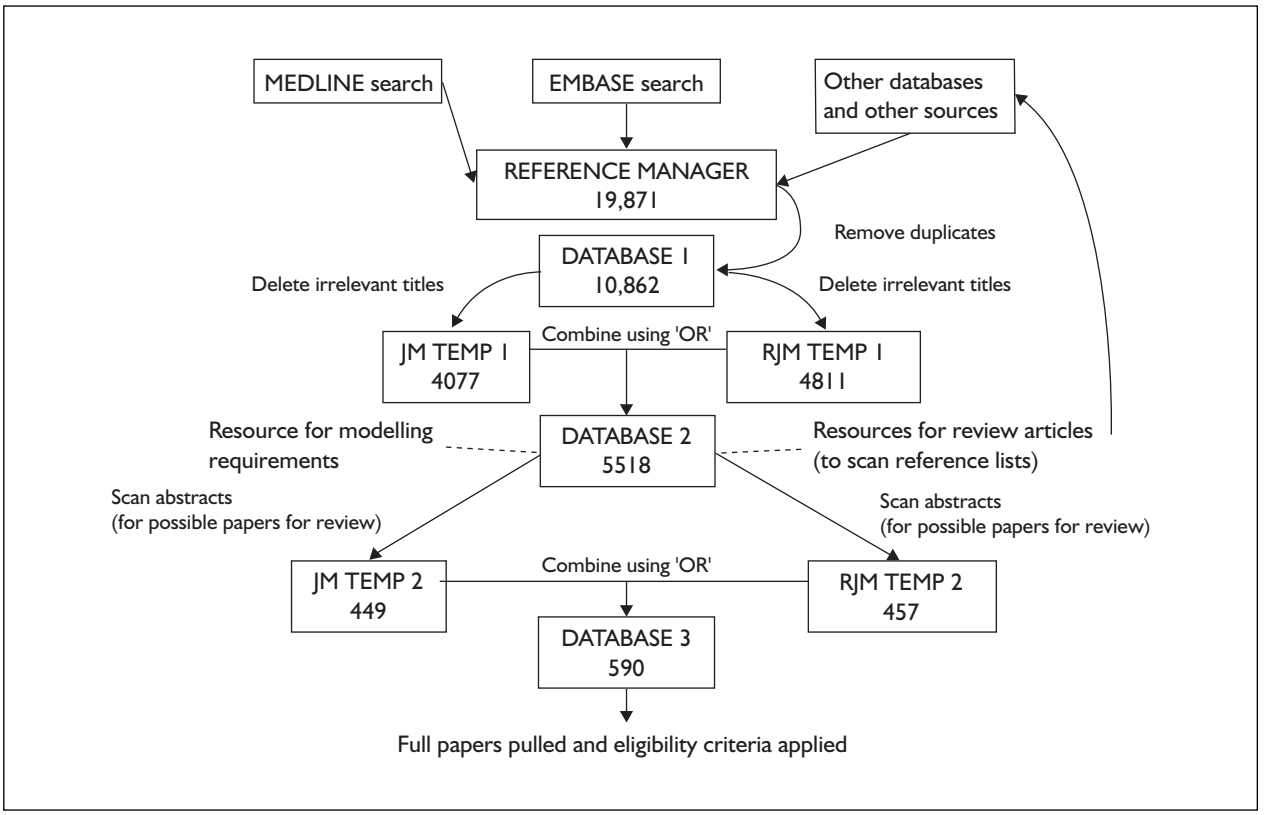

FIGURE 1 *Reference management*

Hand searching

Reference lists of included articles and relevant review articles identified by the searches were scanned to check for relevant studies not identified by the electronic searches.

Focusing the search

The resulting database was then scanned independently by two of the authors (RJM and JM), initially on the basis of title and then abstract. At this stage two broad inclusion criteria were used: in order to be included the study had to be about patients with chest pain (pain thought to be cardiac in nature) and also either to include the use of a diagnostic test or be set in a chest pain clinic. The full text of papers which appeared to be relevant was then requested for more detailed analysis. An outline of this strategy including the number of papers identified in the early stage of the search process is shown in *Figure 1*.

Eligibility criteria

Papers were then considered by pairs of reviewers chosen to include one cardiovascular expert (MKD, RCD or FDRH) and one generalist (RJM, BCD, LH and JM). In order to be eligible for the review, the following inclusion and exclusion criteria were used.

Inclusion criteria

Patients with chest pain, thought to be cardiac in origin who underwent a diagnostic test.
The diagnostic tests considered were as follows.

Acute chest pain

- History/clinical features as a test.
- Resting ECG.
- Combinations of clinical features and resting ECG findings. These had not been included initially in our hypotheses to be tested but, following our searches, it became apparent that a number of authors had examined the ability of physicians to diagnose patients with chest pain on the basis of clinical features and resting ECG in such a way that separate features could not be distinguished, in other words considering a physician's diagnosis as a diagnostic test. These were felt to be important and so were included under the heading 'black box'.

Chronic chest pain

- Resting ECG.
- Exercise ECG.

RACPCs

Papers concerning RACPCs were included. These were defined as studies where patients with recent

onset chest pain were assessed in a dedicated clinic by a specialist cardiology team. Studies of inpatient chest pain observation units and open access clinics that did not involve cardiological assessment (e.g. open access exercise testing) were excluded.

Exclusion criteria

- No original data.
- Studies concerned solely with the prognostic rather than diagnostic value of the tests under evaluation.
- No appropriate outcomes.
- No diagnostic tests.
- Significant proportion of patients included with previous MI (>20%).
- Studies that used a case control design.

Each reviewer stated whether or not a paper was eligible using a standard case report form. Papers that were excluded at this stage are presented in Appendix 3 along with the reasons for exclusion. Disagreements were resolved by arbitration by the steering group.

Data extraction

Papers considered to be eligible were then reviewed in duplicate by the same team for data extraction. A third reviewer (RJM, JM or JJD) then checked extracted data before entry on to a Microsoft Access database. Data were extracted concerning inclusion and exclusion criteria, potential sources of bias, demographic details of included subjects and test performance results (2×2 tables comparing test with gold standard). The potential sources of bias examined were incorporation bias, verification bias, blinding, selection of study sample, study population and the treatment of indeterminate results.[25] These results are presented in Appendix 2.

Analysis

Analysis was performed using STATA version 7. From the numbers of true positives, false positives, true negatives and false negatives in each study, LRs were obtained. A weighted average of the pooled results was calculated using the standard Mantel–Haenszel method for risk ratios, with 95% CIs.[25] Heterogeneity between studies was tested using the chi-squared test.

Acute chest pain model method (Monte Carlo simulation)

The model

A Monte Carlo simulation with a 28-day timeframe was constructed using DATA-Pro (TreeAge Software, Williamstown, MA, USA).[26] The model (*Figures 2–5*) was driven by a combination of a decision tree examining the performance of different diagnostic strategies and a link between the effectiveness of thrombolytic therapy and the time delay from the onset of pain. The outcome measure used was survival at 28 days for patients surviving the first 24 hours.

Four strategies were compared:

1. Patient with chest pain transported to A&E department by 999 ambulance. Decision to give thrombolysis in A&E is based on ECG alone.
2. Patient with chest pain transported to A&E by 999 ambulance. Decision to give thrombolysis in A&E based on ECG and a single POCT for TnT if ECG negative.
3. Patient with chest pain calls ambulance, telemetry ECG performed and pre-hospital thrombolysis given if positive by paramedic team. All patients transported to A&E where further diagnosis based on ECG alone made in patients with negative pre-hospital ECGs.
4. Patient with chest pain calls ambulance, telemetry ECG performed and pre-hospital thrombolysis given if positive by paramedic team. All patients transported to A&E department where further diagnosis based on ECG, and a single POCT for TnT if ECG negative, for patients with negative pre-hospital ECGs.

Assumptions made in the model

Effectiveness

- The effect of timing of thrombolysis was modelled using a table of relative risks for survival between 1 and 28 days post-infarct indexed to the time from the onset of chest pain, and obtained from a systematic review – see *Table 1* and *Figure 6*.[27,28]
- Sensitivity and specificity of the POCT were similarly indexed with time, and the values obtained from a systematic review – see *Table 1* and *Figure 7*.[29]
- Sensitivity and specificity of ECG were based on the results of our systematic review (see *Table 20*).
- Reteplase was given to patients with positive pre-hospital ECGs and streptokinase was given to patients diagnosed in hospital. The effectiveness and the risks of haemorrhage of the two drugs were considered equal.[8]

Uncertainty in the model

Uncertainty in the model consists of two types:

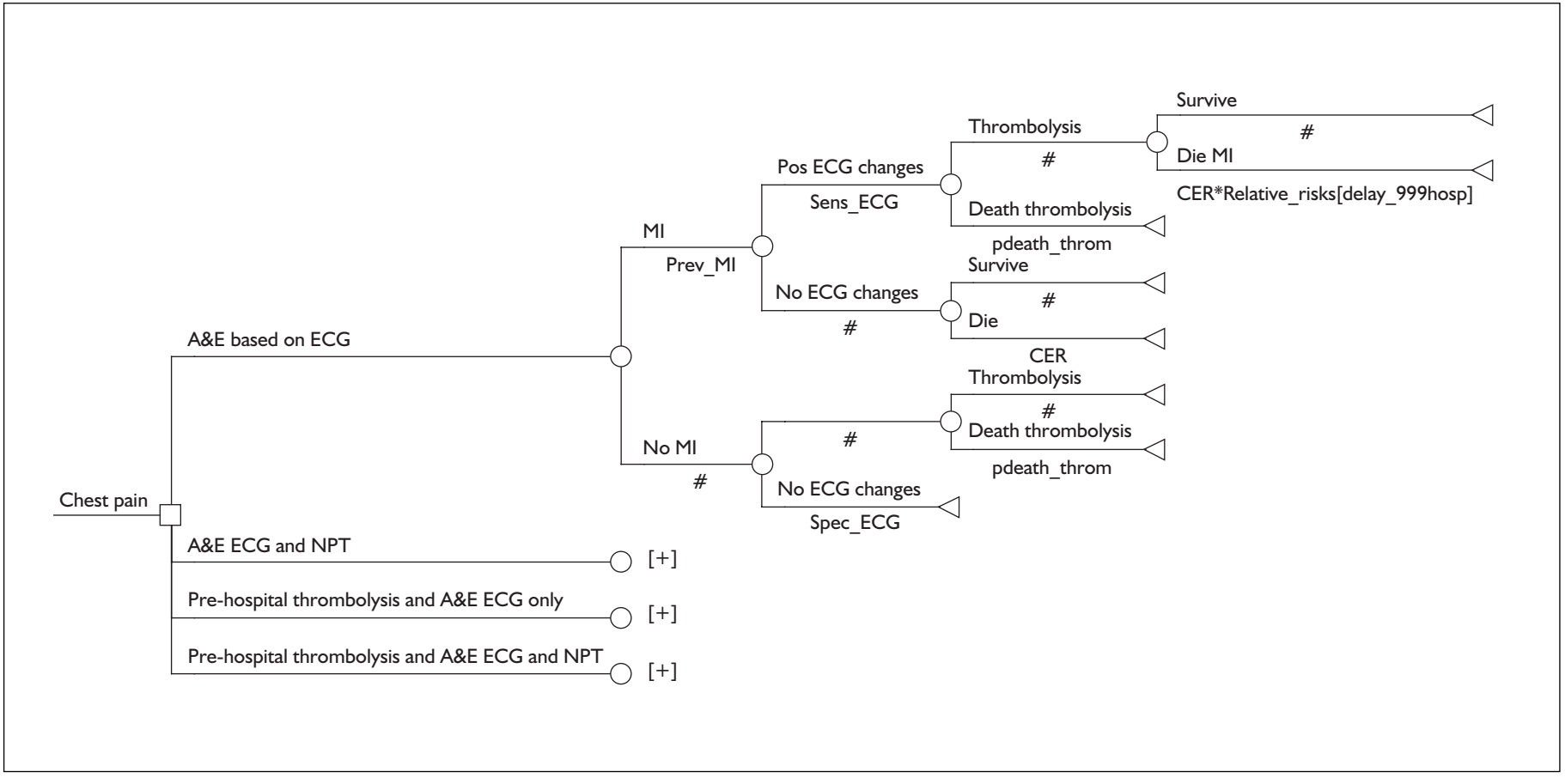

FIGURE 2 *Decision to give thrombolysis in A&E is based on ECG alone. CER, control event rate.*

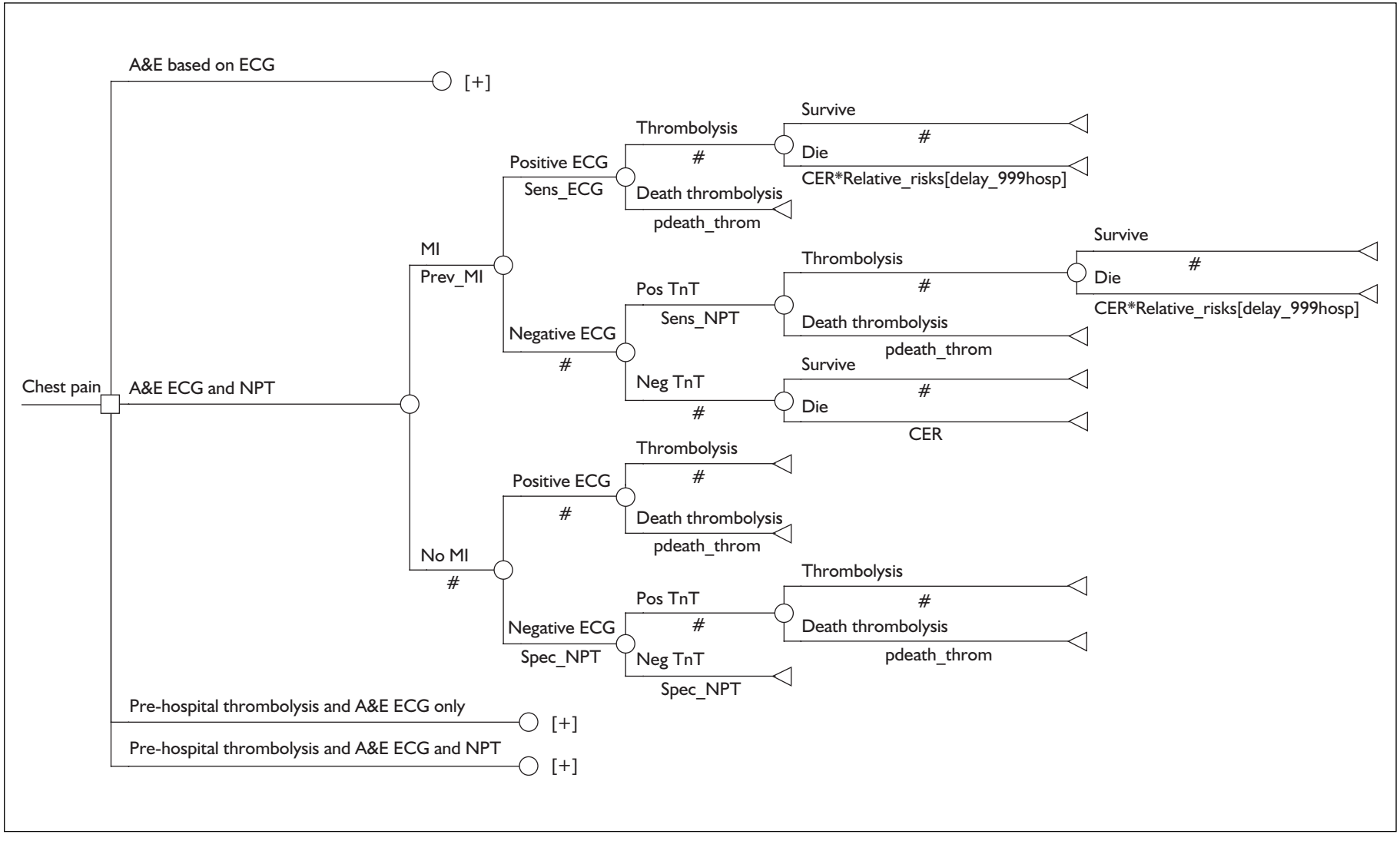

FIGURE 3 *Decision to give thrombolysis in A&E based on ECG and POCT for TnT if ECG negative. NPT, near patient test.*

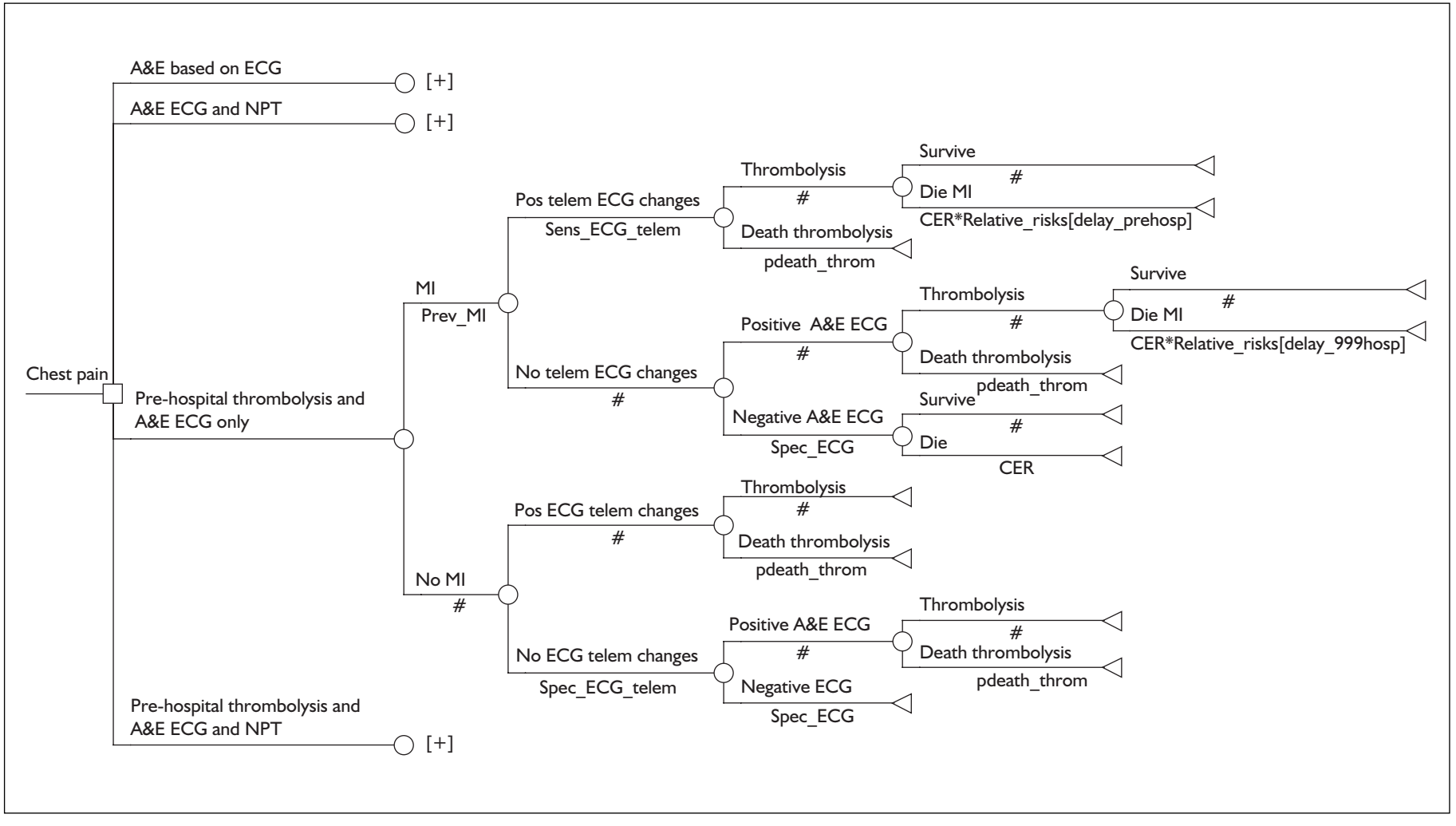

FIGURE 4 *Decision to give thrombolysis either pre-hospital with ECG telemetry or in A&E based on ECG and POCT for TnT if ECG negative*

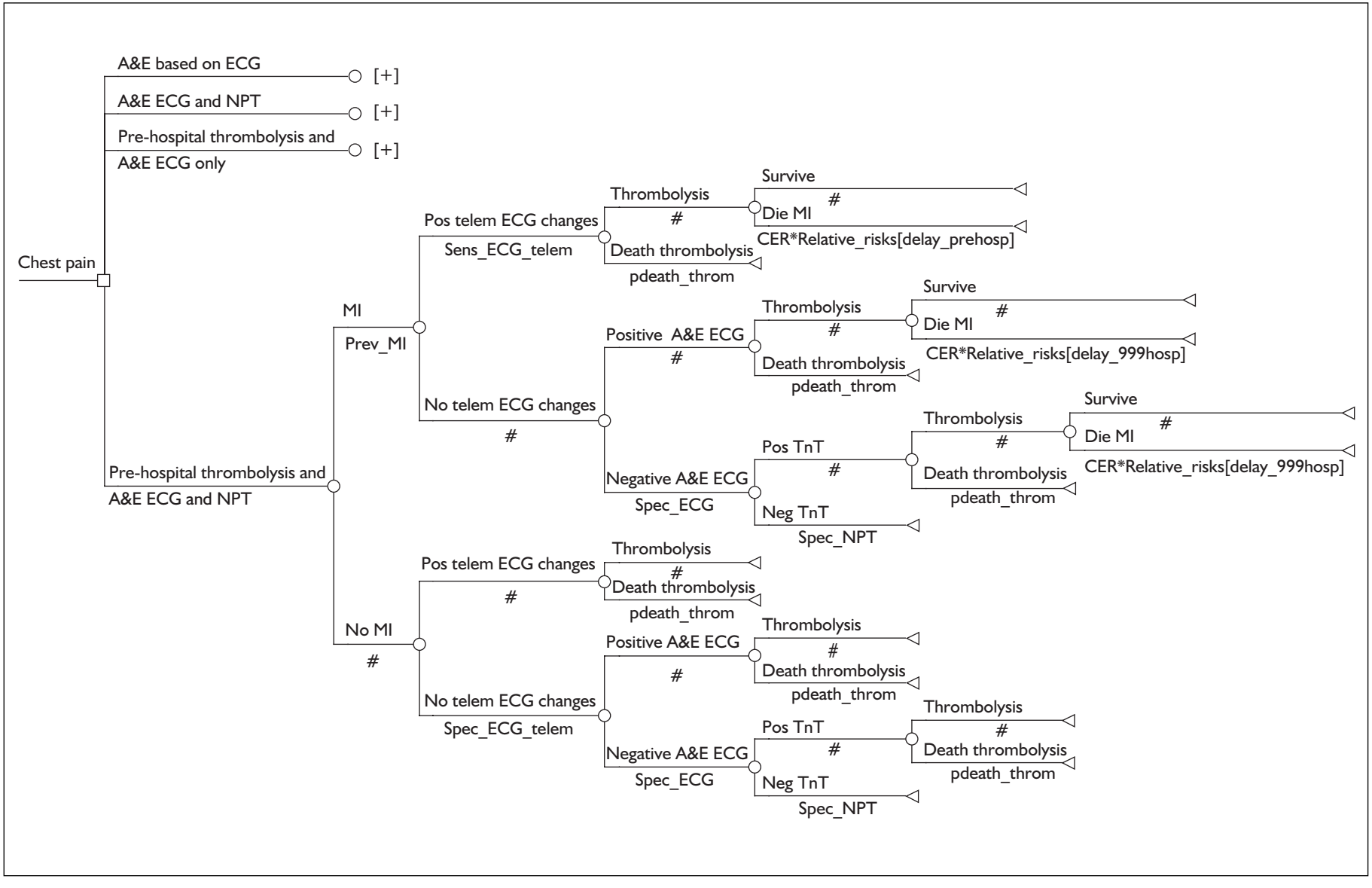

FIGURE 5 *Decision to give thrombolysis either pre-hospital with ECG telemetry or in A&E based on ECG alone*

TABLE 1 *Effectiveness data: parameters of beta distributions*

Parameter	α parameter of Beta distribution	β parameter of Beta distribution	Mean (%) and 95% CI
Sensitivity of telemetry ECG	42	58	42 (33 to 52)
Specificity of telemetry ECG	99.7	0.3	99.7 (94 to 100)
Prevalence of MI	50	50	50 (40 to 60)
Sensitivity of normal A&E ECG	94	6	94 (89 to 98)
Specificity of normal A&E ECG	40	60	40 (30 to 50)
Control event rate (death between 1 and 28 days)	11.5	88.5	11.5 (6 to 18)
Risk of death with thrombolysis	1	99	1 (0.03 to 4)
Sensitivity of Q wave/ST change/T wave	67	33	67 (57 to 76)
Specificity of Q wave/ST change/T wave	87	13	87 (80 to 93)

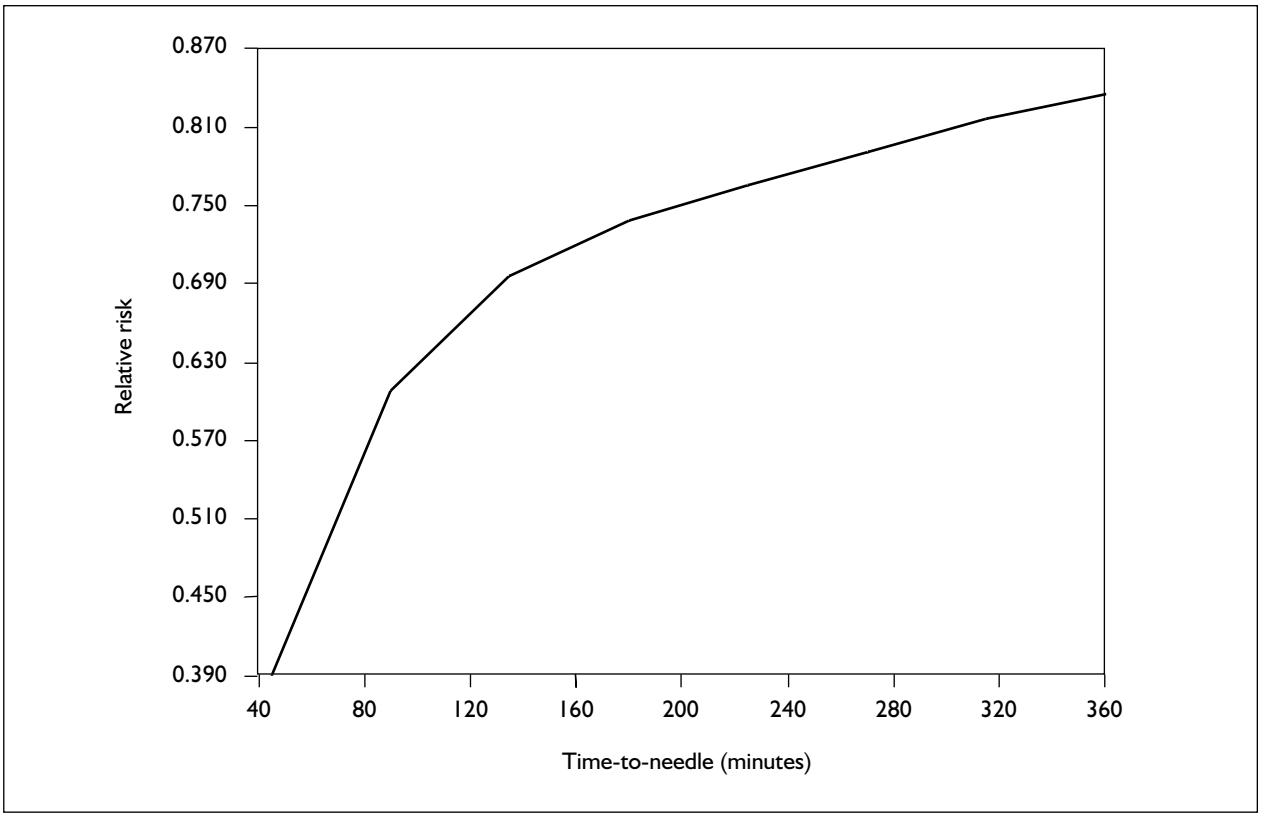

FIGURE 6 *Relative risk of death from MI days 1–28 post-infarct*

- **First order**, which relates to the path taken by an individual patient in the tree, and to variations in costs and in response time for the ambulance service. Exploration of first-order uncertainty was undertaken using sensitivity analysis, varying parameters and changing the output.
- **Second order**, which relates to statistical uncertainty as to the true value of various parameters in the model. These parameters were represented by probability density functions with characteristics chosen to represent the mean and standard deviation of the available data (see *Table 1*). Beta distributions were specified for the prevalence of MI, death rate without thrombolysis, risk of death from haemorrhage and diagnostic performance of telemetry and standard ECG.

Cost-effectiveness analysis

Cost data were obtained from national reference sources and other data from a concurrent systematic review of the literature (*Table 2*).

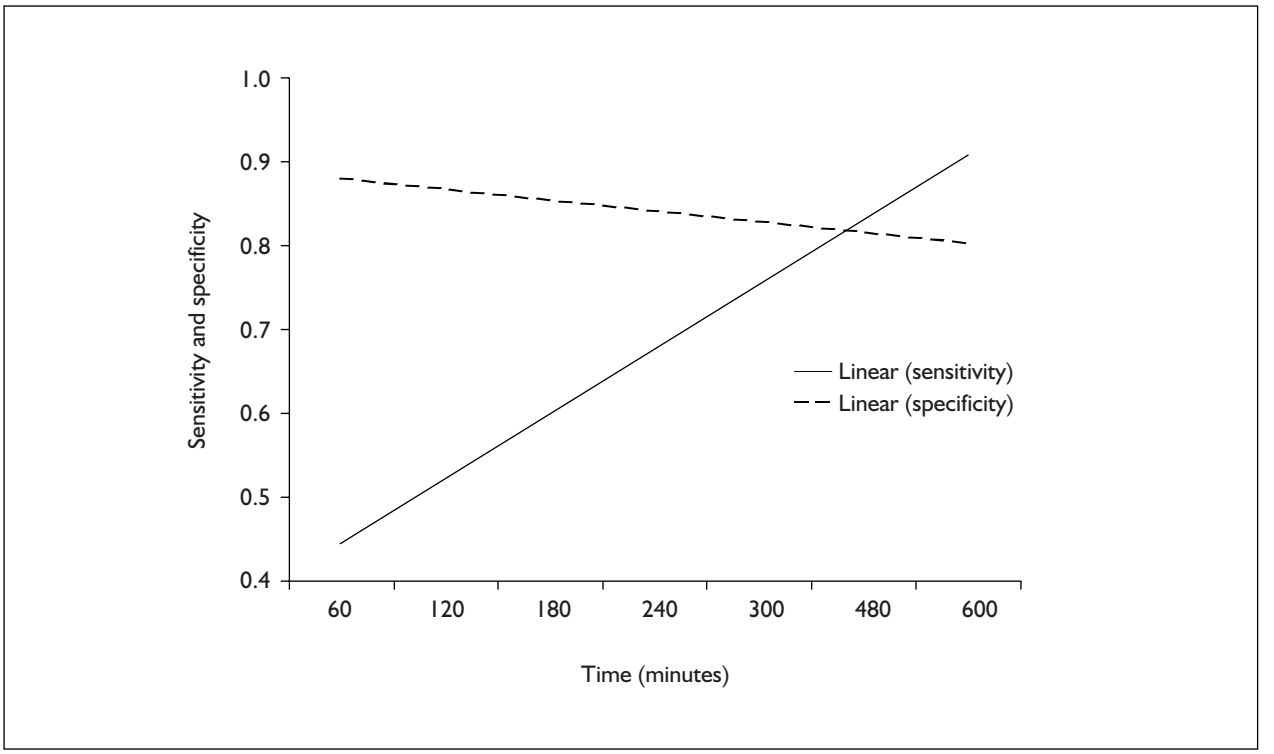

FIGURE 7 *Variation of sensitivity and specificity of the POCT with time*

TABLE 2 *Cost data*

Item	Unit cost (£)	Source
Ambulance call-out	106	National Audit office
Additional cost of telemetry ECG	200	Estimated
Reteplase	716.25	BNF30
Streptokinase	80	BNF30
A&E died	113	Reference costs 2000[31]
A&E referred	54	Reference costs 2000[31]
A&E discharged	46	Reference costs 2000[31]
Treatment of MI	903	Reference costs 2000[31]
TnT test	8.50	Roche diagnostics (personal communication)

The economic analysis considered health service costs incurred in the 28 days after admission, and cost-effectiveness was measured in cost per patient alive at 28 days.

Analysis

1. A second-order Monte Carlo simulation was performed with 10,000 runs sampling every distribution to determine the frequency of strategy choice in terms of maximising effectiveness.
2. A point estimate of cost-effectiveness was obtained and displayed on the cost-effectiveness plane. Incremental cost-effectiveness ratios for non-dominated strategies were calculated as difference in cost/difference in proportion of patients surviving between 1 and 28 days.
3. A further second-order Monte Carlo simulation was performed and the results were displayed as a scattergram on the cost-effectiveness plane and as a cost-effectiveness acceptability curve.
4. Sensitivity analysis was conducted for uncertainty in costs (particularly the cost of providing pre-hospital thrombolysis) and in pain-to-needle time for hospital thrombolysis.
5. Sensitivity of the result to different aspects of second-order uncertainty was explored using the effect of sampling only one distribution at a time on the cost-effectiveness scattergram.

Chronic chest pain model (discrete event simulation)

Aim of the model

The simulation is set up to explore the impact of three different service models of care for the investigation of patients presenting to a GP with chest pain which might be due to exertional angina.

Study population

The model excludes patients with established CHD (whether through previous investigation or past events such as acute MI) and patients with ACS. The model also excludes patients who would not be considered as suitable for angiography because of other factors such as co-morbidity or general frailty. The model considers patients aged between 25 and 79 years. The study population was defined in this way since most of the test performance data that are available are in people without prior MI, and the availability of epidemiological and test performance data are very limited in people over the age of 80 years.

Models of care

The three models of care being evaluated are as follows:

1. RACPC. The type of clinic evaluated here is that promoted by the UK NSF for CHD: "patients who develop new symptoms that their GP thinks might be due to angina can be assessed by a specialist within 2 weeks of referral."[3] In this model, it is assumed that all patients who attend a chest pain clinic are seen by a cardiologist, and the assessment includes an exercise ECG performed on the same day.
2. Open access exercise ECG. In this model of care, the GP may refer patients for an exercise ECG without reference to a cardiologist. It is assumed that patients with a positive exercise test will be subsequently referred on to a cardiologist, and that patients with a negative test will be managed by the GP with a working diagnosis that the pain is not cardiac in origin.
3. Cardiology outpatient clinic. The GP refers patients with suspected angina to a cardiologist, who may arrange for further investigation, including exercise ECG.

Outcome

Three outcome measures are being used: resources needed to provide the model of care; the average time delay before a definitive (correct) diagnosis is reached; and the number of coronary events (including deaths) that occur before definitive diagnosis is made. For this exercise, 'definitive diagnosis' includes not only whether or not a patient has angina, but also a decision as to whether or not (if they had angina) they would benefit from surgery. Thus, for patients with angina, it is assumed that a definitive diagnosis is made once an angiogram has been performed.

Research question

What is the impact of RACPCs compared with open access exercise ECG and cardiology outpatient clinics on the management of patients presenting in primary care with suspected angina?

Construction of the simulation model

The model is a discrete event simulation (DES) model, written in Borland Delphi, using an event-based simulation executive.

The simulation predicts what would happen to a population of 1000 new patients presenting per year with chest pain to their GP under the three different models of care. Patients enter the simulation with pre-determined characteristics in terms of age, gender, underlying cardiac disease and ability to complete an exercise ECG. The frequency of each of these characteristics is determined from published population data where available (see the section 'Data used in the model', p. 18). Patients remain in the model until:

1. a definitive cardiac diagnosis is made on the basis of angiography, or
2. a correct diagnosis of non-cardiac disease is made – referred to in the model as 'benign exit', or
3. the patient suffers an acute MI.

The risks for these events for each type of patient are derived from published literature (see the section 'Data used in the model', p. 18).

Logic of the model

Phase 1. GP assessment and management

A patient consults the GP with chest pain. The GP assesses the (pre-test) probability that the chest pain is due to CHD – in the model this is assigned as a probability between 0 and 1.

If the GP assesses the probability to be 'below threshold' (see the section 'Data used in the model', p. 18), and the patient does not have cardiac disease, then the patient leaves the model as a 'benign exit'. If the patient does have cardiac disease, then it is assumed that after 3 months, the GP will refer on to a cardiologist because of persisting symptoms.

If the GP assesses the probability to be 'above threshold', then the patient is referred on for further investigation.

Phase 2. Initial investigation – exercise ECG and cardiologist assessment

This will depend on which model of care is being tested.

In the open access exercise test model, patients will either be referred to a cardiologist (if well above threshold, or unsuited for an exercise test) or be referred for an exercise test (if just above threshold). If the exercise test is positive, the patient will be referred to a cardiologist (see the next paragraph), and if negative, they will be managed by the GP.

In the cardiology outpatient model, the cardiologist will make a diagnosis of 'definite cardiac', 'possible cardiac' or 'definitely not cardiac'. In the last case, the patient is referred back to the GP without further investigation. Otherwise, the patient is referred for an exercise test, after which the cardiologist will review the patient again, and may revise the diagnosis.

In the chest pain clinic model, patients will either be referred to the chest pain clinic or for a routine cardiology appointment (if just above threshold). If referred to the chest pain clinic, the exercise test is performed on the same day as the patient sees the cardiologist, and the cardiologist makes a diagnosis (as described in the previous paragraph) in the light of the exercise test results.

Phase 3. Referred back to GP as non-cardiac

If at any stage the cardiologist makes a 'definitely not cardiac' diagnosis, the patient is referred back to the GP. If the patient is genuinely non-cardiac, this constitutes a 'benign exit'. If the patient does have cardiac disease, the GP will re-refer after a further 3-month gap. In this case, the cardiologist will send all patients on for angiography.

Phase 4. Further investigation – myocardial perfusion imaging and angiography

After an exercise test has been performed, or a decision has been made not to use an exercise test, further investigations are carried out on patients for which the cardiologist has made a 'definite cardiac' diagnosis or a 'possible cardiac' diagnosis. The former will be referred for angiography, and the latter for myocardial perfusion imaging (MPI).

Angiography is taken as the reference standard for determining cardiac status. Patients may suffer an acute event during angiography (in which case they exit the model as an 'acute event'), or they will exit the model after angiography has been completed as a 'benign exit' (if angiography normal) or as a 'definitive cardiac diagnosis', if the angiogram was positive.

Patients with a positive MPI scan are referred on to angiography. Patients with a negative MPI scan are referred back to the GP as 'non-cardiac'.

Illustration of patient flows

Figures 8–10 illustrate the possible patient flows through the model, depending on what services are available.

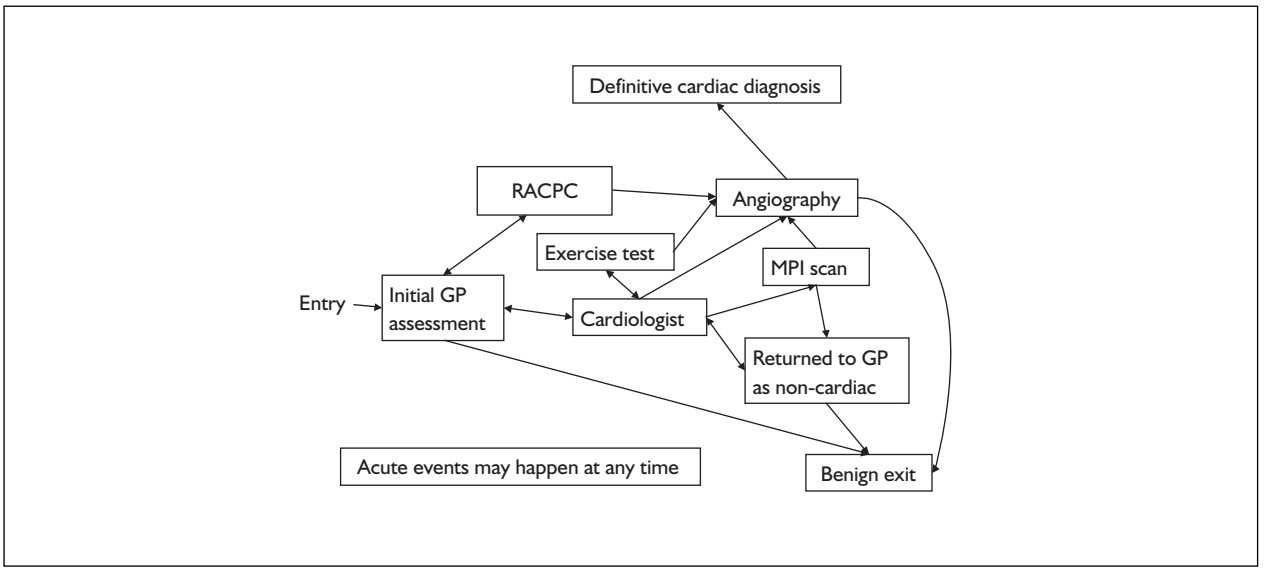

FIGURE 8 *RACPC model*

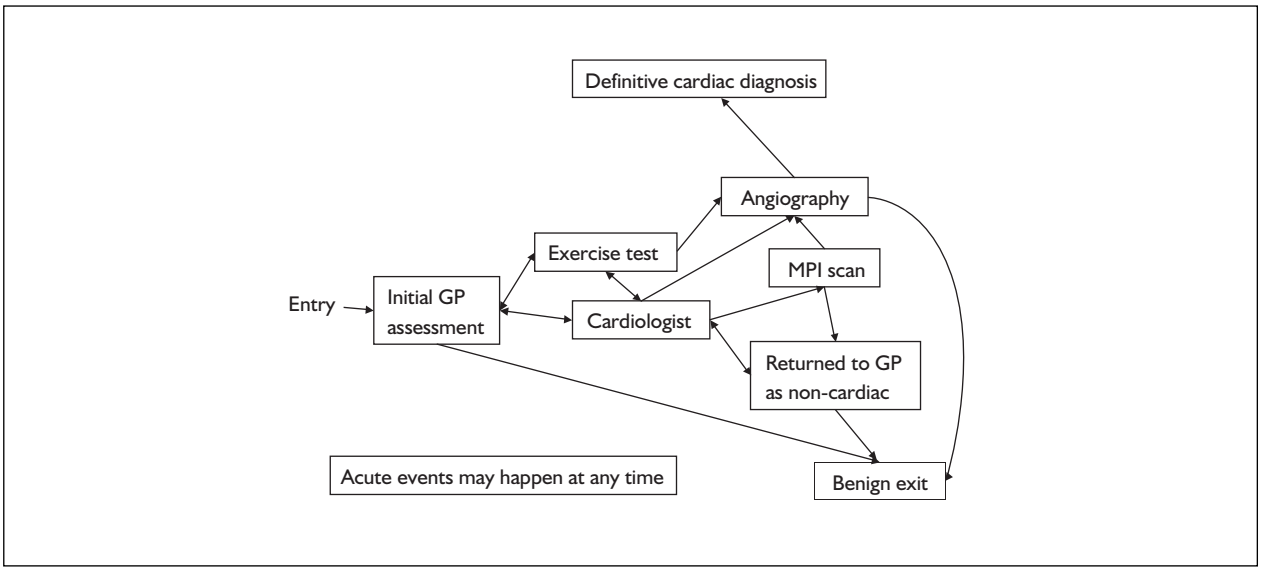

FIGURE 9 *Open access exercise test model*

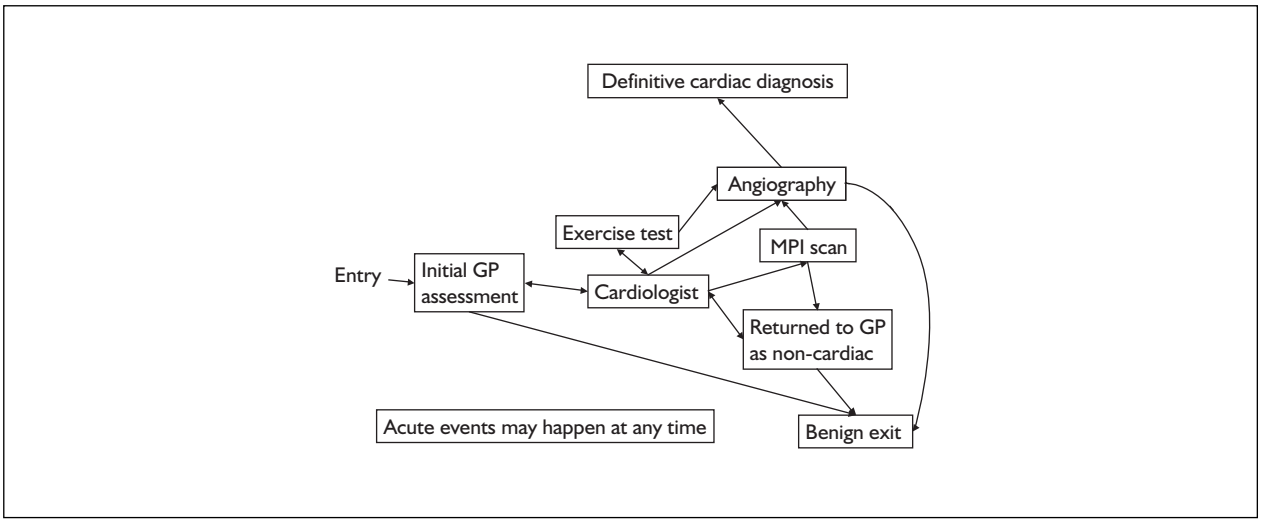

FIGURE 10 *Cardiology outpatient clinic model*

Data used in the model

Queuing discipline

The following assumptions are made:

1. There is no restriction on the availability of GP consultations.
2. Appointments need to be made for referrals to a cardiologist, exercise tests, MPI and angiography. For each of these, there are a limited number available per year. The patient is given the next available appointment subject to a minimum delay of:
   (a) 1 day for an RACPC
   (b) 1 day for an open access exercise test
   (c) 1 week for an exercise test (not open access)
   (d) 1 week for a cardiology outpatient appointment
   (e) 1 week for an MPI scan
   (f) 1 week for an angiogram.

   Thus, for example, the patient will not receive an angiogram within 1 week of referral, even if appointments are available within the week. This is to allow for the time taken to process requests.
3. Appointment waiting times are also subject to maximum waiting times, to be consistent with national targets.[3] These are:
   (a) 13 weeks for cardiology outpatient appointment
   (b) 2 weeks to see cardiologist at RACPC

(c) 2 weeks for an open access exercise test. Where these waiting times would otherwise be exceeded, extra appointment capacity is created as necessary during the running of the model. This is then reflected in the resources required to run each type of clinic.

4. For a patient with underlying cardiac disease that is initially assessed by the GP as being unlikely to be cardiac disease, the GP will refer on to a cardiologist after 3 months of persistent symptoms.
5. If an exercise test was ordered by a cardiologist, the patient will see the cardiologist 7 days after the test was performed.
6. If an exercise test was ordered by a GP, then the patient will see the GP 14 days after the test was performed.
7. For a patient with underlying cardiac disease who is assessed by a cardiologist as 'definitely non-cardiac', the GP will re-refer after a 3-month gap due to persistent symptoms.

Characteristics of patients entering the model

Age and gender

Based on data from the General Practice Morbidity Survey,[32] the distribution by age and gender of patients presenting with chest pain to their GP is as shown in *Table 3*.

TABLE 3 *Age distribution of incident cases (%)*

Age group (years)	Males[a]	Females[a]
25–34	1.58	1.12
35–44	1.57	1.14
45–54	14.85	11.15
55–64	11.46	8.81
65–74	17.78	15.30
75–79	6.96	8.29
All ages	54.2	45.8

[a] Percentages shown are **not** the age-specific incidence of presentations, but rather the proportion that each specific age group contributes to the overall presentation rate in primary care.

One thousand new patients presenting per year with chest pain would be drawn from an underlying practice population of 207,900 adults (aged 25–74 years), since the incidence of chest pain considered potentially to be cardiac in origin in the community is 481 per 100,000 in 25–74 year-olds.[33] Given that 61.5% of the population are in the age range 25–74 years,[34] this equates to a total practice population of around 350,000.

Prevalence of underlying cardiac disease

The prevalence of CHD in patients presenting with chest pain in primary care that the GP considers to be possibly cardiac in origin is around 26%.[33] The prevalence of CHD in patients referred to cardiology outpatients has been reported as 31%.[35] The review of chest pain clinic papers (see the section 'Chest pain clinic results', p. 37) showed that the prevalence of CHD in patients referred to such clinics was 40% (range: 28–51%).

Within this prevalence, the underlying cardiac disease is further defined in terms of underlying coronary artery pathology, drawing on data from the Coronary Artery Surgery Study (CASS)[36] as shown in *Table 4*.

Ability of patient to perform an exercise test

This was based on estimates from the cardiologists (RD & MKD) on the review team, in the absence of any literature (*Table 5*).

Referral threshold of GP

It has been assumed that the GP classifies patients presenting with chest pain in terms of a pre-test probability of cardiac disease that is accurate (thus

TABLE 5 *Percentage unable to perform exercise test*

Age group (years)	Percentage
25–44	1
45–64	5
65–74	20
75–79	50

TABLE 4 *Distribution of cardiac disease (%)*

Age group (years)	Single vessel	Double vessel	Triple vessel	Left main
25–39	43.6	28.7	18.1	9.6
40–49	29.0	31.2	27.3	12.5
50–59	20.0	31.0	34.0	14.9
60–69	15.3	26.8	38.9	18.9
≥ 70	8.2	16.5	50.5	24.7

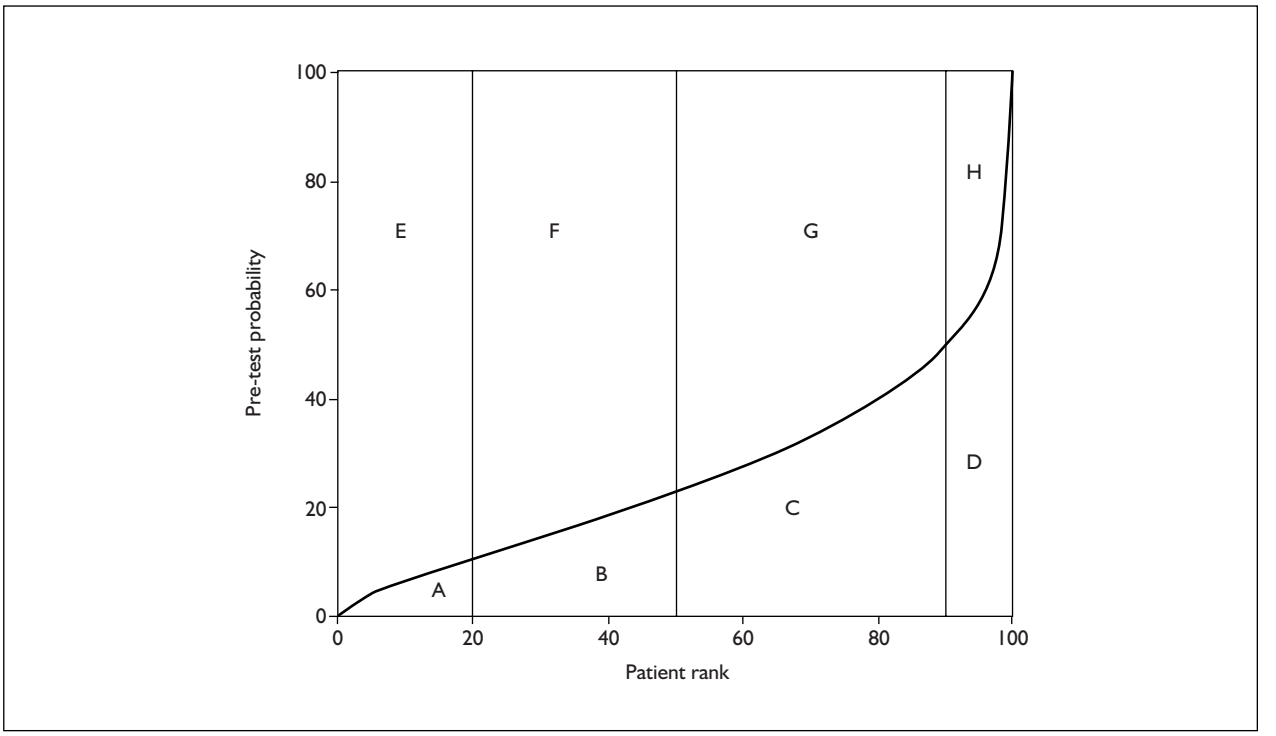

FIGURE 11 *Pre-test probability against patient rank*

30% of patients with a pre-test probability of 0.30 will have underlying cardiac disease). The GP will refer the patient for specialist assessment/further investigation at or above a given threshold, the level of which depends on the service that is available. The threshold is expressed as the proportion of patients (ranked in order of pre-test probability) with suspected cardiac pain who will be referred. The base case model is that the top 80% of patients (in terms of pre-test probability) will be referred for further investigation. If a chest pain clinic is available, the 50% with the highest pre-test probabilities will be referred to the clinic, and the remaining 30% to a routine cardiology outpatient appointment. For open access ECG, it is assumed that the top 10% will be referred directly to a cardiologist, and the 70% below that will be referred for an open access test.

The distribution of pre-test probability against rank is shown in *Figure 11*. Patients below the curve (groups A, B, C and D) actually have CHD whereas those above the curve do not. Groups C, D, G and H are referred to chest pain clinic; groups C and D represent 40% of these. Similarly, when there is no open access available, groups B, C, D, F, G and H are referred to outpatients; groups B, C and D together represent 31% of these. When open access exercise tests are available, groups B, C, F and G are referred to open access exercise tests; groups B and C represent 27% of these. In this case, groups D and H are referred directly to cardiologist outpatient appointments; group D represents 62% of these.

TABLE 6 *Sensitivity of MPI scan according to actual condition*

Actual condition	Sensitivity (%)
Single vessel	78
Double vessel	89
Triple vessel	92
Left main stem	92

Performance of diagnostic tests

The test performance of exercise ECG was taken to be 71% sensitive and 77% specific (see Chapter 4). It was assumed that the test performance of exercise ECG was the same in all three settings, that is, that the test was interpreted by a cardiologist. MPI was taken to have a specificity of 87%, and underlying-condition dependent sensitivity as shown in *Table 6*.[37]

Accuracy of cardiologist diagnosis

Cardiologist diagnosis is as shown in *Tables 7* and *8*. The figures for diagnosis in the absence of an exercise test are drawn from the CASS study.[36] The figures in italics in these tables represent the probability of an incorrect diagnosis. We assumed that the probability of an incorrect diagnosis

TABLE 7 *Probability of cardiologist's diagnosis by actual condition of patient and exercise test result (men)*

Actual condition of patient	Probability (%) of given diagnosis following:								
	No exercise test			Positive exercise test			Negative exercise test		
	Yes[a]	Poss.[b]	No[c]	Yes	Poss.	No	Yes	Poss.	No
Non-cardiac	*14.9*[d]	40.5	44.6	*22.4*[d]	36.9	40.7	*7.5*[d]	44.0	48.5
Single vessel	43.1	44.4	*12.5*[d]	46.2	47.6	*6.2*[d]	40.1	41.2	*18.7*[d]
Multi-vessel	59.0	38.9	*2.1*[d]	59.6	39.3	*1.1*[d]	58.4	38.5	*3.1*[d]

[a] Yes = definitely cardiac.
[b] Poss. = possibly cardiac.
[c] No = definitely non-cardiac.
[d] Figures in italics indicate the probability of an incorrect diagnosis in each case.

TABLE 8 *Probability of cardiologist's diagnosis by actual condition of patient and exercise test result (women)*

Actual condition of patient	Probability (%) of given diagnosis following:								
	No exercise test			Positive exercise test			Negative exercise test		
	Yes[a]	Poss.[b]	No[c]	Yes	Poss.	No	Yes	Poss.	No
Non-cardiac	*9.0*[d]	35.3	55.7	*13.5*[d]	33.5	53.0	*4.5*[d]	37.0	58.5
Single vessel	30.3	55.3	*14.5*[d]	32.8	60.0	*7.2*[d]	27.7	50.6	*21.7*[d]
Multi-vessel	40.9	57.0	*2.2*[d]	41.3	57.6	*1.1*[d]	40.4	56.4	*3.2*[d]

[a–d] See *Table 7*.

would be halved by a 'correct' exercise test result, and multiplied by 1.5 in the case of an incorrect exercise test result.

In the case where a cardiologist makes two diagnoses, one before and one after exercise test, we assumed that the cardiologist will only change diagnosis in the direction indicated by the exercise test. The probability of a diagnosis that would be unacceptable under this rule is added to the probability of an unchanged diagnosis. For example, consider a patient with single vessel disease. If the first diagnosis is possibly cardiac and the exercise test is positive, then the post-exercise test diagnosis will be definitely cardiac with probability 46.2 per cent, and possibly cardiac with probability 53.8 per cent. Here, the 6.2 per cent probability of a diagnosis of definitely not cardiac is reassigned to the diagnosis of possibly cardiac.

Risk of acute event

Risk of acute first events was estimated using data from the Oxford Myocardial Infarction Incidence Study (*Table 9*).[38]

TABLE 9 *Annual risks of first myocardial infarction or coronary death*

Men: age (years)	Event rate[a]	Women: age (years)	Event rate[a]
25–34	2.2	25–34	0.0
35–49	76.0	35–49	16.0
50–64	430.9	50–64	151.2
65–79	926.0	65–79	633.5

[a] Annual rate of first acute event per 100,000 population.

These data were used to estimate risk for patients with non-cardiac chest pain. For cardiac patients, an additional risk multiplier was used based on CASS survival data.[36] Annual mortalities observed in the CASS study are shown in *Table 10*. Clearly the lower mortality for double than for single vessel is a sampling effect: we decided to use the average figure (1.3%) for both groups. The mean age of the trial patients was 51 years and they were 90% male. The annual mortality for 45–54-year-old US males during this time was 0.86%.[39]

TABLE 10 *Annual mortality for CASS patients under medical management*

Actual condition	Mortality (%)
Single vessel	1.4
Double vessel	1.2
Triple vessel	2.1

Comparing this with the figures in *Table 10* gives a base case risk multiplier of 1.6 for single and double vessel and 2.5 for triple vessel. Left main stem was assumed to be the same as triple vessel.

The risk of acute event during angiography is set at 1 in 700 (MKD and RCD estimate).

Cost data

The costs of investigations were based on results of the EMPIRE study:[40]

- exercise ECG: £70
- myocardial perfusion imaging: £220
- coronary angiography: £1100
- outpatient appointment: £70.

Running the model

When the model is started, all queues are empty. Each of the outputs shown in the results is based on a 'warm-up' period of 10 years, followed by a period of 100 years over which the results were collected. The arrival rate was set at 1000 new patients per year. The mean results from three runs are shown.

For each policy option, the first requirement was to assess the required capacity for cardiologist appointments, exercise tests, MPI scans and angiography. To find the average use in an unconstrained run, each of these capacities was set to 2000 per year and the model run once. The capacities were then each set to the nearest multiple of 10 above the average use in the 100-year run of the model and the model re-run.

The next step was to increase, if necessary, the capacities for each type of appointment until each

TABLE 11 *Sensitivity analysis (clinic attributes)*

Clinic attributes Queuing discipline	Base case	Sensitivity analysis
Minimum delay for appointment		
RACPC	1 day	
Open access exercise test	1 day	
Exercise test (not open access)	1 week	
Cardiology outpatient appointment	1 week	
Myocardial perfusion scan	1 week	
Angiogram	1 week	
Maximum waits for appointments[a]		
RACPC	2 weeks	
Open access exercise test	2 weeks	
Exercise test (not open access)	6 weeks	2–10 weeks
Cardiology outpatient appointment	13 weeks	
Myocardial perfusion scan	13 weeks	2–26 weeks
Angiogram	13 weeks	2–26 weeks

[a] Model creates capacity such that 90% of appointments held within maximum time.

TABLE 12 *Sensitivity analysis (patients' characteristics)*

Patients' characteristics	Base case	Sensitivity analysis
Age and gender structure of England and Wales		
Incidence of new onset chest pain possibly cardiac	4.8 per 1000 adults	2.4–9.6 per 1000 adults
Prevalence of CHD		
Patients presenting with chest pain to GP-assessed as possibly cardiac	26%	20–30%
Patients referred to cardiology outpatient departments	31%	24–35%
Patients referred to rapid access clinic	40%	32–44%

TABLE 13 *Sensitivity analysis (physician performance)*

GP referral threshold	**Base case**	**Sensitivity analysis (%)**
RACPC	50% to rapid access 30% to cardiology outpatient department	37.5–62.5 22.5–37.5
Open access exercise test	10% to cardiology outpatient department 70% to exercise test	7.5–12.5 52.5–87.5
Cardiology outpatients	80% referred	60–100
Accuracy of initial cardiologist diagnosis (probability of misdiagnosis)	**Base case**	**Sensitivity analysis (%)**
Non-cardiac patient assessed as cardiac	14.9% in males 9% in females	10–20 5–15
Patient with single vessel disease assessed as non-cardiac	12.5% in males 14.5% in females	8–17 10–20
Patient with multi-vessel disease assessed as non-cardiac	2.1% in males 2.2% in females	1–3 1–3

TABLE14 *Sensitivity analysis (test performance)*

Performance of diagnostic tests	**Base case (%)**	**Sensitivity analysis (%)**
Exercise ECG		
Sensitivity	71	65–76[a]
Specificity	77	72–82[a]
MPI		
Sensitivity	78–92	
Specificity	87	

[a] Corresponds to 95% CIs for test attributes determined from systematic review.

TABLE 15 *Sensitivity analysis (risk of acute event)*

Risks of acute event	**Base case**	**Sensitivity analysis**
During angiography	1 in 700	1 in 350 to 1 in 1000
50–64-year-old men with non-cardiac chest pain	0.43% per annum[a]	
Single/double vessel disease: risk in non-cardiac multiplied by	1.6	1.2–2
Triple/left main stem disease: risk in non-cardiac multiplied by	2.5	2–3

[a] Given as an illustration. Age- and gender-specific rates derived from Volmink *et al.*[38]

was achieving at least 90% with waiting time within the target waiting times listed under 'Queuing discipline' above (p. 18). If any of the four queues averaged under 90% 'on time', the capacity associated with the lowest percentage 'on time' was increased by 10. This was repeated until three consecutive runs of the model had all queues achieving at least 90% 'on time'. For MPI scans and angiography the maximum wait (i.e. 90% performed within the time period) was taken to be 13 weeks, consistent with the NSF second-stage aim and for exercise tests ordered outwith the open access service, 6 weeks.[3]

Sensitivity analyses

Sensitivity analyses were performed, testing the impact of the key assumptions in the model. These are presented in tabular form in *Tables 11–15*.

Chapter 4

Results of the review

The initial search strategy (*Table 16*) identified 10,862 papers, of which 5344 were excluded on the basis of their titles (see *Figure 1*). The number of potentially relevant papers was reduced to 590 after review of abstracts. These papers were reviewed in detail and 170 were subsequently included in one or more of the five review topics.

The evaluation of suspected ACS

The studies that assessed use of clinical features and ECG in the diagnosis of ACS were divided into three categories: those that reported the use of individual symptoms or signs; those that reported the use of single ECG changes; and those that reported the use of combinations of diagnostic information to make a diagnosis. The last group have been labelled 'black box studies' as it was not always clear how the different information was integrated to arrive at a diagnosis.

Quality of studies

Tables 40–45 show the results of the assessment of quality of the included studies. There were a number of general issues of concern in relation to the methodological quality of these studies.

The reference standards used for MI comprised combinations of ECG changes, enzyme rises, typical clinical features (largely chest pain) and in some cases radionucleotide scanning results. The most commonly used criteria were those of the WHO (20/64 comparisons).[23] A number of studies also classified patients with either sudden unexplained death or autopsy evidence of MI as 'true positives'.[41–48] In some studies, the ECG or clinical feature being evaluated was specifically excluded reducing the likelihood of incorporation bias.[44,49–61] However, in many cases the reference standard was applied retrospectively at discharge taking into account all of the clinical details. The potential problem with this approach is that it makes incorporation bias more likely. In other words, whether or not the test ECG or clinical feature being evaluated was present or absent may have influenced whether or not the reference standard diagnosis was positive or negative.

Verification or work-up bias, that is, the extent to which the result of the test ECG or clinical feature influenced whether or not the reference standard could be applied, depended largely on the study setting. Verification bias was not a major problem in those studies which were based on inpatient cohorts, since the data required to apply the gold standard were mostly available via patients' records. Studies where patients attending A&E were studied have more potential for work-up bias in that the diagnostic information available for patients discharged from A&E with a negative diagnosis is likely to be less complete than for those admitted to hospital (*Tables 40*, *42* and *44*).

Those studies based on inpatient cohorts will, however, have introduced the possibility of two further biases. First, it may have been that the results of initial tests helped determine whether or not the patient was admitted – thus, for example, patients with a normal initial ECG may have not

TABLE 16 *Reference sources*

Source	No. of references identified	No. eligible for inclusion in review	Sensitivity (eligible/total)	Precision (eligible/identified)
MEDLINE	8079	132	0.78	0.02
EMBASE	6058	108	0.64	0.02
CINAHL	5093	73	0.43	0.01
Expert panel	40	4	0.02	0.10
Cochrane	601	6	0.04	0.01
Reference lists	237	4	0.02	0.02
Abstracts	0	0	0	0
Total – unique	10,862	170		0.02

TABLE 17 *Clinical symptoms*

Symptom		MI only				MI or unstable angina		
		Studies	LR	95% CI	*P* for heterogeneity	Studies	LR	95% CI
Pleuritic pain	LR+	3[55,62,63]	0.19	0.14 to 0.25	0.5	0		
	LR–		1.17	1.15 to 1.19	0.003			
Sharp pain	LR+	2[53,55]	0.32	0.21 to 0.50	0.3	1	0.41	0.29 to 0.57
	LR–		1.36	1.26 to 1.46	0.4		1.32	1.20 to 1.45
Positional pain	LR+	2[53,63]	0.27	0.21 to 0.36	0.3	1	0.27	0.17 to 1.42
	LR–		1.12	1.11 to 1.14	0.09		1.35	1.25 to 1.47
Pain on palpation	LR+	3[53,55,63]	0.23	0.08 to 0.30	0.15	1	0.17	0.11 to 0.27
	LR–		1.18	1.16 to 1.20	0.001		1.56	1.42 to 1.71
Crushing pain	LR+	6[47,53,55,63–65]	1.44	1.39 to 1.49	0.14	2	1.56	1.36 to 1.78
	LR–		0.63	0.60 to 0.67	0.9		0.63	0.55 to 0.73
Central pain	LR+	3[62–64]	1.24	1.2 to 1.27	0.01	1	1.12	1.07 to 1.17
	LR–		0.49	0.43 to 1.56	0.002		0.31	0.19 to 0.50
Left-sided radiation of pain	LR+	2[63,65]	1.45	1.36 to 1.55	0.004	2	1.22	1.15 to 1.30
	LR–		0.78	0.73 to 0.82	0.02		0.58	0.49 to 0.69
Right-sided radiation of pain	LR+	2[55,65]	2.59	1.85 to 3.70	0.7	1	6.68	2.95 to 15.2
	LR–		0.8	0.72 to 0.88	0.01		0.73	0.65 to 0.81
Any radiation of pain	LR+	2[47,62]	1.43	1.33 to 1.55	0.7	1	1.26	1.13 to 1.40
	LR–		0.8	0.75 to 0.84	0.01		0.27	0.13 to 0.53
Pain duration >1 h	LR+	1[65]	1.3	1.15 to 1.47		1	1.05	0.92 to 1.21
	LR–		0.35	0.19 to 0.64		1	0.84	0.56 to 1.27
Previous MI/angina	LR+	4[47,55,62,63]	1.29	1.22 to 1.36	0.001	1	1.22	1.09 to 1.37
	LR–		0.84	0.81 to 0.88	0.001		0.77	0.67 to 0.90
Nausea/vomiting	LR–	4[52,55,62,64]	1.88	1.58 to 2.23	0.5	1	1.78	1.16 to 2.74
	LR–		0.77	0.71 to 0.84	0.001		0.82	0.72 to 0.95
Sweating	LR+	5[47,55,62–64]	2.06	1.96 to 2.16	0.07	0		
	LR–		0.65	0.62 to 0.67	0.001			

been admitted and therefore excluded from the study. Second, there is likely to be a spectrum bias applying the results of studies done on inpatient cohorts compared with patients in community settings (and also A&E), where the symptoms on average will be less severe and any ECG changes will be less established. This spectrum bias is likely to lead to higher test sensitivity in hospital than in the community.

A general problem with the reporting of the studies was that the majority did not state from what overall number of patients assessed with chest pain the final study sample was chosen.

A 'treatment paradox' occurs if application of the diagnostic test under study leads to treatment that may modify what is the result of the reference standard. This is of potential importance in these studies because patients presenting with symptoms of an MI who were thrombolysed may not have subsequently displayed the required attributes of MI, particularly if thrombolysis was successful in avoiding a 'Q wave infarction'. Unfortunately, whether or not this was a problem was unclear in many of the studies, as it was not stated whether thrombolysis had been given to many/all of the patients.

The evaluation of suspected ACS: clinical signs and symptoms

Twenty-one papers were found that contained data regarding the use of 16 different clinical signs and symptoms in the diagnosis of MI (*Tables 40* and *41*). In 11 studies, the definition of the reference standard was broadened to ACS. *Tables 17* and *18* contain the positive and negative LRs for a number of common elements from the clinical history and examination. None of these in isolation were found to be particularly useful: no

TABLE 18 *Clinical signs*

Sign		MI only				MI or unstable angina		
		Studies	LR	95% CI	*P* for heterogeneity	Studies	LR	95% CI
Pulmonary crackles	LR+	1[55]	2.08	1.42 to 3.05		0	–	–
	LR–		0.76	0.62 to 0.93				
SBP <80 mmHg	LR+	1[66]	3.06	1.80 to 5.22		0	–	–
	LR–		0.97	0.95 to 0.99				
Third heart sound	LR+	1[55]	3.21	1.60 to 6.45		0	–	–
	LR–		0.88	0.79 to 0.99				

SBP, systolic blood pressure.

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.

The evaluation of suspected ACS: resting ECG

Fifty-three papers were found that included data concerning the use of one or more features from a resting ECG in the diagnosis of suspected ACS (*Tables 42* and *43*). Results from these studies are presented in *Table 19*. The diagnosis of unstable angina is not possible using ECG and so for this section only papers concerning the diagnosis of MI were evaluated.[24]

The occurrence of ST elevation (most 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 feature for the diagnosis of MI with a positive LR of 13.1 (95% CI 8.28 to 20.6). The presence of Q waves (LR 5.01, 95% CI 3.56 to 7.06) and ST depression (LR 3.13, 95% CI 2.50 to 3.92) were the next best discriminating single features. When a number of possible features of MI were combined then reasonable discrimination of MI was possible [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 an MI (LR+ 0.14, 95% CI 0.11 to 0.20). Again, the summary results are difficult to interpret because of significant heterogeneity between studies. Nevertheless, a consistent picture emerges that important diagnostic information is conveyed by a single ECG in the evaluation of acute chest pain. It has been assumed for this analysis that previous ECGs or the capacity to do serial ECGs are not available in the emergency evaluation of chest pain in the community, so the differentiation has not been made between new and old ECG changes.

The evaluation of suspected ACS: black box

Fifteen studies investigated real-time decision-making based on combinations of information initially available to physicians (*Tables 44* and *45*). These black box papers were subdivided on the basis of the clinical decision being considered as a diagnostic test (*Table 20*):

TABLE 19 *Resting ECG features for acute chest pain*

		MI only			
		Studies	**LR**	**95% CI**	***P* for heterogeneity**
Normal ECG	LR+	11[11,41,47,53,58,67–72]	0.14	0.11 to 0.20	0.007
	LR–		1.58	1.42 to 1.76	<0.001
Sinus rhythm	LR+	0			
	LR–				
AF	LR+	1[41]	0.57	0.13 to 2.49	
	LR–		1.02	0.98 to 1.05	
ST elevation (STe)	LR+	17[11,41,42,48,55–58,61,66,68,71–76]	13.1	8.28 to 20.6	<0.001
	LR–		0.47	0.42 to 0.54	<0.001
ST depression (STd)	LR+	2[55,66]	3.13	2.50 to 3.92	0.6
	LR–		0.60	0.25 to 1.43	<0.001
T waves	LR+	1	1.87	1.41 to 2.48	
	LR–		0.66	0.50 to 0.87	
Q waves	LR+	1[55]	5.01	3.56 to 7.06	
	LR–		0.45	0.32 to 0.64	
Left BBB	LR+	1[41]	0.49	0.15 to 1.60	
	LR–		1.03	0.99 to 1.08	
Right BBB	LR+	1[41]	0.28	0.04 to 2.12	
	LR–		1.03	1.00 to 1.06	
STe/STd/Q/T	LR+	5[45,47,65,70,77]	5.30	3.66 to 7.70	<0.001
	LR–		0.38	0.21 to 0.65	<0.001
STe/STd/Q/T/BBB	LR+	3[58,60,78]	4.34	2.46 to 7.67	0.08
	LR+		0.36	0.33 to 0.38	0.7
STe/STd/Q/T/BBB or other rhythms	LR+	2[79,80]	2.11	1.17 to 3.78	<0.001
	LR–		0.28	0.16 to 0.50	0.003

AF, atrial fibrillation.

- interpretation of admission ECG for MI[57,78,81] and ACS[57]
- interpretation of clinical data other than the ECG for MI[82]
- A&E initial diagnoses for MI[51,57,83–86] and ACS[57,68–70]
- A&E decisions to admit for MI[50,84,85] and ACS.[50,71–73]

Study quality

For the black box studies there were two main issues regarding the quality of studies. The first was the grade of person whose clinical acumen was being examined. This person(s) should be representative of the type of person normally seeing patients in the setting: in one study a chief cardiologist's diagnosis based on the initial ECG was the diagnostic test evaluated and in another the ECGs were read by consensus.[78,81] The results from these are both likely to be very different from a junior physician reading the same ECG that would be a typical scenario in A&E, or indeed from a GP or paramedic making a diagnosis in the community. Whereas in some studies the clinical features and ECG findings were being interpreted following specific decision rules, in many it was left to the subjective interpretation of the clinician. Another important issue in these studies was the extent of follow-up of patients in order to confirm the reference standard diagnosis. Many studies did not rigorously follow up those not admitted to the A&E, relying on telephone self-reports[83,86] or not following up patients who were not admitted at all.[51,87]

Results

Table 20 contains the results of the 15 black box studies. The better quality studies (those in which the diagnosis evaluated was realistic of the setting in question and where work-up bias was kept to a

TABLE 20 *Black box studies*

	Studies	Sensitivity	Specificity	LR+	LR–
ECG diagnosis					
AMI: adequate quality[a]	1[57]	0.42 (95% CI 0.32 to 0.52)	0.997 (95% CI 0.980 to 0.999)	145 (95% CI 20.2 to 1044)	0.58 (95% CI 0.49 to 0.70)
AMI: all studies	3[57,78,81]	0.25 (95% CI 0.23 to 0.28)	0.995 (95% CI 0.991 to 0.998)	52 (95% CI 7.97 to 339.5)	0.60 (95% CI 0.43 to 0.82)
ACS: adequate quality	1[57]	0.42 (95% CI 0.37 to 0.49)	0.87 (95% CI 0.82 to 0.91)	3.28 (95% CI 2.23 to 4.84)	0.66 (95% CI 0.58 to 0.74)
ACS: all studies	1[57]	0.42 (95% CI 0.37 to 0.49)	0.87 (95% CI 0.82 to 0.91)	3.28 (95% CI 2.23 to 4.84)	0.66 (95% CI 0.58 to 0.74)
Signs+history					
AMI: adequate quality	1[82]	0.94 (95% CI 0.89 to 0.96)	0.23 (95% CI 0.18 to 0.30)	1.22 (95% CI 1.12 to 1.33)	0.28 (95% CI 0.16 to 0.50)
AMI: all studies	1[82]	0.94 (95% CI 0.89 to 0.96)	0.23 (95% CI 0.18 to 0.30)	1.22 (95% CI 1.12 to 1.33)	0.28 (95% CI 0.16 to 0.50)
ACS: adequate quality	0				
ACS: all studies	0				
A&E diagnosis					
AMI: adequate quality	1[57]	0.45 (95% CI 0.35 to 0.55)	0.95 (95% CI 0.92 to 0.97)	9.22 (95% CI 5.50 to 15.5)	0.58 (95% CI 0.48 to 0.70)
AMI: all studies	6[51,57,83,86,87,89]	0.64 (95% CI 0.62 to 0.66)	0.78 (95% CI 0.77 to 0.79)	4.48 (95% CI 2.82 to 7.12)	0.29 (95% CI 0.18 to 0.49)
ACS: adequate quality	3[57,90,91]	0.84 (95% CI 0.81 to 0.87)	0.72 (95% CI 0.69 to 0.74)	4.01 (95% CI 1.55 to 10.4)	0.23 (95% CI 0.07 to 0.75)
ACS: all studies	4[57,87,90,91]	0.81 (95% CI 0.79 to 0.83)	0.73 (95% CI 0.72 to 0.75)	3.54 (95% CI 1.97 to 6.38)	0.25 (95% CI 0.14 to 0.45)
Admission					
AMI: adequate quality	1[85]	0.92 (95% CI 0.90 to 0.95)	0.69 (95% CI 0.66 to 0.72)	3.01 (95% CI 2.73 to 3.31)	0.11 (95% CI 0.08 to 0.16)
AMI: all studies	3[50,84,85]	0.95 (95% CI 0.94 to 0.96)	0.55 (95% CI 0.54 to0.56)	2.55 (95% CI 1.87 to 3.47)	0.08 (95% CI 0.05 to 0.13)
ACS: adequate quality	1[85]	0.85 (95% CI 0.82 to 0.88)	0.74 (95% CI 0.71 to 0.77)	3.24 (95% CI 2.89 to 3.64)	0.20 (95% CI 0.16 to 0.25)
ACS: all studies	4[50,84,85,92]	0.90 (95% CI 0.88 to 0.91)	0.67 (95% CI 0.66 to 0.68)	3.01 (95% CI 2.55 to 3.56)	0.13 (95% CI 0.09 to 0.20)

[a] Studies of 'adequate quality' included a realistic decision being tested (i.e. a decision by a front-line physician, not an outside expert) and adequate follow-up.
AMI, acute myocardial infarction.

minimum) are presented both separately and in combination with all the studies.

Interpretation of admission ECG for MI and ACS

Clinicians could interpret ECGs with a very high specificity for MI [LR 145 (95% CI 20.2 to 1044) in the best quality paper], although the sensitivity was low (LR– 0.58).[57] These results are in marked contrast to the presence or absence of individual ECG features (see above).

Interpretation of clinical data other than the ECG for MI

The one study that examined the exclusive use of clinical data in diagnosing MI had an LR+ of 1.22 (95% CI 1.12 to 1.33) and a LR– of 0.28.[88] This result is consistent with the evaluation of individual symptoms and signs in isolation (see above).

A&E initial diagnoses for MI and ACS

The six studies in which an A&E initial diagnosis

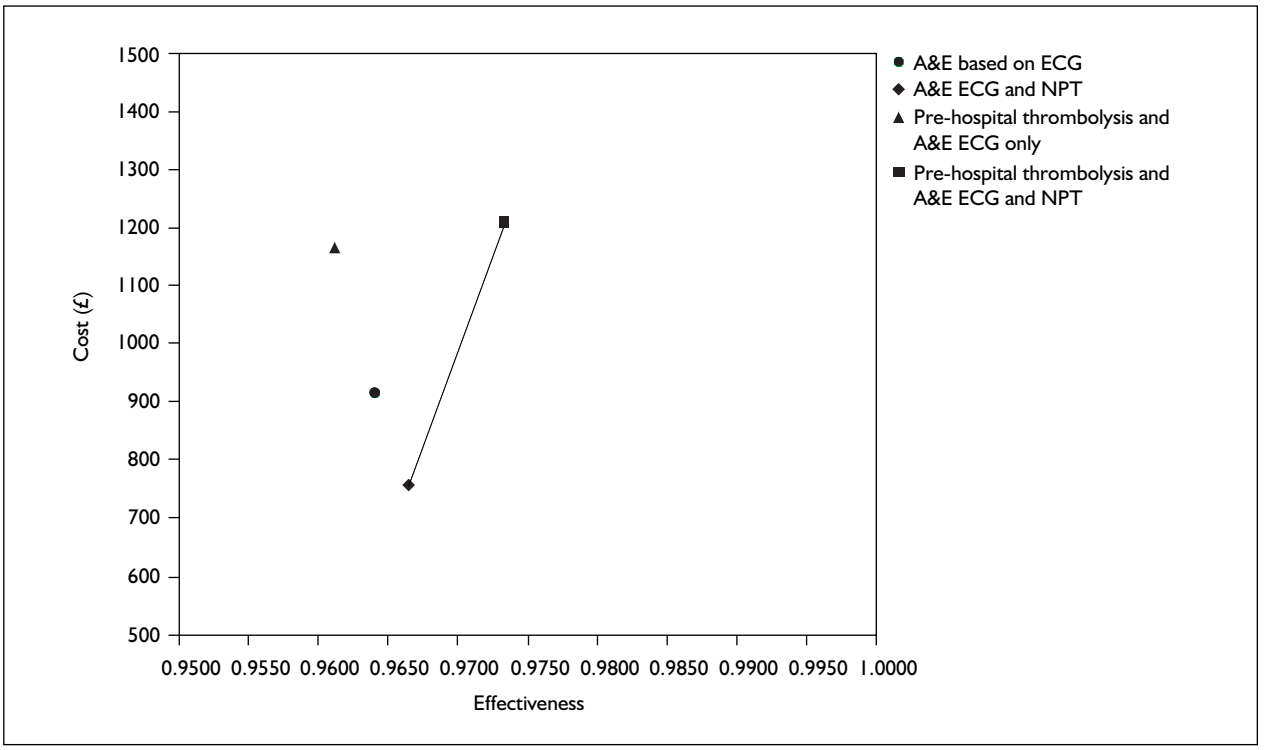

FIGURE 12 *Cost-effectiveness analysis at the chest pain: point estimates on the cost-effectiveness plane.*

for MI was treated as the diagnostic test resulted in an LR+ of 4.48 (95% CI 2.82 to 7.12) and a LR– of 0.29 (95% CI 0.18 to 0.49). When the one better quality study was examined individually, it had a higher LR+ [9.22 (95% CI 5.50 to 15.5)] but also a higher LR– [0.58 (95% CI 0.48 to 0.70)].[85] The LRs when ACS was used as the reference standard were lower.

A&E decisions to admit for MI and ACS

For a diagnosis of MI the LR+ for admission was 2.55 (95% CI 1.87 to 3.47) with an LR– of 0.08 (95% CI 0.05 to 0.13). There was little difference when the better quality study was examined individually [LR+ 3.01 (95% CI 2.73 to 3.31) and LR– 0.11 (95% CI 0.08 to 0.16)]. Results with ACS as the reference standard were similar.

The evaluation of suspected ACS: second-order Monte Carlo simulation

Simple cost-effectiveness analysis

The two strategies that used POCT dominated the two that did not: A&E-based use of POCT was both more effective and less expensive than an A&E-based strategy based on ECG alone (see *Figure 12*). Pre-hospital thrombolysis was more effective when supported by A&E based POCT, and the costs were similar whether or not POCT was used. Pre-hospital thrombolysis without POCT was the least effective strategy overall. Pre-hospital treatment with POCT was more effective but more costly than A&E assessment using POCT. In this circumstance, pre-hospital therapy was associated with an additional seven per 1000 patients surviving at an additional cost of £453 per patient, with an incremental cost-effectiveness ratio (ICER) of £65,825 per patient. This simple cost-effectiveness analysis is also shown in *Table 21*, with A&E use of ECG and POCT as the baseline strategy. This further illustrates that the baseline strategy is both more effective and less expensive than the two strategies not using POCT.

Probabilistic analysis

The Monte Carlo simulation showed considerable uncertainty in this estimate, the scatterplot showing only marginal separation of the two pre-hospital strategies (with and without POCT) (*Figure 13*). The cost-effectiveness acceptability curve shows the probability that, for a given threshold cost at which it is deemed to be cost-effective to prevent a death, switching from an A&E-based to a pre-hospital-based strategy will be cost effective (*Figure 14*). For example, if it is assumed that if it costs more than £90,550 to

TABLE 21 *Cost-effectiveness comparison*

Strategy	Cost per patient (£)	Incremental cost (£)	28-day survival	Incremental difference in survival	ICER (£)
A&E ECG and POCT	757		0.966		
A&E based on ECG	916	159	0.964	–0.003	(Dominated)
Pre-hospital thrombolysis and A&E ECG only	1166	409	0.961	–0.005	(Dominated)
Pre-hospital thrombolysis and A&E ECG and POCT	1209	453	0.973	0.007	65,825

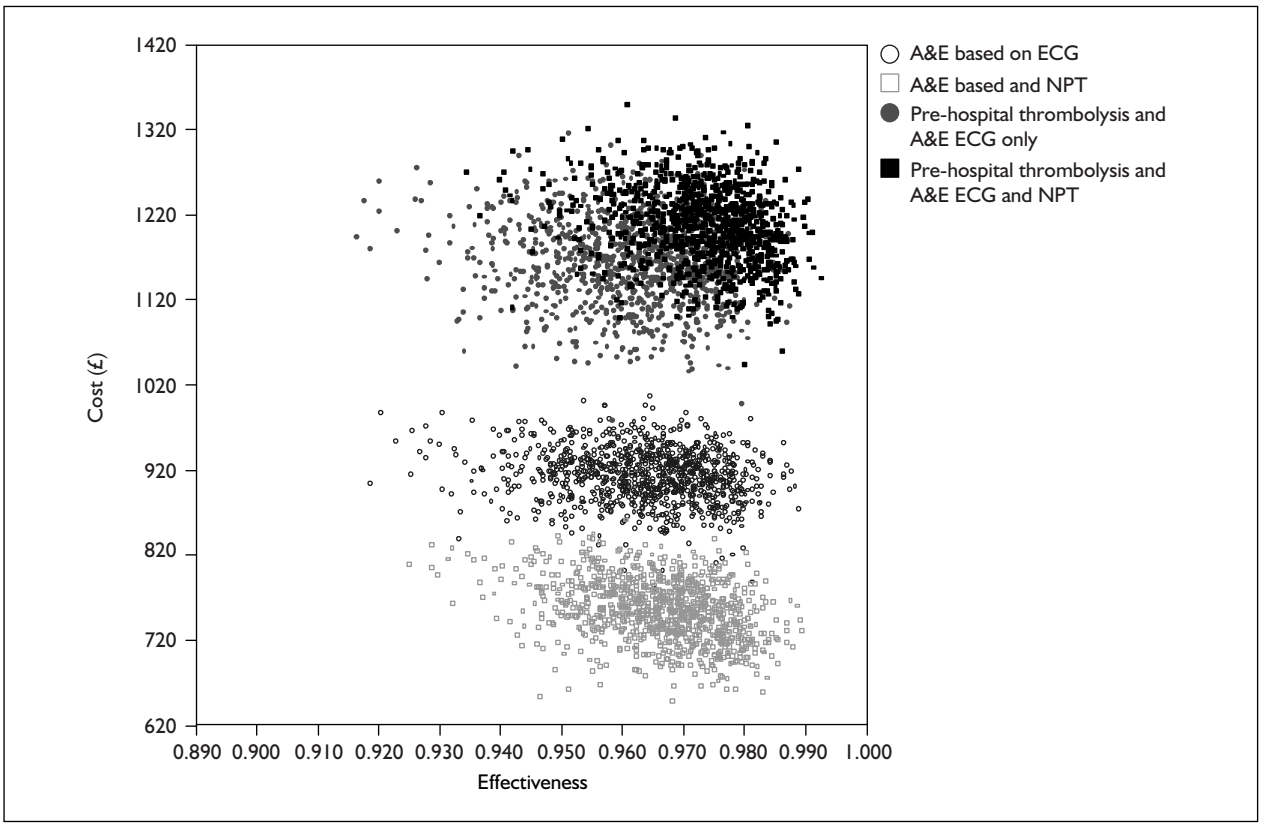

FIGURE 13 *Scatterplot on cost-effectiveness plane: all distributions sampled*

prevent a death, then the policy is not cost-effective; *Figure 14* shows that the model estimates a 70% probability that switching to a pre-hospital strategy would be cost-effective. This curve shows that the 95% CI on the ICER between the strategies A&E ECG and POCT, with and without pre-hospital thrombolysis, extends from £25,000 to £400,000 (*Figure 14*). However, the pre-hospital treatment was more effective in nearly all of the samples (*Figure 15*).

Sensitivity analysis

Sensitivity analysis of the effect of changing the cost of telemetry ECG and pain-to-needle time did not alter the order of dominated strategies, but significantly decreased the cost-effectiveness of pre-hospital treatment when either increased.

Table 22 shows the results of the sensitivity analysis on increasing pain to needle time and *Table 23* those for costs of telemetry. *Figure 16* shows the combined first- and second-order sensitivity analyses. The second-order uncertainty, that is, that of the statistical measures of prevalence, effect size and test performance, is displayed as a probabilistic analysis and a cost-effectiveness acceptability curve. The first-order uncertainty, as to cost and pain to needle time, is shown as a set of five cost-effectiveness acceptability curves, representing different time and cost scenarios.

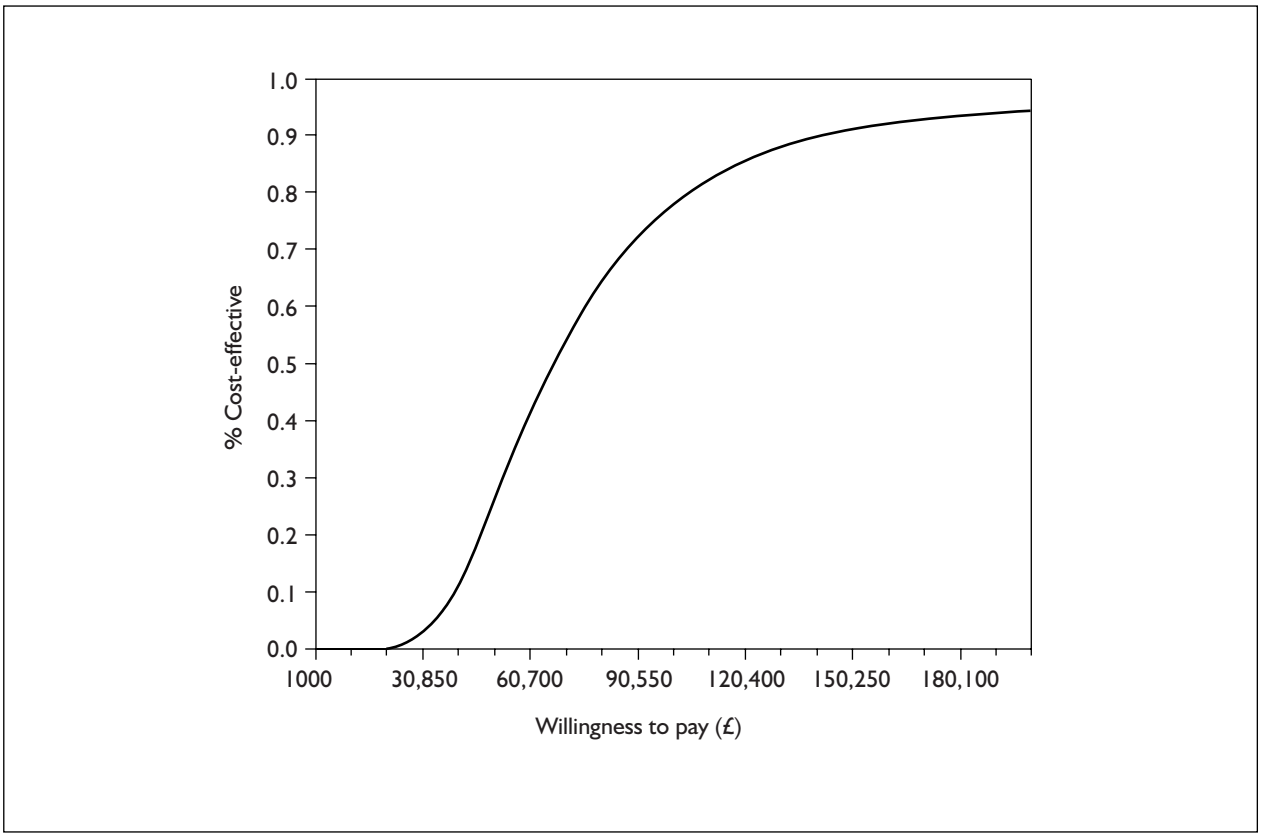

FIGURE 14 *Cost-effectiveness acceptability curve*

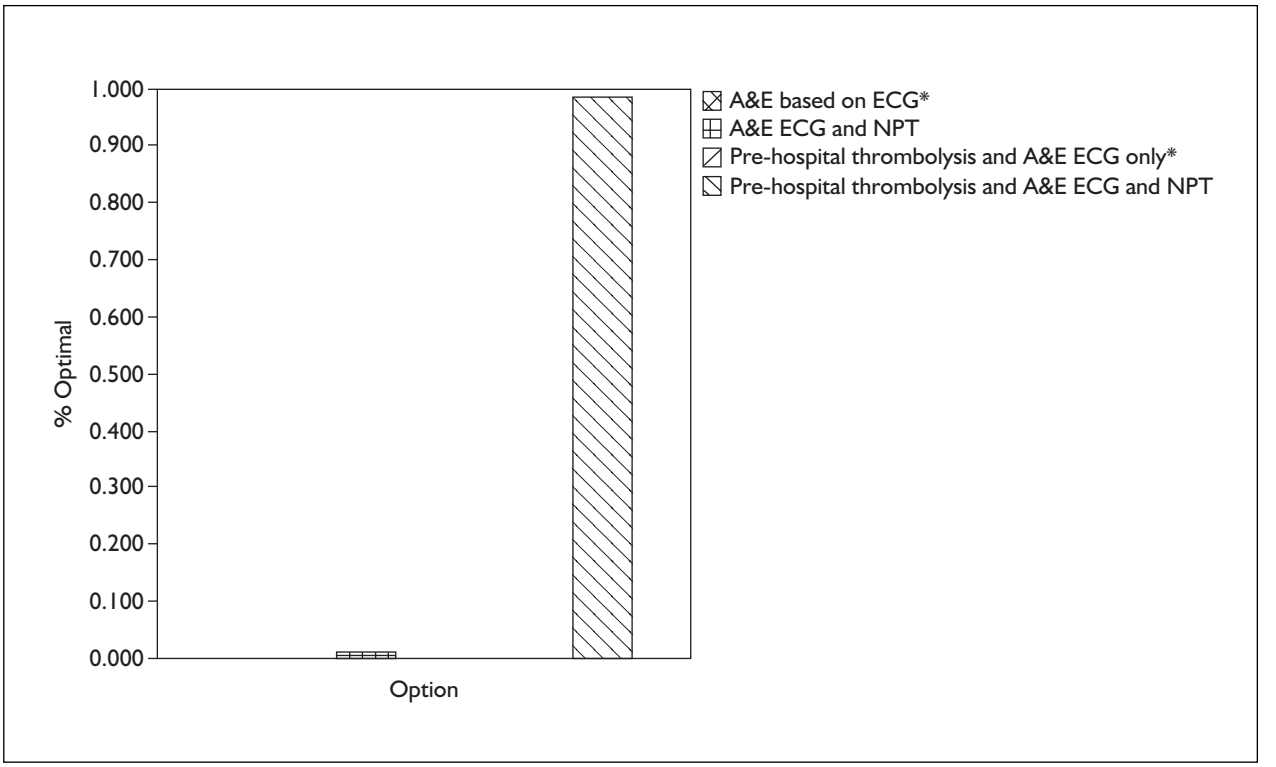

FIGURE 15 *Frequency of optimal choice: Monte Carlo simulation. *These strategies do not appear in the figure, as they never resulted in the optimal outcome.*

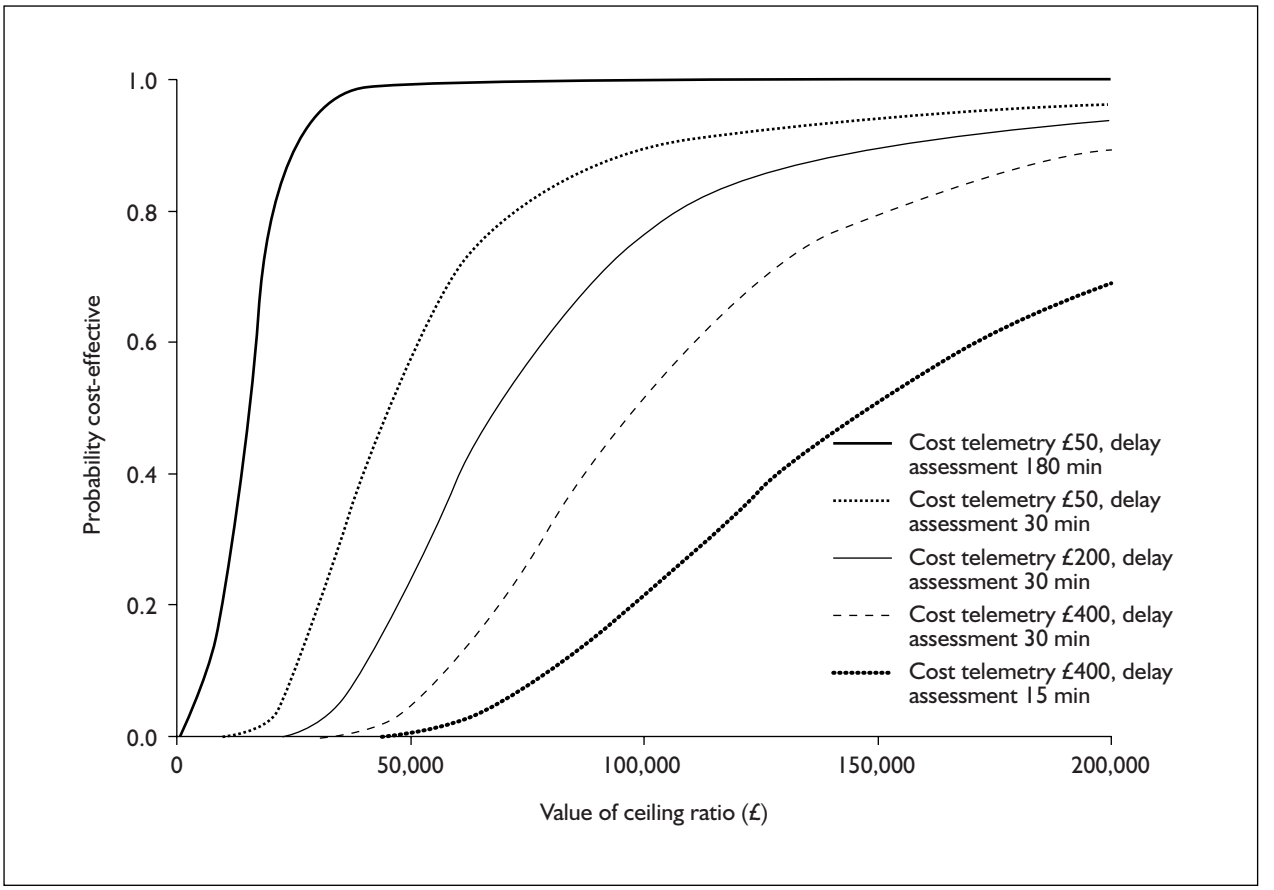

FIGURE 16 *Sensitivity analysis: effect of delay in thrombolysis and cost of providing telemetry ECG*

This shows how increasing either the cost of providing pre-hospital thrombolysis or the difference in time delay between hospital and pre-hospital strategies not only decreases the cost-effectiveness of pre-hospital treatment relative to hospital-based treatment, but also increases the impact of parameter uncertainty (by decreasing the slope of the curve).

The evaluation of suspected exertional angina

The review addressed the utility of resting ECG, exercise ECG and RACPCs in the assessment of suspected exertional angina.

Quality

General description

The majority of papers reviewed used angiography as the reference standard for the diagnosis of CHD (*Tables 46* and *48*). There was variation in the degree of stenosis in a main coronary artery used to define CHD from 30 to 75%. In addition, some of the studies defined a 50% stenosis in the left main stem as significant whilst requiring a 70 or 75% stenosis in other coronary arteries. Three broad types of exercise test were examined in the review: Bruce or modified Bruce tests, other treadmill tests (in general older types of test prior to the near universal adoption of the Bruce protocol) and bicycle ergometer tests.

Potential biases

Data regarding potential biases is presented in *Tables 47* and *49*. Little or no incorporation bias was present in the studies examined as the reference standard (angiography in most cases) was completely separate to the diagnostic tests under evaluation.

Verification bias, in contrast, was a far more serious source of error: very few of the studies examined subjected all potential subjects to the same reference standard, because of the potential morbidity associated with angiography. In fact, most of the studies required angiography to be performed for the patient to be eligible.

TABLE 22 *Sensitivity analysis of pain-to-needle time*

Pain-to-needle time (minutes)	Strategy	Cost (£)	Incremental cost (£)	Effectiveness	Incremental effectiveness	ICER (£)
15	A&E ECG and POCT	756.20		0.9705		
	A&E based on ECG	915.10		0.9679		(Dominated)
	Pre-hospital thrombolysis and A&E ECG only	1165.00		0.9627		(Dominated)
	Pre-hospital thrombolysis and A&E ECG and POCT	1208.30	452.20	0.975	0.0044	102,378.65
56.25	A&E ECG and POCT	756.20		0.9676		
	A&E based on ECG	915.10		0.965		(Dominated)
	Pre-hospital thrombolysis and A&E ECG only	1165.00		0.9616		(Dominated)
	Pre-hospital thrombolysis and A&E ECG and POCT	1208.30	452.20	0.9738	0.0062	72,438.89
97.5	A&E ECG and POCT	756.20		0.9578		
	A&E based on ECG	915.10		0.9555		(Dominated)
	Pre-hospital thrombolysis and A&E ECG only	1165.00		0.9581		(Ext. Dominated)
	Pre-hospital thrombolysis and A&E ECG and POCT	1208.30	452.20	0.97	0.0122	37,047.29
138.75	A&E ECG and POCT	757.90		0.9536		
	A&E based on ECG	915.10		0.9514		(Dominated)
	Pre-hospital thrombolysis and A&E ECG only	1165.00		0.9566		(Ext. Dominated)
	Pre-hospital thrombolysis and A&E ECG and POCT	1208.30	450.40	0.9683	0.0147	30,607.00
180	A&E ECG and POCT	768.00		0.9514		
	A&E based on ECG	915.10		0.9493		(Dominated)
	Pre-hospital thrombolysis and A&E ECG only	1165.00		0.9558		(Ext. Dominated)
	Pre-hospital thrombolysis and A&E ECG and POCT	1211.40	443.50	0.9673	0.016	27,739.22

Blinding with regard to interpretation of the reference standard and the exercise test should have been possible in every case due to the separation in time between the performance of the two tests. However, a number of studies did not report whether or not blinding took place. (*Tables 47* and *49*).

The evaluation of suspected exertional angina: resting ECG

Thirteen studies were found which evaluated the use of a resting ECG in the diagnosis of CHD (*Table 24*). The presence of Q waves was the most frequently evaluated ECG change. This was found to have an LR of 2.56, but the 95% CI was wide (0.89 to 7.30). One paper evaluated the use of QRS notching[93] and found this to have a high positive LR [LR+ 9.96 (95% CI 2.58 to 38.5)]. ST segment plus or minus T wave changes were not found to be useful and neither was the normality or otherwise of the ECG taken as a whole. The absence of any of the ECG features examined (LR– 0.43–1.01) was uninformative.

The evaluation of suspected exertional angina: exercise ECG

A total of 111 papers evaluating the use of exercise ECG in the diagnosis of chronic chest

TABLE 23 *Sensitivity analysis of cost of telemetry ECG*

Pain-to-needle time (minutes)	Strategy	Cost (£)	Incremental cost (£)	Effectiveness	Incremental effectiveness	ICER (£)
50	A&E ECG and POCT	756.20		0.9666		
	A&E based on ECG	915.10		0.964		(Dominated)
	Pre-hospital thrombolysis and A&E ECG only	1015.00		0.9613		(Dominated)
	Pre-hospital thrombolysis and A&E ECG and POCT	1058.30	302.20	0.9734	0.0069	44,108.62
120	A&E ECG and POCT	756.20		0.9666		
	A&E based on ECG	915.10		0.964		(Dominated)
	Pre-hospital thrombolysis and A&E ECG only	1085.00		0.9613		(Dominated)
	Pre-hospital thrombolysis and A&E ECG and POCT	1128.30	372.20	0.9734	0.0069	54,326.80
190	A&E ECG and POCT	756.20		0.9666		
	A&E based on ECG	915.10		0.964		(Dominated)
	Pre-hospital thrombolysis and A&E ECG only	1155.00		0.9613		(Dominated)
	Pre-hospital thrombolysis and A&E ECG and POCT	1198.30	442.20	0.9734	0.0069	64,544.98
260	A&E ECG and POCT	756.20		0.9666		
	A&E based on ECG	915.10		0.964		(Dominated)
	Pre-hospital thrombolysis and A&E ECG only	1225.00		0.9613		(Dominated)
	Pre-hospital thrombolysis and A&E ECG and POCT	1268.30	512.20	0.9734	0.0069	74,763.16
365	A&E ECG and POCT	756.20		0.9666		
	A&E based on ECG	915.10		0.964		(Dominated)
	Pre-hospital thrombolysis and A&E ECG only	1330.00		0.9613		(Dominated)
	Pre-hospital thrombolysis and A&E ECG and POCT	1373.30	617.20	0.9734	0.0069	90,090.43
400	A&E ECG and POCT	756.20		0.9666		
	A&E based on ECG	915.10		0.964		(Dominated)
	Pre-hospital thrombolysis and A&E ECG only	1365.00		0.9613		(Dominated)
	Pre-hospital thrombolysis and A&E ECG and POCT	1408.30	652.20	0.9734	0.0069	95,199.52

TABLE 24 *Resting ECG for chronic chest pain*

Analysis	No. of studies	LR+	LR–
Abnormal ST segment and T wave	2	0.99 (95% CI 0.88 to 1.11)	1.01 (95% CI 0.97 to 1.04)
Resting ST depression	1	1.50 (95% CI 1.16 to 1.94)	0.93 (95% CI 0.89 to 0.97)
Q wave	6	2.56 (95% CI 0.89 to 7.30)	0.75 (95% CI 0.68 to 0.79)
Q wave or ST changes	2	2.44 (95% CI 1.55 to 3.84)	0.43 (95% CI 0.33 to 0.56)
QRS notching	1	9.96 (95% CI 2.58 to 38.5)	0.40 (95% CI 0.30 to 0.53)
Any abnormality	3	1.53 (95% CI 1.01 to 2.33)	0.74 (95% CI 0.48 to 1.15)

TABLE 25 *Exercise ECG for chronic chest pain – different definitions of positive*

Analysis	No. of studies	LR+	LR–
ST depression 1 mm – all studies	71	2.79 (95% CI 2.53 to 3.07)	0.44 (95% CI 0.40 to 0.47)
ST depression 2 mm – all studies	12	3.85 (95% CI 2.49 to 5.98)	0.72 (95% CI 0.65 to 0.81)
ST slope – all data points	13	2.41 (95% CI 1.81 to 3.20)	0.37 (95% CI 0.27 to 0.50)
ST slope – cutoff point <2 μV/beats/minute	7	2.01 (95% CI 1.74 to 2.31)	0.59 (95% CI 0.53 to 0.66)
ST slope – cutoff point >2 μV/beats/minute	6	3.91 (95% CI 2.51 to 6.09)	0.32 (95% CI 0.20 to 0.50)
Combinations	6	1.83 (95% CI 1.72 to 1.95)	0.36 (95% CI 0.33 to 0.40)

pain for patient without known CHD were included in the review (*Table 25*). Many of the studies excluded patients with significant resting ECG abnormalities (see *Table 46*). There were 71 studies that included data for ST depression of 1 mm, 12 studies ST depression of 2 mm, 13 studies ST slope and six studies combinations of features such as treadmill scores. The LR+ for ST depression was 2.79 (95% CI 2.53 to 3.07) for a 1-mm cutoff and 3.85 (95% CI 2.49 to 5.98) if a 2-mm cutoff was used. The LR– values were 0.44 (95% CI 0.40 to 0.47) (1 mm) and 0.72 (95% CI 0.65 to 0.81) (2 mm), respectively. The ST slope showed similar performance with LR+ 2.01 (95% CI 1.74 to 2.31) for cutoffs below 2 μV/beats/minute rising to 3.91 (95% CI 2.51 to 6.09) when slopes steeper than 2 μV/beats/minute were used. The results from the combination scores were LR+ 1.83 (95% CI 1.72 to 1.95) and LR– 0.36 (95% CI 0.33 to 0.40).

Papers concerning the use of exercise ECG to diagnose chest pain thought to be due to CHD were chosen. Those with high proportions of patients (>20%) with known CHD were excluded, as were those where it was clear that participants did not suffer from chest pain. However, in a number of cases the reports did not include enough information for a definitive decision to be made on this basis. In order to investigate this further, the sensitivity analysis separately examined studies where these details were clearly stated (*Table 26*). A lack of previous cardiac history significantly reduced the specificity and LR+ [2.39 (95% CI 2.17 to 2.62)] of ST depression as a test whereas studies where all patients had chest pain tended towards a higher specificity and LR+ [3.09 (95% CI 2.67 to 3.58)]. The sensitivity analysis also examined studies where patients were not taking drugs which might have influenced the exercise tolerance test (ETT) result. These studies achieved greater LR+ [7.05 (95% CI 3.08 to 16.12)] and lower LR– [0.16 (95% CI 0.09 to 0.30)].

The Bruce protocol was the most commonly used (41 studies). There appeared to be a definite shift over time towards this with more recent studies being more likely to use Bruce's method. Sensitivity analysis around the type of exercise test used showed no significant difference in any comparison.

Very few papers specified how equivocal results were dealt with (22/71 reporting ST depression). This is potentially important as a considerable proportion of exercise tests may result in equivocal results, mostly in cases with a negative test result where the patient failed to reach 85% of their target heart rate. Despite this, those studies reporting their treatment of equivocal results (excluded or treated as negative) did not result in significantly different results from those where this detail was omitted.

The relative efficacy of ST depression as a diagnostic tool in men and women separately was examined (*Table 27*): 19 studies were found which gave results for men only and a further 19 concerning women only. When considered alone, the results from men-only studies gave an LR of 2.92 (95% CI 2.17 to 3.93) for 1 mm of ST depression whereas the LR in the 19 studies concerning women alone dropped to 1.92 (95% CI 1.72 to 2.24). Sensitivity analyses were also carried out for these studies (*Table 27*) but are of little value owing to the small numbers of studies involved in the comparisons.

The evaluation of suspected exertional angina: RACPCs

After eligibility review, 34 papers were considered potentially relevant to the RACPCs review and were appraised in detail. Nine of these were eligible for the review (*Table 28*).

Study quality

No randomised controlled trials (RCTs) were found. No study contained a true control group, but two made use of a hypothetical control group

TABLE 26 *Exercise ECG studies for chronic chest pain – sensitivity analysis*

Analysis	No. of studies	LR+	LR–
Overall	71	2.79 (95% CI 2.53 to 3.07)	0.44 (95% CI 0.40 to 0.47)
Other disease and treatment			
<20% previous MI	43	2.39 (95% CI 2.17 to 2.62) $p = 0.001^a$	0.44 (95% CI 0.40 to 0.49) $p = 0.51^a$
Known to have no previous cardiac history	8	2.41 (95% CI 1.95 to 2.98) $p = 0.002^a$	0.41 (95% CI 0.32 to 0.53) $p = 0.71^a$
Known to have no other drugs	9	5.24 (95% CI 3.35 to 8.20) $p = 0.14^a$	0.38 (95% CI 3.35 to 8.20) $p = 0.09^a$
No history or drugs	1	7.05 (95% CI 3.08 to 16.12)	0.16 (95% CI 0.09 to 0.30)
Type of test			
Bruce	41	2.75 (95% CI 2.46 to 3.08)	0.46 (95% CI 0.42 to 0.50)
Bicycle	17	3.20 (95% CI 2.38 to 4.29) $p = 0.54^b$	0.39 (95% CI 0.33 to 0.45) $p = 0.13^b$
Other treadmill	9	2.90 (95% CI 2.31 to 3.65) $p = 0.66^b$	0.37 (95% CI 0.28 to 0.49) $p = 0.18^b$
Bruce with <20% with previous MI	26	2.47 (95% CI 2.23 to 2.75)	0.45 (95% CI 0.39 to 0.51)
Bicycle with <20% with previous MI	12	2.24 (95% CI 1.81 to 2.77) $p = 0.32^c$	0.40 (95% CI 0.33 to 0.49) $p = 0.313^c$
Other treadmill with <20% with previous MI	3	3.05 (95% CI 2.02 to 4.59) $p = 0.38^c$	0.43 (95% CI 0.33 to 0.59) $p = 0.71^c$
Other features			
Studies with 12-lead ECG	39	2.50 (95% CI 2.25 to 2.77) $p = 0.04^a$	0.45 (95% CI 0.44 to 0.47) $p = 0.34^a$
Studies not using 12-lead ECG	32	3.36 (95% CI 2.73 to 4.14) $p = 0.04^a$	0.42 (95% CI 0.38 to 0.46) $p = 0.34^a$
ST-upsloping segments considered abnormal	24	2.96 (95% CI 2.51 to 3.50) $p = 0.55^a$	0.46 (95% CI 0.41 to 0.52) $p = 0.37^a$
Studies with 100% patients with chest pain	34	3.09 (95% CI 2.67 to 3.58) $p = 0.13^a$	0.38 (95% CI 0.34 to 0.43) $p < 0.001^a$
Studies stating proportion of population recruited	11	2.95 (95% CI 3.31 to 3.76) $p = 0.63^a$	0.45 (95% CI 0.37 to 0.56) $p = 0.63^a$
Studies stating method for dealing with equivocal results	22	2.84 (95% CI 2.39 to 3.38) $p = 0.95^a$	0.41 (95% CI 0.35 to 0.47) $p = 0.35^a$

[a] Compared with all studies not fitting this criterion.
[b] Compared with all studies using the Bruce protocol.
[c] Compared with studies using the Bruce protocol with <20% with MI history.

(how would the GP have managed the patient if the clinic had not been available?).[94,95] None presented data prior to the introduction of a chest pain clinic.

Chest pain clinic results

All clinics reviewed patients within 24 hours of referral. Inclusion criteria with respect to referral diagnosis varied between clinics, with some explicitly excluding patients thought to have an ACS whereas others encouraged these patients to be referred unless there was a definite MI clinically. Investigation universally included an ECG but the provision of exercise testing varied from 7 to 58% of clinic attendees. There was wide variation (25–75%) in the number of patients discharged back to their GP. Follow-up of patients attending the clinics to ascertain their subsequent outcomes was attempted in four studies.[94,96–98]

The two studies with hypothetical control groups estimated that the clinic prevented 213 (21% of those attending the clinic) unnecessary admissions over a 22-month period in one study,[95] and 66

TABLE 27 *Exercise ECG for chronic chest pain – males and females (1 mm ST depression)*

Analysis	No. of studies	LR+	LR–
Overall males	19	2.92 (95% CI 2.17 to 3.93)	0.46 (95% CI 0.38 to 0.56)
Other disease and treatment			
Males <20% previous MI	17	2.67 (95% CI 1.97 to 3.62) $p = 0.054^a$	0.46 (95% CI 0.37 to 0.57) $p = 0.97^a$
Males known to have no previous cardiac history	1	3.12 (95% CI 2.26 to 4.32) $p = 0.45^a$	0.54 (95% CI 0.47 to 0.62) $p = 0.79^a$
Males known to have no other drugs	1	6.88 (95% CI 3.30 to 14.33) $p = 0.51^a$	0.51 (95% CI 0.41 to 0.63) $p = 0.78^a$
Overall females	19	1.96 (95% CI 1.72 to 2.24)	0.55 (95% CI 0.49 to 0.65)
Other disease and treatment			
Females <20% previous MI	15	2.04 (95% CI 1.77 to 2.36) $p = 0.18^a$	0.53 (95% CI 0.45 to 0.63) $p = 0.12^a$
Females known to have no previous cardiac history	2	2.66 (95% CI 1.04 to 6.83) $p = 0.74^a$	0.38 (95% CI 0.08 to 1.76) $p = 0.38^a$
Females known to have no other drugs	2	1.45 (95% CI 0.71 to 2.96) $p = 0.161^a$	0.85 (95% CI 0.62 to 1.17) $p = 0.241^a$

[a] Compared with all studies not fitting this criterion.

(38%) such admissions over a 6-month period in the other (*Table 29*).[94] One study estimated that 89 of 144 (62%) patients with an ACS identified in the clinic would otherwise have been managed in the community.[95]

Three studies gave data on the speed of further investigation and surgical treatment of patients with cardiac disease, but none compared these data with current or prior 'best practice'.[97,99] In one study, 22/152 (15%) of patients with a cardiac diagnosis had had a bypass graft or angioplasty after 30 days.[99] The second followed up patients after 6 months and found that 37/140 (26%) had undergone surgery or angioplasty.[98] The last concerned only patients with stable angina and after 15 months' follow-up 20/115 had received surgical intervention or angioplasty.[97]

A diagnosis of non-cardiac chest pain was made in 28–69% of patients referred to rapid access clinics. Three studies followed up these patients to ascertain whether this was the correct final diagnosis. In one, no patients with non-cardiac chest pain had received a cardiac diagnosis at 1-month follow-up.[94] In the second, no patients with a non-cardiac diagnosis developed any cardiac complications after 8 months, but 12% were lost to follow-up.[98] The third study wrote to GPs 6 months after the clinic visit and found two patients with an initial non-cardiac diagnosis had subsequently had an MI.[96]

Simulation model for the evaluation of suspected exertional angina

Base case scenario

The results from running the model using the base case assumptions are shown in *Table 30*. In terms of time to definitive diagnosis, the RACPC model of care achieves the best results, both for excluding disease in people who do not have a cardiac cause for their chest pain and in making a definitive diagnosis in people who do have a cardiac cause for their symptoms. As a result of people spending less time in the model before a diagnosis is made, this model is associated with fewer coronary events, but the number of anticipated events prior to final diagnosis is low in all three patterns of service provision. Comparison of open access exercise test to no open access services shows that the open access exercise test results in more rapid exclusion of cardiac disease in people who do not have underlying CHD, but delays to angiographic diagnosis in people who do have CHD.

TABLE 28 *Characteristics of included RACPC studies*

First author, year, country	Clinic referral criteria	Exclusion criteria	Clinic	ETT	Comparison group	Method of follow-up
Studies with a comparison group						
el Gaylani, 1997, UK[94]	Suspected unstable angina	MI	Seen on day of referral by cardiology registrar; facilities for ECG, ETT and echocardiography	13/175	Retrospective questionnaire to GPs of patients not admitted (139/175) about what GP would have done	Patients admitted had case notes review to determine outcome. Patients discharged were followed up via questionnaires to GP at 1 month
O'Toole, 1995, UK[100]	Chest pain or palpitations of up to 48 hours duration	1. Acute symptoms likely to require admission. 2. Long-standing or established symptoms	Seen within 24 hours of referral. Clinic run Mon.–Fri. 1.30–4.20 p.m. Special referral form. Options = ECG alone or ECG + clinical assessment	35/60	Patients referred to routine cardiology services over same time period	None
Newby, 1998, UK[95]	Suspected cardiac chest pain of acute or recent onset	Suspected ACS	Weekday p.m. clinic. Seen within 24 hours. Full cardiology team, ECG, ETT	610/1001	Prospective proforma: provisional diagnosis and management by GP if clinic unavailable	None
Studies with no comparison group but follow-up of patients						
Duncan, 1976, UK[96]	New or worsening chest pain within previous 4 weeks suggestive of MI. Men aged <70	MI	Daily clinic; patients assessed by cardiologist. All had ECG. ETT when diagnosis in doubt	52/616	None	Patients with new onset angina followed up in clinic for 6 months. Patients not thought to have new onset angina followed up by letter to GP 6 months after clinic attendance
Gandhi, 1995, UK[97]	Suspected stable angina. Age <70	Previous history of known cardiac disease; Suspected ACS	Weekday morning clinic with patients assessed by cardiologist within 24 hours of referral	93/467	None	Only patients with stable angina followed up by patient questionnaire, GP (for cause of death) and hospital records

continued

TABLE 28 *Characteristics of included RACPC studies (cont'd)*

First author, year, country	Clinic referral criteria	Exclusion criteria	Clinic	ETT	Comparison group	Method of follow-up
Davie, 1998, UK[98]	New chest pain, increasing chest pain, chest pain at rest, other chest pain of concern	'Obvious' MI or unstable angina	Mon.–Fri. working hours clinic. Seen within 24 hours, mostly same day. Cardiology trainee and cardiologist, ECG, ETT	Not reported	None	Follow-up by telephone or postal questionnaire 8.5 months after clinic attendance
Studies with no comparison group or follow-up						
Sutcliffe, 2000, UK[101,102]	New chest pain considered to be exertional angina	Known CHD. Suspected ACS	Daily clinic on weekdays. Patients attend via GP without appointment	1132/ 2137	None	None
Timmis, 1999, UK[103]	Recent onset chest pain (last max. 4 weeks) Age: if male, >29; if female, >39	Previous history of CHD. Suspected MI or unstable angina	Daily clinic on weekdays. Patients seen within 24 hours	No data	None	None
Norell, 1992, UK[99]	Patients presenting with chest pain of recent onset	None	Weekday afternoon clinic (2–4 p.m.) Patients seen within 24 hours of referral to cardiology registrar	73/250	None	None

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TABLE 29 *Results of included RACPC studies*

First author, year, country	*N*	Diagnosis made in clinic				Clinic outcome				Follow-up	Comparison group
		ACS	Non-acute cardiac pain	Non-cardiac chest pain	Other/ unclear	Admitted	Further clinic/other outpatient follow-up	Discharged	Other		
Studies with a comparison group											
el Gaylani, 1997, UK[94]	175	34 (20%)	52 (30%)	88 (51%)		35 (20%)	37 (21%)	101 (58%)	(1%) self-discharged	Response rates to GP questionnaires: 98% at 1 month. For 5 of 34 patients with initial diagnosis of ACS, final diagnosis was non-cardiac chest pain. After 1 month: 3 patients thought to have stable angina at clinic were subsequently admitted with ACS. No patients with non-cardiac chest pain had this diagnosis changed	66 (48%) of 139 patients not admitted would have been admitted to hospital and 13 (9%) would have been sent to A&E
O'Toole, 1995, UK[100]	60	5 (8%)	20 (33%)	30 (50%)	5 (8%)	13 (22%)	Not differentiated between chest pain and palpitations				Results not relevant for this review
Newby, 1998, UK[95]	1001	144 (15%)	274 (27%)	511 (51%)	72 (7%): other cardiac problems	145 (14%)	~360 (36%)	~500 (50%)			GP specified provisional plan for 676 (68%) of patients. Out of 106 patients with ACS, 40 (38%) would have been admitted to hospital. Out of 570 patients who did not have ACS, 142 (25%) would have been admitted

continued

TABLE 29 *Results of included RACPC studies (cont'd)*

First author, year, country	*N*	Diagnosis made in clinic				Clinic outcome				Follow-up	Comparison group
		ACS	Non-acute cardiac pain	Non-cardiac chest pain	Other/ unclear	Admitted	Further clinic/other outpatient follow-up	Discharged	Other		
Studies with no comparison group but follow-up of patients											
Duncan, 1976, UK[96]	616	47 (8%), including 21 patients with possible MI and 26 patients with definite MI	31 (5%)	308 (50%)	230 (37%): 'new or worsening angina' (not clear if non-acute angina or ACS)	Not reported				Response rate of GPs to follow-up letter at 6 months not reported. 1 patient with non-acute cardiac pain had MI. 2 patients thought to have non-cardiac pain subsequently had MI. Of 251 patients with 'new or worsening angina', including 21 with 'possible MI', 39 (16%) had MI within 6 months	
Gandhi, 1995, UK[97]	467		110 (24%)		357 (76%) (not recorded)					Follow-up successful for 107/110. Out of these, 12 (11%) patients with angina died or had MI during median follow-up of 16 months	
Davie, 1998, UK[98]	317	51 (16%)	89 (28%)	136 (43%)	39 (12%) (not reported)	51/278 (18%)	77/278 (28%)	150/278 (54%)		Follow-up on 278 (88%). No patients with label of non-cardiac chest pain had MI or died (but no ascertainment of whether non-respondents were still alive)	

continued

TABLE 29 *Results of included RACPC studies (cont'd)*

First author, year, country	*N*	Diagnosis made in clinic				Clinic outcome				Follow-up	Comparison group
		ACS	Non-acute cardiac pain	Non-cardiac chest pain	Other/ unclear	Admitted	Further clinic/other outpatient follow-up	Discharged	Other		
Studies with no comparison group or follow-up											
Sutcliffe, 2000, UK[101,102,104]	2137	102 (5%)	596 (28%)	1439 (67%)		(2%)	(33%)	(65%)			
Timmis, 1999, UK[103a]	2160	(4%)	(25%)	(69%)		(4%)	(20%)	(75%)			
Norell, 1992, UK[99]	250	79 (32%)	73 (29%)	69 (28%)	29 (12%)	66 (28%)	121 (48%)	63 (25%)			

[a]Only percentages quoted in this study.

This table is published in *International Journal of Clinical Practice* 2002;**56**(1):29–33 (McManus RJ *et al*., A systematic review of the evidence for rapid access chest pain clinics), and is reproduced by kind permission of the *IJCP*.

TABLE 30 *Results of base case run of model*

	No open access	Open access exercise test	RACPC
Capacity required (per year)			
Cardiologist appointments	840	500	340
Chest pain clinics	n/a	n/a	510
Exercise tests (excluding those in chest pain clinics)	450	660	170
MPI scans	260	180	320
Angiography	320	310	330
Extra appointments required over and above capacity to achieve targets[a]			
Cardiologist appointments	1.1	5.0	0.8
Chest pain clinics			35.6
Exercise tests		24.1	
Average time (days) to			
Benign exit	46.7	33.3	26.9
Definitive cardiac diagnosis	107.1	126.1	74.0
Acute event	68.9	79.0	57.7
Acute events per year	**1.72**	**1.62**	**1.32**
Total cost[b]	**£487,000**	**£448,000**	**£523,000**

[a] 'Extras per year' refers to the average annual number of extra appointments needed to satisfy the requirement that all appointments are within a fixed time from booking. Note that merely increasing the standard capacity by these amounts would reduce the number of extra appointments needed, but not remove the need for them altogether.
[b] Based on resources used, rather than capacity required.

The capacity requirements are greatest to run the RACPC service, and this is reflected in the highest resource utilisation for this service: £523,000 per annum for a service to a catchment population of 350,000, which is 8% higher than the costs of running a no open access service. The extra costs are not generated by extra appointments with cardiologists (850 capacity required in the chest pain clinic model as compared with 840 without open access), but by extra investigations (principally exercise tests and MPI scans). Open access exercise tests are associated with 8% lower costs than a no open access service as a result of reduced capacity requirements for outpatient cardiology.

Sensitivity analyses

The results of the sensitivity analyses are shown in *Tables 31–39*. The sensitivity analyses had no overall effect on the rank ordering of the costs of the different models of care, so the description below focuses on time to diagnosis and number of coronary events while awaiting diagnosis for each of the different parameters. The effect of open access exercise testing on average time to definitive cardiac diagnosis relative to the other models appeared worse in the base case scenario that in all the sensitivity analyses. This suggests that the play of chance had a significant effect on this particular result.

Waiting times

As waiting times for further investigation lengthened, the advantages of RACPCs lessened (*Table 31*). Thus, if the maximum waiting time for angiography was set for 6 months, then RACPCs were no longer associated with earlier definitive cardiac diagnosis. Indeed, with longer waiting times, the open access exercise test model was associated with shorter times to definitive diagnosis and fewer coronary events while awaiting diagnosis compared with the other models of care.

Patient characteristics

Changing the incidence of chest pain in the population or changing the proportion of people with chest pain who have CHD made no difference to the rank ordering of the models of care (*Tables 32* and *33*). The benefits of RACPCs tended to increase relative to other models of care as the proportion of patients with CHD in the population rose.

TABLE 31 *Sensitivity analysis of queuing discipline*

Waiting times[a]		No OA	OA exercise ECG	RACPC
Average time to benign exit				
Low	Number of days	42.3	22.8	22.7
	Change from no OA service (%)		–20 (46)	–20 (46)
Base	Number of days	46.7	33.3	26.9
	Change from no OA service (%)		–13 (29)	–20 (42)
High	Number of days	47.5	24.6	39.8
	Change from no OA service (%)		–23 (48)	–8 (16)
Average time to definitive cardiac diagnosis				
Low	Number of days	86.4	84.4	48.7
	Change from no OA service (%)		–2 (2)	–38 (44)
Base	Number of days	107.1	126.1	74.0
	Change from no OA service (%)		19 (18)	–33 (31)
High	Number of days	106.4	96.8	110.4
	Change from no OA service (%)		–10 (9)	4 (4)
Acute events while awaiting diagnosis (per year)				
Low	Number of events	1.54	1.35	1.13
	Change from no OA service (%)		–0.2 (12)	–0.4 (26)
Base	Number of events	1.72	1.62	1.32
	Change from no OA service (%)		–0.1 (6)	–0.4 (23)
High	Number of events	1.63	1.53	1.69
	Change from no OA service (%)		–0.1 (6)	0.1 (4)
Total cost per year				
Low	£000	488	449	524
	Change from no OA service (%)		–39 (8)	36 (7)
Base	£000	487	448	523
	Change from no OA service (%)		–39 (8)	36 (7)
High	£000	486	448	526
	Change from no OA service (%)		–38 (8)	40 (8)

[a] Waiting times: low = appointment capacities are set for 90% in under 2 weeks, except for cardiology outpatient appointments, which are set at 90% within 13 weeks; base = appointment capacities set for 90% in under 2 weeks for OA services; 6 weeks for other exercise tests; 13 weeks for cardiology outpatients, MPI scan and angiography; high = same as base case except that appointment capacities are set for 90% within 10 weeks for exercise test (not OA) and 26 weeks for MPI scan and angiography.

OA, open access.

GP referral threshold

Changing the proportion of people with chest pain who are referred on for further investigation by the GP did not affect the rank ordering of the models of care, although the advantages of chest pain clinics appeared greater if the referral threshold was high (i.e. the GP referred fewer patients with chest pain) (*Table 34*).

Performance of diagnostic tests

This sensitivity analysis was performed in two ways. First, the overall accuracy of exercise ECG was varied, that is, both sensitivity and specificity were changed in the same direction (*Table 35*). Second, the 'cutoff' for a positive exercise ECG was changed, by varying the sensitivity and specificity in opposite directions (*Table 36*). For example, if the definition of a positive exercise test was changed from 1 to 2 mm ST depression, this would raise specificity but lower sensitivity. Varying the accuracy of exercise ECG did not change ordering of the different models of care, but the difference between the rapid access models and the outpatient cardiology model was greater the better the test. No clear pattern emerged if the 'cutoff' for a positive test was changed. The RACPC model generally achieved the best results, although time to a correct non-cardiac diagnosis was lower for the open access exercise test model when the sensitivity of the test was high and the specificity low.

TABLE 32 *Sensitivity analysis of incidence of chest pain*

Incidence of chest pain (per 1000)		No OA	OA exercise ECG		RACPC	
Average time to benign exit						
2.4	Number of days	44.7	23.4		30.9	
	Change from no OA service (%)		–21	(48)	–14	(31)
4.8	Number of days	46.7	33.3		26.9	
	Change from no OA service (%)		–13	(29)	–20	(42)
9.6	Number of days	38.1	22.3		27.3	
	Change from no OA service (%)		–16	(42)	–11	(28)
Average time to definitive cardiac diagnosis						
2.4	Number of days	98.1	91.2		65.3	
	Change from no OA service (%)		–7	(7)	–33	(33)
4.8	Number of days	107.1	126.1		74.0	
	Change from no OA service (%)		19	(18)	–33	(31)
9.6	Number of days	95.3	85.8		73.7	
	Change from no OA service (%)		–10	(10)	–22	(23)
Acute events while awaiting diagnosis (per year)						
2.4	Number of events	0.82	0.69		0.61	
	Change from no OA service (%)		–0.1	(16)	–0.2	(26)
4.8	Number of events	1.72	1.62		1.32	
	Change from no OA service (%)		–0.1	(6)	–0.4	(23)
9.6	Number of events	2.99	2.57		2.50	
	Change from no OA service (%)		–0.4	(14)	–0.5	(16)
Total cost per year						
2.4	£000	243	221		261	
	Change from no OA service (%)		–22	(9)	18	(7)
4.8	£000	487	448		523	
	Change from no OA service (%)		–39	(8)	36	(7)
9.6	£000	974	894		1049	
	Change from no OA service (%)		–80	(8)	75	(8)

Accuracy of initial cardiologist diagnosis

Varying the accuracy of the initial cardiologist diagnosis did not change the rank ordering of the models, except that if cardiologist accuracy was low, then open access exercise testing was at least as efficient as rapid access clinics in reaching correct non-cardiac diagnoses (*Table 37*). The more accurate the cardiologist, the better the rapid access clinics performed and the worse the open access exercise testing performed relative to the other models.

Risks of acute events

Varying the likelihood of coronary events during angiography or at any other time did not have any major effect on the rank orderings (*Tables 38* and *39*).

Summary of chronic model results

The general conclusion that an RACPC service is associated with faster definitive diagnoses of both cardiac and non-cardiac chest pain and fewer cardiac events while awaiting definitive diagnosis is robust unless waiting times for angiography are long (maximum wait set at 6 months), in which case open access exercise testing appears the most efficient model. The RACPC service is the most expensive of the three models, and open access exercise testing the cheapest. Open access exercise testing appears to offer some advantages to routine cardiology outpatients in that it is associated with shorter time to definitive non-cardiac diagnosis. The effect of open access exercise testing on time to definitive cardiac diagnosis is unclear: the base case analysis suggests that it is associated with longer time to diagnosis, but this was not supported by the sensitivity analyses.

TABLE 33 *Sensitivity analysis of prevalence of CHD*

Prevalence of CHD[a]		No OA	OA exercise ECG	RACPC
Average time to benign exit				
20%	Number of days	43.1	25.0	25.7
	Change from no OA service (%)		–18 (42)	–17 (40)
26%	Number of days	46.7	33.3	26.9
	Change from no OA service (%)		–13 (29)	–20 (42)
30%	Number of days	40.5	27.2	28.0
	Change from no OA service (%)		–13 (33)	–12 (31)
Average time to definitive cardiac diagnosis				
20%	Number of days	92.6	96.9	66.7
	Change from no OA service (%)		4 (5)	–26 (28)
26%	Number of days	107.1	126.1	74.0
	Change from no OA service (%)		19 (18)	–33 (31)
30%	Number of days	112.2	113.8	71.2
	Change from no OA service (%)		2 (1)	–41 (37)
Acute events while awaiting diagnosis (per year)				
20%	Number of events	1.32	1.16	1.00
	Change from no OA service (%)		–0.2 (12)	–0.3 (24)
26%	Number of events	1.72	1.62	1.32
	Change from no OA service (%)		–0.1 (6)	–0.4 (23)
30%	Number of events	1.83	1.60	1.42
	Change from no OA service (%)		–0.2 (13)	–0.4 (23)
Total cost per year				
20%	£000	420	377	460
	Change from no OA service (%)		–43 (10)	40 (10)
26%	£000	487	448	523
	Change from no OA service (%)		–39 (8)	36 (7)
30%	£000	528	490	564
	Change from no OA service (%)		–38 (7)	36 (7)

[a] 20% prevalence of CHD in patients presenting with chest pain to the GP leads to 24% prevalence at cardiology outpatients and 32% prevalence at chest pain clinic. 30% prevalence of CHD leads to 35% prevalence at cardiology outpatients and 44% prevalence at chest pain clinic.

TABLE 34 *Sensitivity analysis of GP referral threshold*

Proportion referred by GP		No OA	OA exercise ECG		RACPC	
Average time to benign exit						
100%	Number of days	53.7	34.7		40.6	
	Change from no OA service (%)		–19	(35)	–13	(24)
80%	Number of days	46.7	33.3		26.9	
	Change from no OA service (%)		–13	(29)	–20	(42)
60%	Number of days	32.5	16.0		14.8	
	Change from no OA service (%)		–17	(51)	–18	(55)
Average time to definitive cardiac diagnosis						
100%	Number of days	89.8	95.8		61.4	
	Change from no OA service (%)		6	(7)	–28	(32)
80%	Number of days	107.1	126.1		74.0	
	Change from no OA service (%)		19	(18)	–33	(31)
60%	Number of days	121.5	100.9		69.0	
	Change from no OA service (%)		–21	(17)	–52	(43)
Acute events while awaiting diagnosis (per year)						
100%	Number of events	1.69	1.50		1.39	
	Change from no OA service (%)		–0.2	(11)	–0.3	(18)
80%	Number of events	1.72	1.62		1.32	
	Change from no OA service (%)		–0.1	(6)	–0.4	(23)
60%	Number of events	1.64	1.26		1.07	
	Change from no OA service (%)		–0.4	(23)	–0.6	(35)
Total cost per year						
100%	£000	536	483		586	
	Change from no OA service (%)		–53	(10)	50	(9)
80%	£000	487	448		523	
	Change from no OA service (%)		–39	(8)	36	(7)
60%	£000	440	414		467	
	Change from no OA service (%)		–26	(6)	27	(6)

TABLE 35 *Sensitivity analysis of performance of diagnostic tests: changing test performance*

Sensitivity/specificity		No OA	OA exercise ECG	RACPC
Average time to benign exit				
73%/80%	Number of days	64.8	29.5	26.7
	Change from no OA service (%)		–35 (54)	–38 (59)
71%/77%	Number of days	46.7	33.3	26.9
	Change from no OA service (%)		–13 (29)	–20 (42)
68%/75%	Number of days	31.6	26.6	26.2
	Change from no OA service (%)		–5 (16)	–5 (17)
Average time to definitive cardiac diagnosis				
73%/80%	Number of days	129.0	129.2	76.8
	Change from no OA service (%)		0 (0)	–52 (40)
71%/77%	Number of days	107.1	126.1	74.0
	Change from no OA service (%)		19 (18)	–33 (31)
68%/75%	Number of days	88.9	102.7	64.7
	Change from no OA service (%)		14 (16)	–24 (27)
Acute events while awaiting diagnosis (per year)				
73%/80%	Number of events	2.13	1.73	1.31
	Change from no OA service (%)		–0.4 (19)	–0.8 (39)
71%/77%	Number of events	1.72	1.62	1.32
	Change from no OA service (%)		–0.1 (6)	–0.4 (23)
68%/75%	Number of events	1.42	1.37	1.20
	Change from no OA service (%)		0.0 (4)	–0.2 (16)
Total cost per year				
73%/80%	£000	482	442	523
	Change from no OA service (%)		–40 (8)	41 (9)
71%/77%	£000	487	448	523
	Change from no OA service (%)		–39 (8)	36 (7)
68%/75%	£000	487	449	526
	Change from no OA service (%)		–38 (8)	39 (8)

TABLE 36 *Sensitivity analysis of changing cutoff point of test: changing 'cutoff point' for positive*

Sensitivity/Specificity		No OA	OA exercise ECG	RACPC
Average time to benign exit				
65%/82%	Number of days	44.9	26.8	26.6
	Change from no OA service (%)		–18 (40)	–18 (41)
71%/77%	Number of days	46.7	33.3	26.9
	Change from no OA service (%)		–13 (29)	–20 (42)
76%/72%	Number of days	45.9	26.6	32.2
	Change from no OA service (%)		–19 (42)	–14 (30)
Average time to definitive cardiac diagnosis				
65%/82%	Number of days	99.0	113.3	72.8
	Change from no OA service (%)		14 (14)	–26 (27)
71%/77%	Number of days	107.1	126.1	74.0
	Change from no OA service (%)		19 (18)	–33 (31)
76%/72%	Number of days	113.7	109.4	75.2
	Change from no OA service (%)		–4 (4)	–38 (34)
Acute events while awaiting diagnosis (per year)				
65%/82%	Number of events	1.57	1.55	1.20
	Change from no OA service (%)		0.0 (1)	–0.4 (24)
71%/77%	Number of events	1.72	1.62	1.32
	Change from no OA service (%)		–0.1 (6)	–0.4 (23)
76%/72%	Number of events	1.65	1.46	1.38
	Change from no OA service (%)		–0.2 (11)	–0.3 (16)
Total cost per year				
65%/82%	£000	482	436	521
	Change from no OA service (%)		–46 (10)	39 (8)
71%/77%	£000	487	448	523
	Change from no OA service (%)		–39 (8)	36 (7)
76%/72%	£000	490	458	529
	Change from no OA service (%)		–32 (7)	39 (8)

TABLE 37 *Sensitivity analysis of accuracy of initial cardiologist diagnosis*

Misdiagnosis rate[a]		No OA	OA exercise ECG	RACPC
Average time to benign exit				
Low	Number of days	34.4	26.2	30.6
	Change from no OA service (%)		–8 (24)	–4 (11)
Base	Number of days	46.7	33.3	26.9
	Change from no OA service (%)		–13 (29)	–20 (42)
High	Number of days	32.7	31.0	29.1
	Change from no OA service (%)		–2 (5)	–4 (11)
Average time to definitive cardiac diagnosis				
Low	Number of days	83.5	100.0	69.5
	Change from no OA service (%)		17 (20)	–14 (17)
Base	Number of days	107.1	126.1	74.0
	Change from no OA service (%)		19 (18)	–33 (31)
High	Number of days	81.3	119.5	67.0
	Change from no OA service (%)		38 (47)	–14 (18)
Acute events while awaiting diagnosis (per year)				
Low	Number of events	1.23	1.37	1.40
	Change from no OA service (%)		0.1 (11)	0.2 (14)
Base	Number of events	1.72	1.62	1.32
	Change from no OA service (%)		–0.1 (6)	–0.4 (23)
High	Number of events	1.31	1.68	1.20
	Change from no OA service (%)		0.4 (28)	–0.1 (8)
Total cost per year				
Low	£000	470	435	509
	Change from no OA service (%)		–35 (7)	39 (8)
Base	£000	487	448	523
	Change from no OA service (%)		–39 (8)	36 (7)
High	£000	504	458	545
	Change from no OA service (%)		–46 (9)	41 (8)

[a] See *Table 31* for definitions of low, base and high.

TABLE 38 *Sensitivity analysis of risks of acute events during angiography*

During angiography		No OA	OA exercise ECG	RACPC
Average time to benign exit				
1 in 1000	Number of days	47.8	30.4	32.1
	Change from no OA service (%)		–17 (36)	–16 (33)
1 in 700	Number of days	46.7	33.3	26.9
	Change from no OA service (%)		–13 (29)	–20 (42)
1 in 350	Number of days	29.4	26.2	25.6
	Change from no OA service (%)		–3 (11)	–4 (13)
Average time to definitive cardiac diagnosis				
1 in 1000	Number of days	108.0	115.5	71.9
	Change from no OA service (%)		7 (7)	–36 (33)
1 in 700	Number of days	107.1	126.1	74.0
	Change from no OA service (%)		19 (18)	–33 (31)
1 in 350	Number of days	84.3	100.7	62.2
	Change from no OA service (%)		16 (19)	–22 (26)
Acute events while awaiting diagnosis (per year)				
1 in 1000	Number of events	1.63	1.56	1.21
	Change from no OA service (%)		–0.1 (4)	–0.4 (26)
1 in 700	Number of events	1.72	1.62	1.32
	Change from no OA service (%)		–0.1 (6)	–0.4 (23)
1 in 350	Number of events	1.73	1.81	1.59
	Change from no OA service (%)		0.1 (4)	–0.1 (8)
Total cost per year				
1 in 1000	£000	487	447	524
	Change from no OA service (%)		–40 (8)	37 (8)
1 in 700	£000	487	448	523
	Change from no OA service (%)		–39 (8)	36 (7)
1 in 350	£000	486	448	526
	Change from no OA service (%)		–38 (8)	40 (8)

TABLE 39 *Sensitivity analysis of risk of acute cardiac events at any time*

Acute event risk at any time[a]		No OA	OA exercise ECG	RACPC
Average time to benign exit				
Low	Number of days	39.6	24.6	26.9
	Change from no OA service (%)		–15 (38)	–13 (32)
Base	Number of days	46.7	33.3	26.9
	Change from no OA service (%)		–13 (29)	–20 (42)
High	Number of days	37.4	23.5	25.6
	Change from no OA service (%)		–14 (37)	–12 (31)
Average time to definitive cardiac diagnosis				
Low	Number of days	95.0	96.1	63.2
	Change from no OA service (%)		1 (1)	–32 (33)
Base	Number of days	107.1	126.1	74.0
	Change from no OA service (%)		19 (18)	–33 (31)
High	Number of days	88.9	92.6	60.3
	Change from no OA service (%)		4 (4)	–29 (32)
Acute events while awaiting diagnosis (per year)				
Low	Number of events	1.28	1.12	0.92
	Change from no OA service (%)		–0.2 (13)	–0.4 (29)
Base	Number of events	1.72	1.62	1.32
	Change from no OA service (%)		–0.1 (6)	–0.4 (23)
High	Number of events	1.52	1.44	1.18
	Change from no OA service (%)		–0.1 (5)	–0.3 (23)
Total cost per year				
Low	£000	486	450	524
	Change from no OA service (%)		–36 (7)	38 (8)
Base	£000	487	448	523
	Change from no OA service (%)		–39 (8)	36 (7)
High	£000	485	448	524
	Change from no OA service (%)		–37 (8)	39 (8)

[a] See *Table 31* for definitions of low, base and high.

Chapter 5
Discussion

The evaluation of suspected ACS

National guidance is that patients with acute chest pain in whom an ACS is suspected should call for an ambulance. The NSF sets a standard of paramedic attendance within 8 minutes of a call to the ambulance service from a patient with chest pain with the clear intention of speeding time to assessment in a setting where thrombolysis is available.[3] GPs asked to see patients with symptoms suggestive of ACS are advised to call an ambulance before attending the patient. Therefore, the role of the GP is limited in the evaluation of suspected ACS, and is likely to be restricted to patients attending the surgery with atypical symptoms. Nevertheless, it remains relevant to consider the diagnostic value of clinical features and diagnostic tests that are available in primary care. From the GP perspective, clinical features or diagnostic test results with high sensitivity (low LR–) will be particularly useful in a patient in whom the diagnosis is unlikely, since this will enable the patient to be managed in primary care. From the perspective of other primary care services, such as ambulance services and A&E, tests with high specificity (high LR+) are also of value, since these will enable thrombolytic therapy to be commenced if a diagnosis of MI is confirmed. Therefore, systematic reviews were carried out assessing the diagnostic value of the clinical features of chest pain and the resting ECG. Some studies also looked at clinical diagnosis incorporating combinations of clinical features and ECG results, and these have also been reviewed as 'black box' studies. This label was chosen since it was not clear in most of these studies how the various inputs (ECGs results, clinical features, etc.) were assimilated to reach a diagnosis. We excluded papers using computerised decision support systems to aid in the MI diagnostic decision, since these were felt unlikely to be applicable to community settings.

Cardiac troponins, a topic outwith this review, have emerged as a diagnostic test of considerable value in the triaging of patients in A&E, with a sensitivity of over 90% at 8 hours or more after onset of pain, and a specificity of over 80%.[29] The potential impact of POCT for troponins in A&E was assessed using a simulation model.

A further issue in the primary care management of suspected ACS is whether or not pre-hospital thrombolysis should be administered. This was also considered in the simulation model, which incorporated the results of the systematic review of ECG to assess the utility of pre-hospital thrombolysis given on the basis of in-ambulance telemetry ECG. Results from Scotland show that in more rural settings with potentially longer 'call to needle' times, thrombolysis can be effectively given in the community with reductions in 1-year mortality.[105] Furthermore, results from GREAT with early thrombolysis have shown a lack of benefit from thrombolysis in those with clinical symptoms of MI but not ST elevation. This perhaps reflects the potential inaccuracy in the diagnosis of MI using clinical features alone.[106]

Quality of the studies

In general, the studies were of reasonable quality (*Tables 41, 43,* and *45*), although in some studies there was important spectrum bias in that the population was restricted to patients admitted to hospital. This will have resulted in an artificially raised sensitivity (low LR–).

Clinical features of acute chest pain

No sign or symptom exhibited by patients presenting with possible acute MI proved effective enough alone to rule in or out diagnosis of MI.[22] Interestingly, the classical description of central crushing chest pain was not found to be particularly discriminative in isolation (LR 1.44), whereas chest pain radiating to the right side (not particularly common in practice) proved to have the best LRs of any symptom (LR+ 2.59). The most effective sign was the presence of a third heart sound which achieved an LR+ for MI of 3.21, but requires that the physician attending the patient, possibly in their own home or in the street, has the clinical acumen to detect a third heart sound. Pleuritic chest pain proved to be most effective at ruling out MI (LR+ 0.19). However, both GPs and A&E doctors are likely to adopt high-sensitivity, low-specificity strategies when making a decision to admit a patient with chest pain and so unless a sign or symptom (or its absence) has a very low LR (certainly less than 0.1) then it will not be particularly useful. Since this review was completed, a further study of the value

of clinical features in the diagnosis of acute undifferentiated chest pain in a chest pain unit has been published.[19] The overall prevalence of ACS was 9%, so this reflects the lower risk population that the GP may still see. This study also found that no feature had a sufficiently low LR to exclude ACS with any confidence.

Resting ECG in acute chest pain

ST elevation was by far the most effective single ECG feature at discriminating patients with MI (LR+ 13.1) and a normal ECG was fairly effective at ruling out MI (LR– 0.14). Q waves and ST depression also had value, particularly when compared with the clinical factors discussed above. In practical terms, the immediate decision to be made in MI is whether or not to administer thrombolysis and the evidence in this case is in favour of its use in the setting of ST elevation and new onset left bundle branch block.[27] The presence of Q waves and/or ST depression, although indicative of CHD, should not influence a thrombolysis decision. Furthermore, with respect to the timing of appearance of ECG abnormalities, Q waves are a later phenomenon than ST changes.[107]

The effectiveness of ECG changes as a diagnostic tool in the community is likely to be considerably influenced by the experience and ability of GPs to detect accurately a given change. A postal survey of 140 GPs found that their ability to spot specific abnormalities ranged from 9% (true acute posterior MI) to 95% (ventricular extrasystole); 80% were able to identify an acute anterior MI and 67% a normal ECG. Recent qualification, possession of Member of the Royal College of General Practitioners or Royal College of Physicians (MRCP/MRCGP) qualification and frequency of usage were associated with better performance.[108]

McCrea and Saltissi showed 106 GPs a series of six ECGs at an educational meeting and found that 82% were able to identify correctly a normal tracing. Depending on the site of infarction, between 33 and 61% were able to identify correctly an acute MI.[109]

Four studies included patients in a true community setting, either in primary care or in unselected patients calling for a paramedic.[11,44,79,110] All the other studies included those attending A&E or admitted to a ward (often cardiac care unit). It is therefore unclear whether the results achieved in the secondary care settings are reproducible in the spectrum of patients seen in primary care. In the unselected setting of primary care, it is likely that the performance characteristics of any test are likely to be worse owing to the dilution of true positive cases with large numbers of patients without CHD.

As with clinical signs, the relevance of these findings to an urban primary care physician may well be slight owing to the likelihood that a 'scoop and run' policy will be undertaken by the paramedics immediately removing the patient to hospital rather than 'stay and play' where additional tests and treatment are performed before transit. The potential effect of pre-hospital testing is discussed further in the accompanying modelling.

The findings from this review are broadly in line with those of Panju and colleagues, although for most of the ECG features this review included a larger number of studies.[111] Panju and colleagues differentiated between new and all appearances of ECG features, finding that in particular for ST elevation that new changes were considerably more predictive of acute MI than 'any' change. This review has not attempted to make this distinction as it is unlikely in the majority of cases in the UK that an old ECG will be available for comparison in a suitably short timescale. The exception to this would be for patients who had had a previous ECG being attended by their own GP in working hours.

ECG in combination with clinical features: black box studies

The results from the so-called 'black box' papers, where real-time decisions based on combinations of information initially available to physicians were treated as diagnostic test, showed wide variation in ability to diagnose MI. The most effective decisions were those including the use of an ECG which fits with the results from the individual features where ST elevation was considerably more discriminating than any of the historical or examination features. Interestingly, however, the best results were obtained with interpretation of an ECG alone (LR+ 52 for all studies and LR+ 145 for the highest quality study[57]). This may be a reflection of the decision being made: in the highest ranked quality study, the decision was whether or not a patient would receive thrombolysis. Physicians in this case achieved very high specificity with lower sensitivity, as might be expected in a situation where one is trying to ensure that only eligible patients receive the treatment. When this is compared with the results gained from the decision whether or not to admit

a patient with query MI then the LR+ were much lower (2.55–3.01) and specificity was sacrificed for increased sensitivity: in this case physicians tend to avoid sending home a person who is having an MI at the expense of admitting a number of patients unnecessarily. Hence, the LR– was low (0.08–0.11), which raises the question of whether a GP would be able to exclude an MI on the basis of interpreting the ECG in the light of the clinical features. However, these studies were done in A&E departments and so are not directly applicable to a general practice setting. In particular, an A&E physician would be able to assess the patient over a longer period of time than would be available to a GP.

One paper examined the use of history plus signs alone (i.e. without an ECG) in diagnosing MI and found that they were poor at making a diagnosis.[82] This is in keeping with the results from the individual clinical features, which were similarly unimpressive. When overall A&E diagnoses of MI using all available clinical and investigative data are examined, the LR+ of 4.48 is indicative of reasonable predictive value rising to almost 10 in the one better quality paper.[57] In this case, complicated combinations of evidence are being assimilated by A&E physicians. It is likely that the decisions made by primary care physicians or other community-based staff (e.g. paramedics) will be less effective both owing to variations in training in the ability to recognise MI and also with respect to the difference in spectrum seen in the community as opposed to more selected populations.

Models of care for the evaluation of suspected ACS

POCT for TnT are a cost-effective addition to the management of patients with suspected MI, increasing lives saved and decreasing costs. This is particularly the case when hospital-based thrombolysis is used, as a greater proportion of patients are available for assessment.

Pre-hospital thrombolysis has only a modest effect on survival compared with prompt hospital treatment, and is unlikely to be cost-effective, unless hospital treatment is particularly delayed. The use of a probabilistic model fully expresses our uncertainty as to the cost-effectiveness of the four strategies considered. The point estimates suggest that the two strategies using POCT are dominant, with an ICER of £65,000 per patient surviving at 28 days moving from hospital to pre-hospital thrombolysis. The second-order simulation shows considerable uncertainty underlying this statement. The 95% CI for the ICER is very wide, and includes estimates that would be considered highly cost-effective in addition to those that would not. Since the precise threshold at which the intervention could be considered cost-effective is a matter of judgement, it is best displayed as a cost-effectiveness acceptability curve. This shows the trade-off between increasing certainty that the intervention would be cost-effective, and the maximum acceptable cost (*Figure 14*). The 'best estimate' is provided by the 50% probability cost-effective at a willingness to pay of £65,000. The 95% CI goes from ~£31,000 to over £200,000. In addition, *Figure 16* shows how this uncertainty and maximum cost vary according to key assumptions in the model (first-order uncertainty). Hence, with the lowest estimates of cost of telemetry (£50 per patient) and with long delays prior to hospital assessment (3 hours), pre-hospital thrombolysis has a high likelihood of being cost-effective: there is a 50% chance that the ICER will be no higher than £10 000 per life saved. Conversely, if the potential for hospital assessment is rapid (15 minutes), and the cost of telemetry is high, then there is a 50% chance that the ICER will be greater than £160,000 per life saved.

The model does not consider effectiveness in terms of quality-adjusted life-years (QALYs): to do so would require an estimate of life expectancy and quality of life (QoL) for all the potential outcomes, and their variance with the time to thrombolysis. These data are not available. It is therefore not directly comparable with any particular cost per QALY benchmark, but one might expect life expectancy and QoL after an MI to be reduced, and possibly improved by early thrombolysis. Further data in this area could be used to extend the model. If we accept £100,000 per life saved and a decision uncertainty threshold of 80%, it seems likely that pre-hospital thrombolysis could only be cost-effective if the likely delay to hospital was more than 30 minutes and the additional cost of telemetry less than £200. Hence in urban areas, and if expensive capital equipment such as defibrillators incorporating 12-lead ECGs (costing £10,000) were used, pre-hospital therapy is unlikely to be cost-effective and effort would be better spent in rapid assessment on admission to the A&E unit. It has been estimated that around 10% of the UK population live in rural areas more than 30 minutes from the nearest hospital.[106] This was an entry criterion for the GREAT pre-hospital thrombolysis trial which showed benefit from pre-hospital thrombolysis given by GPs as opposed to

paramedics in terms of long-term survival at a marginal cost per life saved at 4 years of £3890 (1990 – 42,820).[112] Unfortunately, in many rural areas, such as Scotland and Wales, satellite transmission would be needed for telemetry, and training of ambulance personnel to read infarct patterns on an ECG might be less costly.

The model does not consider possible advantages of early hospital admission, assuming no difference in effectiveness of defibrillation in hospital and by paramedics, although the potential to treat heartblock and other less common arrhythmias more effectively might favour early hospital admission. There is at present insufficient evidence to favour a national policy of pre-hospital thrombolysis, although particular local circumstances that either prolong hospital transport times or reduce costs may allow local developments.

The evaluation of suspected exertional angina

The diagnosis of suspected angina is one that is made predominately from the clinical history.[113] In this review, the accuracy of two tests was assessed through systematic review of the evidence: the resting ECG and the exercise ECG. The former is usually available in primary care, and the latter is sometimes available through open access services. This review focused on the diagnostic rather than the prognostic value of the exercise ECG. The review did not consider other investigations, such as stress echocardiography or MPI, since these tests are not available in the primary care setting.

Quality of the studies

There were two serious problems identified with the quality of these studies: spectrum bias and verification bias. There is a risk of spectrum bias if the population in whom the study was carried out is different from the patients in whom one would be interested in carrying out the diagnostic test. Verification bias occurs if the result of the diagnostic test being evaluated influences whether or not the gold standard test is applied.

The issue of verification bias in this case is related to that of spectrum bias. Very few of the studies examined subjected all potential subjects to the same reference standard, because of the potential morbidity associated with angiography. In fact, most of the studies required angiography to be performed for the patient to be eligible. Thus, many patients in the population of interest (i.e. people with chest pain possibly cardiac in origin) were excluded, because no angiography was performed. It is difficult to tell in most of the studies to what extent the decision to perform angiography was influenced by the result of the exercise ECG. One group quantified the likely effect of this verification bias by the use of dual reference standards by computing the likelihood of CHD in those patients in the study population who did not undergo angiography.[114,115] They showed, as might be expected, that selective use of angiography as a reference standard is likely to result in an artificially reduced specificity. This is because patients with a low pre-test probability and a negative exercise test (probable true negatives) are likely to be under-represented in a group selected for angiography. Conversely, selective use of angiography is likely to lead to inflated sensitivity owing to the likely higher pre-test probability of those selected. The few studies which required all subjects to undergo angiography were likely to include patients with a greater pre-test probability of coronary artery disease, and therefore reflect significant spectrum bias. This spectrum bias is reflected in the high prevalence of CHD among the study populations ranging from 24 to 88%,[116,117] median 59%, as opposed to evidence from primary care that around 26% of patients with suspected CHD turn out to have this diagnosis.[33]

Resting ECG

The results of the review suggest that a resting ECG is of only limited value in the evaluation of suspected angina. Q waves were the only readily recognised single ECG feature with an LR+ of 2.56. One study examined the use of QRS notching and found it to be useful; however, it seems unlikely that most GPs would recognise this without further training given their known difficulties in ECG reading.[108,109] GPs are reasonably effective at recognising a completely normal ECG (86% in McCrea and Saltissi's study[109]), but the results suggest that the presence or absence of any abnormality was not a good test (LR+ 1.53; LR– 0.74). For example, in one series, 20% of patients with a normal ECG actually had a final diagnosis of unstable angina.[99]

Nevertheless, given the ease of access and relatively low cost of an ECG, it is reasonable to recommend that GPs continue to perform them. Most GPs have their own machines, and those who do not are likely to have arrangements with their local hospital for performing ECGs. One role that they have is to identify previously unrecognised MI

through the identification of Q waves.[118] Also, they will be required before an exercise test is performed.

Exercise ECG

ST depression, the most widely used marker for CHD (71/111 studies), performed only moderately well in the studies reviewed with an LR+ of 2.79. This improved to LR+ 3.85 when a 2-mm cutoff was used. Similar results were achieved when a steep ST slope was used. As with previous reports, the studies showed considerably less ability to diagnose CHD in women compared with men. Our results for LR+ [1.96 (95% CI 1.72, 2.24)] were similar if a little lower than the LR+ found by Kwok and colleagues in their review of exercise testing in women [2.25 (95% CI 1.84, 2.66)].[119] The small difference may reflect our inclusion criteria resulting in a different selection of papers with a reduction in past history of CHD in our set. Normal exercise tests were found to have poor discriminating power in excluding CHD, with a relatively high LR– (0.44 for 1 mm ST depression).

LRs of this order of magnitude are most likely to be of value in the assessment of patients with an intermediate probability of having CHD.[22] Thus, if the pre-test probability of a patient having CHD is 50%, an exercise ECG showing 1 mm of ST depression will increase this probability to 75% – a level at which it would be appropriate to proceed to angiography. Conversely, a negative test would reduce the probability of CHD to around 25%, in which case more conservative management is justified. However, in patients with a higher pre-test probability of CHD with a classical history of chest pain on exertion, a normal exercise test will not significantly reduce the likelihood that they suffer from CHD.

It would have been interesting to explore the effects of patient characteristics other than gender on the accuracy of the exercise ECG as a diagnostic test such as age and the nature of the chest pain. However, since this was not an individual patient data meta-analysis, we were limited to the sub-groups that were reported in the included papers.

These results of the systematic review emphasise that the exercise ECG, although it contributes to the diagnosis of CHD, is a relatively weak diagnostic test, and should not be interpreted in isolation from the clinical history. Although a number of different ways of analysing the exercise ECG were identified in the systematic review, none of these appeared to add significant value to the diagnostic utility of the investigation. Problems with spectrum bias and verification bias cast doubt on the applicability of the studies to a primary care setting, and it is likely that the 'true' sensitivity of the test will be lower and the specificity higher, that is, in primary care, the test will have a higher LR+ (better) and a higher LR– (worse). Furthermore, given that our search strategy only identified published studies, there is the possibility that, through publication bias, the pooled result overestimates the diagnostic accuracy of exercise ECG. However, little is known about the manner in which publication bias acts in studies of diagnostic accuracy, or how it can be investigated.

Models of care for suspected exertional angina

Two components of this review looked at models of care for the evaluation of suspected exertional angina. A systematic review of the evidence for RACPCs was conducted and a simulation exercise was performed to predict the impact of the implementation of a chest pain clinic service with a 2-week maximum wait (in accordance with the NSF targets) or an open access exercise test service as compared with traditional care (the routine cardiology outpatients).

RACPCs

The review identified nine studies concerning the evaluation of RACPCs in the management of patients presenting in primary care. Criteria for attendance at one of these clinics varied across the studies, resulting in a wide variation in investigation, diagnosis and subsequent outcome. No studies were randomised or had a true comparison group. The studies were essentially descriptive rather than evaluative in nature. Therefore, it is not possible to draw any conclusions as to the effectiveness or otherwise of RACPCs. Four theoretical benefits of RACPCs were examined: fewer unnecessary hospital admissions for chest pain; better recognition of patients with ACS; earlier specialist assessment of patients with stable angina; and more rapid and accurate identification of patients with non-cardiac chest pain.

Limited data, from statements of physician intent, suggest that these clinics might reduce unnecessary admissions and identify patients with ACSs who would otherwise not have been admitted. However, comparison with a hypothetical statement of intent to admit or not admit is prone to bias. Retrospective data collected by el Gaylani and colleagues as to

whether GPs would have admitted patients if a chest pain clinic was not available may have been influenced by what actually happened to the patient.[94] The prospective approach by Newby and colleagues is a stronger design, but data were only obtained for 68% of referrals.[95] In both cases, if the rapid access clinics were popular with GPs then their hypothetical responses may have been influenced by a desire to demonstrate the advantage of the service. A study published since the review was completed also suggested that an RACPC led to fewer admissions but, again, this was based on hypothetical statements of intent by the GP, and so is subject to the same biases.[120]

The potential advantages of early assessment of patients with exertional angina are twofold: earlier initiation of optimal medical therapy and earlier access to revascularisation where appropriate. However, without comparative data on what treatment patients would otherwise have received, and how long patients would otherwise have waited for further investigation such as angiography, and further intervention, such as percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG), it is difficult to quantify whether the earlier assessment in chest pain clinics led to faster intervention, be it pharmacological, radiological or surgical. Five studies provided data on the outcome of patients with confirmed CHD in terms of subsequent interventions.[79–81,121,122] In each case around 20% of these had a bypass or angioplasty at the time of follow up, which varied between 30 days and 15 months, possibly reflecting differences in referral criteria.

Some 28–69% of the patients in the studies were given a diagnosis of non-cardiac chest pain. Were these diagnoses accurate? Four out of eight studies included no follow-up of patients by which to confirm the final diagnosis made by the assessing cardiologist. Many patients were seen only once and did not receive objective diagnostic testing. Even where this was done, there is scope for diagnostic error.[123] The three studies with comprehensive follow-up allow some estimate to be made of the accuracy of initial diagnosis.[94,96,98] However, the focus of such follow-up was restricted to subsequent major ischaemic events over relatively short timescales (up to 8 months). Such events are relatively rare, even in cases of confirmed angina and, where follow-up is not universal, it is possible for significant disease or death to be missed.[126] Furthermore, patients with atypical presentations may be harder to diagnose in a one-stop clinic. One study found two patients thought to have gastrointestinal symptoms subsequently suffered MI.[96] A traditional clinic where patients are seen over a period of months may potentially be more effective in diagnosing such atypical cases, but no study was found which tested this hypothesis.

Clinics with a 2-week maximum wait

All study clinics saw patients within 24 hours of GP referral. It is possible that longer waits than this may either result in adverse outcomes for patients with an unrecognised ACS or in GPs referring patients for hospital admission who otherwise might have been seen in the clinic. The NSF proposes patient assessment within 2 weeks of referral.[3] This suggests that the role of NSF clinics will be to fast-track assessment of patients with suspected exertional angina, rather than to identify patients with ACSs and prevent unnecessary hospital admissions of patients with acute chest pain. None of the studies in the review, descriptive or otherwise, evaluated this model of care. A study published since the review was completed compared two clinics in different parts of Glasgow – a daily clinic which aimed to see patients within 24 hours of referral and a weekly clinic which aimed to see patients within 7 days of referral.[127] This found a lower proportion of patients with ACS (3.8% versus 7.8%) and a higher proportion of patients with stable coronary disease (62% versus 37%) referred to the weekly clinic as compared to the daily clinic. Although these differences may simply reflect variation in patients' characteristics or GP behaviour in the two parts of the city, they do corroborate the impression that the longer the waiting time for the clinic, the greater the emphasis on assessment of suspected exertional angina rather than exclusion of ACS (for which a weekly clinic would be an inappropriate route of access to specialist services).

Simulation exercise

Given the lack of data on what impact an RACPC with a 2-week wait might have on care, it was relevant to carry out a modelling exercise to predict what the impact of such clinics might be. As comparators, routine cardiology outpatients and open access exercise test services were used. The former represented the usual pattern of care in the UK prior to the introduction of RACPCs and the latter an innovative model of care that has been used in some parts of the country.[128,129] CPOUs were not modelled,[130] as these play a greater role in the assessment of suspected ACS, and while popular in the USA as a safe way of reducing hospital stay and speeding diagnosis, they may not be applicable in the NHS.[19]

Simple questions were asked of the simulation exercise: what is the overall cost of each model of care? What is the average time delay to make a correct diagnosis of non-cardiac pain? How long does it take on average to make a diagnosis of angiographically confirmed CHD? How many coronary events occur before a definitive correct diagnosis is made?

The 'base case' runs of the model were built upon the assumptions that all the government waiting times for investigations were met, and estimates from the literature (and from this systematic review) of the accuracy of the diagnostic tests and the epidemiology of chest pain and coronary heart disease in the community.

Differences in costs of the different services

The base case scenario suggested that the capacity requirements of the system were greatest for the RACPC model, since this resulted in the highest number of investigations such as exercise tests, MPI and angiography. It was estimated that for a population of 350,000, the annual extra costs of running an RACPC were of the order of £36,000. The difference is not great, since the primary difference between the two models is one of waiting time, not throughput. Once the flow of patients in the different models of care has reached equilibrium, the rate of seeing patients in the different models will be similar in order to maintain the waiting time targets. Nevertheless, this is likely to be an underestimate of the true cost difference, since the model has assumed that the referral threshold is the same regardless of service available, that is, GPs will refer 80% of patients in whom they suspect CHD. However, it is likely that the threshold will be lower the easier access is to the service. For example, the study by Byrne and colleagues found a lower prevalence of CHD in patients referred to a daily RACPC as compared with a weekly clinic.[127] Therefore, the difference in capacity requirements to run an RACPC as compared with a routine cardiology outpatient service for people with chest pain is likely to be greater. An estimate of the likely extra costs can be gained from looking at the results of the sensitivity analyses. In *Table 34*, it can be seen that if the referral threshold of the GP goes up from 80 to 100%, then the costs of running the service increase by a further £63,000, making the overall cost difference as compared with a routine cardiology outpatient service about £100,000 per annum.

The base case scenario also suggested that the open access exercise test was the least expensive service, principally because it was associated with the fewest assessments by a cardiologist and fewer investigations (with the exception of exercise testing). The open access service was £39,000 per annum cheaper than the cardiology outpatient service, and £75,000 per annum cheaper than the RACPC service. However, as with the RACPC, this cost advantage is negated over routine cardiology outpatients if associated with a lowering of the referral threshold. However, for the difference to disappear, more extreme differences in referral thresholds are required. Thus, in *Table 34*, it can be seen that an open access exercise test service would become more expensive than a routine cardiology service if 100% of possible patients were referred to the service, and if only 60% of possible patients were referred to the routine cardiology service (£483,000 versus £440,000).

The purpose of the sensitivity analyses was to assess the impact of changing the different key assumptions that went into the construction of the model. Changing these assumptions made no difference to the rank ordering of costs of the services, with RACPCs always being the most expensive and open access exercise testing the least expensive model of care. The relative difference in costs between the models of care changed depending on the assumptions made, but not the rank ordering, unless the models were compared using different underlying assumptions at the same time. This is plausible with regard to GP referral threshold, as discussed above, but not with regard to the other assumptions, such as test accuracy and prevalence of CHD in the population, which are independent of the model of care.

The costs were based on the results of a single study and may be prone to error. Although this may have some effect on the absolute cost differences between the different models of care, it is unlikely to have a significant effect on their relative rankings.

Differences in average time to correct non-cardiac diagnosis ('benign exit')

In the base case scenario, the RACPC was associated with the fastest average time to correct non-cardiac diagnosis, reducing the average time to diagnosis by approximately 3 weeks as compared with the routine cardiology service. The open access exercise test service also led to faster correct non-cardiac diagnoses, reducing the time taken by about 2 weeks. The importance of this time difference is difficult to evaluate, in the absence of any data on patient-centred health status. Hence, the patient benefit will depend

upon how reassuring they find a 'negative' diagnosis. There is evidence to suggest that 'negative' diagnoses are not always reassuring.[131] The emphasis in chest pain clinics on excluding cardiac diagnoses may mean that alternative diagnoses are not actively considered, and the patient may be dissatisfied if the cause of their pain is not identified.

The effect of RACPCs and open access exercise testing on time to correct non-cardiac diagnosis was robust in that none of the sensitivity analyses changed the rank ordering of the different models of care in relation to this outcome.

Differences in average time to diagnose angiographically confirmed CHD

In the base case scenario, the RACPC was associated with important reductions in average time to angiographically confirmed CHD, reducing the time delay by just over 1 month compared with the routine cardiology outpatient service. In contrast, the open access exercise test service appeared to result in an additional 20-day delay to diagnosis. The importance of earlier angiographic diagnosis is twofold. First, it will lead to earlier recognition of which patients are suitable for revascularisation, whether by PTCA or by CABG. Second, it will guide optimal medical treatment both to control symptoms and reduce risks of further vascular events.[113] Given that new-onset exertional angina is associated with a poorer prognosis than stable angina that has been present for several months, these are important considerations.[97] It is difficult to quantify the size of these benefits since the studies of revascularisation have in general been performed in people with stable angina that may have been present for longer than in the sort of patients who will be identified in RACPCs.

This benefit of RACPCs over the other models of care was robust to change in the underlying assumptions of the simulation exercise, with the exception of changing the waiting times. If the waiting time for angiography is set so that 90% of patients receive their angiogram within 6 rather than 3 months, the advantage of RACPCs disappears (*Table 31*). Under this circumstance, the open access exercise test service is associated with the shortest times to diagnosis.

The relatively poor performance of open access exercise testing in the base case analysis did not appear robust to changing the assumptions. In most of the sensitivity analyses, the open access exercise test service was associated with shorter times to angiographic diagnosis than routine cardiology outpatients. This suggests that random variation may have had an influence on the result of the base case model with respect to open access exercise testing. Random variation was reduced in the simulation by running each model three times for 100 years. However, this does not eliminate the possibility of chance affecting the outcome, since if a queue builds up for a service, it may take several years to dissipate.

Differences in number of coronary events that occur prior to definitive diagnosis

The number of coronary events that occur is essentially a consequence of how long people remain in the simulation before a diagnosis is made. The simulation assumes a risk of a coronary event both for people with and without CHD, with the higher risks for the latter being estimated from data from the Coronary Artery Surgery Study (CASS), and being dependent upon the underlying nature of the CHD.[36] Hence the differences between the models do not reflect changes in coronary events rates, which is outwith the scope of the model, and would be expected to be influenced by initiation of optimal medical therapy and, in the long run, by revascularisation where appropriate. Hence, in the base case scenario, the RACPC was associated with the fewest events per year, which was a consequence of the shorter average time spent in the simulation exercise of both patients with and without CHD. However, this difference disappears if the waiting times for investigation are lengthened, since this eliminates the time advantage of the RACPC.

The differences in the number of expected coronary events per year were small. This reflects the short time on average that patients spent in the simulation exercise. Thus, although the RACPC was associated with 40% fewer events compared with the cardiology outpatient model, this represented only 0.4 events per year. This may be an underestimate, since the risks of coronary events were based on CASS data, and this reflects risk after angiography. Risk in the short term for patients with newly diagnosed exertional angina may be higher than this.[97] Nevertheless, this is unlikely to have had a major effect on the results, since the sensitivity analysis did not suggest any major effect if the risk differential between cardiac and non-cardiac patients was increased (see *Table 39*).

Limitations of the simulation exercise

In the absence of data from controlled studies, a simulation exercise offers the best estimate of the likely impact of RACPCs as compared with other

models of service provision. However, it is subject to a number of limitations.

First, assumptions need to be made about the key inputs into the model, such as physician behaviour, performance of diagnostic tests, the epidemiology of chest pain and CHD and the achievement of waiting list targets. Although some of these assumptions have a good evidence base, others (e.g. proportion of people able to complete an exercise test) are best guesses by clinical experts. The impact of these assumptions was tested by sensitivity analyses which explored what difference it would have made to the results if the assumptions in the 'base case' model were changed. These sensitivity analyses explored the impact of altering: clinic attributes (waiting times, *Table 31*); patient characteristics (incidence of new onset chest pain, *Table 32*; prevalence of CHD, *Table 33*; and prognosis, *Table 39*); physician performance (GP referral threshold, *Table 34*; and accuracy of cardiologist diagnosis, *Table 37*), exercise ECG performance (*Tables 35* and *36*) and risks associated with angiography (*Table 38*). These sensitivity analyses suggest that for the outcome measures used in this exercise, the results were not significantly different if the assumptions were changed (with the exception of waiting times). Thus, for example, the sensitivity analysis shows that changing the prevalence of disease (or pre-test probability), as would occur if the case mix was changed (e.g. more people with diabetes, or a higher proportion of older people) would not affect the overall result. Similarly, altering the accuracy of exercise testing, which might be affected by who reports the test and how (e.g. use of computer-generated reports), does not significantly change the results of the model. The prognosis estimates were based on average survival from the CASS registry data, which, although robust, may have limited applicability to current patients. Nevertheless, making different assumptions about prognosis (e.g. by including a higher proportion of people with worse left ventricular function) did not influence the findings of the model.

However, the model also has to make the assumption that the clinicians within the system behave in a consistent manner. Thus, it is assumed that GPs in the open access exercise test model will follow clinical guidelines, and refer on for specialist assessment all those in whom they make a diagnosis of exertional angina, and not manage them in primary care.[113] In practice, one of the concerns raised with open access exercise tests is that not all patients with positive tests may be referred on for specialist review and/or further investigation.[128,129] Second, it has been assumed that patients referred to a RACPC will undergo exercise testing if suitable. The wide variation in practice between RACPCs (see *Table 28*) suggests that this is not policy in all clinics. If RACPCs are more selective in their use of exercise testing, then the associated costs will be lower.

It is beyond the scope of the simulation exercise to test the cost-effectiveness of the different models of care. Cost estimates have been made of the different models, but effectiveness in terms of improvements in QoL or reduction in cardiovascular morbidity and mortality has not been assessed. Too many assumptions would have had to be made for such an analysis to be performed with any accuracy. Instead, the exercise has focused on the more limited outcomes of how long it takes to make a diagnosis and how many cardiovascular events are likely to occur during this diagnostic process.

Finally, as discussed above, the simulation exercise is affected by random variation. The sensitivity analyses suggested that chance played a major role in the relatively poor performance of open access exercise testing with regard to time taken to definitive cardiac diagnosis.

Interpretation of the evidence

The evidence base for the introduction of RACPCs is weak. In particular, no evidence was found to support a RACPC with a 2-week target waiting time. The simulation exercise suggests that such an RACPC will lead to more rapid diagnosis, but that this model of care is also more expensive. It is not possible from the available data to state whether or not the extra expenditure represents value for money. In particular, the opportunity costs of transferring resources to chest pain clinics from other services need to be considered, as do the relative merits of fast-tracking chest pain patients over and above other patients with cardiac problems such as arrhythmias and heart failure. Indeed, it has been argued that the model of rapid assessment of chest pain should be extended to these other presentations of cardiac disease.[132]

A concern with RACPCs that was raised by the simulation exercise of particular relevance to the NHS is that the benefits from the clinics depended upon reasonable waiting times for further investigation. If the second-stage NSF targets are met (e.g. 3-month waiting time for angiography), then these benefits will be realised. If however, the waiting times are 6 months (the first-stage target

for the NSF) or longer, then the benefits in terms of earlier diagnosis have been lost, and the service will be more costly. Furthermore, once angiography has been performed, optimising the benefits will depend on the ability of the system to offer revascularisation where appropriate. The potential problem will be that the health service simply shifts the waiting list. Parallel investment is occurring in expanding the capacity of revascularisation services, but it may be unrealistic to assume that capacity will expand quickly enough to meet the new case load identified from RACPCs.

It is not at issue whether or not it is rational to provide rapid assessment for patients with suspected angina. There is a strong evidence base for effective treatments for such patients,[113] and it is not in dispute that earlier treatment is likely to lead to better outcome. What is at issue is whether RACPCs offer the optimal way of achieving this rapid assessment. Indeed, the simulation exercise suggests that open access exercise testing costs less and may lead to more rapid diagnosis when waiting lists are long. As the NSF is implemented, evaluation needs to be built in to the setting up and running of the RACPCs.

Chapter 6
Conclusions

Implications for healthcare

Assessment of suspected ACS

- No clinical features were identified that had strong predictive value in ruling out an ACS in a patient presenting with chest pain. Therefore, in patients in whom an ACS is suspected, urgent referral for further assessment in a specialist setting is justified.
- Certain ECG changes, in particular ST elevation, are highly specific for MI, with a high LR+. Interpretation of the ECG taken as a whole can make the ECG even more specific in the diagnosis of MI. Therefore, in patients with these changes, thrombolysis can be initiated provided that there are no contraindications.
- Normal ECGs, although they are associated with a reasonably low LR–, cannot be taken to exclude an ACS. Therefore, performing an ECG in primary care to exclude ACSs is not justified. If an ACS is suspected, emergency referral is justified regardless of the result of the ECG.
- The simulation exercise suggests that POCT with TnT is a useful tool to identify patients with acute coronary syndrome in A&E. Use of this test is justified in patients in whom this diagnosis is suspected.
- The simulation exercise suggests that pre-hospital thrombolysis is marginally more effective than hospital thrombolysis, but is more expensive. There is substantial uncertainty around the ICER of changing from a policy of hospital thrombolysis to a pre-hospital policy. If ambulance telemetry costs are low, expertise is available to read the telemetry ECG, and if the travel time to hospital is long, then pre-hospital thrombolysis may be justified.

Assessment of suspected exertional angina

- The resting ECG provides little diagnostic information in the assessment of suspected exertional angina, though it may be of some value in diagnosing the presence of CHD (e.g. old MI), and is necessary prior to an exercise test.
- Exercise ECG provides both prognostic and diagnostic information. This review was concerned simply with the latter. In this regard, the traditional interpretation of an abnormal exercise ECG result (1 mm ST depression) has an LR+ of 2.79 and an LR– of 0.44. It is not a strongly diagnostic test, whether positive or negative. Therefore, taken in isolation, it is of only limited value in the diagnosis of CHD. The specificity may be increased (at the cost of lower sensitivity) by raising the definition of abnormality to 2 mm ST depression.
- Use of different criteria from ST depression or use of treadmill scores does not dramatically improve the performance of the test.
- Exercise testing is less accurate when performed in women than in men, in terms of both sensitivity and specificity. The poor performance should be taken into account in interpreting the results in this population.
- No strong evidence was found to support the use of RACPCs as a model of care to ensure rapid assessment of patients with suspected exertional angina.
- A simulation exercise suggested that a 2-week RACPC would lead to more rapid differentiation of chest pain due to CHD as compared with chest pain due to other causes. However, this exercise also suggested that the potential advantages of RACPCs would be lost if such a service existed in the context of long waiting times (e.g. 6 months) for further investigation such as angiography.
- No evidence was found, and it was beyond the scope of the simulation model as to whether the RACPC model is more cost-effective than other models of care.

Recommendations for further research

Assessment of ACS

Good evidence is available on the diagnostic value of clinical features and ECGs and, more recently, on the performance of tests such as cardiac troponins. The next step is to ascertain what is the most appropriate model of care to ensure accurate triaging of patients with suspected ACS. There is some evidence (not formally appraised in this review) that CPOUs which provide short-stay admissions may be appropriate, but most of the evidence comes from the USA, and the applicability to the UK needs to be tested.[19,113] The simulation model suggests that use of

ambulance telemetry to guide pre-hospital thrombolysis is most likely to be effective in rural areas with longer anticipated delays before arrival at hospital. Different models that could be tested include: ECG recording by paramedics with thrombolysis on arrival at hospital; thrombolysis decision taken after transmission (and review) of ECG to hospital; and thrombolysis initiated by paramedics on the basis of their own interpretation of the ECG. Further RCTs exploring this model of care are justified.

Relevant research questions therefore include:

- What is the most appropriate model of care to ensure accurate triaging of patients with suspected ACS?
- What is the cost effectiveness of pre-hospital thrombolysis in rural areas?

RACPCs

RACPCs are already being introduced as a result of implementation of the NSF for CHD. Therefore, although their evidence base is weak, it is impractical to recommend RCTs of this pattern of service as compared with traditional cardiology outpatients. Nevertheless, a trial of RACPCs against other innovative models, such as open access exercise testing, is justified. The modelling undertaken in this review was restricted to people without a previously established diagnosis of CHD. There would be merit in evaluating the role of RACPCs in the management of patients with established CHD presenting with new or worsening angina. There is considerable variation in how RACPCs are being set up, and it would be possible to carry out non-randomised studies to explore the impact of these variations. Key differences between clinics include the proportion of patients in whom exercise tests are carried out, the wait after referral until the patient is seen and who runs the clinic (nurse led or cardiologist led). Furthermore, it would be possible to pool data from clinics to assess the accuracy of the chest pain clinic diagnosis (in particular, those with the label of non-cardiac disease) through long-term follow-up looking at the occurrence of new coronary events, and comparing this with the expected incidence in the general population. It is also relevant to test different ways of providing follow-up care for people presenting with chest pain who are given a non-cardiac diagnosis.

Relevant research questions therefore include:

- What is the relative cost-effectiveness of RACPCs as compared with other innovative models of care such as open access exercise testing?
- What role should RACPCs play in the management of patients with established CHD presenting with new or worsening angina?
- How should RACPCs be managed? (e.g. proportion of exercise ECGs performed; skill mix of staff; maximum waiting time from referral).
- What is the long-term outcome of patients discharged from RACPCs?
- How should patients with non-cardiac chest pain be followed up?

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Contribution of authors

The study outline was developed by BCD and FDRH. JM wrote the detailed protocol, with contributions from BCD, JJD, RCD and FDRH. The method was refined following funding with additional contributions from RJM, PMB and MKD.

JM, RJM and RALO were responsible for coordinating and running the study. The search strategies were developed by RALO, with contributions from the other authors. The searches were performed by RALO. RJM and JM reviewed the titles and abstracts of identified papers. Full texts of papers were reviewed by MKD, RCD, FDRH, RJM, BCD, LH and JM. The analysis of the data was developed and executed by JJD. The acute chest pain model was developed and carried out by BCD, with expert cardiological input from RCD and MKD. The chronic chest pain model was developed and carried out by PMB with cardiological input from RCD and MKD. The writing up of the first and second drafts was coordinated and edited by JM and RJM, with all authors contributing to specific sections.

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Appendix 1

Search strategies

MEDLINE search

Medical subject headings	Textwords
CHEST PAIN	chest pain
MYOCARDIAL INFARCTION	angina
MYOCARDIAL ISCHEMIA	heart attack$
CORONARY	clammy
CORONARY VASOSPASM	sweat$
ANGINA PECTORIS	myocard$ isch?em$
HYPERHIDROSIS	myocard$ infarc$
EXERCISE TEST	diaphore$
HEART AUSCULTATION	exercise$ test$
PULSE	auscultat$
MEDICAL HISTORY TAKING	pulse
CLINICAL MEDICINE	(history adj2 tak$)
CLINICAL COMPETENCE	diagnos$ different$
"DIAGNOSTIC TECHNIQUES AND PROCEDURES"	(clinical adj5 competenc$)
DIAGNOSTIC TESTS, ROUTINE	diagnos$ test$
PHYSICAL EXAMINATION	physical exam$
AUSCULTATION	body temperature
BODY TEMPERATURE	palpat$
PALPATION	percussion
PERCUSSION	(heart adj5 catheteri?ation)
ANGIOCARDIOGRAPHY	stress$ echo$
CORONARY ANGIOGRAPHY	stress$ test$
HEART CATHETERIZATION	angiocardio$
FUNCTION TESTS	coronary angiogr$
ECHOCARDIOGRAPHY	echocardiogr$
ELECTROCARDIOGRAPHY	electrocardiogr$
RADIONUCLIDE IMAGING	ecg
TECHNETIUM TC 99M SESTAMIBI	radionuc$
THALLIUM RADIOISOTOPES	sestamibi
PREDICTIVE VALUE OF TESTS	techne?ium
"SENSITIVITY AND SPECIFICITY"	thallium
"REFERRAL AND CONSULTATION"	ekg
AMBULATORY CARE FACILITIES	predictive value$
OUTPATIENT CLINICS, HOSPITAL	sensitivit$
PAIN CLINICS	specificit$
	likelihood ratio$
	interobserver
	intraobserver
	accuracy
	precision
	reliability
	(referral$ adj5 consultat$)
	(ambula$ adj5 care)
	open access
	(chest pain$ adj5 clinic$)
	pain clinic$

EMBASE search

Medical subject headings	Textwords
THORAX PAIN	chest pain$
HEART INFARCTION	angina
HEART MUSCLE ISCHEMIA	heart attack$
CORONARY ARTERY DISEASE	clammy
CORONARY ARTERY SPASM	sweat$
ANGINA PECTORIS	myocard$ isch?em$
DIAPHORESIS	myocard$ infarc$
HYPERHIDROSIS	diaphore$
EXERCISE TEST	hyperhidro$
HEART AUSCULTATION	exercise$ test$
PULSE RATE	auscultat$
ANAMNESIS	pulse
CLINICAL MEDICINE	(history adj2 tak$)
COMPETENCE	diagnos$ different$
DIAGNOSTIC TEST	(clinical adj5 competenc$)
PHYSICAL EXAMINATION	diagnos$ test$
AUSCULTATION	physical exam$
BODY TEMPERATURE	body temperature
ANGIOCARDIOGRAPHY	palpat$
HEART CATHETERIZATION	percussion
HEART FUNCTION TEST	(heart adj5 catheteri?ation)
ECHOCARDIOGRAPHY	stress$ echo$
CONTRAST ECHOCARDIOGRAPHY	stress$ test$
DOPPLER ECHOCARDIOGRAPHY	angiocardio$
M MODE ECHOCARDIOGRAPHY	coronary angiogr$
TRANSESOPHAGEAL ECHOCARDIOGRAPHY	echocardiogr$
TWO DIMENSIONAL ECHOCARDIOGRAPHY	electrocardiogr$
ELECTROCARDIOGRAPHY	ecg
SCINTISCANNING	radionuc$
HEART SCINTISCANNING	sestamibi
SCINTIANGIOGRAPHY	techne?ium
METHOXY ISOBUTYL ISONITRILE TECHNETIUM TC 99M	thallium
THALLIUM	ekg
PREDICTION	predictive value$
PATIENT REFERRAL	sensitivit$
OUTPATIENT DEPARTMENT	specificit$
PAIN CLINIC	likelihood ratio$
	interobserver
	intraobserver
	accuracy
	precision
	reliability
	(referral$ adj5 consultat$)
	(ambula$ adj5 care$)
	open access
	(chest pain$ adj5 clinic$)

CINAHL search

Medical subject headings	Textwords
CHEST PAIN	chest pain$
MYOCARDIAL INFARCTION	angina
MYOCARDIAL ISCHEMIA	heart attack$
CORONARY DISEASE	clammy
CORONARY VASOSPASM	sweat$
ANGINA PECTORIS	myocard$ isch?em$
HYPERHIDROSIS	myocard$ infarc$
EXERCISE TEST	diaphore$
HEART AUSCULTATION	exercise$ test$
PULSE	auscultat$
MEDICAL HISTORY TAKING	pulse
CLINICAL MEDICINE	(history adj2 tak$)
CLINICAL COMPETENCE	diagnos$ different$
"DIAGNOSTIC TECHNIQUES AND PROCEDURES"	(clinical adj5 competenc$)
DIAGNOSTIC TESTS, ROUTINE	diagnos$ test$
PHYSICAL EXAMINATION	physical exam$
AUSCULTATION	body temperature
BODY TEMPERATURE	palpat$
PALPATION	percussion
PERCUSSION	(heart adj5 catheteri?ation)
ANGIOCARDIOGRAPHY	stress$ echo$
CORONARY ANGIOGRAPHY	stress$ test$
HEART CATHETERIZATION	angiocardio$
HEART FUNCTION TESTS	coronary angiogr$
ECHOCARDIOGRAPHY	echocardiogr$
ELECTROCARDIOGRAPHY	electrocardiogr$
RADIONUCLIDE IMAGING	ecg
TECHNETIUM TC 99M SESTAMIBI	ekg
THALLIUM RADIOISOTOPES	radionuc$
PREDICTIVE VALUE OF TESTS	sestamibi
"SENSITIVITY AND SPECIFICITY"	techne?ium
"REFERRAL AND CONSULTATION"	thallium phore$
AMBULATORY CARE FACILITIES	predictive value$
OUTPATIENT CLINICS, HOSPITAL	sensitivit$
PAIN CLINICS	specificit$
	likelihood ratio$
	interobserver
	intraobserver
	accuracy
	precision
	reliability
	(referral$ adj5 consultat$)
	(ambula$ adj5 care)
	open access
	(pain$ adj5 clinic$)

Cochrane search

Issue 1 2000 was searched.

Appendix 2

Details of studies included in the review

TABLE 40 *Acute clinical features: general details*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Berger *et al*., 1990, Switzerland[65]	Secondary care	All patients admitted to hospital complaining chiefly of CP	Chest trauma; patients transferred from another hospital with a diagnosis	57			191	87	278
Buclin *et al*., 1988, France[133]	Secondary care	Patients whose principal complaint was thoracic CP	None specified	M 60–70[b] F 70–80[b]			N/S	N/S	278
Craig, 1982, Australia[134]	Secondary care	Admission diagnosis of MI, myocardial ischaemia, CHD, CP or angina	None specified	N/S			137	77	214
Dalton *et al*., 1999, USA[49]	A&E	Patients admitted to ED with CP	Not specified	65	40	84	18	10	28
Doyle *et al*., 1988, Ireland[92]	A&E	Anterior or left-sided CP	Age <18 years	53			270	181	451
Goldman *et al*., 1982, USA[50]	A&E	≥ 30; chief complaint anterior, precordial or left lateral CP unexplained by obvious local trauma or CXR abnormalities	Obvious local trauma or chest-film abnormalities Age <30 year in Yale, <25 year in Brigham (non-signing of consent form only in Brigham)	N/S			N/S	N/S	482
Gray *et al*., 1993 UK[51]	Secondary care	Patients admitted with CP who had serial cardiac enzymes + ECG	Working diagnosis not clear (1–17%)	N/S			N/S	N/S	15135
Grijseels *et al*., 1995, The Netherlands[79]	Primary and secondary care	Symptoms suggestive of MI	No hospital final diagnosis	67			484	422	906
Herlihy *et al*., 1987, USA[52]	Secondary care	Chest pain and 'ECG changes' admitted to CCU	Pre-existing disease that could produce nausea; medications that could produce nausea; received thrombolysis	N/S			N/S	N/S	265
Herlitz *et al*., 1995, Sweden[82]	Primary and secondary care	Age <75 CP of between 15 minutes and 2 hours 45 minutes duration	Contraindications to thrombolysis: diastolic BP ≥ 120	N/S			N/S	N/S	352
Jonsbu *et al*., 1991, Norway[64]	Secondary care	Suspected acute MI	Unable to give reliable medical history	N/S			N/S	N/S	200
Karlson *et al*., 1991, Sweden[87]	A&E	Presenting to ER with 'CP or other symptoms suggestive of AMI' and subsequently admitted to hospital		N/S			N/S	N/S	7157

continued

TABLE 40 *Acute clinical features: general details (cont'd)*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Lee *et al*., 1985, USA[53]	A&E	Presenting to A&E with anterior or left-sided CP	Patients aged <25 years	56			286	310	596
Logan *et al*., 1986, New Zealand[54]	Secondary care	Admission to CCU	Received opiates in previous 12 hours		32	77	67	31	98
Mair *et al.*, 1995, Austria.[78]	A&E	CP	Admissions 10 p.m. – 6 a.m.; trauma	60[a]	21	89	77	37	114
Pozen *et al*., 1984, USA[90]	A&E	Male ≥ 30 years, female ≥ 40 years. Chief symptom CP, jaw or left arm pain and SOB or changed pattern of angina	Male <30 years, female <40 years. Presenting at inconvenient time of day	62			1299	1021	2320
Rohl *et al.*, 1992, Germany[89]	Secondary care	Patients with MI or acute CP. Age >30 years	Patients with traumatic/non-cardiac CP; life-threatening arrhythmia; haemodynamic instability needing intensive care	N/S			N/S	N/S	615
Short, 1981,UK[62]	Primary and secondary care	Patients presenting to their GP with ≥ 1 attack of spontaneous CP who were referred for specialist cardiology opinion	Patients seen >14 days after the attack	62	24	84	216	167	383
Solomon *et al.*, 1989, USA[63]	A&E	Age >30 years. Chief complaint of anterior, precordial or left lateral CP unexplained by local trauma or CXR abnormality presenting to A&E between Dec. 1983 and Aug. 1985	Age <30 years Obvious local trauma or X-ray abnormality to explain CP. Only first 3 visits of each patient included	30–64 = 50 ≥ 65 = 73			3838	3896	7734
Tierney *et al.*, 1985, USA[135]	A&E	Men ≥ 30 years, females ≥ 40 years with CP attending the ER	Prisoners; recent trauma to chest; smoke inhalation; chronic indigestion	56			N/S	N/S	540
Tierney *et al.*, 1986, USA[55]	A&E	Male ≥ 30 years female ≥ 40 years. Anterior CP presenting to ER	No initial consent form filled in or no follow-up data available	56			N/S	N/S	492

[a] ED, emergency department; ER, emergency room; CXR, chest X-ray; CP, chest pain; CCU, critical care unit; SOB, shortness of breath; BP, blood pressure.
[b] Median.

TABLE 41 *Acute clinical features: reference standard and potential biases*

Paper	Reference standard description	Reference standard for MI unless stated otherwise				Incorporation bias	Blinding	Verification/ work-up bias (%)	Selection of the study sample	Study population	Sub-groups	Indeterminate results
		ECG[a]	Enzymes[a]	Clinical	Other							
Berger *et al.*, 1990, Switzerland[65]	Discharge diagnosis taking into account:	ECG changes indicating MI	CK peaking within first 36 h with CKMB >6% total	CP		No	Unclear	No	Consecutive	Single	No	
Buclin *et al.*, 1988, France[133]	Discharge diagnosis taking into account:	ECG changes	Enzyme rise	Clinical features		Unclear	No	No	Consecutive	Single	No	Not specified
Craig, 1982, Australia[134]	WHO criteria[b]	WHO criteria[b]	WHO criteria[b]	WHO criteria[b]		Yes	No	No	Consecutive	Single	No	Classed as not MI
Dalton *et al.*, 1999, USA[49]	Enzymes alone		Raised CK			Yes	Yes	No	Random	Single	No	Not specified
Doyle *et al.*, 1988, Ireland[92]		MI not defined	MI not defined	Cardiac CP defined by Rose criteria	Unstable angina = typical pain, serial ST/T changes + normal or less than 2-fold inc. in cardiac enzymes	Unclear	Yes	No	Consecutive	Single	Yes inpatients vs. outpatients	Excluded
Goldman *et al.*, 1982, USA[50]	1 or more ECG or enzyme changes	New Q waves + at least 25% decrease in amplitude of following R wave	SGOT ≥ 2× admission value; or CKMB ≥ 5% total CK or LDH1 >LDH2		Focal uptake technetium-99	Unclear	Unclear	No 58	Consecutive	Single	No	Excluded

continued

TABLE 41 *Acute clinical features: reference standard and potential biases (cont'd)*

Paper	Reference standard description	Reference standard for MI unless stated otherwise				Incorporation bias	Blinding	Verification/ work-up bias (%)	Selection of the study sample	Study population	Sub-groups	Indeterminate results
		ECG[a]	Enzymes[a]	Clinical	Other							
Gray *et al.*, 1993, UK[51]	ECG or enzyme changes	Evolution of sequential ST segment changes with new path Q waves	≥ 2 × ULN rise in cardiac enzymes			No	No	No	Consecutive	Single	No	Classified as no MI
Grijseels *et al.*, 1995, The Netherlands[79]	WHO criteria[b]	WHO criteria[b]	WHO criteria[b]	WHO criteria[b]		Yes	No	No	Consecutive	Single	Yes Abnormal ECG	Excluded
Herlihy *et al.*, 1987, USA[52]	ECG or enzyme changes	ST elevations >1 mm (only specifies leads II, III, AVF) 2 waves	CK elevations (not specified how much)			No	Unclear	No	Consecutive	Single	No	Not specified
Herlitz *et al.*, 1995, Sweden[82]	2 or more from ECG, enzymes and clinical features	Appearance of Q waves in first 3 days in at least 2 leads	At least 2 values above normal range of CK/CK-MB	Pain indicative of MI ≥ 15 minutes duration		Yes	Unclear	No	Consecutive	Single	Yes outside hospital	Not specified evaluation, inside hospital evaluation
Jonsbu *et al.*, 1991, Norway[64]		'Standard criteria'	'Standard criteria'	'Standard criteria'		Yes	No	No	Consecutive	Single	No	Not specified
Karlson *et al.*, 1991, Sweden[87]	2 or more from ECG, enzymes and clinical features	New Q waves in ≥ 2 leads	AST > ULN on ≥ 2 different days	CP for ≥ 15 minutes		Yes	Unclear	No	Consecutive	Single	No	Not specified

continued

TABLE 41 *Acute clinical features: reference standard and potential biases (cont'd)*

Paper	Reference standard description	Reference standard for MI unless stated otherwise				Incorporation bias	Blinding	Verification/ work-up bias (%)	Selection of the study sample	Study population	Sub-groups	Indeterminate results
		ECG[a]	Enzymes[a]	Clinical	Other							
Lee *et al.*, 1985, USA[53]	1 or more from ECG, or enzyme changes or positive scintiscan	New Q waves with reduction in R wave	Enzyme rise >ULN		Focal uptake of Tc-99m on scintiscan	No	Yes	Enzymes available for 71%	Consecutive	Separate	Yes: gender; age; PMH of CHD; pain quality	Not specified
Logan *et al.*, 1986, New Zealand[54]		Q wave plus ST segment/T wave	CPK + SGOT elevation (are double normal)			No	No	No	Consecutive	Single	No	Excluded
Mair *et al.*, 1995, Austria[78]	WHO criteria[b]	WHO criteria[b]	WHO criteria[b]	WHO criteria[b]		Unclear	Unclear	No	Other	Single	No	Not specified
Pozen *et al.*, 1984, USA[90]	Final blinded physician's diagnosis	WHO criteria[b]	WHO criteria[b]	WHO criteria[b]		Yes	Yes	No	Consecutive	Separate	No	Not specified
Rohl *et al.*, 1992, Germany[89]	2 or more from	Pathological Q waves or ST-T waves characteristic of MI	Revised CK with CK-MB ≥ 6%	Angina ≥ 30 minutes duration not responding to nitrates		Unclear	Unclear	No	Consecutive	Single	No	Excluded
Short, 1981, UK[62]	Combination of:	Evolving ECG consistent with infarction	Rise of AST to ≥ 2 × upper limit	CP consistent with CHD		Yes	No	No	Consecutive	Single	Yes: PMH of CHD	Not specified

continued

TABLE 41 *Acute clinical features: reference standard and potential biases (cont'd)*

Paper	Reference standard description	Reference standard for MI unless stated otherwise				Incorporation bias	Blinding	Verification/ work-up bias (%)	Selection of the study sample	Study population	Sub-groups	Indeterminate results
		ECG[a]	Enzymes[a]	Clinical	Other							
Solomon *et al.*, 1989, USA[63]		Q waves (>0.04 minutes duration) with 25% decrease in following R wave as compared with ED ECG	Characteristic evolution of enzymes including CKMB	Sudden unexplained death	If late presentation (i.e. enzymes peak likely prior to admission) and no PMH of MI or valvular calcification then local area of uptake in cardiac area of scintiscan	Yes	Unclear	Yes	Consecutive	Single	Yes: Age <65 vs >65 years	Excluded
Tierney *et al.*, 1 from 1985, USA[135]		Pathological Q waves on FU ECG not present on the A&E tracing. ECG criteria only used where enzymes not available	Raised total CK + CKMB >4% total or LDH1 ≥ LDH2 for patients without renal infarction or haemolysis			No	Yes	No	Consecutive	Single	Yes: gender; age; ethnicity	Excluded

continued

TABLE 41 *Acute clinical features: reference standard and potential biases (cont'd)*

Paper	Reference standard description	Reference standard for MI unless stated otherwise				Incorporation bias	Blinding	Verification/ work-up bias (%)	Selection of the study sample	Study population	Sub-groups	Indeterminate results
		ECG[a]	Enzymes[a]	Clinical	Other							
Tierney *et al.*, 1986, USA[55]	I from	If no enzyme available, MI diagnosis of new abnormal Q waves on following ECG	Elevated total CK with CKMB >4% or LDH1 isoenzyme ≥ LDH2			No	Yes	No	Consecutive	Single	No	Excluded

[a] FU, follow-up; LDH, lactate dehydrogenase
[b] WHO criteria for myocardial infarction: 2 or more from: (1) evolution of unequivocal findings for myocardial infarction on serial ECGs in at least 2 leads of the same territory (i.e. diagnostic Q waves or QS complexes); (2) serial CK and CKMB rise and fall with peak ≥ 2 × ULN; (3) typical prolonged severe CP and related symptoms >20 minutes.

TABLE 42 *Acute resting ECG: general details*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Adams *et al.*, 1993, UK[11]	Primary and secondary care	Study of suspicion of AMI; CP <4 hours; current to GREAT study of pre-hospital thrombolysis	Randomisation to pre-hospital arm of study	63			98	39	137
Aufderheide *et al.*, 1990, USA[56]	A&E	Stable adult patients seeking paramedic evaluation for chief complaint of non-traumatic CP	If acquisition of ECG would alter patient care; lack of verbal consent	63			98	39	137
Aufderheide *et al.*, 1992, USA[57]	A&E and secondary care	Cooperative; initially stable; adult pre-hospital patients with a chief complaint of non-traumatic CP of presumed ischaemic origin	Patients with VT; VF; 2nd or 3rd degree heart block; SBP <90 or if in the opinion of the paramedics, the acquisition of a pre-hospital 12 lead ECG or study info would alter patient care	N/S			N/S	N/S	439
Aufderheide *et al.*, 1992, USA[110]	A&E and primary care	Cooperative; stable (SBP >90; no VT; VF or heat blocks) Adult (>18 years), with non-traumatic CP of presumed ischaemic origin	'Acquisition of pre-hospital study information would interfere with patient care.' No ECG transmitted; no medical record; taken to different hospital; non co-operative patients; unstable clinically.	66	27	94	202	237	439
Behar *et al.*, 1977, Israel[85]	A&E	Presumed MI	ECG not available	N/S			N/S	N/S	1578
Bell *et al.*, 1990, Australia[80]	Secondary care	Suspected acute MI admitted to CCU with 12-lead ECG carried out before CCU admission	Referred from other hospital with complications; arrest prior to 12-lead; pacemaker; patients receiving thrombolysis	59			308	102	410
Berger *et al.*, 1990, Switzerland[65]	Secondary care	All patients admitted to hospital complaining of chiefly of CP	Chest trauma; patients transferred from another hospital with a diagnosis	57			191	87	278

continued

TABLE 42 *Acute resting ECG: general details (cont'd)*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Bertini *et al.*, 1991, Italy[136]	Secondary care	All patients requiring interventions in Florence MCCU for CP thought to be coronary artery disease in 1986	N/S	66			392	213	605
Buclin *et al.*, 1988, France[133]	Secondary care	Patients whose principal complaint was thoracic CP	None recorded	M 60–70[b] F 70–80[b]			N/S	N/S	278
Craig, 1982, Australia[134]	Secondary care	Admission diagnosis of MI; myocardial ischaemia; CHD; CP or angina	None recorded	N/S			137	77	214
Doyle *et al.*, 1988, Ireland[92]	A&E	Anterior or left-sided CP	Age under 18	53			270	181	451
Fesmire *et al.*, 1989, USA[41]	A&E and secondary care	Patients admitted from A&E suspected of having MI	Transfers from other hospitals	58	96	20	233	207	440
Fesmire *et al.*, 1998, USA[42]	A&E and secondary care	Consecutive patients with CP suspicious for coronary ischaemia who were admitted and had ECG plus serial ECG for at least 1 hour	Cocaine use; tachycardia; pulmonary oedema; Pacemaker. Non admission of patient	56	23	94	611	389	1000
Foster *et al.*, 1994, USA[77]	Primary and secondary care	Non-trauma-related chest, epigastric, arm, shoulder, neck or jaw discomfort	No discomfort as inclusion criteria; advanced malignancy; do not resuscitate documented; <21 years old; unable to give history; cardiac arrest	N/S			N/S	N/S	155
Foy *et al.*, 1991, New Zealand[58]	Secondary care	Admitted to CCU with suspected AMI	N/S	N/S			N/S	N/S	40
Gama *et al.*, 1990, UK[137]	Secondary care	Admissions to Acute Geriatric Unit (for any reason)	No ECG or enzymes done	81			91	179	270

continued

TABLE 42 *Acute resting ECG: general details (cont'd)*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Goldman *et al.*, 1982, USA[50]	A&E	Age ≥ 30 years. Chief complaint anterior, precordial or left lateral chest pain unexplained by obvious local trauma or CXR abnormalities	Obvious local trauma or chest – film abnormalities Age <30 in Yale, <25 in Brigham (non-signing of consent form only in Brigham)	N/S			N/S	N/S	482
Gray *et al.*, 1993, UK[51]	Secondary care	Initial working diagnosis of MI	No working diagnosis could be determined from retrospective analysis of notes	N/S			N/S	N/S	15135
Grijseels *et al.*, 1995, The Netherlands[79]	Primary and secondary care	Symptoms suggestive of MI	No hospital final diagnosis; incomplete data	67			484	422	906
Grim *et al.*, 1989, USA[76]	A&E and primary care	48 patients with the complaint of 'chest discomfort'. Age >30 years; <70 years; CP for >20 minutes and <4 h; pain not relieved by sublingual nitroglycerine; ECG ST elevation >1 mm in >2 leads; able to give consent	Bleeding disorder; CVA or TIA; oral anticoagulants; gastrointestinal/genitourinary bleeding, major surgery/trauma in previous month; severe hypertension; systolic BP >180 mmHg or diastolic BP >110 mmHg; IDDM; bleeding ulcer	65			19	29	48
Gustafsson *et al.*, 1996, Sweden[73]	Secondary care	Acute CP of <12 h duration plus suspicion of AMI admitted during working hours Mon.–Fri.	SBP <100 or HB <110 g/l Technically poor results	67	42	88	79	28	107
Hands *et al.*, 1988, USA[59]	Secondary care	Left BBB in patients recruited to MILIS study	MI within 2/52 prior to presentation	N/S			N/S	N/S	35
Hedges *et al.*, 1992, USA[138]	A&E	Age ≥ 30 years; chest discomfort; clinical suspicion of MI sufficient to warrant ECG; initial ECG < 0.1 mv ST elevation or no ST elevation.	Chest discomfort CXR/trauma; cardioversion within 24 h; transfers; no consent; haematocrit <30%; haemodynamically unstable; potential thrombolysis candidate with presentation	61	31	96	218	43	261

continued

TABLE 42 *Acute resting ECG: general details (cont'd)*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Jonsbu *et al.*, 1993, Norway[43]	A&E and secondary care	Admitted with CP	Not specified	N/S			N/S	N/S	1252
Justis *et al.*, 1992, USA[75]	A&E	Presenting to ED with CP	N/S	56			131	57	188
Karlson *et al.*, 1991, Sweden[87]	A&E	Presenting to ER with 'CP or other symptoms suggestive of AMI' and subsequently admitted to hospital		N/S			N/S	N/S	7157
Kellett, 1997, Ireland[67]	Secondary care	Suspected MI	None given	64			N/S	N/S	600
Kudenchuk *et al.*, 1998, USA[44]	Primary and secondary care	Suspected symptoms of AMI	'Clinical contraindications to thrombolysis'	60			2001	1026	3027
Lee *et al.*, 1985, USA[53]	A&E	Presenting to A&E with anterior or left sided CP	Patients aged <25 years	56			286	310	596
Lee *et al.*, 1989, USA[45]	A&E	Age >30 years. Chief symptom anterior, precordial or left-sided acute CP	Obvious local trauma; abnormality on CXR patients refusing FU who were not diagnosed as having MI	N/S			N/S	N/S	7734
Lee *et al.*, 1990, USA[84]	A&E	Age >30 years. Chief complaint anterior, precordial or left-sided CP unexplained by trauma or CXR	Patients not admitted who would not consent to FU at 48–72 h. No information on prior trace. No ECG interpretation. Self-discharges	59			2879	2794	5673
Mair *et al.*, 1995, Austria[78]	A&E	CP	Trauma Admitted between 10 p.m. and 6 a.m.	60[b]	21	89	77	37	114

continued

TABLE 42 *Acute resting ECG: general details (cont'd)*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Mair *et al.*, 1995, Austria[69]	A&E	Non-traumatic CP	Nil	60[b]	32	89	43	17	60
Miller *et al.*, 1987, USA[61]	Secondary care	Suspected acute MI	Chest pain <30 minutes duration. BBB	65	30	93	62	38	100
Otto *et al.*, 1994, USA[71]	Primary care	Non-traumatic CP of presumed ischaemic origin. Adults >18 years; alert and oriented; English speaking; able to cooperate; perceived as reliable; BP >90 mmHg systolic; no 2nd/3rd degree block; VF; VT	Not one of the inclusion criteria or acquisition of 12-lead ECG would interfere with patient care	66	27	95	193	235	428
Patel *et al.*, 1996, UK[46]	Secondary care	Age 30–75 years; Within 24 h of typical anginal pain; willing to give informed comment	Prolonged CP; evidence of persistent ST elevation; Death; evolutionary Q waves: LVH with strain pattern; left BBB drugs which might influence ST segment changes	59	30	77	169	43	212
Pozen *et al.*, 1984, USA[90]	A&E	Male ≥ 30 years, female ≥ 40 years Chief symptom CP; jaw or left arm pain and SOB or changed pattern of angina	Male <30 years Female <40 years Presenting at inconvenient time of day	62			1299	1021	2320
Rohl *et al.*, 1992, Germany[89]	Secondary care	Patients with MI or acute CP. Age >30 years	Patients with traumatic/non-cardiac CP; life-threatening arrhythmia; haemodynamic instability needing intensive care	N/S			N/S	N/S	615
Rouan *et al.*, 1989, USA[47]	A&E	Age >30 years with anterior, precordial or left lateral CP. 1st 3 visits only	Chest trauma; abnormal CXR; >3 visits to A&E in study period	N/S			4625	2490	7115

continued

TABLE 42 *Acute resting ECG: general details (cont'd)*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Rude *et al.*, 1983, USA[60]	Secondary care	≥ 30 minutes pain thought to be acute myocardial ischaemia in whom a suspected or definite MI was one of the admission diagnoses	Age >75 years; pregnant; pacemaker terminal illness; multi-organ failure; cardiomyopathy; acute stroke; in other study or unable to attend FU	61			2292	1405	3697
Sgarbossa *et al.*, 1996, USA[139]	Secondary care	In GUSTO study. Cases: (1) acute MI documented by serum enzyme changes; (2) left BBB on baseline ECG Controls: (1) angiographically demonstrated CAD; (2) left BBB; (3) no acute CP at time of ECG	Not left BBB. Contraindications to GUSTO study	69[b]			84	47	131
Shlipak *et al.*, 1999, USA[140]	A&E	Age >18 years old Left BBB 'Acute cardiopulmonary symptoms' presenting to ED of UCSF – Moffit–Long Hospital	Intermittent left BBB; patients not tested for elevation of cardiac enzymes within 12 h	N/S			N/S	N/S	83
Short, 1981, UK[62]	Primary and secondary care	CP		62	24	84	216	167	383
Singer *et al.*, 1997, USA[68]	A&E and secondary care	Age >30 years. Symptoms of chest discomfort; SOB; syncope; CCF; pulmonary oedema; epigastric pain or new onset symptoms <12 h	Unclear time of onset. Unavailable ECGs	59			316	210	526
Solomon *et al.*, 1989, USA[63]	A&E	Age >30 years. Chief complaint of anterior, precordial or left lateral CP unexplained by local trauma or CXR abnormality presenting to ERs between Dec. 1983 and Aug. 1985	Age <30 years. Obvious local trauma or X-ray abnormality to explain CP. Only first 3 visits of each patient included; subsequent visits in time	30–64 = 50 ≥ 65 = 73			3838	3896	7734

continued

TABLE 42 *Acute resting ECG: general details (cont'd)*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Tierney *et al.*, 1985, USA[135]	A&E	Male ≥ 30 years, female ≥ 40 years attending A&E with CP	Prisoners. Recent trauma to chest. Smoke inhalation. Chronic indigestion.	56			N/S	N/S	540
Tierney *et al.*, 1986, USA[55]	A&E	Men aged ≥ 30 years, women aged ≥ 40 years. Anterior CP on presentation to A&E	No initial consent form filled in or no follow-up data available	56			N/S	N/S	492
Tighe *et al.*, 1996, Ireland[141]	Secondary care	Acute CP	None	63	31	90	N/S	N/S	264
Weaver *et al.*, 1990, USA[66]	Primary care and A&E	Patient alert and orientated; CP of suspected cardiac origin; CP ≥ 15 minutes and <6 h; systolic BP >80 and <180; diastolic BP <120; systolic BP difference between arms <20 mmHg	Age ≥ 75 years; bleeding condition; history of strokes; seizures or TIAs; major surgery in last 2/12; GI bleed in last year; cancer or terminal illness; liver disease/jaundice; renal insufficiency; IDDM; active colitis; recent trauma or central line placement; warfarin therapy	N/S	35	74	N/S	N/S	2472
Yusuf *et al.*, 1984, UK[72]	Secondary care	Suspected uncomplicated MI in last 12 h		56			402	73	475
Zalenski *et al.*, 1993, USA[74]	Secondary care	Presenting to A&E with CP, SOB, etc. who were admitted to CCU with provisional diagnosis of MI or unstable angina	Not admitted to CCU; <18 years old. Provisional diagnosis of other causes of CP. Admitted 11 p.m.–5 a.m.	64			84	65	149

continued

TABLE 42 *Acute resting ECG: general details (cont'd)*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Zalenski *et al.*, 1997, USA[48]	A&E and secondary care	Age ≥ 35 years old. CP suggestive of ischaemia; infarction and admitted to CCU	Transfer from another hospital; too clinically unstable to allow extra leads; took >5 minutes to separate 12 leads and additional 6 leads; no follow-up ECG; <2 CK determinations	66			333	200	533

[a] CCF, congestive cardiac failure; GI, gastrointestinal; IDDM, insulin-dependent diabetes mellitus; MCCU, mobile coronary care unit; VF, ventricular fibrillation; VT, ventricular tachycardia.
[b] Median.
CVA, cerebrovascular accident; LVM, left ventricular hypertrophy; TIA, transient ischaemic attack.

TABLE 43 *Acute resting ECG: reference standard and potential biases*

Paper	Reference standard description	Reference standard for MI unless stated otherwise[a]				Incorporation bias	Blinding	Verification/ work-up bias (%)	Selection of the study sample	Study population	Sub-groups	Indeterminate results
		ECG	Enzymes	Clinical	Other							
Adams *et al.*, 1993, UK[11]	WHO criteria	WHO criteria	WHO criteria	WHO criteria		Yes	Yes	No	Consecutive	Single	No	Classified as no MI
Aufderheide *et al.*, 1990, USA[56]	Final hospital diagnosis		MI: abnormal elevation of CPK and/or LDH iso-enzymes within 72 h after hospital admission			No	Yes	No	Consecutive	Single	No	Excluded
Aufderheide *et al.*, 1992, USA[57]			For MI – abnormal elevation of CKMB and/or LDH within 72 h of admission	For angina – the diagnosis was determined by the safety committee investigators after hospital chart review		No	Unclear	No	Consecutive	Single	No	Excluded
Aufderheide *et al.*, 1992, USA[110]	WHO criteria	WHO criteria	WHO criteria	WHO criteria		Unclear	Unclear	No	Consecutive	Single	No	Excluded
Behar *et al.*, 1977, Israel[85]	WHO criteria	WHO criteria	WHO criteria	WHO criteria		No	No	Yes	Consecutive	Single	No	Excluded
Bell *et al.*, 1990, Australia[80]	2 or more from	New path Q waves	2 × ULN or +ve CKMB	Focal Tc-99tech uptake		Unclear	Yes	No	Consecutive	Single	No	N/S
Berger *et al.*, 1990, Switzerland[65]	Discharge diagnosis taking into account	ECG changes indicating MI	CK peaking within first 36 h with CKMB >6% total	CP		Yes	Unclear	No	Consecutive	Single	No	

continued

TABLE 43 *Acute resting ECG: reference standard and potential biases (cont'd)*

Paper	Reference standard description	Reference standard for MI unless stated otherwise[a]				Incorporation bias	Blinding	Verification/ work-up bias (%)	Selection of the study sample	Study population	Sub-groups	Indeterminate results
		ECG	Enzymes	Clinical	Other							
Bertini *et al.*, 1991, Italy[136]	1 or more from	New pathological Q waves OR	Characteristic rise of CK and CKMB (values not stated)			No	Yes	No	Consecutive	Single	No	Treated as negative
Buclin *et al.*, 1988, France[133]	Discharge diagnosis taking into account	ECG changes	Enzyme rise	Clinical features		Unclear	No	No	Consecutive	Single	No	N/S
Craig, 1982, Australia[134]	WHO criteria	WHO criteria	WHO criteria	WHO criteria		Yes	No	No	Consecutive	Single	No	Classed as no MI
Doyle *et al.*, 1988, Ireland[92]		MI not defined	MI not defined	Cardiac CP defined by Rose criteria	MI not defined. Unstable angina = typical pain, serial ST/T changes + normal or less than 2-fold inc. in cardiac enzymes	Yes	Yes	No	Consecutive	Separate	Yes: inpatients vs outpatients	Excluded
Fesmire *et al.*, 1989, USA[41]	1 or more from	If no rise in CK, then new pathological Q waves	CK >269 IU/l plus CKMB >2.2% plus characteristic rise + fall in serial enzymes		If rapid demise then autopsy proven MI	Yes	Yes	No	Consecutive	Single	No	Excluded
Fesmire *et al.*, 1998, USA[42]	WHO criteria and/or sudden death	WHO criteria	WHO criteria	WHO criteria	Patient death within 24 h	Yes	Yes	No	Consecutive	Single	Yes AMI, angina	N/S

continued

TABLE 43 *Acute resting ECG: reference standard and potential biases (cont'd)*

Paper	Reference standard description	Reference standard for MI unless stated otherwise[a]				Incorporation bias	Blinding	Verification/ work-up bias (%)	Selection of the study sample	Study population	Sub-groups	Indeterminate results
		ECG	Enzymes	Clinical	Other							
Foster *et al.*, 1994, USA[77]		'Conventional ECG criteria for MI'	Conventional 'enzyme criteria for MI'			No	Yes	No	Consecutive	Single	No	N/S
Foy *et al.*, 1991, New Zealand[58]	Enzymes alone		Peak CK ≥ 2 × ULN			Yes	Yes	No	Consecutive	Single	No	N/S
Gama *et al.*, 1990, UK[137]	Clinical features plus one or more from	'Characteristic ECG changes'	Raised enzymes 2 × ULN	'Characteristic history'		Yes	No	No	Consecutive	Single	No	Treated as negative
Goldman *et al.*, 1982, USA[50]	1 or more from	New Q waves + at least 25% decrease in amplitude of following R wave	SGOT ≥ 2 × admission value; or CKMB ≥ 5% total CK or LDH1 >LDH2		Focal Tc-99 uptake	Unclear	Unclear	No	Consecutive	Single	No	Excluded
Gray *et al.*, 1993, UK[51]	1 or more from	Sequential ST segment changes with new path Q waves	≥ 2 × ULN rise in cardiac enzymes			Unclear	No	No	Consecutive	Single	No	Classified as no MI
Grijseels *et al.*, 1995, The Netherlands[79]	WHO criteria	WHO criteria	WHO criteria	WHO criteria		Yes	No	No	Consecutive	Single	Yes Abnormal ECG	Excluded
Grim *et al.*, 1989, USA[76]		Admission ECG: ST changes compatible with AMI	CK increase; CKMB ≥ 5%; LDH +ve			Yes	Yes	No	Other		No	

continued

TABLE 43 *Acute resting ECG: reference standard and potential biases (cont'd)*

Paper	Reference standard description	Reference standard for MI unless stated otherwise[a]				Incorporation bias	Blinding	Verification/ work-up bias (%)	Selection of the study sample	Study population	Sub-groups	Indeterminate results
		ECG	Enzymes	Clinical	Other							
Gustafsson *et al.*, 1996, Sweden[73]	2 or more from	ECG changes in 2 leads: Q waves or ST elevation followed by T wave inversion	Increase in CK or CKMB typical of AMI in first 24 h	>20 minutes typical CP		Unclear	Unclear	No	Consecutive	Single	No	Excluded
Hands *et al.*, 1988, USA[59]	Enzymes only		Rises above 13 IU/l in CKMB in serial samples			No	Yes	No	Consecutive	Separate	Yes: PMH CHD	N/S
Hedges *et al.*, 1992, USA[138]	WHO criteria	WHO criteria	WHO criteria	WHO criteria		No	Yes	No	Consecutive	Single	No	Excluded
Jonsbu *et al.*, 1993, Norway[43]	Consensus diagnosis taking into account all available patient information including	ECG changes	Enzymes changes	Clinical characteristics	Radionucleotide scan where available; autopsy where available	Yes	Yes	Unclear	Consecutive	Single	No	N/S
Justis *et al.*, 1992, USA[75]		TIMI -II criteria for diagnosis of MI	Peak CKMB ≥ 23 IU/ml			No	Yes	Yes	Consecutive	Single	No	Excluded
Karlson *et al.*, 1991, Sweden[87]	2 of following: for 'confirmed AMI'	New 2 mm in ≥ 2 leads	AST > normal from ≥ 2 different days	CP duration ≥ 15 minutes		Yes	Unclear	No	Consecutive	Single	No	Other
Kellett, 1997, Ireland[67]	WHO criteria	WHO criteria and/ or TnT	WHO criteria and/or TnT	WHO criteria and/ or TnT		Unclear	Unclear	No	Consecutive	Single	No	Other (sensitivity analysis

continued

TABLE 43 *Acute resting ECG: reference standard and potential biases (cont'd)*

Paper	Reference standard description	Reference standard for MI unless stated otherwise[a]				Incorporation bias	Blinding	Verification/ work-up bias (%)	Selection of the study sample	Study population	Sub-groups	Indeterminate results
		ECG	Enzymes	Clinical	Other							
Kudenchuk *et al.*, 1998, USA[44]	Final hospital diagnosis of MI or ACS		Elevation	Characteristic symptoms	Autopsy/ angiography	Unclear	Yes	No	Consecutive	Single	Yes: randomised Y/N; thrombolysis: pre-hospital/ in hospital	N/S
Lee *et al.*, 1985, USA[53]	1 or more from	New Q waves with reduction in R wave	Enzyme rise >ULN		Focal uptake of Tc-99m on scintiscan	No	Yes	Enzymes available for 71%	Consecutive	Separate	Yes: gender, age PMH CHD, pain quality	N/S
Lee *et al.*, 1989, USA[45]	1 or more from	New Q + at least 25% amplitude of the following R wave. A hospital official ECG reader acted as reference standard	Characteristic elevation of serum enzyme levels including CKMB		Scintiscan showing local uptake of technetium-99m, stannous pyrophosphate or sudden unexplained death within 72 h of presentation	No	Yes	No	Consecutive	Single	No	Excluded
Lee *et al.*, 1990, USA[84]	1 from	New pathological Q waves (≥ 0.04 s duration) with reduction of ≥ 25% in following R wave	Characteristic elevation of serum enzyme levels	Sudden death within 72 h if clinical course/ECG most consistent with acute MI	Focal uptake of technetium-99m, stannous pyrophosphate	No	Yes	No	Consecutive	Single	Yes: presence of previous ECG	N/S

continued

TABLE 43 *Acute resting ECG: reference standard and potential biases (cont'd)*

Paper	Reference standard description	Reference standard for MI unless stated otherwise[a]				Incorporation bias	Blinding	Verification/ work-up bias (%)	Selection of the study sample	Study population	Sub-groups	Indeterminate results
		ECG	Enzymes	Clinical	Other							
Mair *et al.*, 1995, Austria[78]	WHO criteria	WHO criteria	WHO criteria	WHO criteria		Unclear	Unclear	No	Other	Single	No	N/S
Mair *et al.*, 1995, Austria[69]	WHO criteria	WHO criteria	WHO criteria	WHO criteria		Unclear	Yes	No	Other	Single	No	Other
Miller *et al.*, 1987 USA[61]	Enzymes only		CK > ULN			Yes	No	No	Consecutive	Single	Yes: PMH MI	N/S
Otto *et al.*, 1994, USA[71]	WHO criteria	WHO criteria	WHO criteria	WHO criteria		No	Yes	No	Consecutive	Single	Yes: Gender	N/S
Patel *et al.*, 1996, UK[46]	Prolonged CP plus ECG or enzyme changes	Development of new Q waves	Rise ≥ 2 × ULN	Prolonged CP	Cardiac death	Yes	Yes	No	Consecutive		No	N/S
Pozen *et al.*, 1984, USA[90]	Final blinded physician's diagnosis	WHO criteria	WHO criteria	WHO criteria		Yes	Yes	No	Consecutive	Separate	No	
Rohl *et al.*, 1992, Germany[89]	2 or more from	Pathological Q waves or ST-T waves characteristic of MI	Revised CK with CKMB ≥ 6%	Angina ≥ 30 minutes duration not responding to nitrates		Unclear	Unclear	No	Consecutive	Single	No	Excluded
Rouan *et al.*, 1989, USA[47]	1 or more from the following	New Q waves (≥ 0.04 s duration, ≥ 25% decrease of R wave following) compared to 1st ECG	CK: trace or ≥ 5% elevation MB with typical rise and fall; LDH elevation		(1) Local uptake of technetium on scintiscan; (2) sudden unexplained death within 72 h	Unclear	Yes	Yes (43% had follow-up enzymes)	Consecutive	Single	Yes: suggestive vs normal ECG	Excluded

continued

TABLE 43 *Acute resting ECG: reference standard and potential biases (cont'd)*

Paper	Reference standard description	Reference standard for MI unless stated otherwise[a]				Incorporation bias	Blinding	Verification/ work-up bias (%)	Selection of the study sample	Study population	Sub-groups	Indeterminate results
		ECG	Enzymes	Clinical	Other							
Rude *et al.*, 1983, USA[60]	Enzymes only		Elevation of CK or CK isoenzymes within 72 h of admission			No	Yes	No	Consecutive	Single	No	Other
Sgarbossa *et al.*, 1996, USA[139]	All patients had left BBB + CP	Left BBB on baseline ECG	CKMB elevated			No	Yes	Unclear	Other	Separate	No	N/S
Shlipak *et al.*, 1999, USA[140]	Consensus of three investigators using		Elevation: Troponin I ≥ 1.5 mg/l or CKMB ≥ 7u/l; 73% total	'Characteristic clinical presentation'		No	Yes	No	Consecutive	Single	No	N/S
Short, 1981, UK[62]	Combination of	Evolving ECG consistent with infarction	Rise of AST to ≥ 2 × upper limit	CP consistent with CHD		Yes	No	No	Consecutive	Single	Yes: PMH CHD	N/S
Singer *et al.*, 1997, USA[68]	International diagnostic criteria	'Diagnostic ECG findings'	'Typical increases and decreases'	'Prolonged myocardial ischaemic symptoms'		Unclear	Yes	No	Consecutive	Single	No	Excluded

continued

TABLE 43 *Acute resting ECG: reference standard and potential biases (cont'd)*

Paper	Reference standard description	Reference standard for MI unless stated otherwise[a]				Incorporation bias	Blinding	Verification/ work-up bias (%)	Selection of the study sample	Study population	Sub-groups	Indeterminate results
		ECG	Enzymes	Clinical	Other							
Solomon *et al.*, 1989, USA[63]	1 or more from	Q waves (>0.04 minutes duration) with 25% decrease in following R wave as compared with ED ECG	CKMB present or CKMB ≥ 5% of elevated total CK, with typical rise and fall of LDH in absence of lysis or renal impairment or CK rise and fall, with peak at least 2 × ULN	Sudden unexplained death	If late presentation (i.e. enzymes peak likely prior to admission) and no PMH of MI or valvular calcification, then local area of uptake in cardiac area of scintiscan	Yes	Unclear	Yes	Consecutive	Single	Yes: age	N/S
Tierney *et al.*, 1985, USA[135]	1 from	Pathological Q waves on FU ECG not present on the A&E tracing ECG. Criteria only used where enzymes not available	Raised total CK + CKMB >4% total or LDH1 ≥ LDH2 for patients without renal infarction or haemolysis			No	Yes	No	Consecutive	Single	Yes: gender, age, ethnicity	Excluded

continued

TABLE 43 *Acute resting ECG: reference standard and potential biases (cont'd)*

Paper	Reference standard description	Reference standard for MI unless stated otherwise[a]				Incorporation bias	Blinding	Verification/ work-up bias (%)	Selection of the study sample	Study population	Sub-groups	Indeterminate results
		ECG	Enzymes	Clinical	Other							
Tierney *et al.*, 1986, USA[55]	1 from	If no enzyme available, MI diagnosed if new abnormal Q waves on following ECG	Elevated total CK with CKMB >4% or LDH1 isoenzyme ≥ LDH2			No	Yes	No	Consecutive	Single	No	Excluded
Tighe *et al.*, 1996, Ireland[141]	Combination of	Evolutionary ECG changes	CK > 2 × ULN			No	Yes	No	Consecutive	Single	No	N/S
Weaver *et al.*, 1990, USA[66]	Discharge diagnosis of MI. No specific features given	Not stated	Not stated	Not stated		Unclear	Unclear	No	Consecutive	Single	No	Treated as negative
Yusuf *et al.*, 1984, UK[72]	1 or more from	20% reduction in 'R wave score'	CKMB > twice normal limit			No	No	Yes (95.2)	Consecutive	Single	No	Treated as positive
Zalenski *et al.*, 1993, USA[74]	Discharge diagnosis of MI plus 1 or more from	New pathological Q waves, or existing Q waves if with ST elevation	CKMB/CK rise of 5% or more			Unclear	Unclear	No	Other	Single	No	Other
Zalenski *et al.*, 1997, USA[48]	WHO criteria and/or sudden death	WHO criteria	WHO criteria	WHO criteria	Patient died on first day with consistent clinical features of AMI	Yes	Unclear	No	Consecutive	Single	No	N/S

[a] IU, international unit.

TABLE 44 *Black box: general details*

Paper	Setting	Inclusion criteria	Exclusion criteria	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Aufderheide *et al.*, 1992, USA[57]	A&E and secondary care	Cooperative; initially stable; adult pre-hospital patients with a chief complaint of non-traumatic CP of presumed ischaemic origin	Patients with VT; VF; 2nd- or 3rd-degree heart block; SBP <90 or, if in the opinion of the paramedics, the acquisition of a pre-hospital 12-lead ECG or study info would alter patient care	N/S			N/S	N/S	439
Baxt *et al.*, 1996, USA[83]	A&E	Presenting to ED with anterior CP, ≥ aged 18 years	Age <18 years	54			780	290	1070
Baxt, 1991, USA[86]	Secondary care	Age >18 years presenting to A&E with CP	Where no FU was available	52			192	139	331
Behar *et al.*, 1977, Israel[85]	A&E	Presumed MI	ECG not available	N/S			N/S	N/S	1578
Doyle *et al.*, 1988, Ireland[92]	A&E	Anterior or left-sided CP	Age <18 years	53			270	181	451
Goldman *et al.*, 1982, USA[50]	A&E	Age ≥ 30 years. Chief complaint anterior, precordial or left lateral CP unexplained by obvious local trauma or CXR abnormalities	Obvious local trauma or chest-film abnormalities. Age <30 years in Yale, <25 years in Brigham (non-signing of consent form only in Brigham ≤ 30)	N/S			N/S	N/S	482
Gray *et al.*, 1993, UK.[51]	Secondary care	Patients admitted with CP who had serial cardiac enzymes + ECG	Working diagnosis not clear (1–17%)	N/S			N/S	N/S	15135
Heden *et al.*, 1997, Sweden[81]	A&E	Patients attending A&E 1990–95 who had an ECG	Uninterpretable ECG; pacemakers	65			5974	5598	11572
Herlitz *et al.*, 1995, Sweden[82]	Primary and secondary care	Age <75 years CP of between 15 minutes and 2 hours 45 minutes duration	Contraindications to thrombolysis: diastolic BP ≥ 120	N/S			N/S	N/S	352

continued

TABLE 44 *Black box: general details (cont'd)*

Paper	Setting	Inclusion criteria	Exclusion criteria	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Karlson *et al.*, 1991, Sweden[87]	A&E	Presenting to ER with 'CP or other symptoms suggestive of AMI' and subsequently admitted to hospital		N/S			N/S	N/S	7157
Lee *et al.*, 1990, USA[84]	A&E	Age >30 years, with chief complaint of anterior, precordial, or left-sided CP unexplained by trauma or CXR	Patients not admitted who would not consent to FU at 48–72 h. No information on prior trace. No ECG interpretation. Self-discharges	59			2879	2794	5673
Mair *et al.*, 1995, Austria[78]	A&E	CP	Trauma. Admitted between 10 p.m. and 6 a.m.	60[a]	21	89	77	37	114
Pozen *et al.*, 1980, USA[91]	A&E and secondary care	'Suspected acute CHD'. Male >30 years, female >40 years		55			245	156	401
Pozen *et al.*, 1984, USA[90]	A&E	Consent given. Male ≥ 30 years, female ≥ 40 years. Chief symptoms CP, jaw or left arm pain and SOB or changed pattern of angina	Male <30 years, female <40 years. No consent. Presenting at inconvenient time of day	62			1299	1021	2320
Rohl *et al.*, 1992, Germany[89]	Secondary care	Patients with MI or acute CP. Age >30 years	Patients with traumatic/non-cardiac CP; life-threatening arrhythmia; haemodynamic instability needing intensive care	N/S			N/S	N/S	615

[a] Median.

TABLE 45 *Black box: reference standard and potential biases*

Paper	Type of test	Reference standard description	Reference standard for MI unless stated otherwise				Incorporation bias	Blinding	Verification/ work-up bias	Selection of the study sample	Study population	Sub-groups	Indeterminate results
			ECG	Enzymes	Clinical	Other							
Aufderheide *et al.*, 1992, USA[57]	ECG A&E diagnosis			For MI – Abnormal elevation of CKMB and/or LDH within 72 h of admission		For angina – the diagnosis was determined by the safety committee investigators after hospital chart review	No	Unclear	No	Consecutive	Single	No	Excluded
Baxt *et al.*, 1996, USA[83]	A&E diagnosis	1 or more from	New pathological Qs (at least 0.04 s) and at least 25% decrease in following R wave amplitude	Raised CK with CKMB ≥ 5%			No	Yes	No	Consecutive	Single	Unclear	Excluded
Baxt, 1991, USA[86]	A&E diagnosis	1 or more from	New Q waves (at least 0.05 s) + at least 25% decrease in the amplitude of the following r wave	Characteristic of serum enzyme level including CKMB ≥ 5% total CK or LDH1 >LDH2		Scintiscan showing local uptake of technetium-99 in cardiac area if enzymes peaked before hospital	No	Yes	No	Consecutive	Single	No	Excluded
Behar *et al.*, 1977, Israel[85]	Admission to hospital	WHO criteria	WHO criteria	WHO criteria	WHO criteria	Yes	No	No	Consecutive	Single	No	Excluded	

continued

TABLE 45 *Black box: reference standard and potential biases (cont'd)*

Paper	Type of test	Reference standard description	Reference standard for MI unless stated otherwise				Incorporation bias	Blinding	Verification/ work-up bias	Selection of the study sample	Study population	Sub-groups	Indeterminate results
			ECG	Enzymes	Clinical	Other							
Doyle *et al.*, 1988, Ireland[92]	Admission to hospital		MI not defined	MI not defined	Cardiac chest pain defined by Rose criteria	Unstable angina = typical pain, serial ST/T changes + normal or less than 2-fold inc. In cardiac enzymes	Unclear	Yes	No	Consecutive	Single	Yes inpatients vs. outpatients	Excluded
Goldman et al., 1982, USA[50]	Admission to hospital	1 or more from	New Q waves and at least 25% decrease in amplitude of following R wave	SGOT >2 × admission value; OR CKMB above 5% total CK or LDH1 (isoenzyme) > LDH2		Focal uptake of technetium-99	Unclear	Unclear	No	Consecutive	Single	No	Excluded
Gray *et al.*, 1993, UK[51]	A&E diagnosis	1 or more from	Evolution of sequential ST segment changes with new pathological Q waves	Elevation of serum cardiac enzymes to ≥ 2 × ULN			No	No	No	Consecutive	Single	No	Not specified

continued

TABLE 45 *Black box: reference standard and potential biases (cont'd)*

Paper	Type of test	Reference standard description	Reference standard for MI unless stated otherwise				Incorporation bias	Blinding	Verification/ work-up bias	Selection of the study sample	Study population	Sub-groups	Indeterminate results
			ECG	Enzymes	Clinical	Other							
Heden *et al.*, 1997, Sweden[81]	ECG	2 or more from	Serial changes – new Q waves in at least 2 adjacent leads and/or persistent T inversions in ≥ 2 leads after newly developed ST elevation in same lead	CKMB >0.23μkat/l with typical rise and fall	Characteristic CP >20 minutes		Yes	Yes	No	Other	Separate	No	Excluded
Herlitz *et al.*, 1995, Sweden[82]	History and examination	2 or more from	Appearance of Q waves in 1st 3 days in at least 2 leads	At least 2 values above normal range of CK/CKMB	>15 minutes pain indicative of AMI		Yes	Unclear	No	Consecutive	Single	No	Not specified
Karlson *et al.*, 1991, Sweden[87]	A&E diagnosis	2 or more from	New Q waves in ≥ 2 leads	AST > ULN on ≥ 2 different days	CP ≥ 15 minutes		Yes	Unclear	No	Consecutive	Single	No	Not specified
Lee *et al.*, 1990, USA[84]	Admission to hospital	1 or more from	New pathological Q waves (≥ 0.04 s duration) with reduction of ≥ 25% in following R wave	Characteristic evolution of serum enzyme levels	Sudden death within 72 h if clinical course/ ECG most consistent with acute MI	Focal uptake of technetium-99m, stannous pyrophosphate	No	Yes	No	Consecutive	Single	Yes: presence of previous ECG	

continued

TABLE 45 *Black box: reference standard and potential biases (cont'd)*

Paper	Type of test	Reference standard description	Reference standard for MI unless stated otherwise				Incorporation bias	Blinding	Verification/ work-up bias	Selection of the study sample	Study population	Sub-groups	Indeterminate results
			ECG	Enzymes	Clinical	Other							
Mair *et al.*, 1995, Austria[78]	ECG	WHO criteria, judged by independent cardiologist	WHO criteria	WHO criteria	WHO criteria		Unclear	Unclear		Other	Single	No	Not specified
Pozen *et al.*, 1980, USA[91]	A&E diagnosis	Combination of	Standard criteria	Standard criteria	Standard criteria		No	No	No	Consecutive	Single	No	Excluded
Pozen *et al.*, 1984, USA[90]	A&E diagnosis	Final blinded physician's diagnosis using WHO criteria	WHO criteria	WHO criteria	WHO criteria		Yes	Yes	No	Consecutive	Separate	No	
Rohl *et al.*, 1992, Germany[89]	A&E diagnosis	2 or more from	Pathological Q waves or ST-T waves characteristic of MI	Revised CK with CKMB ≥ 6%	Angina ≥ 30 minutes duration not responding to nitrates		Unclear	Unclear	No	Consecutive	Single	No	Excluded

AST, aspastate aminotransferase.

TABLE 46 *Chronic exercise ECG: general details*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Acanfora *et al.*, 1991, Italy[142]	Secondary care	CP	PMH MI; HT; cardiogram op. AF; paced valve disease; heart failure; severe arrhythmias; severe systematic disease; LVH or RVH; BBB; pre-excitation syndrome	42	28	76	126	38	164
Alexander *et al.*, 1998, USA[143]	Secondary care	Evaluation for CP; angio within 90 days of ETT	Cardiac catheterization; CABG; acute MI; Significant valvular or congenital disease; resting ST changes; BBB	50			2249	976	3225
Alijarde-Guimera *et al.*, 1983, Spain[144]	Secondary care	Patients referred for the assessment of CP who had had coronary angiography and maximal treadmill stress tests	Previous MI; unstable angina; cardiomyopathy; valvular or congenital heart disease; Prinzmetal's angina; mitral valve prolapse; intraventricular conduction delay or obvious ECG LVH and those on β-blockers or digoxin during preceding 48 h or amiodarone during last 2 months. Also patients without exercise-induced ST segment changes who did not achieve 85% or the maximal age-predicted HR	48	38	71	87	18	105
Aparici *et al.*, 1989, Spain[145]	Secondary care	Suspected coronary artery disease presenting at institution	Digoxin; antiarrhythmics; PMH MI	60			154	0	154
Ascoop *et al.*, 1971, The Netherlands[146]	Secondary care	CP + ETT + angio; normal ECG at rest; no other cardiac abnormalities	Abnormal ECG; other non-ischaemic cardiac abnormalities	46	30	63	85	11	96
Atwood *et al.*, 1998, USA and Hungary[147]	Secondary care	Males who had exercise tests and coronary angios to evaluate CP or other findings thought to be due to coronary disease	Incomplete data; females; previous cardiac surgery; valve disease; left BBB; WPWs; previous MI excluded from diagnostic sub-group	59			1384	0	1384
Balnave *et al.*, 1978, UK[148]	Secondary care	Not clear	Not clear	50	35	66	57	13	70

continued

TABLE 46 *Chronic exercise ECG: general details (cont'd)*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Baron *et al.*, 1980, UK[149]	Secondary care	Patients referred for investigation of CP	Patients with rest pain; digoxin therapy; left BBB; hypertrophic cardiomyopathy	52			71	22	93
Barthelemy *et al.*, 1996, France[150]	Secondary care	Patients referred for suspicion of CAD based on symptoms, positive ETT or referred for angio	Abnormal ECG at rest; ST segment decrease; T wave changes included by hyperventilation; PMH MI; CCF; cardiomyopathy; valvular heart disease	55	31	76	236	0	236
Berman *et al.*, 1980, USA[151]	Secondary care	Bruce ETT + angio within 6 weeks	BBB	49	21	69	167	63	230
Bonoris *et al.*, 1978, USA[152]	Secondary care	ETT + angio + referred for evaluation of CP	Cardiac valve disease; cardiomyopathy; conduction defects; premature ventricular complexes or HT; digitalis; β-blockers; GTN; diuretics	52	35	71	67	22	89
Bungo *et al.*, 1983, USA[153]	Secondary care	CP or symptoms suggestive of CHD	Medications that would influence results	48[b]	23	70	59	22	81
Campos *et al.*, 1983, USA[154]	Secondary care	Patients who had had cardiac catheterization and who went on to have ETT (and/or RNA)	Previous cardiac surgery or significant valvular disease	N/S			N/S	N/S	233
Cantor *et al.*, 1998, Israel[155]	Secondary care	Female patients undergoing exercise testing and thallium scanning for detection of CHD	Intraventricular conduction defects; valvular heart disease; LVH; cardiomyopathy; those receiving anti-arrhythmics	55	27	83	0	101	101
Chaitman *et al.*, 1978, Canada[156]	Secondary care	CP + ETT + angio	PMH MI; abnormal resting ECG	49	31	62	100	0	100
Cheng *et al.*, 1999, USA[157]	Secondary care	History of CP with ETT + angio within 2 months	MI <3 months from test date; valvular heart disease; CABG; left BBB	59			176	74	250
Chikamori *et al.*, 1994, Japan[158]	Secondary care	Suspected CAD	Complete BBB; previous MI; WPW; digitalis treatment	62	34	85	224	123	347

continued

TABLE 46 *Chronic exercise ECG: general details (cont'd)*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Chikamori *et al.*, 1995, Japan[159]	Secondary care	Consecutive patients suspected of having CAD	Complete BBB; WPW; digitalis	62	34	85	234	132	366
Ciaroni *et al.*, 1998, Switzerland[160]	Secondary care	Patients investigated for CP query angina	Murmur; old MI on ECG; dilated cardiomyopathy; valve disease; CABG; angioplasty; chronic chest disease; left BBB; right BBB; WPW; calcium channel blockers; nitrates; β-blocks; digoxin	56	46	69	431	357	788
Currie *et al.*, 1983, Australia[161]	Secondary care	Age <66 years; no MI; no other cardiac disease or conduction abnormality. Undergoing angio because of CP	Not specified	51	30	64	105	0	105
Curzen *et al.*, 1996, USA[162]	Secondary care	All women with CP who underwent coronary angio + ETT	Path Q; left/right BBB on resting ECG; valvular or congenital heart disease; previous CHD on angio; inability to perform ETT	57	25	93	0	205	205
Demange *et al.*, 1992, France[163]	Secondary care	CP	PMM MI; very old; unstable angina; valve disease; AF; left BBB; digitalis; amiodarone	57	38	75	76	24	100
Detrano *et al.*, 1984, USA[164]	Secondary care	Suspected coronary disease	Previous MI; valvular disease; unstable angina; serious arrhythmia; left BBB; extreme obesity; unable to do ETT	54			111	43	154
Detrano *et al.*, 1986, USA[165]	Secondary care	Referred for angio with suspected CAD	Refusal to undergo ETT; severe valvular or cardiomyopathic disease; unstable angina; serious arrhythmia; left BBB; extreme obesity or neurological or orthopaedic conditions precluding performance of an ETT	54	29	77	206	97	303

continued

TABLE 46 *Chronic exercise ECG: general details (cont'd)*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Detrano *et al.*, 1987, USA[166]	Secondary care	Patients referred for angio who did not have a history or ECG evidence of MI	Refusal to undergo ETT; severe valvular or cardiomyopathic disease; unstable angina; serious arrhythmia; left-BBB; extreme obesity or neurological or orthopaedic conditions precluding performance of an ETT	54	29	77	185	86	271
Detry *et al.*, 1977, USA[167]	Secondary care	CP	BBB; valvular heart disease; digitalis	48	27	65	231	47	278
Detry et al., 1978, Belgium[168]	Secondary care	Typical or atypical CP	Prior MI; valvular heart disease; cardiomyopathy; HT; BBB; ECG LVH	47	33	64	0	53	53
Do *et al.*, 1997, USA[17]	Secondary care	Underwent exercise ECG for suspected CAD with complete data available on coronary angio within 3 months of exercise test	Previous MI or CABG; valvular heart disease; left BBB; Q waves on resting ECG	N/S			718	0	718
Dressendorfer *et al.*, 1989, USA.[169]	Secondary care	Patients with exertional CP referred for angio with a preliminary diagnosis of definite or possible angina	Orthopaedic limitations; unstable angina; heart failure; clinical history of MI; uncontrolled HT; digitalis; previous angio; abnormal 12-lead ECG	56	45	68	48	17	65
Egloff *et al.*, 1987, Italy[170]	Secondary care	Patients referred because of CP or previous MI. Athletes referred for evaluation	Valvular heart disease; cardiomyopathy; conduction defects; pre-excitation syndromes and mitral valve prolapse. Those on digoxin, β-blockers, calcium antagonists or diuretics	49	23	67	130	0	130
Froelicher *et al.*, 1998, USA[171]	Secondary care	Men $\geq$ 18 years with probable or definite stable angina	Previous MI or abnormal angiogram	58			814	0	814

continued

TABLE 46 *Chronic exercise ECG: general details (cont'd)*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Hecht *et al.*, 1980, USA[172]	Secondary care	Patients undergoing diagnostic cardiac catheterisation with suspected CHD. Selected on the basis of availability of the isotope for thallium testing	Not specified	53	31	71	104	2	106
Helfant *et al.*, 1973, USA[173]	Secondary care	Stable chest discomfort for ≥ 3 months; normal resting ECG	Valvular or congenital heart defects; cardioactive medications	N/S			N/S	N/S	65
Herpin *et al.*, 1995, France[174]	Secondary care	Referred to clinic with history of CP	Prior MI; taking digitalis or amiodarone; unstable angina; patent hypertrophic cardiomyopathy; valvular disease; left BBB; AF	60	34	76	113	47	160
Herpin *et al.*, 1996, France[175]	Secondary care	Patients referred for the evaluation of CP. None had prior MI	Taking digoxin or amiodarone; unstable angina; hypertrophic cardiomyopathy; valvular disease; left BBB or AF	60	34	76	113	47	160
Herpin *et al.*, 1998, France[176]	Secondary care	CP; 'moderate or high risk of CAD'	Previous MI; taking digoxin or amiodarone; unstable angina; patent hypertrophic cardiomyopathy or valve disease; LBBB; AF	59	34	76	148	52	200
Hoberg *et al.*, 1991, Germany[177]	Secondary care	Clinically stable angina; β-blockers	LBBB; on digoxin; ≥ 1 mm ST depression on resting ECG; previous MI; or ECG evidence on previous MI; unstable angina; cardiomyopathy; AF	55	37	70	143	29	172
Ibrahim *et al.*, 1998, USA[178]	Secondary care	Left BBB + ETT + angio	Left BBB induced by exercise; pharmacological stress; pacemakers; >3 months between angio and treadmill	N/S			N/S	N/S	41

continued

TABLE 46 *Chronic exercise ECG: general details (cont'd)*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Ilsley *et al.*, 1982, UK[179]	Secondary care	Women being investigated for CP and who had 12-lead ETT and cardiac catheterization at the National Heart Hospital	ECG evidence of prior MI; conduction defects such as BBB or AF; those taking digoxin; those with rheumatic or congenital heart disease or hypertrophic cardiomyopathy	51	29	64	0	62	62
Jelinkova *et al.*, 1997, Czech Republic[180]	Secondary care	Typical angina pectoris	BBB; ventricular hypertrophy; ventricular pre-excitation; MI <3 months ago; cardiac surgery; PTCA; valvular or congenital heart disease; patients receiving digitalis	50			0	102	102
Kajinami *et al.*, 1995, Japan[181]	Secondary care	Patients undergoing elective angio. CP or ECG suggesting ischaemia	Unstable condition; PMH CABG or angioplasty; Q waves	56	16	86	174	77	251
Kisacik *et al.*, 1996, Turkey[182]	Secondary care	Patients for investigation of CP	Unstable angina; uncontrolled HT; recent (<2 months) MI; major ventricular arrhythmias; cardiomyopathy; permanent pacemaker; CCF; significant valvular disease; patients with a poor basal echocardiographic window; patients unable to exercise adequately	51	29	70	58	11	69
Kramer *et al.*, 1978, USA[183]	Secondary care	Referred for evaluation of CP syndrome	Valvular or congenital heart disease; HT; LVH; BBB; previous cardiac surgery; inotropic drugs	47	29	68	87	28	115
Lachterman *et al.*, 1990, USA[184]	Secondary care	Men; routine clinical exercise testing and angio	Women; recent MI; left BBB; Had PTCA or CABG	59			328	0	328
Lachterman *et al.*, 1991, USA[185]	Secondary care	Most were referred because of CP	No angiogram; left BBB women; MI; CABG; angioplasty	59			271	0	271

continued

TABLE 46 *Chronic exercise ECG: general details (cont'd)*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Linhart *et al.*, 1974, USA[116]	Secondary care	Angio + ETT (mostly CP)	Not specified	46	18	66	0	98	98
Liu *et al.*, 1998, Taiwan[186]	Secondary care	Patients with CP who underwent ETT and thallium imaging	History of MI within last 8 weeks; prior revascularisation; left BBB	59			68	22	90
Lu *et al.*, 1993, Denmark[187]	Secondary care	Patients having angio and ETT	BBB; pre-excitation syndrome; recent MI; cardiac surgery; angioplasty; valvular or congenital heart disease	55	28	76	165	48	213
Macieira-Coelho *et al.*, 1990, Portugal[188]	Secondary care	CP	Previous MI; cardiomyopathy; valvular or congenital heart disease; intraventricular conduction defect	53	32	70	93	20	113
Malczewska *et al.*, 1999, Poland[189]	Secondary care	Women referred for investigation of CP	Pre-excitation syndrome; valvular heart disease; mitral prolapse; cardiac insufficiency; severe renal or liver disease	42			0	106	106
Marcomichelakis *et al.*, 1980, UK[190]	Secondary care	Anginal type CP	Previous MI; BBB on ECG or other conduction abnormalities	48	32	64	50	0	50
McNeer *et al.*, 1978, USA[191]	Secondary care	Patients attending for investigation of CP	No exercise test; too ill for test	N/S			N/S	N/S	1472
Melendez *et al.*, 1979, Canada[192]	Secondary care	Patients with CP	Not specified	N/S			23	20	43
Melin *et al.*, 1985, Belgium[193]	Secondary care	CP; female; having coronary angio	Evidence of MI; valve disease cardiomyopathy; past CABG; BBB or LVH on ECG. Use of digitalis	52	27	69	0	135	135

continued

TABLE 46 *Chronic exercise ECG: general details (cont'd)*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Michaelides *et al.*, 1990, Greece[194]	Secondary care	Patients who underwent a maximal ETT and coronary arteriography within 4 months of each other	BBB; ventricular hypertrophy; ventricular pre-excitation; recent MI (<3 months); history of cardiac surgery; angioplasty; valvular or congenital heart disease; on digoxin	51			232	14	246
Michaelides *et al.*, 1999, Greece[195]	Secondary care	Patients with symptoms resembling angina	Refused angio; left/right BBB; LVH; RVH; ventricular pre-excitation; MI; valvular disease; congenital heart disease; aorto-coronary bypass surgery; angioplasty; digitalis	52	32	74	218	27	245
Moons *et al.*, 1997, The Netherlands[196]	Secondary care	Normal resting ECG; no previous MI; no digitalis	Not specified	N/S	28	70	222	73	295
Morise *et al.*, 1992, USA[197]	Secondary care	Referred to stress laboratory 1983–90 for evaluating whether had CAD. Normal resting ECG	History of MI; coronary angiography; current diagnosis	54			235	185	420
Morise *et al.*, 1995, USA[198]	Secondary care	Referred for 'evaluation of presence of CAD' to a stress laboratory	Previous MI; previous coronary arteriography	56			1007	661	1668
Morise *et al.*, 1995, USA[199]	Secondary care	Presenting to exercise lab. with suspected coronary disease. Coronary angio within 3 months	Angio not due in next 3 months; previous MI; previous angio; on digitalis; uninterpretable ECG (BBB/LVH/WPW, etc.)	52			74	47	121
Morise *et al.*, 1995, USA[200]	Secondary care	Patients referred for the purpose of evaluating CAD	PMH MI or angio; digitalis; other cardiac diagnoses including valvular disease; cardiomyopathy; LVH; left BBB; WPW; ST depression on resting ECG	53			2824	1643	4467

continued

TABLE 46 *Chronic exercise ECG: general details (cont'd)*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Morise *et al.*, 1997, USA[115]	Secondary care	Referral to exercise lab. with 'suspected CAD'	Prior MI or angio; on digitalis; 'uninterpretable exercise ECGs,' left BBB; LVH; WPW; 'other ST-T changes that displace resting ST segment'	46			742	616	1358
Morise *et al.*, 1997, USA[114]	Secondary care	Referral to exercise lab. with 'suspected CAD'	Previous MI or coronary angio; on diagnosis; other cardiac diagnosis: valvular heart disease; myopathy; left BBB; LV hypertrophy; WPW; ST-T changes	53			400	381	781
Morris *et al.*, 1978, USA[201]	Secondary care	ETT + angio; 'known or suspected CAD'	Not specified	50	17	69	348	112	460
Nair *et al.*, 1983, USA[202]	Secondary care	CP; normal ECG at rest; no PVCS at rest	Prior MI; cardiomyopathy; valvular heart disease; anaemia; thyroid disease or electrolyte imbalance	55			197	83	280
Nallamothu *et al.*, 1995, USA[203]	Secondary care	Exercise thallium single photon emission computed tomography and coronary angio within 3 months of each other, normal resting ECG	Digitalis; coronary revascularisation; valvular or congenital heart disease or primary cardiomyopathy	57			241	80	321
Nasrallah *et al.*, 1975, USA[204]	Secondary care	Patients undergoing ETT + angio with CP who had non-specific ST-T changes on resting ECG or normal ECG but on digitalis	ECG showing: MI; LVH; conduction disorder; abnormal hyperventilatory changes before ETT	51			62	31	93
Newman *et al.*, 1980, USA[205]	Secondary care	CP suggestive of CAD and no other evidence of active disease ETT and angio >1 month	MI in last 3 months; lack of consent; participation in physician conditioning programme	51	33	69	53	19	72
Newman *et al.*, 1988, USA[206]	Secondary care	CP	Arteriograms and surgery antedating the exercise test	N/S	65	84	100	53	153

continued

TABLE 46 *Chronic exercise ECG: general details (cont'd)*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Nowak *et al.*, 1993, Sweden[117]	Secondary care	Suspected angina	Presence of pre-excitation; AF or frequent ectopics on resting ECG	61	28	81	145	54	199
Oguzhan *et al.*, 1997, Turkey[207]	Secondary care	Patients referred to clinic for investigation of CP	Unstable angina; recent (<2 months) MI; cardiomyopathy; CCF; significant valvular disease; uncontrolled HT; major arrhythmias; permanent pacemaker and patients with a poor echo window or medical conditions that precluded ETT	51	29	70	59	11	70
Okin *et al.*, 1994, USA[208]	Secondary care	Stable angina	Significant valvular disease; MI in the last 6 weeks or LBBB on resting ECG	59			152	32	184
Paillole *et al.*, 1995, France[209]	Secondary care	NIDDM or IDDM patients suspected of having CAD because complained of either typical angina, atypical angina, rest constricting angina or exercise dyspnoea or because exhibited resting ECG abnormalities including abnormal ST-T segment	Previous MI; ECG resting Q wave abnormalities; unstable angina; left BBB or valvular heart disease; clinical diabetic neuropathy and severe renal insufficiency (creatinine clearance of less than 45 ml/minute). Also patients with asthma.	59	40	70	36	23	59
Papazoglou *et al.*, 1991, Greece[210]	Secondary care	2 exercise tests + coronary angio	Valvular disease; cardiomyopathy; LVH; RVH; left BBB; pre-excitation; prescribed with antiarrhythmics	58			101	8	109
Patterson *et al.*, 1982, USA[211]	Secondary care	Patients referred by their physicians for cardiac catheterization for the evaluation of CP	Valve heart disease; previous MI; cardiomyopathy; previous CABG	52	26	71	64	32	96

continued

TABLE 46 *Chronic exercise ECG: general details (cont'd)*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Piessens *et al.*, 1974, Belgium[212]	Secondary care	CP warranting coronary angio	Congenital heart disease; hypertensive heart disease; rheumatic heart disease; intermittent claudication or a cardiothoracic ratio >0.5. Treatment with digoxin; quinidine; procainamide or β-blockers	47	30	61	59	11	70
Pruvost *et al.*, 1987, France[213]	Secondary care	ETT + angio; 96% for the investigation of CP	Prior MI; valvular disease; cardiomyopathy; complete BBB; WPW; digitalis; diuretics. Did not read 85% of predicted HR with a named ECG	50	20	75	558	0	558
Quyyumi *et al.*, 1984, UK[214]	Secondary care	Patients being investigated for CP and were having angio	Patients on nitrates; calcium antagonists or digoxin; LV aneurysm; uncontrolled HT; left BBB; cardiac arrhythmias	N/S	35	78	61	17	78
Rijneke et al., 1980, The Netherlands[215]	Secondary care	Patients being investigated for CP	An abnormal repolarisation pattern on standard 12-lead ECG, no other heart disease other than CAD; no medication that might influence the depolarisation pattern, e.g. digitalis; anti-arrhythmics; psychotropic drugs	51			565	58	623
Ritchie *et al.*, 1977, USA[216]	Secondary care	'Known or suspected CHD'	Patients with prolonged rest pain	50	24	68	94	7	101
Rodriguez *et al.*, 1993, USA[217]	Secondary care	Patients having exercise testing and angio within 3 months of each other	Digoxin treatment; had MI; underwent CABG surgery; left BBB; LVH; Q waves; ST depression on resting ECG	60			147	0	147
Roitman *et al.*, 1970, USA[218]	Secondary care	Patients with CP who had had both angio and ETT	Unfit for ETT; ECG unsatisfactory; coronary angio unsatisfactory	46	22	68	84	16	100
Rowe *et al.*, 1982, USA[219]	Secondary care	Patients with left BBB	Not specified	N/S			N/S	N/S	57

continued

TABLE 46 *Chronic exercise ECG: general details (cont'd)*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Salazar *et al.*, 1976, Mexico[220]	Secondary care	CP or abnormal ECG	Cardioactive drugs (digitalis; diuretics; β-blockers or coronary vasodilators)	43	22	65	36	14	50
San Roman *et al.*, 1998, Spain[221]	Secondary care	Patients with typical CP and no previous history of CAD	Previous MI; Q wave on ECG; previous revascularization; previous positive stress test; previous angiographically proven CAD; unstable angina; CCF; congenital or valvular heart disease; cardiomyopathy	64			50	52	102
Santinga *et al.*, 1982, USA[222]	Secondary care	Coronary arteriograms within 1 month of exercise electrocardiography	MI; digoxin; LVH; left BBB	51			85	28	113
Santoro *et al.*, 1998, Italy[223]	Secondary care	CP of suspected coronary cause	Documented CAD; known angina; previous MI or arrhythmias; valve disease; cardiomyopathy. Also abnormal baseline ECG; inability to exercise; CIs to exercise; dipyridamole; dobutamine + poor acoustic echo window	N/S			N/S	N/S	60
Sato *et al.*, 1988, Japan[224]	Secondary care	Consecutive patients who underwent both angio and ETT within 3 weeks	Acute or remote MI; unstable angina; vasospastic angina; post-coronary bypass surgery; post-percutaneous transluminal coronary angioplasty; cardiomegaly; HT; resting ECG abnormality; conduction defect; severe arrhythmia; on digoxin	57	30	71	109	33	142
Silverberg *et al.*, 1980, USA[225]	Secondary care	Patients with suspected CAD who underwent diagnostic coronary angio within 2 days	Left BBB; LVH; clinical contraindications to treadmill	52	34	72	96	34	130

continued

TABLE 46 *Chronic exercise ECG: general details (cont'd)*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Sketch *et al.*, 1975, USA[226]	Secondary care	CP; ETT; angio	Valvular heart disease; myocarditis or pericarditis; primary myocardial disease; anaemia; thyroid disease; electrolyte imbalance; digoxin; propranolol; quinidine sulphate	49			195	56	251
Sullivan *et al.*, 1994, UK[227]	Secondary care	Women referred to one cardiologist during 1987–91 with a clinical diagnosis of angina, who went on to have angio. They were matched to men with comparative angiographic outcomes	10 patients were excluded because of valvular or congenital heart disease	N/S			684	202	886
Thwaites *et al.*, 1986, UK[228]	Secondary care	Referred for investigation of CP	Hypertension; BBB; LV aneurysm; arrhythmias or unstable angina	N/S	31	75	66	15	81
Tsuda *et al.*, 1993, Japan[229]	Secondary care	Patient undergoing both exercise test and selective coronary angio to assess the cause of CP	PMH MI; overt heart failure; valvular heart disease; cardiomyopathy	55	33	74	132	49	181
Tucker *et al.*, 1976, USA[230]	Secondary care	Patients who underwent ETT and subsequent cardiac catheterization and coronary angio within 1 week of ETT	Patients on cardiac glycosides; had BBB or had had coronary surgery were excluded		18	70	85	15	100
Turner *et al.*, 1979, New Zealand[231]	Secondary care	Patients suspected as having angina or who gave a past history of MI with subsequent angina	Digoxin effects or other drugs known to influence ST segment response	48			107	18	125
Vovan *et al.*, 1987, France[232]	Secondary care	Patients hospitalised with pain suspected to be angina who had had ETT and angio within 8 days	Aortic or mitral valve disease; LBBB; pre-excitation syndrome; LVH	53			178	49	227

continued

TABLE 46 *Chronic exercise ECG: general details (cont'd)*

Paper	Setting	Inclusion criteria[a]	Exclusion criteria[a]	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Walling *et al.*, 1993, USA[233]	Secondary care	Woman without diagnosed CAD referred for evaluation of CP whose CP was suggestive enough of CAD to warrant angio or if they had several risk factors associated with atypical pain	PMH MI; revascularization; valve disease; conduction disturbances or cardiomyopathy	55	37	79	0	62	62
Weiner *et al.*, 1979, USA and Canada[234]	Secondary care	Symptomatic patients who underwent ETT within 1 month of cardiac catheterization	Unstable angina; previous MI; digitalis treatment; failure to reach 85% of maximum HR in conjunction with a negative test	N/S			1465	580	2045
Weintraub *et al.*, 1984, USA[235]	Secondary care	CP	Cardiac surgery; ECG evidence of myocardial infarction; left BBB; digoxin; congenital; valvular or myopathic heart disease	55			105	42	147
Weintraub *et al.*, 1985, USA[236]	Secondary care	CP	Cardiac surgery; ECG evidence of MI (Q waves); congenital; valvular or myopathic heart disease; left BBB; digitalis	55			105	42	147
Wetherbee *et al.*, 1988, USA[237]	Secondary care	Having tests for evaluation of CP or possible CHD	Valvular heart disease; cardiomyopathy; severe HT; left BBB; pre-excitation or marked ST/T changes on resting ECG	57			132	0	132
Wilson *et al.*, 1993, USA[238]	Secondary care	Flow exercise ECG for 'clinical reasons'	Intraventricular conduction delay; MI within 6 weeks of exercise stress test; AF; heart transplantation; valve disease; prior CABG; premature ventricular contractions or intermittent ventricular pacing	57	27	84	96	33	129

[a] LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy; HT, hypertension; angio, angiography; WPW, Wolff–Parkinson–White syndrome; CCF, congestive cardiac failure; GTN, glyceryl trinitrate RNA< radionuclide angiocardiography; CAD coronary artery disease; PVCS, premature ventricular complexes; NIDDM, non-insulin-dependent diabetes mellitus; HR, heart rate.
[b] Median.

TABLE 47 *Chronic exercise ECG: reference standard and potential biases*

Paper	Type of exercise test	Angiographic reference standard	Other reference standard	Incorporation bias	Blinding	Verification/ work-up bias	Selection of the study sample	Study population	Sub-groups	Indeterminate ETT results
Acanfora *et al.*, 1991, Italy.[142]	Bicycle	>70%		No	Yes	No	Consecutive	Separate	No	Not specified
Alexander *et al.*, 1998, USA[143]	Bruce	>75%		No	Unclear	No	Consecutive	Single	Yes: gender	Not specified
Alijarde-Guimera *et al.*, 1983, Spain[144]	Bruce	>70%		No	Unclear	No	Consecutive	Single	No	Not specified
Aparici *et al.*, 1989, Spain[145]	Bicycle	>70% or >50% LMS		No	Unclear	No	Consecutive	Single	Yes : age	Excluded
Ascoop *et al.*, 1971, The Netherlands[146]	Bicycle	>50%		No	Unclear	No	Other	Single	No	Not specified
Atwood *et al.*, 1998, USA and Hungary[147]	Other treadmill	>50%		No	No	No	Consecutive	Single	No	Not specified
Balnave *et al.*, 1978, UK[148]	Bruce	>50%		No	Yes	No	Other	Single	No	Not specified
Baron *et al.*, 1980, UK[149]	Bruce	>70%		No	Unclear	No	Consecutive	Single	No	Not specified
Barthelemy *et al.*, 1996, France[150]	Bicycle	>70%		No	Yes	No	Consecutive	Single	No	Not specified
Berman *et al.*, 1980, USA[151]	Bruce	>70%		No	Unclear	No	Other	Single	No	Excluded
Bonoris *et al.*, 1978, USA[152]	Other treadmill	>70%		No	Yes	No	Other	Single	No	Not specified
Bungo *et al.*, 1983, USA[153]	Bruce	>70%		No	Unclear	No	Consecutive	Single	No	Not specified
Campos *et al.*, 1983, USA[154]	Bruce	>75%		No	Yes	No	Consecutive	Single	No	Excluded

continued

TABLE 47 *Chronic exercise ECG: reference standard and potential biases (cont'd)*

Paper	Type of exercise test	Angiographic reference standard	Other reference standard	Incorporation bias	Blinding	Verification/ work-up bias	Selection of the study sample	Study population	Sub-groups	Indeterminate ETT results
Cantor *et al.*, 1998, Israel[155]	Bruce		Radionucleotide scan: At least one area clearly ischaemic at effort with redistribution at rest, 4 h after exercise	No	Yes	No	Consecutive	Single	Yes: age	Not specified
Chaitman *et al.*, 1978, Canada[156]	Bruce	>70%		No	Yes	No	Consecutive	Single	No	Excluded
Cheng *et al.*, 1999, USA[157]	Other treadmill	>70%		No	Yes	No	Consecutive	Single	Yes	Not specified
Chikamori *et al.*, 1994, Japan[158]	Bruce	>75%		No	Yes	No	Consecutive	Single	No	Not specified
Chikamori *et al.*, 1995, Japan[159]	Bruce	>75%		No	Yes	No	Consecutive	Single	No	Not specified
Ciaroni *et al.*, 1998, Switzerland[160]	Bicycle	>70% or >50% LMS		No	Unclear	No	Consecutive	Single	Yes: gender	Not specified
Currie *et al.*, 1983, Australia[161]	Bicycle	>50%		No	Yes	No	Consecutive	Single	No	Not specified
Curzen *et al.*, 1996, USA[162]	Not specified	>50%		No	Unclear	No	Consecutive	Single	Yes: age	Not specified
Demange *et al.*, 1992, France[163]	Bicycle	>50%		No	Unclear	No	Consecutive	Single	No	Not specified
Detrano *et al.*, 1984, USA[164]	Bruce	>50%		No	Yes	No	Consecutive	Single	No	Not specified
Detrano *et al.*, 1986, USA[165]	Bruce	>50%		No	Yes	No	Consecutive	Single	No	Excluded

continued

TABLE 47 *Chronic exercise ECG: reference standard and potential biases (cont'd)*

Paper	Type of exercise test	Angiographic reference standard	Other reference standard	Incorporation bias	Blinding	Verification/ work-up bias	Selection of the study sample	Study population	Sub-groups	Indeterminate ETT results
Detrano *et al.*, 1987, USA[166]	Bruce	>50%		No	Yes	No	Consecutive	Single	No	Not specified
Detry *et al.*, 1977, USA[167]	Bicycle	>50%		No	Unclear	No	Consecutive	Single	Yes: gender; PMH CHD	Not specified
Detry *et al.*, 1978, Belgium[168]	Bicycle	>70%		No	Yes	No	Other	Single	No	Not specified
Do *et al.*, 1997, USA[17]	Other treadmill	>70% or >50% LMS		No	Yes	No	Random	Single	No	Not specified
Dressendorfer *et al.*, 1989, USA[169]	Bruce	>70%		No	Yes	No	Consecutive	Single	Yes: use of β-blockers	Not specified
Egloff *et al.*, 1987, Italy[170]	Bicycle	>70% or >50% LMS		No	Unclear	No	Consecutive	Single	No	Not specified
Froelicher *et al.*, 1998, USA[171]	Other treadmill	>50%		No	Yes	No	Consecutive	Single	No	Not specified
Hecht *et al.*, 1980, USA[172]	Bruce	>50%		No	Yes	No	Consecutive	Single	No	Treated as negative
Helfant *et al.*, 1973, USA[173]	Bicycle	>75%		No	Unclear	No	Other	Single	No	Excluded
Herpin *et al.*, 1995, France[174]	Bicycle	>50%		No	Yes	No	Consecutive	Single	No	Excluded
Herpin *et al.*, 1996, France[175]	Bicycle	>50%		No	Yes	No	Consecutive	Single	No	Excluded
Herpin *et al.*, 1998, France[176]	Bicycle	>70% or >50% LMS		No	Yes	No	Consecutive	Single	No	Not specified
Hoberg *et al.*, 1991, Germany[177]	Not specified	>70%		No	No	Unclear	Consecutive	Single	Yes: gender	Not specified
Ibrahim *et al.*, 1998, USA[178]	Other treadmill	>70%		Yes	Unclear	No	Consecutive	Single	No	Excluded

continued

TABLE 47 *Chronic exercise ECG: reference standard and potential biases (cont'd)*

Paper	Type of exercise test	Angiographic reference standard	Other reference standard	Incorporation bias	Blinding	Verification/ work-up bias	Selection of the study sample	Study population	Sub-groups	Indeterminate ETT results
Ilsley *et al.*, 1982, UK[179]	Bruce	>50%		No	Yes	N/S	Consecutive	Single	No	Not specified
Jelinkova *et al.*, 1997, Czech Republic[180]	Bicycle	>70% or >50% LMS		No	Yes	No	Consecutive	Single	No	Excluded
Kajinami *et al.*, 1995, Japan[181]	Bruce	>50%		No	Yes	No	Consecutive	Single	No	Not specified
Kisacik *et al.*, 1996, Turkey[182]	Bruce	>50%		No	Yes	No	Consecutive	Single	No	Not specified
Kramer *et al.*, 1978, USA[183]	Other treadmill	>60%		No	Yes	No	Consecutive	Single	No	Excluded
Lachterman *et al.*, 1990, USA[184]	Other treadmill	>75%		No	Unclear	No	Consecutive	Single	No	Not specified
Lachterman *et al.*, 1991, USA[185]	Other treadmill	>75%		No	Unclear	No	Consecutive	Single	No	Not specified
Linhart *et al.*, 1974, USA[116]	Bruce	>50%		No	Unclear	No	Other	Single		Not specified
Liu et al., 1998, Taiwan[186]	Bruce	>50%		No	Yes	No	Consecutive	Single	Yes: Group 1 = sub-optimal ETT (peak HR <85% maximal predicted); group 2 = optimal ETT (peak HR >85%)	Included as sub-group
Lu *et al.*, 1993, Denmark[187]	Bruce	>70% or >50% LMS		No	Unclear	No	Consecutive	Single	No	Excluded

continued

TABLE 47 *Chronic exercise ECG: reference standard and potential biases (cont'd)*

Paper	Type of exercise test	Angiographic reference standard	Other reference standard	Incorporation bias	Blinding	Verification/ work-up bias	Selection of the study sample	Study population	Sub-groups	Indeterminate ETT results
Macieira-Coelho *et al.*, 1990, Portugal[188]	Bicycle	>75%		No	Yes	No	Consecutive	Single	No	Not specified
Malczewska *et al.*, 1999, Poland[189]	Bruce	>50%		No	Unclear	No	Consecutive	Separate	No	Not specified
Marcomichelakis *et al.*, 1980, UK[190]	Bruce	>50%		No	Unclear	No	Consecutive	Separate	Yes: (a) angina symptoms; (b) no pain but abnormal ECG	Not specified
McNeer *et al.*, 1978, USA[191]	Bruce	>75%		No	No	No	Consecutive	Single	Yes: β-blockers, HR	Excluded
Melendez *et al.*, 1979, Canada[192]	Bruce	>50%		No	Yes	No	Consecutive	Single	Yes: typical/ atypical CP	Negative
Melin *et al.*, 1985, Belgium[193]	Bicycle	>50%		No	Yes	No	Consecutive	Single	No	Not specified
Michaelides *et al.*, 1990, Greece[194]	Other treadmill	>70% or >50% LMS		No	Yes	No	Consecutive	Single	Yes	Excluded
Michaelides *et al.*, 1999, Greece[195]	Bruce	>70% or >50% LMS		No	Yes	No	Consecutive	Single	No	Excluded
Moons *et al.*, 1997, The Netherlands[196]	Bicycle	Visual reduction in luminal diameter of a ≥ 1 major artery		No	Yes	No	Consecutive	Single	Yes: age	Not specified
Morise *et al.*, 1992, USA[197]	Bruce	>50%		No	Yes	No	Consecutive	Single	No	Not specified
Morise *et al.*, 1995, USA[200]	Bruce	>50%	Probability of CAD independent of angio + ST depression in exercise test	No	Yes	Yes 18% had angios	Consecutive	Single	Yes: angio or not	Not specified

continued

TABLE 47 *Chronic exercise ECG: reference standard and potential biases (cont'd)*

Paper	Type of exercise test	Angiographic reference standard	Other reference standard	Incorporation bias	Blinding	Verification/ work-up bias	Selection of the study sample	Study population	Sub-groups	Indeterminate ETT results
Morise *et al.*, 1995, USA[198]	Bruce	>50%		No	Yes	No	Consecutive	Single	Yes: gender, derivation/ validation, group	Not specified
Morise *et al.*, 1995, USA[199]	Bruce	>50%		No	Yes	No	Consecutive	Separate	No	Excluded
Morise *et al.*, 1997, USA[115]	Bruce	>50%	Probabilistic method using clinical data where angio not available	Yes	Yes	Yes: 11% had angio, remainder used probabilistic method	Consecutive	Single	Yes: (1) max. HR ≥ 85% predicted; (2) had angio	Not specified
Morise *et al.*, 1997, USA[114]		>50%	Probabilistic method using clinical data where angio not available	No	Yes	No	Consecutive	Single	Yes: gender, oestrogen status	Not specified
Morris *et al.*, 1978, USA[201]	Other treadmill	>75%		No	Unclear	No	Consecutive	Single	Yes: gender	Not specified
Nair *et al.*, 1983, USA[202]	Bruce	>50%		No	Yes	No	Other	Single	Yes: gender; VEs or not	Not specified
Nallamothu *et al.*, 1995, USA[203]	Bruce	>50%		No	Yes	No	Consecutive	Single	Yes: conclusive ETT	Excluded
Nasrallah *et al.*, 1975, USA[204]	Other treadmill	>60%		No	Yes	No	Consecutive	Separate	Yes: digoxin, non-specific ST changes	Not specified
Newman *et al.*, 1980, USA[205]	Bruce	>75%		No	Unclear	No	Other	Single	No	Excluded
Newman *et al.*, 1988, USA[206]	Other treadmill	>50%		No	Unclear	Yes	N/S	Single	No	Excluded
Nowak *et al.*, 1993, Sweden[117]	Bicycle	>50%		No	Yes	No	Consecutive	Single	No	Excluded

continued

TABLE 47 *Chronic exercise ECG: reference standard and potential biases (cont'd)*

Paper	Type of exercise test	Angiographic reference standard	Other reference standard	Incorporation bias	Blinding	Verification/ work-up bias	Selection of the study sample	Study population	Sub-groups	Indeterminate ETT results
Oguzhan *et al.*, 1997, Turkey[207]	Bruce	>70%		No	Yes	No	Consecutive	Single	No	Not specified
Okin *et al.*, 1994, USA[208]	Other treadmill	>50%		No	Yes	Yes	Consecutive	Separate	Yes	Not specified
Paillole *et al.*, 1995, France[209]	Bicycle	>70% or >50% LMS		No	Yes	No	Consecutive	Single	No	Not specified
Papazoglou *et al.*, 1991, Greece[210]	Bruce/other treadmill	>50%		No	No	No	N/S	Single	No	Not specified
Patterson *et al.*, 1982, USA[211]	Bruce	>50%		No	Yes	No	Consecutive	Single	No	Excluded
Piessens *et al.*, 1974, Belgium[212]	Bicycle	>75%		No	Yes	No	Other	Single	No	Not specified
Pruvost *et al.*, 1987, France[213]	Bruce	>50%		No	Yes	No	Consecutive	Single	No	Excluded
Quyyumi *et al.*, 1984, UK[214]	Bicycle	>75%		No	Yes	No	Random	Single	No	Excluded
Rijneke *et al.*, 1980, The Netherlands[215]	Bicycle	>50% >70%		No	Yes	No	Consecutive	Single	No	Not specified
Ritchie *et al.*, 1977, USA[216]	Bruce	>50%		No	Yes	No	Other	Single	No	Not specified
Rodriguez *et al.*, 1993, USA[217]	Other treadmill	>70% or >50% LMS		No	Unclear	No	Consecutive	Single	No	Not specified
Roitman et al., 1970, USA[218]	Other treadmill	>50%		Yes	Yes	No	Consecutive	Single	Yes: interpretable ETT	Excluded
Rowe *et al.*, 1982, USA[219]	Bruce	>70%		No	Unclear	No	Other	Separate	Yes: the test performed	Not specified
Salazar *et al.*, 1976, Mexico[220]	Bruce	>50%		No	Yes	No	Consecutive	Single	No	Not specified

continued

TABLE 47 *Chronic exercise ECG: reference standard and potential biases (cont'd)*

Paper	Type of exercise test	Angiographic reference standard	Other reference standard	Incorporation bias	Blinding	Verification/ work-up bias	Selection of the study sample	Study population	Sub-groups	Indeterminate ETT results
San Roman *et al.*, 1998, Spain[221]	Bruce	>50%		No	No	No	Consecutive	Single	No	Not specified
Santinga *et al.*, 1982, USA[222]	Other treadmill	>50%		No	Yes	No	Consecutive	Single	Yes: gender history	Not specified
Santoro *et al.*, 1998, Italy[223]	Bicycle	>70%		No	Unclear	No	Unclear	Single	No	Not specified
Sato *et al.*, 1988, Japan[224]	Bruce	>75% or >50% LMS		No	Unclear	No	Consecutive	Single	No	Not specified
Silverberg *et al.*, 1980, USA[225]	Bruce	>50%		No	Yes	No	Other	Single	No	Excluded
Sketch *et al.*, 1975, USA[226]	Bruce	>75%		No	Unclear	No	Other	Single	Yes: gender	Other (sensitivity analysis)
Sullivan *et al.*, 1994, UK[227]	Not specified	>30%		No	Yes	No	Consecutive	Single	Yes: gender	Not specified
Thwaites *et al.*, 1986, UK[228]	Bruce and Bicycle	>75%		No	Yes	No	Random	Single	No	Excluded
Tsuda *et al.*, 1993, Japan[229]	Bruce	>70%		No	Yes	No	Consecutive	Single	Yes: hypertension vs non-hypertension	Not specified
Tucker *et al.*, 1976, USA[230]	Other treadmill	>70%		No	Unclear	No	Consecutive	Single	Yes: patients with exercise-induced ventricular premature beats	Excluded
Turner *et al.*, 1979, New Zealand[231]	Other treadmill	>75%		No	Unclear	No	Consecutive	Single	No	Excluded
Vovan *et al.*, 1987, France[232]	Bruce	>75%		No	Yes	No	Other	Single	Yes: no. of vessels involved	Excluded

continued

TABLE 47 *Chronic exercise ECG: reference standard and potential biases (cont'd)*

Paper	Type of exercise test	Angiographic reference standard	Other reference standard	Incorporation bias	Blinding	Verification/ work-up bias	Selection of the study sample	Study population	Sub-groups	Indeterminate ETT results
Walling *et al.*, 1993, USA[233]	Bruce	>50%		No	Yes	No	Consecutive	Single	No	Excluded
Weiner *et al.*, 1979, USA[234]	Bruce	>70%		No	Yes	No	Consecutive	Single	Yes: 3 groups depending on clinical likelihood of angina; gender	Excluded
Weintraub *et al.*, 1984, USA[235]	Bicycle	>75% or >50% LMS		No	Yes	No	Consecutive	Single	Yes: gender; CP typical or atypical	Excluded
Weintraub *et al.*, 1985, USA[236]	Bicycle	>75% or >50% LMS		No	Yes	No	Consecutive	Single	Yes: gender; CP typical or not	Excluded
Wetherbee *et al.*, 1988, USA[237]	Bruce/ Bicycle	>70% or >50% LMS		No	Yes	No	Consecutive	Single	No	Treated as negative
Wilson *et al.*, 1993, USA[238]	Bruce	>50%		No	Yes	No	Consecutive	Single	Yes: gender	Not specified

LMS, left main stem.

TABLE 48 *Chronic resting ECG: general details*

Paper	Setting	Inclusion criteria	Exclusion criteria	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Atwood *et al.*, 1998, USA and Hungary[147]	Secondary care	Males who had exercise tests and coronary angios to evaluate CP or other findings thought to be due to coronary disease	Incomplete data; females; previous cardiac surgery; valve disease; left BBB; WPW; previous MI excluded from diagnostic sub-group	59			1384	0	1384
Detry *et al.*, 1978, Belgium[168]	Secondary care	Typical or atypical CP	Prior MI; valvular heart disease; cardiomyopathy; HT; BBB; ECG LVH	47	33	64	0	53	53
France *et al.*, 1990, USA[93]	Secondary care	Patients referred for cardiac catheterization during a 2-year. period	LVH; RVH; BBB; prior CABG; cardiomyopathy	62			63	59	122
Jelinek *et al.*, 1976, USA[239]	Secondary care	Clinically suspected of having CAD	Anaemia; alcoholism; thyroid disease; valvular heart disease; primary myocardial or pericardial disease; cardiac conduction defects; electrolyte abnormalities; recent MI or unstable angina	N/S			153	0	153
Joswig *et al.*, 1985, USA[240]	Secondary care	Patients presenting with recurrent CP	PH of MI or cardiac surgery	N/S			N/S	N/S	184
McGowan *et al.*, 1977, USA[241]	Secondary care	Having coronary angio as evaluation for CAD	Left BBB; previous CABG	N/S			N/S	N/S	160
Moussa *et al.*, 1992, USA[242]	Secondary care	Exercise test and angio within 3 months of testing	Females; left BBB; PTCA or CABG; digoxin; resting ST abnormalities	59	23	80	328	0	328
Murray *et al.*, 1976, UK[243]	Secondary care	Patients presenting with CP warranting selective coronary arteriography	Rheumatic heart disease; digoxin treatment	47	32	64	91	11	102
Okin *et al.*, 1994, USA[208]	Secondary care	Stable angina	Significant valvular disease; MI in the last 6 weeks; or left BBB on resting ECG	58			168	47	215

continued

TABLE 48 *Chronic resting ECG: general details (cont'd)*

Paper	Setting	Inclusion criteria	Exclusion criteria	Age (years)			Gender		Total No. of patients
				Mean	Min.	Max.	Male	Female	
Riecansky *et al.*, 1988, Italy[244]	Secondary care	Referred with angina for investigation	Not specified	N/S	22	59	41	9	50
Roitman *et al.*, 1970, USA[218]	Secondary care	Patients with CP who had had both angio and ETT	Unfit for exercise test; ECG unsatisfactory; coronary angio unsatisfactory	46	22	68	84	16	100
Weiner *et al.*, 1979, USA and Canada[234]	Secondary care	Symptomatic patients who underwent ETT within 1 month of cardiac catheterization	Unstable angina; previous MI; digitalis treatment; failure to reach 85% of maximum HR in conjunction with a negative test	N/S			1465	580	2045

TABLE 49 *Chronic resting ECG: reference standard and potential biases*

Paper	Angiographic reference standard	Other reference standard	Incorporation bias	Blinding	Verification/ work-up bias	Selection of the study sample	Study population	Sub-groups	Indeterminate results
Atwood *et al.*, 1998, USA and Hungary[147]	>50% reduction in luminal diameter of major coronary artery		No	No	Unclear	Consecutive	Single	No	Not specified
Detry *et al.*, 1978, Belgium[168]	>70% reduction in luminal diameter of major coronary artery		No	Yes	No	Other	Single	No	Not specified
France *et al.*, 1990, USA[93]	>70% reduction in luminal diameter of major coronary artery		No	Yes	No	Consecutive	Single	No	Not specified
Jelinek *et al.*, 1976, USA[239]	>75% reduction in luminal diameter of major coronary artery		No	Unclear	No	Consecutive	Single	No	Not specified
Joswig *et al.*, 1985, USA[240]	>50% reduction in luminal diameter of major coronary artery		No	Unclear	No	Consecutive	Single	No	Not specified
McGowan *et al.*, 1977, USA[241]	>70% reduction in luminal diameter of major coronary artery or previous MI		No	Unclear	No	Consecutive	Single	No	Treated as negative
Moussa *et al.*, 1992, USA[242]	>70% reduction in luminal diameter of major coronary artery or > 50% LMS		No	Unclear	No	Consecutive	Single	No	Not specified
Murray *et al.*, 1976, UK[243]			No	Yes	No	Consecutive	Single	No	Not specified

continued

TABLE 49 *Chronic resting ECG: reference standard and potential biases (cont'd)*

Paper	Angiographic reference standard	Other reference standard	Incorporation bias	Blinding	Verification/ work-up bias	Selection of the study sample	Study population	Sub-groups	Indeterminate results
Okin *et al.*, 1994, USA[208]	>50% luminal diameter stenosis of major coronary artery	Clinical features for part of the group clinically defined as normal (free of CP, no history of CHD, on no medication, normal on examination, normal ECG and pain free on ETT) or defined as clinically stable angina (stable retrosternal CP, provoked by exercise and relieved by rest)	No	Yes	Yes	Consecutive	Separate	Yes: (1) patients with angiographically normal coronary arteries; (2) patients with catheterization-proved coronary	Not specified
Riecansky *et al.*, 1988, Italy[244]	>50% reduction in luminal diameter of major coronary artery		No	Unclear	No	N/S	Unclear	No	Not specified
Roitman *et al.*, 1970, USA[218]	>50% reduction in luminal diameter of major coronary artery		No	Yes	No	Consecutive	Single	Yes	Excluded
Weiner *et al.*, 1979, USA and Canada[234]	≥ 70% reduction in luminal diameter of major coronary artery		No	Unclear	No	Consecutive	Separate	Yes: clinical likelihood of angina	Excluded

Appendix 3

List of excluded papers and reasons for exclusion

TABLE 50

Citation	Reason for exclusion
Abben R, Denes P, Rosen KM. Evaluation of criteria for diagnosis of myocardial infarction: study of 256 patients with intermittent left bundle branch block. *Chest* 1979;**75**:575–8.	Not CP
Abdul-Mohsen MF, al-Quorain A, al-Hamdan AA, Husain A, Qutub H, Ladipo GO. Clinical profile of patients admitted to the coronary care unit with possible myocardial infarction without diagnostic ECG and/or enzyme changes. *East Afr Med J* 1993;**70**:777–81.	Not CP
Acanfora D, De Caprio L, Cuomo S, Canonico V, Cicatiello AM, Rengo C, *et al*. Postexercise systolic blood pressure to heart rate ratio: a new exercise criterion for diagnosing coronary artery disease. *Am J Noninvas Cardiol* 1991;**5**:365-71.	No appropriate outcome/results
Ackermann RJ, Vogel RL. Electrocardiographic diagnosis of acute myocardial infarction in the presence of left bundle-branch block. *N Engl J Med* 1996;**335**:131–2.	No original data
Aeschlimann A, Steinmann E, Conen D, Dubach UC. Importance of ECG and chest x-ray of ambulant patients with chest pain. *Schweiz Med Wochenschr; J Suisse Med* 1986;**116**:1720–2.	No appropriate outcome/results
Ahmed SS, Gupta RC, Brancato RR. Significance of nausea and vomiting during acute myocardial infarction. *Am Heart J* 1978;**95**:671–2.	Not a diagnostic test; no appropriate outcome/results
Aldrich RF, Brensike JF, Battaglini JW, Richardson JM, Loh IK, Stone NJ, *et al*. Coronary calcifications in the detection of coronary artery disease and comparison with electrocardiographic exercise testing. Results from the National Heart, Lung, and Blood Institute's type II coronary intervention study. *Circulation* 1979;**59**:1113–24.	Not CP
Alpert JS, Sloss LJ, Cohn PF, Grossman W. The diagnostic accuracy of combined clinical and noninvasive cardiac evaluation: comparison with findings at cardiac catheterization. *Catheter Cardiovasc Diag* 1980;**6**:359–70.	Not CP; no appropriate outcome/results
Alpman A, Guldal M, Berkalp B, Diker E, Erol C, Oral D. Importance of notching and slurring of the resting QRS complex in the diagnosis of coronary artery disease. *J Electrocardiol* 1995;**28**:199–208.	No appropriate outcome/results
Andersen HR, Falk E, Nielsen D. Right ventricular infarction: diagnostic accuracy of electrocardiographic right chest leads V3R to V7R investigated prospectively in 43 consecutive fatal cases from a coronary care unit. *Br Heart J* 1989;**61**:514–20.	No appropriate outcome/results
Andersen HR, Nielsen D, Falk E. Right ventricular infarction: diagnostic value of ST elevation in lead III exceeding that of lead II during inferior/posterior infarction and comparison with right-chest leads V3R to V7R. *Am Heart J* 1989;**117**:82–6.	No appropriate outcome/results
Anon. Prodromal symptoms of myocardial infarction. *WHO Chron* 1972;**26**:112–15.	No appropriate outcome/results
Anshelevich Y, Kalvelis AD. Comparison of the informative value of electrocardiographic criteria of myocardial infarction with the use of different lead systems. *Cor Vasa* 1986;**28**:8–14.	Not CP; not diagnostic test
Aparici M, Peteiro J, Fernandez dAC, Hidalgo R, Cabanero J, Barba J. Utility and tolerance of stress testing in geriatric patients. *Rev Port Cardiol* 1990;**9**:819–22.	Case–control
Assali AR, Herz I, Vaturi M, Adler Y, Solodky A, Birnbaum Y, *et al*. Electrocardiographic criteria for predicting the culprit artery in inferior wall acute myocardial infarction. *Am J Cardiol* 1999;**84**:87–9.	No appropriate outcome/results
Assali AR, Sclarovsky S, Herz I, Adler Y, Porter A, Solodky A, *et al*. Comparison of patients with inferior wall acute myocardial infarction with versus without ST-segment elevation in leads V5 and V6. *Am J Cardiol* 1998;**81**:81–3.	No appropriate outcome/results

continued

TABLE 50 *(cont'd)*

Citation	Reason for exclusion
Aufderheide TP, Rowlandson I, Lawrence SW, Kuhn EM, Selker HP. Test of the acute cardiac ischemia time-insensitive predictive instrument (ACI-TIPI) for prehospital use. *Ann Emerg Med* 1996;**27**:193–8.	No original data; no appropriate outcome/results
Balady GJ, Weiner DA, McCabe CH, Ryan TJ. Value of arm exercise testing in detecting coronary artery disease. *Am J Cardiol* 1985;**55**:37–9.	No appropriate outcome/results
Baltazar RF, Grant A, O'Mara V, Effron MB. The use of a low-level stage during exercise testing in predicting severe coronary disease. *Md Med J* 1991;**40**:1079–81.	Not CP; no appropriate outcome/results
Barlow JB. The 'false positive' exercise electrocardiogram: value of time course patterns in assessment of depressed ST segments and inverted T waves. *Am Heart J* 1985;**110**:1328–36.	No original data
Barthwal SP, Agarwal R, Sarkari NB, Agarwal DK, Shukla SK. Diagnostic significance of T I < T III and TV1 > TV6 signs in ischaemic heart disease. *J Assoc Phys India* 1993;**41**:26–7.	Not CP; no appropriate outcome/results
Beattie JM, Seibert GB, Blomqvist CG. Lead specificity of the maximum ST/heart rate slope response. *Br Heart J* 1985;**53**:349.	No original data
Beker A, Pinchas A, Erel J, Abboud S. Analysis of high frequency QRS potential during exercise testing in patients with coronary artery disease and in healthy subjects. *Pacing Clin Electrophysiol* 1996;**19**:2040–50.	Not CP; no appropriate outcome/results
Ben-Haim SA, Gil A, Edoute Y. Beat-to-beat morphologic variability of the electrocardiogram for the evaluation of chest pain in the emergency room. *Am J Cardiol* 1992;**70**:1139–42.	No appropriate outcome/results
Bergman KS, Stevenson WG, Tillisch JH, Stevenson LW. Effect of body position on the diagnostic accuracy of the electrocardiogram. *Am Heart J* 1989;**117**:204–6.	Not CP; no appropriate outcome/results
Berman JA, Wynne J, Mallis G, Cohn PF. Improving diagnostic accuracy of the exercise test by combining R-wave changes with duration of ST segment depression in a simplified index. *Am Heart J* 1983;**105**:60–6.	No appropriate outcome/results
Berman JL, Wynne J, Cohn PF. A multivariate approach for interpreting treadmill exercise tests in coronary artery disease. *Circulation* 1978;**58**:505–12.	No appropriate outcome/results
Bobbio M, Detrano R, Schmid JJ, Janosi A, Righetti A, Pfisterer M, *et al*. Exercise-induced ST depression and ST/heart rate index to predict triple-vessel or left main coronary disease: a multicenter analysis. *J Am Coll Cardiol* 1992;**19**:11–18.	Not CP; no appropriate outcome/results
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Bosco M, Schon W, Pugliese G. Critical evaluation of combined use of exercise stress test and 201Tl exercise scintigraphy for the diagnostic accuracy of coronary heart disease. *G Ital Cardiol* 1982;**12**:25–33.	No original data
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Bresler MJ, Gibler WB. Acute myocardial infarction: subtleties of diagnosis in the emergency department. *Ann Emerg Med* 1990;Suppl:1–15.	No original data
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Citation	Reason for exclusion
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Calvert AF, Ayres B, Ilicic V, Dunn B. True sensitivity of cardiac exercise testing. A combined clinical evaluation of multiple parameters. *Med J Aust* 1984;**140**:131–5.	No appropriate outcome/results
Calvert AF, Pater G, Pye D, Mann J, Chalmers D, Ayres B. A matched pairs comparison of cycle ergometry and treadmill exercise testing in the evaluation of coronary heart disease. *Aust N Z J Med* 1987;**17**:472–8.	No appropriate outcome/results
Cannon CP, Thompson B, McCabe CH, Mueller HS, Kirshenbaum JM, Herson S, *et al*. Predictors of non-Q-wave acute myocardial infarction in patients with acute ischemic syndromes: an analysis from the Thrombolysis in Myocardial Ischemia (TIMI) III trials. *Am J Cardiol* 1995;**75**:977–81.	No appropriate outcome/results
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Chikamori T, Doi Y, Yonezawa Y, Kuzume O, Furuno T, Ozawa T, *et al*. Clinical significance of prominent negative T waves induced by exercise test. *J Cardiol* 1989;**19**:741–8.	Not diagnostic test
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Cohn K, Kamm B, Feteih N, Brand R, Goldschlager N. Use of treadmill score to quantify ischemic response and predict extent of coronary disease. *Circulation* 1979;**59**:286–96.	Not CP
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Cooke RA, Smeeton N, Chambers JB. Comparative study of chest pain characteristics in patients with normal and abnormal coronary angiograms. *Heart* 1997;**78**:142–6.	Case–control study
Corey GA, Merenstein JH. Applying the acute ischemic heart disease predictive instrument. *J Fam Pract* 1987;**25**:127–33.	Not CP
Craig IH. Accuracy of hospital diagnosis of myocardial infarction. *Aust N Z J Med* 1982;**12**:14–18.	No appropriate outcome/results
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Citation	Reason for exclusion
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De Bacquer D, De Backer G, Kornitzer M, Blackburn H. Prognostic value of ECG findings for total, cardiovascular disease, and coronary heart disease death in men and women. *Heart* 1998;**80**:570–7.	Not CP
De Bacquer D, De Backer G, Kornitzer M, Myny K, Doyen Z, Blackburn H. Prognostic value of ischemic electrocardiographic findings for cardiovascular mortality in men and women. *J Am Coll Cardiol* 1998;**32**:680–5.	Not CP; no appropriate outcome/results
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De Bruyne MC, Hoes AW, Kors JA, Hofman A, van Bemmel JH, Grobbee DE. QTc dispersion predicts cardiac mortality in the elderly. The Rotterdam Study. *Circulation* 1998;**97**:467–72.	Not CP
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DeCaprio L, Ascione L, Cuomo S, Vigorito C, Brienza A, Acanfora D, *et al*. Evaluation of exercise-induced Q-wave amplitude changes and their clinical value. *J Electrocardiol* 1988;**21**:45–53.	Not a diagnostic test
Deckers JW, Rensing BJ, Simoons ML, Roelandt JR. Diagnostic merits of exercise testing in females. *Eur Heart J* 1989;**10**:543–50.	Not CP
Deckers JW, Rensing BJ, Tijssen JG, Vinke RV, Azar AJ, Simoons ML. A comparison of methods of analysing exercise tests for diagnosis of coronary artery disease. *Br Heart J* 1989;**62**:438–44.	No appropriate outcome/results
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Dekker JM, Schouten EG, Klootwijk P, Pool J, Kromhout D. ST segment and T wave characteristics as indicators of coronary heart disease risk: the Zutphen Study. *J Am Coll Cardiol* 1995;**25**:1321–6.	Not CP
Dekker JM, Schouten EG, Klootwijk P, Pool J, Swenne CA, Kromhout D. Heart rate variability from short electrocardiographic recordings predicts mortality from all causes in middle-aged and elderly men. The Zutphen Study. *Am J Epidemiol* 1997;**145**:899–908.	Not CP
Deluche L, Douard H, Binquet C, Chene G, Broustet JP. Diagnostic value of ST depression corrected for heart rate in the post-exercise recovery period. *Arch Mal Coeur Vaiss* 1998;**91**:287–94.	Not CP
Detrano R. Predictive value of exercise ST-segment depression versus ST-segment/heart rate index. *Cardiol Board Rev* 1992;**9**:73–6, 83.	No appropriate outcome/results
Dilger J, Pietsch-Breitfeld B, Stein W, Overkamp D, Ickrath O, Renn W, *et al*. Simple computer-assisted diagnosis of acute myocardial infarction in patients with acute thoracic pain. *Methods Infor Med* 1992;**31**:263–7.	No appropriate outcome/results

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Citation	Reason for exclusion
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Dunn PM, Levinson W. The lack of effect of clinical information on electrocardiographic diagnosis of acute myocardial infarction. *Arch Intern Med* 1990;**150**:1917–19.	No original data
Edenbrandt L, Pahlm O, Lyttkens K, Albrechtsson U. Vectorcardiogram more sensitive than 12-lead ECG in the detection of inferior myocardial infarction. *Clin Physiol* 1990;**10**:551–9.	Not CP
Edhouse JA, Sakr M, Angus J, Morris FP. Suspected myocardial infarction and left bundle branch block: electrocardiographic indicators of acute ischaemia. *J Accident Emerg Med* 1999;**16**:331–5.	No appropriate outcome/results
Eisenstein I, Sanmarco ME, Madrid WL, Selvester RH. Electrocardiographic and vectorcardiographic diagnosis of posterior wall myocardial infarction. Significance of the T wave. *Chest* 1985;**88**:409–16.	Not CP
Ellestad MH, Allen W, Wan MC, Kemp GL. Maximal treadmill stress testing for cardiovascular evaluation. *Circulation* 1969;**39**:517–22.	No appropriate outcome/results
Ellestad MH, Lerman S, Thomas L. The limitations of the diagnostic power of exercise testing. *Am J Noninvas Cardiol* 1989;**3**:139–46.	Not CP
Ellestad MH, Savitz S, Bergdall D, Teske J. The false positive stress test. Multivariate analysis of 215 subjects with hemodynamic, angiographic and clinical data. *Am J Cardiol* 1977;**40**:681–5.	No appropriate outcome/results
Ellestad MH, Thomas L, Ong R, Loh J. The predictive value of the time course of ST segment depression during exercise testing in patients referred for coronary angiograms. *Am Heart J* 1992;**123**:904–8.	Not CP
Ellestad MH, Greenberg PS. Multivariate approach to the treadmill stress test: prospective study. *Cardiology* 1981;**68** Suppl 2:27–34.	Not CP
Eshchar Y, Yahini JH, Atlas P, Kishon Y, Deutsch V, Neufeld HN. Exercise tests in patients with severe angina pectoris: an angiographic correlation. *Angiology* 1980;**31**:32–8.	No appropriate outcome/results
Estes NA, Salem DN. Predictive value of the electrocardiogram in acute coronary syndromes. *JAMA* 1999;**281**:753–4.	No appropriate outcome/results
Evans AT, Shaw LK, Pryor DB. Sensitivity and specificity of the history and physical examination for coronary artery disease. *Ann Intern Med* 1994;**120**:344–5.	No original data
Feneley MP, Gavaghan TP, Kuchar D, Thorburn CW, Baron DW, Morgan JJ. New electrocardiographic criteria for inferior myocardial infarction. *Eur Heart J* 1984;**5**:806–13.	Not CP
Fesmire FM, Percy RF, Bardoner JB, Wharton DR, Calhoun FB, Coronado BE, *et al*. Serial ECGs were more sensitive than an initial ECG for diagnosing chest pain. *Evid-Based Med* 1998;**3**:123.	No original data
Finkelhor RS, Newhouse KE, Vrobel TR, Miron SD, Bahler RC. The ST segment/heart rate slope as a predictor of coronary artery disease: comparison with quantitative thallium imaging and conventional ST segment criteria. *Am Heart J* 1986;**112**:296–304.	Not CP
Fisher LD, Kennedy JW, Chaitman BR, Ryan, TJ, McCabe C, Weiner D *et al*. Diagnostic quantification of CASS (coronary artery surgery study) clinical and exercise test results in determining presence and extent of coronary artery disease. A multivariate approach. *Circulation* 1981;**63**:987–1000.	No appropriate outcome/results
Friedewald VE Jr. Maximal-stress, multiple-lead exercise testing: the significance of ST-segment changes in the detection of coronary arterial occlusive disease. *Heart Lung* 1976;**5**:91–6.	No original data
Friesingerg GC, Smith RF. Correlation of electrocardiographic studies and arteriographic findings with angina pectoris. *Circulation* 1972;**46**:1173–84.	No original data
Frogner FJ, Juul-Moller S. ECG diagnosis of coronary artery disease: a comparison of 3-lead ambulatory ECG registration and exercise testing. *Ann Noninvas Electrocardiol* 1997;**2**:141–5.	No appropriate outcome/results

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Citation	Reason for exclusion
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Gaul G. Stress testing in persons above the age of 65 years: applicability and diagnostic value of a standardized maximal symptom-limited testing protocol. *Eur Heart J* 1984;**5** Suppl E:51–3.	No appropriate outcome/results
Gehring J, Koenig W, Donner M, Wex R, Klein G. The diagnostic value of signal-averaged stress cardiokymography compared with exercise electrocardiography. *J Noninvasive Cardiol* 1998;**2**:32–41.	Not CP
Gemmill JD, Lifson WK, Rae AP, Hillis WS, Dunn FG. Assessment by general practitioners of suitability of thrombolysis in patients with suspected acute myocardial infarction. *Br Heart J* 1993;**70**:503–6.	No appropriate outcome/results
Gerard A, Parmar R, Zhao D, Potter M, Urestsky BF, Runge MS, *et al*. Stress testing markedly underestimates the prevalence of coronary artery disease in a 'low risk' chest pain unit: results of a prospective randomized trial. *Circulation* 1997;**96**:272–3.	No appropriate outcome/results
Gitter MJ, Goldsmith SR, Dunbar DN, Sharkey SW. Cocaine and chest pain: clinical features and outcome of patients hospitalized to rule out myocardial infarction. *Ann Intern Med* 1991;**115**:277–82.	Not a diagnostic test
Gjorup T, Kelbaek H, Nielsen D, Kreiner S, Godtfredsen J. Interpretation of the electrocardiogram in suspected myocardial infarction: a randomized controlled study of the effect of a training programme to reduce interobserver variation. *J Intern Med* 1992;**231**:407–12.	Not a diagnostic test; no appropriate outcome/results
Goldman L, Cook EF, Mitchell N, Flatley M, Sherman H, Rosati R, *et al*. Incremental value of the exercise test for diagnosing the presence or absence of coronary artery disease. *Circulation* 1982;**66**:945–53.	No appropriate outcome/results
Goldschlager N, Selzer A, Cohn K. Treadmill stress tests as indicators of presence and severity of coronary artery disease. *Ann Intern Med* 1976;**85**:277–86.	No appropriate outcome/results
Gorgels AP, Vos MA, Mulleneers R, de Zwaan C, Bar FW, Wellens HJ. Value of the electrocardiogram in diagnosing the number of severely narrowed coronary arteries in rest angina pectoris. *Am J Cardiol* 1993;**72**:999–1003.	No appropriate outcome/results
Grande P, Christiansen C, Pedersen A, Christensen MS. Optimal diagnosis in acute myocardial infarction. A cost-effectiveness study. *Circulation* 1980;**61**:723–8.	No appropriate outcome/results
Green L, Smith M. Evaluation of two acute cardiac ischemia decision-support tools in a rural family practice. *J Fam Pract* 1988;**26**:627–32.	No appropriate outcome/results
Green LA, Yates JF. Influence of pseudodiagnostic information on the evaluation of ischemic heart disease. *Ann Emerg Med* 1995;**25**:451–7.	No appropriate outcome/results
Greenberg PS, Bible M, Ellestad MH. Prospective application of the multivariate approach to enhance the accuracy of the treadmill stress test. *J Electrocardiol* 1982;**15**:143–7.	Not CP
Greenberg PS, Cangiano B, Leamy L, Ellestad MH. Use of the multivariate approach to enhance the diagnostic accuracy of the treadmill stress test. *J Electrocardiol* 1980;**13**:227–36.	Not CP; no appropriate outcome/results
Greenberg PS, Ellestad MH, Clover RC. Comparison of the multivariate analysis and CADENZA systems for determination of the probability of coronary artery disease. *Am J Cardiol* 1984;**53**:493–6.	No appropriate outcome/results; not CP
Grijseels EWM, Deckers JW, Hoes AW, Boersma E, Hartman JAM, Van der Does E, *et al*. Implementation of a pre-hospital decision rule in general practice. Triage of patients with suspected myocardial infarction. *Eur Heart J* 1996;**17**:89–95.	No appropriate outcome/results
Grubb JP, Newton WP. Rapid diagnosis of acute myocardial infarction. *J Fam Pract* 1997;**44**:442–3.	No appropriate outcome/results
Haines DE, Raabe DS, Gundel WD, Wackers FJ. Anatomic and prognostic significance of new T-wave inversion in unstable angina. *Am J Cardiol* 1983;**52**:14–18.	No appropriate outcome/results

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Citation	Reason for exclusion
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Hambye AS, Vervaet A, Lieber S, Ranquin R. Diagnostic value and incremental contribution of bicycle exercise, first-pass radionuclide angiography, and 99mTc-labeled sestamibi single-photon emission computed tomography in the identification of coronary artery disease in patients without infarction. *J Nucl Cardiol* 1996;**3**:464–74.	No appropriate outcome/results
Haraphongse M, Kappagoda T, Tymchak W, Rossall RE. The value of sum of ST segment depression in 12-lead electrocardiogram in relation to change in heart rate during exercise to predict the extent of coronary artery disease. *Can J Cardiol* 1986;**2**:64–7.	No appropriate outcome/results
Harlan WR, Cowie CC, Oberman A, Mitchell RE, MacIntyre NR. Prediction of subsequent ischemic heart disease using serial resting electrocardiograms. *Am J Epidemiol* 1984;**119**:208–17.	Not CP
Harlan WRJ, Graybiel A, Mitchell RE, Oberman A, Osborne RK. Serial electrocardiograms: their reliability and prognostic validity during a 24-yr. period. *J Chron Dis* 1967;**20**:853–67.	Not CP
Harris FJ, DeMaria AN, Lee G, Miller RR, Amsterdam EA, Mason DT. Value and limitations of exercise testing in detecting coronary disease with normal and abnormal resting electrocardiograms. *Adv Cardiol* 1978;11–15.	No appropriate outcome/results
Hasegawa K, Nezuo S, Sawayama T. Systolic blood pressure response during treadmill exercise test in detecting presence and severity of angina pectoris. *Respir Circ* 1985;**33**:1145–50	No appropriate outcome/results
Hegge FN, Tuna N, Burchell HB. Coronary arteriographic findings in patients with axis shifts or S-T-segment elevations on exercise-stress testing. *Am Heart J* 1973; **86:**603–15.	No appropriate outcome/results
Herlitz J, Hjalmarson A, Waldenstrom J. The diagnostic value of different enzymes and standard ECG in acute myocardial infarction. *Scand J Clin Lab Invest* 1985;**45**:413–20.	No appropriate outcome/results
Herlitz J, Karlson BW, Lindqvist J, Sjolin M. Predictors and mode of death over 5 years amongst patients admitted to the emergency department with acute chest pain or other symptoms raising suspicion of acute myocardial infarction. *J Intern Med* 1998;**243**:41–8.	Not a diagnostic test; no appropriate outcome/results
Herlitz J, Karlsson T, Dellborg M, Karlson B, Engdahl J, Sanden W. Occurrence, characteristics, and outcome of patients hospitalized with a diagnosis of acute myocardial infarction who do not fulfill traditional criteria. *Clin Cardiol* 1998;**21**:405–9.	Not chest pain; no appropriate outcome/results
Herpin D, Gaudeau B, Boutaud P, Amiel A, Boijoux C, Demange J. Increase in the amplitude of R waves in exertion: a bad diagnostic criterion for coronary insufficiency. *Ann Cardiol Angeiol* 1986;**35**:135–40.	Not CP
Herzog J, Pandya A, Messenger K, Ellestad MH. Analysis of the Athens Score in the diagnosis of ischemia during exercise testing. *J Noninvas Cardiol* 1998;**2**:7–11.	Not CP
Hlatky MA, Pryor DB, Harrell FEJ, Califf RM, Mark DB, Rosati RA. Factors affecting sensitivity and specificity of exercise electrocardiography. Multivariable analysis. *Am J Med* 1984;**77**:64–71.	No appropriate outcome/results
Hoberg E, Lemke R, Wermuth G, Klaus D. ST-segment depression and R-amplitude changes during bicycle stress test in patients with coronary artery disease (author's transl.). *Z Kardiol* 1981;**70**:776–80.	Not CP
Hoffman JR, Igarashi E. Influence of electrocardiographic findings on admission decisions in patients with acute chest pain. *Am J Med* 1985;**79**:699–707.	No appropriate outcome/results
Hofgren C, Karlson BW, Herlitz J. Prodromal symptoms in subsets of patients hospitalized for suspected acute myocardial infarction. *Heart Lung* 1995;**24**:3–10.	Not a diagnostic test
Hollenberg M, Budge WR, Wisneski JA, Gertz EW. Treadmill score quantifies electrocardiographic response to exercise and improves test accuracy and reproducibility. *Circulation* 1980;**61**:276–85.	No appropriate outcome/results
Hornsten TR, Bruce RA. Computed ST forces of Frank and bipolar exercise electrocardiograms. *Am Heart J* 1969;**78**:346–57.	No appropriate outcome/results

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Citation	Reason for exclusion
Huang S-K, Hung H-F, Liou J-Y, Lin S-C, Kuan P, Cheng J-J. Differential diagnosis of acute chest pain clinically manifested as acute myocardial infarction with angiographically normal coronary artery. *Acta Cardiol Sin* 1997;**13**:93–100.	Not diagnostic test
Hurd HP, Starling MR, Crawford MH, Dlabal PW, O'Rourke RA. Comparative accuracy of electrocardiographic and vectorcardiographic criteria for inferior myocardial infarction. *Circulation* 1981;**63**:1025–9.	Not CP
Ingram DA, Fulton RA, Portal RW, Aber CP. Vomiting as a diagnostic aid in acute ischaemic cardiac pain. *BMJ* 1980;**281**:636–7.	No appropriate outcome/results
Inoue S, Mitsunami K, Kinoshita M. Comparison of electron beam computed tomography and exercise electrocardiography in detecting coronary artery disease in the elderly. *Nippon Ronen Igakkai Zasshi; Jpn J Geriatr* 1998;**35**:626–30.	No appropriate outcome/results
Izumi C, Iga K, Kijima T, Himura Y, Gen H, Konishi T. Limitations of electrocardiography in the diagnosis of acute myocardial infarction–comparison with two-dimensional echocardiography. *Intern Med* 1995;**34**:1061–3.	Not CP
James KB, Obarski TP, Underwood DA. Electrocardiographic criteria for anterior myocardial infarction. *Cleve Clin J Med* 1990;**57**:618–21.	Not CP
Janosi A, Varaljai T, Hankoczy J, Nemeth J, Kadar A, Gyorgy M, *et al*. Sensitivity and specificity of ECG-stress tests in the diagnosis of coronary artery stenosis. *Orv Hetil* 1986;**127**:203–5.	No appropriate outcome/results
Janota M, Fabian J, Rohac J, Belan A. The diagnostic value of R-wave amplitude changes during exercise testing. *Cor Vasa* 1983;**25**:168–76.	No appropriate outcome/results
Jayes RIJ, Beshansky JR, D'Agostino RB, Selker HP. Do patients' coronary risk factor reports predict acute cardiac ischemia in the emergency department? A multicenter study. *J Clin Epidemiol* 1992;**45**:621–6.	No appropriate outcome/results
Jonasson R, Landou C, Orinius E. Exercise electrocardiogram in patients with normal and abnormal coronary arteriogram. *Scand J Clin Lab Invest* 1980;**40**:775–82.	No appropriate outcome/results
Kansal S, Roitman D, Sheffield LT. Stress testing with ST-segment depression at rest. An angiographic correlation. *Circulation* 1976;**54**:636–9.	No appropriate outcome/results
Karlson BW, Herlitz J, Hallgren P, Liljeqvist JA, Oden A, Hjalmarson A. Emergency room prediction of mortality and severe complications in patients with suspected acute myocardial infarction. *Eur Heart J* 1994;**15**:1558–65.	No appropriate outcome/results
Kasser IS, Bruce RA. Comparative effects of aging and coronary heart disease on submaximal and maximal exercise. *Circulation* 1969;**39**:759–74.	No appropriate outcome/results
Kaul S, Abbott RD. Evaluation of chest pain in the emergency department. *Ann Intern Med* 1994;**121**:976–7.	No original data
Kellermann JJ, Frank A, Drory Y, Fisman E. Adjusted single load exercise test. A new exercise test for improved diagnosis of coronary heart disease. *Cardiology* 1980;**65**:121–7.	No appropriate outcome/results
Kennedy RL, Burton AM, Fraser HS, McStay LN, Harrison RF. Early diagnosis of acute myocardial infarction using clinical and electrocardiographic data at presentation: derivation and evaluation of logistic regression models. *Eur Heart J* 1996;**17**:1181–91.	Not a diagnostic test
Klaeboe G, Otterstad JE, Winsnes T, Espeland N. Predictive value of prodromal symptoms in myocardial infarction. *Acta Med Scand* 1987;**222**:27–30.	No appropriate outcome/results
Kligfield P, Okin PM, Ameisen O, Borer JS. Evaluation of coronary artery disease by an improved method of exercise electrocardiography: the ST segment/heart rate slope. *Am Heart J* 1986;**112**:589–98.	Not CP; no original data
Knutsen R, Knutsen SF, Curb JD, Reed DM, Kautz JA, Yano K. The predictive value of resting electrocardiograms for 12-year incidence of coronary heart disease in the Honolulu Heart Program. *J Clin Epidemiol* 1988;**41**:293–302.	Not CP
Kokurina EV, Metelitsa VI, Aleksandrov AA, Ostrovskaya, TP, Ignat'eva IF, Dubinina LT, *et al*. Detection of ischaemic heart disease by electrocardiography in clinical practice and in mass population studies. Comparative investigation. *Cor Vasa* 1983;**25**:321–8.	Not CP

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Citation	Reason for exclusion
Kornreich F, Montague TJ, Rautaharju PM, Block P, Warren JW, Horacek MB. Identification of best electrocardiographic leads for diagnosing anterior and inferior myocardial infarction by statistical analysis of body surface potential maps. *Am J Cardiol* 1986;**58**:863–71.	Not CP
Kornreich F, Rautaharju PM, Warren J, Montague TJ, Horacek BM. Identification of best electrocardiographic leads for diagnosing myocardial infarction by statistical analysis of body surface potential maps. *Am J Cardiol* 1985;**56**:852–6.	Not CP; no appropriate outcome/results
Kornreich F, Selvester RH, Montague TJ, Rautaharju PM, Saetre HA, Ahmad J. Discriminant analysis of the standard 12-lead ECG for diagnosing non-Q wave myocardial infarction. *J Electrocardiol* 1992;**24** Suppl:163–72.	Not CP
Kornreich F. Identification of best electrocardiographic leads for diagnosing acute myocardial ischemia. *J Electrocardiol* 1998;**31** Suppl:157–63.	Not a diagnostic test; no appropriate outcome/results
Kreger BE, Anderson KM, Levy D. QRS interval fails to predict coronary disease incidence: the Framingham Study. *Arch Intern Med* 1991;**151**:1365–8.	Not CP
Kudenchuk PJ, Ho MT, Weaver WD, Litwin PE, Martin JS, Eisenberg MS, *et al*. Accuracy of computer-interpreted electrocardiography in selecting patients for thrombolytic therapy. MITI Project Investigators. *J Am Coll Cardiol* 1991;**17**:1486–91.	Not a diagnostic test; no appropriate outcome/results
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Larsson H, Jonasson T, Ringqvist I, Fellenius C, Wallentin L. Diagnostic and prognostic importance of ST recording after an episode of unstable angina or non-Q-wave myocardial infarction. *Eur Heart J* 1992;**13**:207–12.	No appropriate outcome/results
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Lee HS, Cross SJ, Rawles JM, Jennings KP. Patients with suspected myocardial infarction who present with ST depression. *Lancet* 1993;**342**:1204–7.	No appropriate outcome/results
Lee TH, Rouan GW, Weisberg MC, Brand DA, Cook EF, Acampora D, *et al*. Sensitivity of routine clinical criteria for diagnosing myocardial-infarction within 24 hours of hospitalization. *Ann Intern Med* 1987;**106**:181–6.	Not a diagnostic test
Lehtinen R, Sievanen H, Turjanmaa V, Niemela K, Malmivuo J. Effect of ST segment measurement point on performance of exercise ECG analysis. *Int J Cardiol* 1997;**61**:239–45.	No appropriate outcome/results
Lehtinen R, Sievanen H, Uusitalo A, Malmivuo J. Accurate detection of coronary artery disease by combining exercise and recovery ST/HR analysis. *Jpn Heart J* 1994;**35**:535–6.	No appropriate outcome/results

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TABLE 50 *(cont'd)*

Citation	Reason for exclusion
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Lehtinen R, Sievanen H, Viik J, Turjanmaa V, Niemela K, Malmivuo J. Accurate detection of coronary artery disease by integrated analysis of the ST-segment depression/heart rate patterns during the exercise and recovery phases of the exercise electrocardiography test. *Am J Cardiol* 1996;**78**:1002–6.	Not CP; no appropriate outcome/results
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Lesbre P, Campeau L, Bourrassa M, Huot R, Quiret JC, Bernasconi P. Effort electrocardiogram in women. *Arch Mal Coeur Vaiss* 1976;**69**:935–42.	Not CP
Levenson J. Electrocardiographic diagnosis of acute myocardial infarction in the presence of left bundle-branch block. *N Engl J Med* 1996;**335**:132.	No original data
Lopez EAJ, Araoye MA, McManus CD. The electrocardiographic diagnosis of myocardial infarction in the presence of ventricular conduction defects. A new attempt to solve an old problem. *J Electrocardiol* 1981;**14**:325–32.	Not CP
Lopez EAJ, From AH, Araoye MA, Pipberger HV. Q-wave abnormalities in chronic obstructive pulmonary disease and myocardial infarction. *J Electrocardiol* 1980;**13**:173–80.	Not CP; no appropriate outcome/results
Lopez-Sendon J, Coma-Canella I, Alcasena S, Seoane J, Gamallo C. Electrocardiographic findings in acute right ventricular infarction: sensitivity and specificity of electrocardiographic alterations in right precordial leads V4R, V3R, V1, V2, and V3. *J Am Coll Cardiol* 1985;**6**:1273–9.	No appropriate outcome/results
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Maseri A, Kaski JC, Crea F, Araujo L. Electrocardiographic diagnosis of transient myocardial ischemia. Sensitivity, specificity, and practical significance. *Ann N Y Acad Sci* 1990;**601**:51–60.	No original data
McConahay DR, McCallister BD, Smith RE. Postexercise electrocardiography: correlations with coronary arteriography and left ventricular hemodynamics. *Am J Cardiol* 1971;**28**:1–9.	Not CP
McCrea WA, Saltissi S. Electrocardiogram interpretation in general practice: relevance to prehospital thrombolysis. *Br Heart J* 1993;**70**:219–25.	Not CP
McGuinness JB, Begg TB, Semple T. First electrocardiogram in recent myocardial infarction. *BMJ* 1976;**ii**:449–51.	No appropriate outcome/results
McQueen MJ, Holder D, El-Maraghi NR. Assessment of the accuracy of serial electrocardiograms in the diagnosis of myocardial infarction. *Am Heart J* 1983;**105**:258–61.	No appropriate outcome/results
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TABLE 50 *(cont'd)*

Citation	Reason for exclusion
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Merrill SL, Pearce ML. An autopsy study of the accuracy of the electrocardiogram in the diagnosis of recurrent myocardial infarction. *Am Heart J* 1971;**81**:48–54.	Not CP; no appropriate outcome/results
Meyers DG, Bendon KA, Hankins JH, Stratbucker RA. The effect of baseline electrocardiographic abnormalities on the diagnostic accuracy of exercise-induced ST segment changes. *Am Heart J* 1990;**119**:272–6.	Not CP
Michaelides AP, Dilaveris PE, Psomadaki ZD, Richter DJ, Andrikopoulos GK, Pitsilides N, *et al*. QRS prolongation on the signal-averaged electrocardiogram versus ST-segment changes on the 12-lead electrocardiogram: which is the most sensitive electrocardiographic marker of myocardial ischemia? *Clin Cardiol* 1999;**22**:403–8.	Not a diagnostic test
Michaelides AP, Vyssoulis GP, Katsimichas AT, Lalos ST, Georgiades NA, Psomadaki ZD, *et al*. Exercise-induced ST-segment variability may discriminate false positive tests. *J Electrocardiol* 1998;**31**:197–202.	Not CP
Miranda CP, Lehmann KG, Froelicher VF. Correlation between resting ST segment depression, exercise testing, coronary angiography, and long-term prognosis. *Am Heart J* 1991;**122**:1617–28.	No appropriate outcome/results
Miranda CP, Liu J, Kadar A, Janosi A, Froning J, Lehmann KG, *et al*. Usefulness of exercise-induced ST-segment depression in the inferior leads during exercise testing as a marker for coronary artery disease. *Am J Cardiol* 1992;**69**:303–7.	No appropriate outcome/results
Mittal SR, Jain S. Electrocardiographic diagnosis of right ventricular infarction in the presence of left ventricular posterior infarction. *Int J Cardiol* 1999;**68**:125–8.	Not a diagnostic test; no appropriate outcome/results
Mittal SR, Jain SK. Electrocardiographic criteria for the diagnosis of right ventricular involvement in the setting of acute inferior infarction. *Int J Cardiol* 1997;**60**:321–3.	No appropriate outcome/results
Miyakoda H, Endo A, Kato M, Kato T, Omodani H, Osaki S, *et al*. Exercise-induced U-wave changes in patients with coronary artery disease – correlation with tomographic thallium-201 myocardial imaging. *Jpn Cir J* 1996;**60**:641–51.	Not CP
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Morise AP, Detrano R, Bobbio M, Diamond GA. Development and validation of a logistic regression-derived algorithm for estimating the incremental probability of coronary artery disease before and after exercise testing. *J Am Coll Cardiol* 1992;**20**:1187–96.	No appropriate outcome/results
Morise AP, Singh HP, Duval RD. Correlation of reported exercise test results with recommendation for coronary angiography in men and women with suspected coronary artery disease. *Am J Cardiol* 1995;**75**:180–2.	No appropriate outcome/results
Morise AP, Duval RD. Comparison of three Bayesian methods to estimate posttest probability in patients undergoing exercise stress testing. *Am J Cardiol* 1989;**64**:1117–22.	Not CP
Morise AP, Duval RD. The estimation of post-test probability of coronary disease following exercise testing using the sequential application of two Bayesian methods. *Am Heart J* 1990;**120**:1292–7.	No appropriate outcome/results
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TABLE 50 *(cont'd)*

Citation	Reason for exclusion
Nahormek PA, Chahine RA, Raizner AE, Thornby JI, Ishimori T, Montero A, *et al*. The magnitude of exercise-induced ST segment depression and the predictive value of exercise testing. *Clin Cardiol* 1979;**2**:286–90.	Not CP
Ness J, Mendelson G, Mendelson AH, Aronow WS. Comparison of Q wave MI diagnosis in older persons by an electrocardiogram computer system, three recently board certified physicians, and an experienced cardiologist. *J Noninvas Cardiol* 1998;**2**:11–12.	Not CP
Nowak J, Nilsson T, Sylven C, Jogestrand T. Potential of carotid ultrasonography in the diagnosis of coronary artery disease: a comparison with exercise test and variance ECG. *Stroke* 1998;**29**:439–46.	No appropriate outcome/results
O'Hara MJ, Subramanian VB, Davies AB, Raftery EB. Changes of Q wave amplitude during exercise for the prediction of coronary artery disease. *Int J Cardiol* 1984;**6**:35–45.	Not a diagnostic test
Okada M, Yotsukura M, Shimada T, Ishikawa K. Clinical implications of isolated T wave inversion in adults: electrocardiographic differentiation of the underlying causes of this phenomenon. *J Am Coll Cardiol* 1994;**24**:739–45.	Not CP
Okin PM, Bergman G, Kligfield P. Heart rate adjustment of the time–voltage ST segment integral: identification of coronary disease and relation to standard and heart rate-adjusted ST segment depression criteria. *J Am Coll Cardiol* 1991;**18**:1487–92.	Not CP; no appropriate outcome/results
Okin PM, Chen J, Kligfield P. Effect of baseline ST segment elevation on test performance of standard and heart rate-adjusted ST segment depression criteria. *Am Heart J* 1990;**119**:1280–6.	Not CP; no appropriate outcome/results
Okin PM, Kligfield P, Ameisen O, Goldberg HL, Borer JS. Identification of anatomically extensive coronary artery disease by the exercise ECG ST segment/heart rate slope. *Am Heart J* 1988;**115**:1002–13.	No appropriate outcome/results
Okin PM, Kligfield P, Ameisen O, Goldberg HL, Borer JS. Improved accuracy of the exercise electrocardiogram: identification of three-vessel coronary disease in stable angina pectoris by analysis of peak rate-related changes in ST segments. *Am J Cardiol* 1985;**55**:271–6.	No appropriate outcome/results
Okin PM, Lauer MS, Kligfield P. Chronotropic response to exercise. Improved performance of ST-segment depression criteria after adjustment for heart rate reserve. *Circulation* 1996;**94**:3226–31.	Case–control
Okin PM, Kligfield P. Gender-specific criteria and performance of the exercise electrocardiogram. *Circulation* 1995;**92**:1209–16.	Not CP
Okin PM, Kligfield P. Identifying coronary artery disease in women by heart rate adjustment of ST-segment depression and improved performance of linear regression over simple averaging method with comparison to standard criteria. *Am J Cardiol* 1992;**69**:297–302.	No appropriate outcome/results
Okin PM, Kligfield P. Limited diagnostic value of R-wave amplitude changes with exercise for assessment of the presence and severity of coronary disease. *Cardiovasc Rev Rep* 1994;**15**:11–17, 42.	Not CP
O'Rourke MF, Cook A, Carroll G, Gallagher D, Hall J. Accuracy of a portable interpretive ECG machine in diagnosis of acute evolving myocardial infarction. *Aust N Z J Med* 1992;**22**:9–13.	No appropriate outcome/results
Ouzan J, Chapoutot L, Carre E, Liehn JC, Elaerts J. A multivariate analysis of the diagnostic values of clinical examination, exercise testing and exercise radionuclide angiography in coronary artery disease. *Cardiology* 1993;**83**:197–204.	No appropriate outcome/results
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Panju AA, Hemmelgarn BR, Guyatt GH, Simel DL. Is this patient having a myocardial infarction? *JAMA* 1998;**280**:1256–63.	No original data
Pellinen TJ, Virtanen KS, Valle M, Frick MH. Studies on ergometer exercise testing. II. Effect of previous myocardial infarction, digoxin, and beta-blockade on exercise electrocardiography. *Clin Cardiol* 1986;**9**:499–507.	No appropriate outcome/results

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TABLE 50 *(cont'd)*

Citation	Reason for exclusion
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Pfisterer ME, Williams RJ, Gordon DG, Swanson SM, Battler A, Ceretto WJ, *et al*. Comparison of rest/exercise ECG, thallium-201 scans and radionuclide angiography in patients with suspected coronary artery disease. *Cardiology* 1980;**66**:43–55.	Not CP; no appropriate outcome/results
Pic A, Broustet JP. Diagnostic value of amplitude variations of the QRS complex during computerized exercise testing. *Arch Mal Coeur Vaiss* 1984;**77**:54–63.	Not CP
Pirwitz MJ, Lange RA, Landau C, MeShack BM, Hillis LD, Willard JE. Utility of the 12-lead electrocardiogram in identifying underlying coronary artery disease in patients with depressed left ventricular systolic function. *Am J Cardiol* 1996;**77**:1289–92.	Not CP
Polak MJ, Zhou SH, Rautaharju PM, Armstrong WW, Chaitman BR. Using automated analysis of the resting twelve-lead ECG to identify patients at risk of developing transient myocardial ischaemia – an application of an adaptive logic network. *Physiol Meas* 1997;**18**:317–25.	Not CP, no appropriate outcome/results
Poprawski K, Piszczek I, Smukowski T, Paradowski S. Comparison of the diagnostic value of echocardiographic, ecg and enzymatic investigations in acute myocardial infarction. *Pol Arch Med Wewn* 1991;**85**:167–73.	No appropriate outcome/results
Pratt CM, Francis MJ, Divine GW, Young JB. Exercise testing in women with chest pain. Are there additional exercise characteristics that predict true positive test results? *Chest* 1989;**95**:139–44.	No appropriate outcome/results
Pruvost P, Lablanche JM, Thieuleux FA, Fourrier JL, Traisnel G, Bertrand ME. Value of the computerized analysis of ST segment depression during exercise without myocardial infarction. Apropos of 807 cases. *Arch Mal Coeur Vaiss* 1986;**79**:1878–83.	Not CP
Qian Y. A comparative study of the two-dimensional echocardiography, ECG and selective coronary arteriography in detecting coronary artery disease. *Chung-Hua Hsin Hsueh Kuan Ping Tsa Chih [Chin J Cardiol]* 1992;**19**:345–7.	No appropriate outcome/results
Radice M, Giudici V, Albertini A, Castelli R, Mannarini A. Effect of posture on exercise-induced ischemia: Comparison of supine and sitting bicycle stress testing. *J Appl Cardiol* 1991;**6**:447–54.	Not CP; no appropriate outcome/results
Reczuch K, Porada A, Wrabec K. The influence of sex on the diagnostic value of clinical history and electrocardiographic exercise test in patients with coronary artery disease. *Kardiol Pol* 1996;**45**:198–204.	Not CP
Riabykina GV, Saltykova MM, Sobolev AV. Diagnosis of ischaemic heart disease based on data of precordial mapping. *Cor Vasa* 1989;**31**:444–50.	Not CP; not a diagnostic test
Richardson MT, Holly RG, Amsterdam EA, Wang MQ. The value of ten common exercise tolerance test measures in predicting coronary disease in symptomatic females. *Cardiology* 1995;**86**:243–8.	No appropriate outcome/results
Rifkin RD, Hood WB, Jr. Bayesian analysis of electrocardiographic exercise stress testing. *N Engl J Med* 1977;**297**:681–6.	No original data; no appropriate outcome/results
Risenfors M, Zukauskiene I, Albertsson P, Hartford M, Lomsky M, Herlitz J. Early thrombolytic therapy in suspected acute myocardial infarction – role of the electrocardiogram: results from the TEAHAT Study. *J Intern Med Suppl* 1991;19–25.	No appropriate outcome/results
Robert AR, Melin JA, Detry JM. Logistic discriminant analysis improves diagnostic accuracy of exercise testing for coronary artery disease in women. *Circulation* 1991;**83**:1202–9.	No appropriate outcome/results
Roberts R, Kleiman NS. Earlier diagnosis and treatment of acute myocardial infarction necessitates the need for a 'new diagnostic mind-set'. *Circulation* 1994;**89**:872–81.	No original data
Rodriguez M, Moussa I, Froning J, Kochumian M, Froelicher VF. Improved exercise test accuracy using discriminant function analysis and 'recovery ST slope'. *J Electrocardiol* 1992;**25**:27.	No appropriate outcome/results

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Citation	Reason for exclusion
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Romano M, Caiazzo MR, Di Maro T, Carella G, Golia B, Chiariello M, *et al*. Increased recovery systolic blood pressure after upright bicycle exercise: its incidence and usefulness for detecting coronary artery disease. *Am J Noninvas Cardiol* 1988;**2**:259–63.	Not CP
Romano M, Caiazzo MR, Di Maro T, de Arcangelis E, Carella G, Golia B, *et al*. Abnormal recovery systolic blood pressure response for detecting coronary artery disease in men and women investigated by upright bicycle exercise. *Acta Cardiol* 1991;**46**:153–9.	Not CP; no appropriate outcome/results
Romano M, Cardei S, Monteforte I, Lembo LM, Campopiano A, Scarpato P, *et al*. Different protocols generate variations in systolic blood pressure response after exercise in patients with coronary artery disease. *J Cardiol* 1995;**25**:297–301.	No appropriate outcome/results
Rupprecht HJ, Sohn HY, Kearney P, Bickel C, Nafe B, Meyer J. Clinical predictors of unstable coronary lesion morphology. *Eur Heart J* 1995;**16**:1526–34.	No appropriate outcome/results
Sakai M, Torii Y, Nomura H, Saito Y, Ohnishi S, Hirai H, *et al*. Evaluation of patients with ischemic heart disease by exercise thallium-201 myocardial imaging: comparison with coronary arteriography and graded treadmill exercise testing. *J Cardiogr* 1983;**13**:833–44.	No appropriate outcome/results
Sansoy V, Watson DD, Beller GA. Significance of slow upsloping ST-segment depression on exercise stress testing. *Am J Cardiol* 1997;**79**:709–12.	No appropriate outcome/results
Santinga JT, Brymer JF, Smith F, Flora J. The influence of lead strength on the S-T changes with exercise electrocardiography (correlative study with coronary arteriography). *J Electrocardiol* 1977;**10**:387–91.	Not CP; no appropriate outcome/results
Schabitz J, Behn P. Reliability of various ECG derivations in the diagnosis of heart infarction. *Z Ges Inn Med Grenzgeb* 1967;**22**:657–64.	Not CP
Schiariti M, Ciavolella M, Puddu PE, Giannitti C, Scali D, Schad N, *et al.* ST/HR slope and improved exercise ECG detection of myocardial ischemia in patients with suspected coronary artery disease. *J Electrocardiol* 1991;**24**:307–14.	Not CP
Schmidt H, Strauss H-J, Pielesch W. Diagnosis for angina pectoris: dipyridamol test is no alternative to exercise testing. *Med Klin* 1985;**80**:214–17.	No appropriate outcome/results
Schreck DM, Ng L, Schreck BS, Bosco SF, Allegra JR, Zacharias D, *et al*. Detection of coronary artery disease from the normal resting ECG using nonlinear mathematical transformation. *Ann Emerg Med* 1988;**17**:132–4.	Not CP
Schreck DM, Ng L, Schreck BS, Zacharias D, Grunau CF. Nonlinear transformation of the resting electrocardiogram in the diagnosis of coronary artery disease. *Ann Emerg Med* 1986;**15**:897–900.	No appropriate outcome/results
Schreck DM, Terndrup TE, Bosco SF, Zacharias D, Ng L, Schreck BS. Correlation of nonlinear mathematical transformation of the normal electrocardiogram with the severity of coronary artery disease. *Crit Care Med* 1989;**17**:269–73.	Not CP; no appropriate outcome/results
Schutzenberger W, Leisch F, Herbinger W. R amplitude changes and ST segment lowering in the exercise ECG compared with angiographic findings. *Dtsch Med Wochenschri* 1980;**105**:1285–9.	No appropriate outcome/results
Schweitzer P. The electrocardiographic diagnosis of acute myocardial infarction in the thrombolytic era. *Am Heart J* 1990;**119**:642–54.	No original data; no appropriate outcome/results
Sclarovsky S, Davidson E, Lewin RF, Strasberg B, Arditti A, Agmon J. Unstable angina pectoris evolving to acute myocardial infarction: significance of ECG changes during chest pain. *Am Heart J* 1986;**112**:459–62.	No appropriate outcome/results
Sederholm M, Grottum P, Kjekshus J, Erhardt L. Course of chest pain and its relation to CK release and ST/QRS vector changes in patients with acute myocardial infarction randomized to treatment with intravenous timolol or placebo. *Am Heart J* 1985;**110**:52–8.	Not a diagnostic test

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TABLE 50 *(cont'd)*

Citation	Reason for exclusion
Selker HP, Beshansky JR, Griffith JL, Aufderheide TP, Ballin DS, Bernard SA, *et al*. Use of the acute cardiac ischemia time-insensitive predictive instrument (ACI-TIPI) to assist with triage of patients with chest pain or other symptoms suggestive of acute cardiac ischemia. A multicenter, controlled clinical trial. *Ann Intern Med* 1998;**129**:845–55.	Not CP; no appropriate outcome/results
Selker HP, D'Agostino RB, Laks MM. A predictive instrument for acute ischemic heart disease to improve coronary care unit admission practices: a potential on-line tool in a computerized electrocardiograph. *J Electrocardiol* 1988;**21** Suppl:S11–S17.	Not CP; no appropriate outcome/results
Sgarbossa EB, Pinski SL, Gates KB, Wagner GS. Early electrocardiographic diagnosis of acute myocardial infarction in the presence of ventricular paced rhythm. *Am J Cardiol* 1996;**77**:423–4.	No appropriate outcome/results
Shah A, Wagner GS, Green CL, Crater SW, Sawchak ST, Wildermann NM, *et al*. Electrocardiographic differentiation of the ST-segment depression of acute myocardial injury due to the left circumflex artery occlusion from that of myocardial ischemia of nonocclusive etiologies. *Am J Cardiol* 1997;**80**:512–13.	Not CP
Shah CP, Thakur RK, Reisdorff EJ, Lane E, Aufderheide TP, Hayes OW. QT dispersion may be a useful adjunct for detection of myocardial infarction in the chest pain center. *Am Heart J* 1998;**136**:496–8.	No appropriate outcome/results
Shah PK, Amin DK, Hulse S. Diagnosis of posterolateral infarction: lack of accuracy of commonly used EKG criteria. *Fed Proc* 1985;**44**:807.	No appropriate outcome/results
Short D. Clinical significance of minor ST-T depression in resting electrocardiogram. *Br Heart J* 1972;**34**:377–82.	Not CP
Short D. Electrocardiography and the family doctor. *BMJ* 1970;i:560–1.	No original data; no appropriate outcome/results
Sidorenko BA, Liakishev AA, Akhmedzhanov NM, Matveeva LS, Mazaev VP. The bicycle ergometry test in the diagnosis of ischemic heart disease in women (a comparison with selective coronary angiographic data). *Kardiologiia* 1984;**24**:62–8.	No appropriate outcome/results
Sievanen H, Karhumaki L, Vuori I, Malmivuo J. Compartmental multivariate analysis of exercise ECGs for accurate detection of myocardial ischaemia. *Med Bio Eng Comput* 1994;**32**:S3–S8.	No appropriate outcome/results
Silber SH, Leo PJ, Katapadi M. Serial electrocardiograms for chest pain patients with initial nondiagnostic electrocardiograms: implications for thrombolytic therapy. *Acad Emerg Med* 1996;**3**:147–52.	Not CP; no appropriate outcome/results
Simon H, Silberhorn M. Prodromal symptoms of acute myocardial infarction. *Dtsch Med Wochenschr* 1979;**104**:573–7.	Not CP
Simoons ML, Hugenholtz PG. Estimation of the probability of exercise-induced ischemia by quantitative ECG analysis. *Circulation* 1977;**56**:552–9.	Not CP
Solomon AJ, Tracy CM. The signal-averaged electrocardiogram in predicting coronary artery disease. *Am Heart J* 1991;**122**:1334–9.	No appropriate outcome/results
Sornmo L, Wohlfart B, Berg J, Pahlm O. Beat-to-beat QRS variability in the 12-lead ECG and the detection of coronary artery disease. *J Electrocardiol* 1998;**31**:336–44.	Not CP; no appropriate outcome/results
Stewart S, Haste M. Prediction of right ventricular and posterior wall ST elevation by coronary care nurses: the 12-lead electrocardiograph versus the 18-lead electrocardiograph. *Heart & Lung* 1996;**25**:14–23.	No appropriate outcome/results
Stoletniy LN, Pai RG. Value of QT dispersion in the interpretation of exercise stress test in women. *Circulation* 1997;**96**:904–10.	No appropriate outcome/results
Stowers M, Short D. Warning symptoms before major myocardial infarction. *BMJ* 1970;**32**:833–8.	Not CP
Styliadis I, Nouskas I, Parharidis G, Efthimiadis G, Kitikidou K, Gemitzis K, *et al.* The ST-segment in precordial leads in acute inferior myocardial infarction, with or without right ventricular involvement. *Cuore* 1996;**13**:7–14.	Not CP; no appropriate outcome/results

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TABLE 50 *(cont'd)*

Citation	Reason for exclusion
Sugiura T, Iwasaka T, Takehana K, Nagahama Y, Hasegawa, Inada M. Precordial ST segment depression in patients with Q wave inferior myocardial infarction: role of infarction-associated pericarditis. *Am Heart J* 1993;**125**:672–5.	No appropriate outcome/results
Takeda T, Ishikawa N, Akisada M, Ajisaka R, Akatsuka T, Matsuda M. Regional myocardial perfusion abnormality demonstrated by intra-arterial digital subtraction angiogram at capillary phase. A comparison of DSA with left ventriculography and thallium-201 myocardial scintigraphy. *Nippon Igaku Hoshasen Gakkai Zasshi – Nippon Acta Radiol* 1988;**48**:1069–77.	No appropriate outcome/results
Talbot S, Dreifus LS, Watanabe Y, Chiang R, Morris K, Reich M. Diagnostic criteria for computer-aided electrocardiographic 15-lead system. Evaluation using 12 leads and Frank orthogonal leads with vector display. *Br Heart J* 1976;**38**:1247–61.	Not CP; no appropriate outcome/results
Tamura A, Kataoka H, Mikuriya Y, Nasu M. Inferior ST segment depression as a useful marker for identifying proximal left anterior descending artery occlusion during acute anterior myocardial infarction. *Eur Heart J* 1995;**16**:1795–9.	No appropriate outcome/results
Tandberg D, Kastendieck KD, Meskin S. Observer variation in measured ST-segment elevation. *Ann Emerg Med* 1999;**34**:448–52.	No appropriate outcome/results
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continued

TABLE 50 *(cont'd)*

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continued

TABLE 50 *(cont'd)*

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