Question: What are the education and information needs in adults presenting with chest pain to optimise their understanding of the diagnostic process and their participation in decisions about their investigations?
Information sheets for patients with acute chest pain: randomised controlled trial

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

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

Ref ID 25415 Brit Med J b541 to b546 2009

Study Type Randomised Controlled Trial Funding Health Foundation Leadership Practice Award

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

Inclusion/Exclusion Criteria Subjects were patients who were investigated for chest pain of possible cardiac origin, were aged over 25, had no changes for acute coronary syndrome on a diagnostic electrocardiogram, had no suspected life threatening non-cardiac disease and did not have known coronary heart disease presenting with recurrent or prolonged episodes of cardiac type chest pain. Patients were excluded if they were unable to read or comprehend the trial documentation.

Patient Characteristics The study population had a mean age of 48.6 years, and 61.6% were men. Information sheets were deemed suitable for 19 patients with a diagnosis of angina (mean age 69.58% men) 162 with a diagnosis of definite benign non-cardiac pain (mean age 43, 65% men), 61 with a diagnosis of uncertain cause requiring further cardiology investigation (mean age 52, 49% men), and 458 with a diagnosis of uncertain cause suitable for expectant management (mean age 49, 62% men).

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

Setting Chest pain unit, emergency centre, Sheffield

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

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

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

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

Results 494 of 700 (70.6%) responses. Compared with those receiving standard verbal advice those receiving advice and an information sheet had significantly lower anxiety scores 7.61 versus 8.63 (95% CI 0.20 to 1.84, p=0.015) and depression scores 4.14 versus 5.28 (95% CI 0.41 to 1.86, p=0.002). On the anxiety subscale, intervention was associated with a shift from mild or moderate anxiety to no anxiety; on the depression subscale the intervention was associated with a shift towards lower scores among those with no depression and also a reduction in the proportion with moderate depression. The number needed to treat to avoid one case of anxiety was 9.0 and the NNT for depression was 13.1. Patients in the intervention group had significantly higher scores for mental health (p<0.007) and general health perception (p<0.006) on the SF-36 than those in the control group. There were no other significant differences between the two groups.

Safety and adverse effects None reported

15 May 2009 Page 3 of 196
| **Does the study answer the question?** | Provision of an information sheet to patients with acute chest pain can reduce anxiety and depression and improve mental health and perception of general health but does not alter satisfaction with care or other outcomes. The authors of the study conclude that as the information sheets are simple to administer and outcomes were on balance positive, the use of these sheets should be recommended in patients receiving diagnostic assessment for acute chest pain. |
| **Effect due to factor in study?** | There are some limitations which may bias the outcome of this study: it is not blinded; there was a 30% non response rate to the questionnaire; there was potential for contamination between groups by the nurses giving the information on the information sheet verbally to the control group. |
| **Consistency of results with other studies?** | There are no other studies in this field. |
| **Directly applicable to guideline population?** | This study population excluded all patients who could not read English. Thus it may not be generalisable to all individuals with chest pain. |
| **Internal Validity** | Subjects are not blinded; 29% non response |
Question: What is the incremental benefit and cost effectiveness of a clinical history, risk factors and physical examination in evaluation of individuals with acute chest pain of suspected cardiac origin?
Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

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

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

Ref ID 10251 Br J Gen Pract 2008

Study Type Meta-analysis Funding Not reported

Number of participants 28 prospective and retrospective observational studies

Inclusion/Exclusion Criteria Studies had to describe at least 1 of the 10 signs and symptoms for diagnosing ACS or AMI, and based on original data

Patient Characteristics Patients with signs and symptoms for the diagnosis of acute MI, unstable angina or ACS.

Recruitment
Setting Secondary and primary care

Interventions/ Test/ Factor being investigated
The signs and symptoms considered were pain in left arm and/or shoulder, pain in right arm and/or shoulder, pain in both arms, pain in neck, pain in back, epigastric pain, oppressive pain, vomiting and/or nausea, sweating or absence of chest wall tenderness

Comparisons Signs and symptoms to diagnose chest pain

Length of Study/ Follow-up

Outcome measures studied

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

See narrative for question 1; Table 2: Bruyninckx et al, 2004
See narrative for question 1; Table 3: Bruyninckx et al, 2004
The sensitivity of absence of tenderness was high, namely 92% (95% CI = 85.5 to 96.4) for acute myocardial infarction and 94% (95% CI = 91.4 to 96.1) for acute coronary syndrome. Oppressive pain followed with a sensitivity of 60% (95% CI = 53.7 to 66.0 for acute myocardial infarction). Sweating had the highest LR+, namely 2.92 (95% CI = 1.97 to 4.32 for acute myocardial infarction). The LR+ of right arm or shoulder pain was 2.89 (95% CI = 1.40 to 5.38) for acute myocardial infarction (one study). The other LR+ fluctuated between 1.05 and 1.49 for acute coronary syndrome. Absence of tenderness had a LR- of 0.23 (95% CI = 0.18 to 0.29) for acute myocardial infarction and 0.17 (95% CI = 0.11 to 0.26) for acute coronary syndrome. Other LR- varied between 0.69 (oppressive pain and sweating for acute myocardial infarction) and 0.98 (epigastric pain) for acute coronary syndrome.

Safety and adverse effects
None reported
5606 papers were initially identified of these 28 papers met the inclusion criteria for the use of 10 signs and symptoms, the studies included were prospective and retrospective observational studies, more than half of the studies were published since Mant et al's selection for the HTA published in 2004. A total of 46,908 patients were included in the review. The signs and symptoms considered were pain in left arm and/or shoulder, pain in right arm and/or shoulder, pain in both arms, pain in neck, pain in back, epigastric pain, oppressive pain, vomiting and/or nausea, sweating or absence of chest wall tenderness. Of the 28 papers, 11 were set in the emergency department, 10 were set in coronary care unit or the patients had been admitted to hospital, 3 were on the paramedics in an ambulance, 2 were set in GPs, 1 was carried out by a cardiologist and 1 was in a chest pain observational unit. 16 of the studies had non-selected patients, 11 had selected patients and 1 was from a chest pain observation unit. Selected patients were those who were recruited by coronary care units and cardiologists. All studies included patients had chest pain, in two studies patients also had pulmonary oedema. The mean age of the participants in all the studies was 53-71 years old, and the % of males was from 40-71%.

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

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

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

<table>
<thead>
<tr>
<th>Effect due to factor in study?</th>
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<tr>
<td>Consistency of results with other studies?</td>
<td>Consistent</td>
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<td>Directly applicable to guideline population?</td>
<td>Correct population</td>
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</table>

**Internal Validity**

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

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

<table>
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<tr>
<td>Study Type</td>
<td>Systematic Review</td>
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**Funding**

NHS R&D Health Technology Assessment Programme

15 May 2009
The signs and symptoms considered were pleuritic pain, sharp pain, positional pain, pain on palpation, crushing pain, central pain, left-sided radiation pain, right-sided radiation pain, any radiation of pain, pain duration of longer than 1 hour, previous MI/angina, nausea/vomiting, sweating, pulmonary crackles, systolic blood pressure under 80 mmHg or a third heart sound.

None of the signs and symptoms in isolation were found to be particularly useful: no sign or symptom achieved an LR of <0.1 or >10.22. Indeed, only one of the upper limits of the 95% CIs exceeded 10 – for right-sided radiation of pain in diagnosis of ACS – which was based on only one study. Similarly, only one of the lower limits (for pain on palpation) was <0.1. The results for presence of a sign or symptom (LR+) were more informative than those for the absence of a symptom or sign (LR–) which were non-contributory to making a diagnosis in every case. Systolic hypotension, the presence of a third heart sound and right-sided radiation of chest pain, achieved the highest positive LRs (LR+ 3.21–2.59) for diagnosis of MI. Where the reference standard was MI or unstable angina, right-sided radiation was associated with a higher positive LR (6.68). Clinical features most helpful in ruling out the diagnosis were the presence of pleuritic, sharp or positional pain, and pain produced by palpation (LR+ 0.19–0.32). It should be noted that there was considerable heterogeneity in the results, particularly (although not exclusively) for the negative LRs. This makes the summary statistics difficult to interpret. Nevertheless, there is no evidence that any single symptom or sign taken in isolation is of much value in the diagnosis of acute chest pain.

See narrative for question 1; Table 4: Mant et al, 2004

Safety and adverse effects
None reported

Does the study answer the question?
10862 papers were initially identified of these 21 papers met the inclusion criteria for the use of 16 difference clinical signs and symptoms. A total of 38638 patients were included in the review. The signs and symptoms considered were pleuritic pain, sharp pain, positional pain, pain on palpation, crushing pain, central pain, left-sided radiation pain, right-sided radiation pain, any radiation of pain, pain duration of longer than 1 hour, previous MI/angina, nausea/vomiting, sweating, pulmonary crackles, systolic blood pressure under 80 mmHg or a third heart sound. Of the 21 papers, 8 were set in secondary care, 10 in A&E, and 3 in primary and secondary care. The mean age of the participants in all the studies was 50-73 years old, and the % of males was from 50-71%.

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See tables for detailed results; See narrative for question 1; Table 4: Mant et al, 2004

### Effect due to factor in study?
Yes

### Consistency of results with other studies?
Consistent

### Directly applicable to guideline population?
Correct population

### Internal Validity

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

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

Ref ID 728

Study Type Systematic Review

Number of participant 21 observational studies

Inclusion/Exclusion Criteria papers used at least one of the signs and symptoms in the diagnosis of chest pain

Patient Characteristics

Setting 8 secondary care, 10 A&E, 3 primary&secondary care

Interventions/ Test/ Factor being investigated The signs and symptoms considered were pluritic pain, sharp pain, positional pain, pain on palpation, crushing pain, central pain, left-sided radiation pain, right-sided radiation pain, any radiation of pain, pain duration of longer than 1 hour, previous MI/angina, nausea/vomiting, sweating, pulmonary crackles, systolic blood pressure under 80 mmHg or a third heart sound

Comparisons Signs and symptoms to diagnose chest pain

Length of Study/ Follow-up

Outcome measures studied

Results None of the signs and symptoms in isolation were found to be particularly useful: no sign or symptom achieved an LR of <0.1 or >10.22 Indeed, only one of the upper limits of the 95% CIs exceeded 10 – for right-sided radiation of pain in diagnosis of ACS – which was based on only one study. Similarly, only one of the lower limits (for pain on palpation) was <0.1. The results for presence of a sign or symptom (LR+) were more informative than those for the absence of a symptom or sign (LR−) which were non-contributory to making a diagnosis in every case. Systolic hypotension, the presence of a third heart sound and right-sided radiation of chest pain, achieved the highest positive LRs (LR+ 3.21–2.59) for diagnosis of MI. Where the reference standard was MI or unstable angina, right-sided radiation was associated with a higher positive LR (6.68). Clinical features most helpful in ruling out the diagnosis
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See narrative for question 22; Table 1: Mant et al, 2004

Safety and adverse effects

Does the study answer the question?

None reported

Effect due to factor in study?

Yes

Consistency of results with other studies?

Consistent

Directly applicable to guideline population?

Correct population

Internal Validity

Swap CJ; Nagurney JT;

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

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

Study Type Systematic Review

Funding Not reported

Number of participant 28 prospective and retrospective observational studies and systematic reviews

Inclusion/Exclusion Criteria Studies needed to be observational studies including at least 80 patients. Studies needed to include at least 1 chest pain characteristic and make a diagnosis of ACS or AMI with appropriate diagnostic tests

15 May 2009
Patients described at least one chest pain characteristic which was diagnosed as ACS or AMI.

The studies considered the following chest pain characteristics: quality, location, radiation, size of area or distribution, severity, time of onset and is it continuing, duration, first occurrence frequency, similar to previous cardiac ischemic episodes and the following precipitating or aggravating factors: pleuritic, positional, palpable, exercise, emotional stress, relieving factors, associated symptoms.

Chest pain characteristics for diagnosing chest pain

Certain chest pain characteristics decrease the likelihood of ACS or AMI, namely, pain that is stabbing, pleuritic, positional, or reproducible by palpation (likelihood ratios [LRs] 0.2 to 0.3). Conversely, chest pain that radiates to one shoulder or both shoulders or arms or is precipitated by exertion is associated with LRs (2.3 to 4.7) that increase the likelihood of ACS. The chest pain history itself has not proven to be a powerful enough predictive tool to obviate the need for at least some diagnostic testing. Combinations of elements of the chest pain history with other initially available information, such as a history of CAD, have identified certain groups that may be safe for discharge without further evaluation, but further study is needed before such a recommendation can be considered reasonable. See narrative for question 1; Table 1: Swap and Nagurney, 2005.

Safety and adverse effects

None reported

Does the study answer the question?

28 papers were initially identified that were relevant to the evaluation of chest pain using signs and symptoms, the studies included were prospective and retrospective observational studies and systematic reviews, considering both predictors of AMI and ACS. The studies considered the following chest pain characteristics: quality, location, radiation, size of area or distribution, severity, time of onset and is it continuing, duration, first occurrence frequency, similar to previous cardiac ischemic episodes and the following precipitating or aggravating factors: pleuritic, positional, palpable, exercise, emotional stress, relieving factors, associated symptoms.

Risk stratification for ACS according to components of chest pain history:
Low risk: pain that is pleuritic, positional, or reproducible with palpation or is described as stabbing
Probable low risk: pain not related to exertion or that occurs in a small inframammary area of the chest wall
Probable high risk: pain described as pressure, is similar to that of prior MI or worse than prior anginal pain or is accompanied by nausea, vomiting or diaphoresis
High risk: pain that radiates to one or both shoulders or arms or is related to exertion

See narrative for question 1; Table 1: Swap and Nagurney, 2005

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The authors concluded that although certain elements of the chest pain history are associated with increased (LR = 2.3 to 4.7) or decreased (LR = 0.2 to 0.3) likelihoods of a diagnosis of ACS or AMI, none of them alone or in combination identify a group of patients that can be safely discharged without further diagnostic testing.
See table for detailed results

**Effect due to factor in study?**
Yes

**Consistency of results with other studies?**
Consistent

**Directly applicable to guideline population?**
Correct population

**Internal Validity**
### Grading: 2++

High-quality systematic reviews of case–control or cohort studies. High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal.


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

<table>
<thead>
<tr>
<th>Ref ID</th>
<th>American heart journal</th>
<th>Pages</th>
<th>2002</th>
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</table>

#### Study Type
Cohort

#### Number of participants
13 762 patients

#### Inclusion/Exclusion Criteria
- Inclusion: over 18 years old, chest pain defined as pain in the thoracic region, independent of duration, radiation, or relation to exercise, occurring in the last 24 hours and lasting minutes to hours

#### Patient Characteristics
- The mean age was 65±18 years and 43% were women
- Those who were categorised as being at high risk (21%) had a mean age of 63±10 years, 33% were female, 35% smoked, 25% had diabetes, 38% had hypertension, 13.4% died during the follow up.
- Those who were categorised as being at intermediate risk (47%) had a mean age of 64±11 years, 38% were female, 33% smoked, 28% had diabetes, 41% had hypertension, 2.2% died during the follow up.
- Those who were categorised as being at low risk (32%) had a mean age of 38±15 years, 66% were female, 12% smoked, 8% had diabetes, 22% had hypertension, 0.2% died during the follow up.

#### Recruitment
Admitted to emergency department with chest pain as described above

#### Setting
ED. Careggi General Hospital, Florence, Italy

#### Interventions/ Test/ Factor being investigated
Diagnosing chest pain

#### Comparisons
The chest pain score was based on: location of pain, radiation of pain, character of pain, history of angina

#### Length of Study/ Follow-up
6 months

#### Outcome measures studied
Effectiveness of chest pain score in diagnosing chest pain

#### Results
The chest pain score was based on the following elements each of which was given a value: location of pain: substernal or precordial = +3, left chest, neck, lower jaw or epigastrum = +1, apex = -1; radiation of pain: arm, shoulder, back, neck or lower jaw = +1; character of pain: crushing, pressing or heaviness = +2 sticking, pleuritic or pinprick = -1; associated symptoms: dyspnea, nausea or diaphoresis = +2; history of angina = +3. The mean age was 65±18 years. Patients were classified into 1 of 4 groups.
1) Patients at low risk with obvious noncardiac causes of chest pain, chest pain score <4, normal ECG, and normal serum markers of cardiac injury obtained at least 6 hours from symptoms, were sent home and followed up. (2672 patients)
2) Patients at low risk with chest pain score ≥ 4, normal ECG, normal serum cardiac markers, independent of age or coexisting coronary risk factors, were not admitted and underwent a second-line evaluation and short-term observation in the CPU area, including chest radiography, serial 12-lead ECG, serial troponins and cardiac enzymes, echocardiography and arterial blood gas analysis. When at least one of these tests or procedure results was found to be suggestive of AMI, unstable angina or CAD or left ventricular failure was detected these patients were considered for angiography with no additional testing. After an observation period up to 6 hours

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Page 13 of 196
patients without ongoing cardiovascular events underwent exercise tolerance test or SPECT or stress echocardiography. (1755 patients)
3) Patients at intermediate risk with clinical score ≥ 4 and abnormal ECG (ST-segment elevation <1mm or ST-segment depression <1mm at 60ms from J point) were admitted and managed in the CPU area.
4) Patients at high risk with ECG suggestive for AMI (defined as ST elevation ≥1 mm at 60ms from J point, ≥2 contiguous leads) were directly transferred to the coronary care unit and patients with suspected major cardiovascular disease, such as aortic arch dissection, pulmonary embolism, pneumothorax and acute pericarditis, were admitted and managed with arterial blood gas analysis, chest radiography, echocardiography, and thorax computed tomography if required by clinical assessment.

At six month follow up 0.2% of these patients were recognised as having nonfatal coronary artery disease, hence, the negative predictive value of a chest pain score of < 4 and normal ECG was > 99%

Of the patients with a chest pain score ≥ 4 and normal or non diagnostic electrocardiogram results (1755 patients, 40%), 20% of the low risk group with chest pain score < 4 (group 1) (885 patients) had documented coronary artery disease, 18% of which were by recurrent angina, delayed ECG changes, late rise in markers, the other 2% was by positive stress test.
There were 9335 intermediate and high risk patients, of which 2420 patients (26%) had an MI, 3764 patients (40%) had unstable angina, 129 (1.4%) had aortic dissection and 408 (4%) had pulmonary embolism, other major cardiovascular conditions were diagnosed, including aortic arch dissection, pulmonary embolism, pneumothorax, and acute pericarditis. 2256 patients had atypical chest pain diagnosed as multi-organ disease including chronic and stable ischemic heart disease, defined as known stable angina, previous myocardial infarction, or angiographically documented CAD

Safety and adverse effects

Does the study answer the question?

Of the patients with a chest pain score > 4 and normal electrocardiogram results, 20% (885 patients) had documented coronary artery disease. There were 9335 intermediate and high risk patients, of which 2420 patients (26%) had an MI, 3764 patients (40%) had unstable angina, 129 (1.4%) had aortic dissection and 408 (4%) had pulmonary embolism. Other multi-organ disease was found in 2256 patients.

The authors concluded that the chest pain score screening programme was effective and could significantly reduce admissions and optimise the care of those with an intermediate or high risk score. The authors also concluded that the screening programme could aid the diagnosis of alternative causes of chest pain in patients who do not have evidence of coronary artery disease

Effect due to factor in study?

Yes

Consistency of results with other studies?

Consistent

Directly applicable to guideline population?

Correct population

Internal Validity

Well covered

Sanchis J; Bodý V; Llßcer A; N-èez J; Consuegra L; Bosch MJ; Bertomeu V; Ruiz V; Chorro FJ;...

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

Ref ID 459 Heart (British Cardiac Society ) 1013 - 1018 2005

Study Type Cohort  Number of participant 609 patients

Funding Not reported

15 May 2009
**Inclusion/Exclusion Criteria**

Inclusion: Patients with chest pain of suspected cardiac origin as determined by a cardiologist on call with a negative troponin I concentration (measured at baseline, at 6, 8 and 12 hours). Exclusion: ST elevation, Left Bundle Branch Block, and heart failure, Killip > 1

**Patient Characteristics**

The mean age was 64±12 years, 33% were women, 20% were current smokers, 59% had hypertension, 53% had hypercholesterolemia, 25% had diabetes, 44% had a history of IHD, 13% had a family history of IHD, 7% had had coronary surgery, 12% had ST depression, 9% had T wave inversion

**Recruitment**

Patients admitted to the emergency department in a teaching hospital in Spain

**Setting**

ED, teaching hospital in Spain

**Interventions/ Test/ Factor being investigated**

Diagnosing chest pain

**Comparisons**

The chest pain score was based on: location, radiation, character, severity, what influenced the pain, associated symptoms, history of exertional angina. A clinical history, ECG and for those in the low risk group an early (<24 hours) exercise test

**Length of Study/ Follow-up**

6 months

**Outcome measures studied**

Effectiveness of chest pain score in diagnosing chest pain

**Results**

Troponin I concentrations were taken at arrival, 6 hours (is patient arrived within 2 hours of onset of pain), 8 hours and 12 hours after pain onset. All patients had normal troponin concentrations at each measurement.

Patients underwent a chest pain score assessment, an ECG, and for those in the low risk group an early (<24 hours) exercise test. The chest pain score was based on: location (substernal) = +3, (precardial) = +2, (neck, jaw or epigastrium) = +1, (apical) = -1; radiation (either arm) = +2, (shoulder, back, neck or jaw) = +1; character (crushing, pressing or squeezing) = +3, (heaviness or tightness) = +2, (sticking, stabbing, pinprick or catching) = -1; severity (severe) = +2, (moderate) = +1; influenced by (glyceryl trinitrate) = +1, (stature) = -1, (breathing) = -1; associated symptoms (dyspnoea) = +2, (nausea or vomiting) = +2, (diaphoresis) = +2; history of exertional angina = +3. A clinical history was also taken (age, smoking, hypertension, hypercholesterolemia, diabetes, family history of IHD, history of IHD, previous coronary surgery)

During a 6 month follow up, 25 patients (4.1%) had an acute MI, 9 (1.5%) died of cardiac causes and 29 (4.8%) had a major event (AMI or cardiac death).

Those who could have had a negative exercise test had a very good prognosis compared to those who did not have a negative exercise test or those who could not exercise and do and exercise test.

See narrative for question 2; Table 2: Sanchis et al, 2005, Heart
See narrative for question 2; Table 3: Sanchis et al, 2005, Heart

For predictors of AMI the univariate and multivariate analysis showed: chest pain score (per point univariate P = 0.003, multivariate P = 0.009, odds ratio (OR) 1.2, 95%CI 1.1 to 1.4), age (per year univariate P = 0.02, multivariate P = 0.04, OR 1.04, 95%CI 1.01 to 1.09), men (univariate P = 0.008, multivariate P = 0.02, OR 3.7, 95%CI 2.2 to 11.1), smoking (univariate P = 0.2, multivariate P = not applicable (N.A.), OR N.A., 95%CI N.A.), hypertension (univariate P = 0.3, multivariate P = N.A., OR N.A., 95%CI N.A.), hypercholesterolemia (univariate P = 0.7, multivariate P = N.A., OR N.A., 95%CI N.A.), diabetes (univariate P = 0.3, multivariate P = 0.02, OR 2.5, 95%CI 1.1 to 5.7), family history of IHD (univariate P = 0.3, multivariate P = N.A., OR N.A., 95%CI N.A.), history of IHD (univariate P = 0.02, multivariate P = not significant (N.S.), OR N.A., 95%CI N.A.), coronary surgery (univariate P = 0.09, multivariate P = N.S., OR N.A., 95%CI N.A.)

For predictors of a major event (AMI or cardiac death) the univariate and multivariate analysis showed: chest pain score (per point univariate P = 0.002, multivariate P = 0.001, odds ratio (OR) 1.2, 95%CI 1.1 to 1.4), age (per year univariate P = 0.01, multivariate P = N.S., OR N.A., 95%CI N.A.), men (univariate P = 0.2, multivariate P = N.A., OR N.A., 95%CI N.A.), smoking (univariate P = 0.5, multivariate P = N.A., OR
During a 6 month follow up, 25 patients (4.1%) had an acute MI, 9 (1.5%) died of cardiac causes and 29 (4.8%) had a major event (AMI or cardiac death), these were chest pain score, diabetes, previous coronary surgery and ST-segment depression. The event rate increased with the number of risk factors: no risk factors 2.5% event rate, 1 risk factor 2.9% event rate, 2 risk factors 10.2% event rate, 3 or 4 risk factors 29.2% event rate. Three risk categories were defined: low risk: no or 1 risk factor 2.7% event rate, intermediate risk: 2 risk factors 10.2% event rate, high risk: 3 or 4 risk factors 29.2% event rate. The differences between the 3 categories were all significant: high and intermediate (P = 0.001), high and low (P = 0.0001), intermediate and low (P = 0.008).

Safety and adverse effects

Does the study answer the question?

During a 6 month follow up, 25 patients (4.1%) had an acute MI, 9 (1.5%) died of cardiac causes and 29 (4.8%) had a major event (AMI or cardiac death). Multivariate analysis confirmed the four independent risk factors associated with a major event (AMI or cardiac death), these were chest pain score, diabetes, previous coronary surgery and ST-segment depression. The event rate increased with the number of risk factors: no risk factors 2.5% event rate, 1 risk factor 2.9% event rate, 2 risk factors 10.2% event rate, 3 or 4 risk factors 29.2% event rate. Three risk categories were defined: low risk: no or 1 risk factor 2.7% event rate, intermediate risk: 2 risk factors 10.2% event rate, high risk: 3 or 4 risk factors 29.2% event rate. The differences between the 3 categories were all significant: high and intermediate (P = 0.001), high and low (P = 0.0001), intermediate and low (P = 0.008).

Safety and adverse effects

Does the study answer the question?

During a 6 month follow up, 25 patients (4.1%) had an acute MI, 9 (1.5%) died of cardiac causes and 29 (4.8%) had a major event (AMI or cardiac death). Multivariate analysis confirmed the four independent risk factors associated with a major event (AMI or cardiac death), these were chest pain score, diabetes, previous coronary surgery and ST-segment depression. The event rate increased with the number of risk factors: no risk factors 2.5% event rate, 1 risk factor 2.9% event rate, 2 risk factors 10.2% event rate, 3 or 4 risk factors 29.2% event rate. Three risk categories were defined: low risk: no or 1 risk factor 2.7% event rate, intermediate risk: 2 risk factors 10.2% event rate, high risk: 3 or 4 risk factors 29.2% event rate. The differences between the 3 categories were all significant: high and intermediate (P = 0.001), high and low (P = 0.0001), intermediate and low (P = 0.008).

Effect due to factor in study?

Consistent

Consistency of results with other studies?

Correct population

Directly applicable to guideline population?

Yes

Internal Validity

Well covered

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

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

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

Study Type

Cohort

Funding

Not reported

Number of participant

609 patients

Inclusion/Exclusion Criteria

Inclusion: Patients with chest pain of suspected cardiac origin as determined by a cardiologist on call with a negative troponin I concentration (measured at baseline, at 6, 8 and 12 hours). Exclusion: ST elevation, Left Bundle Branch Block, and heart failure, killip > 1

15 May 2009
The mean age was 64±12 years, 33% were women, 20% were current smokers, 59% had hypertension, 53% had hypercholesterolemia, 25% had diabetes, 44% had a history of IHD, 13% had a family history of IHD, 7% had had coronary surgery, 12% had ST depression, 9% had T wave inversion.

Patients admitted to the emergency department in a teaching hospital in Spain.

Diagnosing chest pain

The chest pain score was based on: location, radiation, character, severity, what influenced the pain, associated symptoms, history of exertional angina. A clinical history, ECG and for those in the low risk group an early (<24 hours) exercise test.

Effectiveness of chest pain score in diagnosing chest pain

Troponin I concentrations were taken at arrival, 6 hours (is patient arrived within 2 hours of onset of pain), 8 hours and 12 hours after pain onset. All patients had normal troponin concentrations at each measurement.

Patients underwent a chest pain score assessment, an ECG, and for those in the low risk group an early (<24 hours) exercise test. The chest pain score was based on: location (subternal) = +3, (precordial) = +2, (neck, jaw or epigastrum) = +1, (apical) = -1; radiation (either arm) = +2, (shoulder, back, neck or jaw) = +1; character (crushing, pressing or squeezing) = +3, (heaviness or tightness) = +2, (sticking, stabbing, pinprick or catching) = -1; severity (severe) = +2, (moderate) = +1; influenced by (glyceryl trinitrate) = +1, (stature) = -1, (breathing) = -1; associated symptoms (dyspnœa) = +2, (nausea or vomiting) = +2, (diaphoresis) = +2; history of exertional angina = +3. A clinical history was also taken (age, smoking, hypertension, hypercholesterolemia, diabetes, family history of IHD, history of IHD, previous coronary surgery).

During a 6 month follow up, 25 patients (4.1%) had an acute MI, 9 (1.5%) died of cardiac causes and 29 (4.8%) had a major event (AMI or cardiac death).

Those who could have had a negative exercise test had a very good prognosis compared to those who did not have a negative exercise test or those who could not exercise and do an exercise test.

See narrative for question 1; Table 6: Sanchis et al, 2005, Heart
See narrative for question 1; Table 7: Sanchis et al, 2005, Heart
For predictors of AMI the univariate and multivariate analysis showed: chest pain score (per point univariate P = 0.003, multivariate P = 0.009, odds ratio (OR) 1.2, 95%CI 1.1 to 1.4), age (per year univariate P = 0.02, multivariate P = 0.04, OR 1.04, 95%CI 1.01 to 1.09), men (univariate P = 0.008, multivariate P = 0.02, OR 3.7, 95%CI 1.2 to 11.1), smoking (univariate P = 0.4, multivariate P = not applicable (N.A.), OR N.A., 95%CI N.A.), hypertension (univariate P = 0.3, multivariate P = N.A., OR N.A., 95%CI N.A.), hypercholesterolemia (univariate P = 0.7, multivariate P = N.A., OR N.A., 95%CI N.A.), diabetes (univariate P = 0.03, multivariate P = 0.02, OR 2.5, 95%CI 1.1 to 5.7), family history of IHD (univariate P = 0.3, multivariate P = N.A., OR N.A., 95%CI N.A.), history of IHD (univariate P = 0.02, multivariate P = not significant (N.S.), OR N.A., 95%CI N.A.), coronary surgery (univariate P = 0.09, multivariate P = N.S., OR N.A., 95%CI N.A.)

For predictors of a major event (AMI or cardiac death) the univariate and multivariate analysis showed: chest pain score (per point univariate P = 0.002, multivariate P = 0.001, odds ratio (OR) 1.2, 95%CI 1.1 to 1.4), age (per year univariate P = 0.01, multivariate P = N.S., OR N.A., 95%CI N.A.), men (univariate P = 0.2, multivariate P = N.A., OR N.A., 95%CI N.A.), smoking (univariate P = 0.5, multivariate P = N.A., OR N.A., 95%CI N.A.), hypertension (univariate P = 0.2, multivariate P = N.A., OR N.A., 95%CI N.A.), hypercholesterolemia (univariate P = 1, multivariate P = N.A., OR N.A., 95%CI N.A.), diabetes (univariate P = 0.03, multivariate P = 0.03, OR 2.3, 95%CI 1.1
to 4.7), family history of IHD (univariate \( P = 1 \), multivariate \( P = N.A., \) OR N.A., 95%CI N.A.), history of IHD (univariate \( P = 0.007 \), multivariate \( P = N.S. \), OR N.A., 95%CI N.A.), coronary surgery (univariate \( P = 0.01 \), multivariate \( P = 0.01 \), OR 3.1, 95%CI 1.3 to 7.6)

The patients were stratified according to the four independent risk factors associated with a major event (AMI or cardiac death), these were chest pain score, diabetes, previous coronary surgery and ST-segment depression. The event rate increased with the number of risk factors: no risk factors 2.5% event rate, 1 risk factor 2.9% event rate, 2 risk factors 10.2% event rate, 3 or 4 risk factors 29.2% event rate. Three risk categories were defined: low risk: no or 1 risk factor 2.7% event rate, intermediate risk: 2 risk factors 10.2% event rate, high risk: 3 or 4 risk factors 29.2% event rate. The differences between the 3 categories were all significant: high and intermediate \( (P = 0.001) \), high and low \( (P = 0.0001) \), intermediate and low \( (P = 0.008) \).

Safety and adverse effects

Does the study answer the question?

During a 6 month follow up, 25 patients (4.1%) had an acute MI, 9 (1.5%) died of cardiac causes and 29 (4.8%) had a major event (AMI or cardiac death). Multivariate analysis found that the following were independent factors in predicting an acute MI: higher chest pain score (per point, odds ratio (OR) 1.2, 95%CI 1.1 to 1.4, \( P = 0.009 \)), older age (per year, OR 1.04, 95% CI 1.01 to 1.09, \( P = 0.04 \)), male sex (OR 3.7, 95% CI 1.2 to 11.1, \( P = 0.02 \)), and diabetes (OR 2.5, 95% CI 1.1 to 5.7, \( P = 0.02 \)). For prediction of major events (AMI or cardiac death), the following were independent predictors: higher chest pain score (OR 1.2, 95% CI 1.1 to 1.4, \( P = 0.01 \)), diabetes (OR 2.3, 95% CI 1.1 to 4.7, \( P = 0.03 \)), ST segment depression (OR 2.8, 95% CI 1.13 to 6.3, 95%, \( P = 0.003 \)), and previous coronary surgery (OR 3.1, 95% CI 1.3 to 7.6, \( P = 0.01 \)). Further analysis found that the event rate increased progressively with the progression of the number of independent risk factors, with the event rate increasing with the number of risk factors: no risk factors 2.5% event rate, 1 risk factor 2.9% event rate, 2 risk factors 10.2% event rate, 3 or 4 risk factors 29.2% event rate. From this 3 risk categories, low intermediate and high, were formed with the difference between each being significant.

NB there is overlap of patients included in this study and the study Sanchis et al 2005, JACC (New Risk Score for Patients with Acute Chest Pain, Non-ST-Segment Deviation, and Normal Troponin Concentrations).

Effect due to factor in study? Yes

Consistency of results with other studies? Consistent

Directly applicable to guideline population? Correct population

Internal Validity Well covered

Sanchis J; BodY V; N-quez J; Bertomeu G; Gmez C; Bosch MJ; Consuegra L; Bosch X; Chorro FJ; Llcer A;

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

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

Study Type Cohort

Number of participant 646 patients

Inclusion/Exclusion Criteria

Inclusion criteria: acute chest pain of possible cardiac origin Exclusion: if the initial ECG showed ST-segment deviation (≥1mm elevation or depression) or if they had troponin I elevation
The mean age was 64±12 years and 32% were women. 20% were smokers, 59% had hypertension, 53% had hypercholesterolemia, 26% had diabetes mellitus, 7% insulin dependant diabetes mellitus, 12% had a family history of IHD, 13% had at least 3 risk factors, 24% had prior coronary stenosis ≥ 50%, 43% had used aspirin in the previous 7 days, 25% had a prior MI, 9% had prior PTCA, 8% had prior CABG, 2% had a history of heart failure. On ECG 10% had T-wave inversion, 9% had confounding ECG

Setting
Patients admitted with acute chest pain to the emergency department in a teaching hospital in Spain during a 34 month period between 15th January 2001 and 30th November 2003

Interventions/Test/Factor being investigated
Diagnosing chest pain

Comparisons
The chest pain score and other variables, described in results

Length of Study/Follow-up
1 year

Outcome measures studied
The primary end point was all cause mortality or nonfatal myocardial infarction, the secondary end point was all cause mortality, nonfatal myocardial infarction or urgent revascularisation at 14 day follow up.

Results
Troponin I concentrations were taken at arrival, 6 hours (if patient arrived within 2 hours of onset of pain), 8 hours and 12 hours after pain onset. All patients had normal troponin concentrations at each measurement.

Patients underwent a chest pain score assessment based on: location (substernal) = +3, location (precordial) = +2, location (neck, jaw or epigastrum) = +1, location (apical) = -1; radiation (either arm) = +2, radiation (shoulder, back, neck or jaw) = +1; character (crushing, pressing or squeezing) = +3, character (heaviness or tightness) = +2, character (sticking, stabbing, pinprick or catching) = -1; severity (severe) = +2, severity (moderate) = +1; influenced by glyceryl trinitrate = +1, influenced by stature = -1, influenced by breathing = -1; associated symptoms (dyspnoea) = +2, (nausea or vomiting) = -2; history of exertional angina = +3. A clinical history was also taken (age, smoking, hypertension, hypercholesterolemia, diabetes, family history of coronary artery disease, history of coronary artery disease, previous coronary surgery). The following other variables were also determined: gender, age, smoking, arterial hypertension, diabetes mellitus, insulin-dependant diabetes mellitus (IDDM), hypercholesterolemia, at least 3 risk factors for coronary artery disease, ≥ 2 chest pain episodes in last 24 hours, Killip class >1 at presentation, evidence of prior coronary stenosis ≥ 50%, use of aspirin in the last 7 days, prior PCI, prior CABG, and a history of heart failure. An ECG was recorded in the emergency room.

At 1 year follow up, the primary end point (all-cause mortality or non-fatal MI) occurred in forty three patients (6.3%). At a 14 day follow up, the secondary end point (all-cause mortality or nonfatal myocardial infarction or urgent revascularisation) occurred in 35 patients (5.4%). The mean chest pain score was 10.4±2.8, 53% had ≥2 chest pain episodes in the previous 24 hours.

See narrative for question 1; Table 8: Sanchis et al, 2005, JACC
The univariate analysis showed that for: pain score ≥ 10 points (P = 0.001), ≥2 chest pain episodes in previous 24 hours (P = 0.001), Killip >1 (P = 0.1), age ≥67 (P = 0.004), men (P = 0.4), current smokers (P = 0.2), hypertension (P = 0.4), hypercholesterolemia (P = 0.6), diabetes mellitus (P = 0.001), IDDM (P = 0.001), family history of IHD (P = 0.6), diabetes mellitus (P = 0.001), at least 3 risk factors (P = 0.8), prior coronary stenosis ≥ 50% (P = 0.1), use of aspirin in previous 7 days (P = 0.02), prior MI (P = 0.1), prior PCI (P = 0.05), prior CABG (P = 0.1), history of heart failure (P = 0.6).

See narrative for question 1; Table 8: Sanchis et al, 2005, JACC
The multivariate analysis showed that for: pain score ≥ 10 points (hazard ratio (HR) 2.5, 95%CI 1.2-5.6, P = 0.02), ≥2 chest pain episodes in previous 24 hours (HR 2.2, 95%CI 1.2-4.2, P = 0.01), age ≥67 (HR 2.3, 95%CI 1.2-4.4, P = 0.01), IDDM (HR 4.2, 95%CI 1.1-8.4, P = 0.0001), prior PTCA (HR 2.2, 95%CI 1.1-4.8, P = 0.04). The multivariate analysis gave P values for the following: Killip >1 (P = 0.7), diabetes mellitus (P = 0.2), prior coronary stenosis ≥ 50% (P = 0.7), use of aspirin in previous
Multivariate analysis found that the following were independent factors in predicting all cause mortality or nonfatal myocardial infarction; a chest pain score $\geq 10$ points (hazard ratio (HR) 2.5, 95% CI 1.2 to 5.6, $P = 0.02$), $\geq 2$ chest pain episodes in last 24 hours (HR 2.2, 95% CI 1.2 to 4.2, $P = 0.01$), age $\geq 67$ years (HR 2.3, 95% CI 1.2 to 4.4, $P = 0.01$), IDDM (HR 4.2, 95% CI 2.1 to 8.4, $P = 0.0001$), and prior PCI (HR 2.2, 95% CI 1.1 to 4.8, $P = 0.04$).

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

The new risk score was then compared with calculated TIMI scores. The new risk score had an accuracy C index of 0.78 ($P = 0.0001$) compared with the TIMI score C index of 0.66 ($P = 0.0001$), and the accuracy of the new score was significantly greater compared with the TIMI score ($P = 0.0002$).

The accuracy of both the new risk score and the TIMI score were tested for the secondary end point (death, MI or urgent revascularization at 14 days, which the TIMI score was originally designed for). The new risk score had a C index of 0.70 ($P = 0.0001$) and the TIMI score and a C index of 0.66 ($P = 0.002$) were correlated to the secondary end point but there was no significant difference ($P = 0.1$).

Safety and adverse effects

None reported

Does the study answer the question?

Multivariate analysis found that the following were independent factors in predicting all cause mortality or nonfatal myocardial infarction; a chest pain score $\geq 10$ points (hazard ratio (HR) 2.5, 95%CI 1.2 to 5.6, $P = 0.02$), $\geq 2$ chest pain episodes in last 24 hours (HR 2.2, 95% CI 1.2 to 4.2, $P = 0.01$), age $\geq 67$ years (HR 2.3, 95% CI 1.2 to 4.4, $P = 0.01$), IDDM (HR 4.2, 95% CI 2.1 to 8.4, $P = 0.0001$), and prior PCI (HR 2.2, 95% CI 1.1 to 4.8, $P = 0.04$).

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

The new risk score was then compared with calculated TIMI scores. The new risk score had an accuracy C index of 0.78 ($P = 0.0001$) compared with the TIMI score C index of 0.66 ($P = 0.0001$), and the accuracy of the new score was significantly greater compared with the TIMI score ($P = 0.0002$).

The accuracy of both the new risk score and the TIMI score were tested for the secondary end point (death, MI or urgent revascularization at 14 days, which the TIMI score was originally designed for). The new risk score had a C index of 0.70 ($P = 0.0001$) and the TIMI score and a C index of 0.66 ($P = 0.002$) were correlated to the secondary end point but there was no significant difference ($P = 0.1$).
index of 0.66 (P = 0.0001), and the accuracy of the new score was significantly greater compared with the TIMI score (P = 0.0002). The accuracy of both the new risk score and the TIMI score were tested for the secondary end point (death, MI or urgent revascularization at 14 days, which the TIMI score was originally designed for). The new risk score had a C index of 0.70 (P = 0.0001) and the TIMI score and a C index of 0.66 (P = 0.002) were correlated to the secondary end point but there was no significant difference (P = 0.1).

NB there is overlap of patients included in this study and the study Sanchis et al 2005, Heart J (Risk Stratification of Patients with Acute Chest Pain and Normal Troponin Concentrations).

**Effect due to factor in study?**  Yes

**Consistency of results with other studies?**  Consistent

**Directly applicable to guideline population?**  Correct population

**Internal Validity**  Well covered

Sanchis J; Bod Y V; N-àez J; Bertomeu G; G-àmez C; Bosch MJ; Consuegra L; Bosch X; Chorro FJ; LlÓcer A;

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

**Study Type**  Cohort

**Number of participant**  646 patients

**Inclusion/Exclusion Criteria**  Inclusion criteria: acute chest pain of possible cardiac origin Exclusion: if the initial ECG showed ST-segment deviation (≥1mm elevation or depression) or if they had troponin I elevation

**Patient Characteristics**  The mean age was 64±12 years and 32% were women. 20% were smokers, 59% had hypertension, 53% had hypercholesterolemia, 26% had diabetes mellitus, 7% insulin dependant diabetes mellitus, 12% had a family history of IHD, 13% had at least 3 risk factors, 24% had prior coronary stenosis ≥ 50%, 43% had used aspirin in the previous 7 days, 25% had a prior MI, 9% had prior PTCA, 8% had prior CABG, 2% had a history of heart failure. On ECG 10% had T-wave inversion, 9% had confounding ECG

**Recruitment**  Patients admitted with acute chest pain to the emergency department in a teaching hospital in Spain during a 34 month period between 15th January 2001 and 30th November 2003

**Setting**  ED in a teaching hospital in Spain

**Interventions/ Test/ Factor being investigated**  Diagnosing chest pain

**Comparisons**  The chest pain score and other variables, described in results

**Length of Study/ Follow-up**  1 year

**Outcome measures studied**  The primary end point was all cause mortality or nonfatal myocardial infarction, the secondary end point was all cause mortality, nonfatal myocardial infarction or urgent revascularisation at 14 day follow up.
Results

Troponin I concentrations were taken at arrival, 6 hours (is patient arrived within 2 hours of onset of pain), 8 hours and 12 hours after pain onset. All patients had normal troponin concentrations at each measurement.

Patients underwent a chest pain score assessment based on: location (substernal) = +3, location (precordial) = +2, location (neck, jaw or epigastrium) = +1, location (apical) = -1; radiation (either arm) = +2, radiation (shoulder, back, neck or jaw) = +1; character (crushing, pressing or squeezing) = +3, character (heaviness or tightness) = +2, character (sticking, stabbing, pinprick or catching) = -1; severity (severe) = +2, severity (moderate) = +1; influenced by glyceryl trinitrate = +1, influenced by stature = -1, influenced by breathing = -1; associated symptoms (dyspnoea) = +2, (nausea or vomiting) = +2, (diaphoresis) = +2; history of exertional angina = +3. A clinical history was also taken (age, smoking, hypertension, hypercholesterolemia, diabetes, family history of coronary artery disease, history of coronary artery disease, previous coronary surgery). The following other variables were also determined: gender, age, smoking, arterial hypertension, diabetes mellitus, insulin-dependant diabetes mellitus (IDDM), hypercholesterolemia, at least 3 risk factors for coronary artery disease, ≥ 2 chest pain episodes in last 24 hours, Killip class > 1 at presentation, evidence of prior coronary stenosis ≥ 50%, use of aspirin in the last 7 days, prior PCI, prior CABG, and a history of heart failure. An ECG was recorded in the emergency room.

At 1 year follow up, the primary end point (all-cause mortality or non-fatal MI) occurred in forty three patients (6.3%). At a 14 day follow up, the secondary end point (all-cause mortality or nonfatal myocardial infarction or urgent revascularisation) occurred in 35 patients (5.4%). The mean chest pain score was 10.4±2.8, 53% had ≥2 chest pain episodes in the previous 24 hours.

See narrative for question 2; Table 4: Sanchis et al, 2005, JACC

The univariate analysis showed that for: pain score ≥ 10 points (P = 0.001), ≥2 chest pain episodes in previous 24 hours (P = 0.001), Killip >1 (P = 0.1), age ≥67 (P = 0.004), men (P = 0.4), current smokers (P = 0.2), hypertension (P = 0.4), hypercholesterolemia (P = 0.6), diabetes mellitus (P = 0.001), IDDM (P = 0.0001), family history of IHD (P = 0.6), at least 3 risk factors (P = 0.8), prior coronary stenosis ≥ 50% (P = 0.1), use of aspirin in previous 7 days (P = 0.02), prior MI (P = 0.1), prior PTCA (P = 0.05), prior CABG (P = 0.1), history of heart failure (P = 0.6).

See narrative for question 2; Table 4: Sanchis et al, 2005, JACC

The multivariate analysis showed that for: pain score ≥ 10 points (hazard ratio (HR) 2.5, 95%CI 1.2-5.6, P = 0.02), ≥2 chest pain episodes in previous 24 hours (HR 2.2, 95%CI 1.2-4.4, P = 0.01), age ≥67 (HR 2.3, 95% CI 1.2-4.4, P = 0.01), IDDM (HR 4.2, 95% CI 2.1-8.4, P = 0.0001), prior PTCA (HR 2.2, 95%CI 1.1-4.8, P = 0.04). The multivariate analysis gave P values for the following: Killip >1 (P = 0.7), diabetes mellitus (P = 0.2), prior coronary stenosis ≥ 50% (P = 0.7), use of aspirin in previous 7 days (P = 0.6), prior MI (P = 0.9), prior CABG (P = 0.8). The multivariate analysis did not give results for: men, current smokers, hypertension, hypercholesterolemia, family history of IHD, at least 3 risk factors, history of heart failure.

From the multivariate analysis it was shown that the following were independent factors in predicting all cause mortality or nonfatal myocardial infarction; a chest pain score ≥ 10 points (hazard ratio (HR) 2.5, 95%CI 1.2 to 5.6, P = 0.02), ≥2 chest pain episodes in last 24 hours (HR 2.2, 95% CI 1.2 to 4.2, P = 0.01), age ≥67 years (HR 2.3, 95% CI 1.2 to 4.4, P = 0.01), IDDM (HR 4.2, 95% CI 2.1 to 8.4, P = 0.0001), and prior PCI (HR 2.2, 95% CI 1.1 to 4.8, P = 0.04).

The study constructed a risk score from 5 variables which were shown to be independently related to the primary end point. The variables with similar HR (chest pain score ≥ 10, ≥2 chest pain episodes in the last 24 hours, age ≥67 years and prior PCI) were assigned a 1 point value. IDDM was assigned a 2 point value as the HR value was twice the HR value of the other variables. This risk score gave the following patient population distribution: 0 points: n=111 (17.2%), 1 point: n=198 (30.7%), 2 points: n=206 (31.9%), 3 points: n=103 (15.9%), 4 points: n=16 (2.5%), 5 points: n=11 (1.7%), 6 points: n=1 (0.2%). The study combined 4-6 points due to the low number of patients giving the distribution: 4-6 points: n=25 (4.3%). The study then distinguished the 5 points values as: very low-risk (0 points, primary end point = 0%), low-risk (1 points, primary end point = 3.1%), intermediate-risk (2 points, primary end point = 5.4%), high-risk (3 points, primary end point = 17.6%) and very high-risk (≥4 points, primary end point = 29.6%). These were statistically significant with a P = 0.00001. The differences between the groups were also significant (comparing very low-, low-, intermediate-risk to very high-risk P = 0.0001, P = 0.0001, P = 0.0001).
Multivariate analysis found that the following were independent factors in predicting all cause mortality or nonfatal myocardial infarction; a chest pain score ≥ 10 points (hazard ratio (HR) 2.5, 95% CI 1.2 to 5.6, P = 0.02), ≥ 2 chest pain episodes in the last 24 hours (HR 2.2, 95% CI 1.2 to 4.2, P = 0.01), age ≥ 67 years (HR 2.3, 95% CI 1.2 to 4.4, P = 0.01), IDDM (HR 4.2, 95% CI 2.1 to 8.4, P = 0.0001), and prior PCI (HR 2.2, 95% CI 1.1 to 4.8, P = 0.04). The accuracy of both the new risk score and the TIMI score were tested for the secondary end point (death, MI or urgent revascularization at 14 days, which the TIMI score was originally designed for). The new risk score had a C index of 0.70 (P = 0.0001) and the TIMI score and a C index of 0.66 (P = 0.002) were correlated to the secondary end point but there was no significant difference (P = 0.1).

The new risk score was then compared with calculated TIMI scores. The new risk score had an accuracy C index of 0.78 (P = 0.0001) compared with the TIMI score C index of 0.66 (P = 0.0001), and the accuracy of the new score was significantly greater compared with the TIMI score (P = 0.0002).

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

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Multivariate analysis found that the following were independent factors in predicting all cause mortality or nonfatal myocardial infarction; a chest pain score ≥ 10 points (hazard ratio (HR) 2.5, 95% CI 1.2 to 5.6, P = 0.02), ≥ 2 chest pain episodes in last 24 hours (HR 2.2, 95% CI 1.2 to 4.2, P = 0.01), age ≥ 67 years (HR 2.3, 95% CI 1.2 to 4.4, P = 0.01), IDDM (HR 4.2, 95% CI 2.1 to 8.4, P = 0.0001), and prior PCI (HR 2.2, 95% CI 1.1 to 4.8, P = 0.04).

The study constructed a risk score from 5 variables which were shown to be independently related to the primary end point. The variables with similar HR (chest pain score ≥ 10, ≥ 2 chest pain episodes in the last 24 hours, age ≥ 67 years and prior PCI) were assigned a 1 point value. IDDM was assigned a 2 point value as the HR value was twice the HR value of the other variables. This risk score gave the following patient population distribution: 0 points: n=111 (17.2%), 1 point: n=198 (30.7%), 2 points: n=206 (31.9%), 3 points: n=103 (15.9%), 4 points: n=16 (2.5%), 5 points: n=11 (1.7%), 6 points: n=1 (0.2%). The study combined 4-6 points due to the low number of patients giving the distribution: 4-6 points: n=25 (4.3%). The study then distinguished the 5 points values as: very low-risk (0 points, primary end point = 0%), low-risk (1 points, primary end point = 3.1%), intermediate-risk (2 points, primary end point = 5.4%), high-risk (3 points, primary end point = 17.6%) and very high-risk (≥4 points, primary end point = 29.6%). These were statistically significant with a P = 0.00001. The differences between the groups were also significant (comparing very low-, low-, intermediate-risk to very high-risk P = 0.0001, P = 0.0001, P = 0.0001 respectively; comparing very low-, low-, intermediate-risk to high-risk P = 0.002, P = 0.0001, P = 0.0001 respectively).
Grading: 2+  Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

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

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

Ref ID 735  Wiener klinische Wochenschrift  pp. 83 to 89  2004

Study Type  Cohort  Funding  Not reported

Number of participant  1288 patients

Inclusion/Exclusion Criteria

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

Patient Characteristics

The mean age of the population was 49±17 years, 41% were women, 29% had hypertension, 9% had diabetes mellitus, 35% had hyperlipidaemia, 32% were current smokers, 26% were obese (BMI>28), 20% had a family history of MI, 15% had a history of prior MI, 23% had a history of coronary artery disease, 2% had a history of congestive heart failure, 3% had valvular heart disease

Recruitment

Patients presenting with chest pain at a non-trauma emergency department

Setting

University hospital in Helsinki, Finland

Interventions/ Test/ Factor being investigated

Diagnosing chest pain

Comparisons

Seven pre-defined criteria are evaluated and were assigned as either typical or atypical

Length of Study/ Follow-up

6 months

Outcome measures studied

Prediction or exclusion of acute MI and major adverse coronary events (MACE) at six months

Results

Seven pre-defined criteria are evaluated and were assigned as either typical or atypical; namely, location of chest pain (typical: left sided, atypical: right sided), character of pain (typical: crushing / sneezing / burning / tightness, atypical: stabbing / single spot / superficial), radiation (typical to the left or both arms, neck, back, atypical: not radiating), appearance of chest pain (typical: exercise induced / undulating / relieved with rest or nitroglycerin, atypical: inducible by pressure / abrupt palpitations / sustained / position dependent / respiration dependent / cough dependent), vegetative signs (typical dyspnea / nausea / diaphoresis atypical: absence of vegetative signs), history of coronary artery disease (typical: MI / PTCA / CABD, atypical: none) and risk factors for coronary artery disease namely; smoking, obesity, hypertension, diabetes, hyperlipidaemia, and family history all typical, atypical was defined as absence or only one risk factor. The positive predictive value (PPV) and LR of typical and atypical criteria were evaluated for prediction or exclusion of acute MI and major adverse coronary events (MACE) at six months.

Thirteen percent (168 patients) of patients had an acute MI and 19% (240 patients) had a MACE (CVD, percutaneous coronary interventions, bypass surgery or MI) at six months follow up.

See narrative for question 1; Table 5: Schillinger et al, 2004

From the typical symptoms or history the likelihood ratios (LR) to predict an MI were: 1 typical symptom or history LR = 1.15; 2 typical symptoms and/or history LR = 1.32; 3 typical symptoms and/or history LR = 1.48; 4 typical symptoms and/or history LR = 1.77; 5 typical symptoms and/or history LR = 1.88; 6 typical symptoms and/or history
The presence of four or more typical criteria was associated with a PPV of 0.21 (95% CI 0.17 to 0.25) to predict acute MI and 0.30 (95% CI 0.25 to 0.35) for 6 month MACE. Increasing numbers of atypical chest pain criteria was associated with increasing PPVs for excluding acute MI and 6 month MACE. The presence of four or more typical criteria was associated with a PPV of 0.94 (95% CI 0.92 to 0.96) to exclude acute MI and 0.93 (95% CI 0.90 to 0.96) for 6 month absence of MACE. The authors concluded that the evaluation of criteria atypical for MI may identify patients suitable for early discharge; however criteria typical of MI have little diagnostic value.
The mean age of the population was 49±17 years, 41% were women, 29% had hypertension, 9% had diabetes mellitus, 35% had hyperlipidaemia, 32% were current smokers, 26% were obese (BMI>28), 20% had a family history of MI, 15% had a history of prior MI, 23% had a history of coronary artery disease, 2% had a history of congestive heart failure, 3% had valvular heart disease.

Patients presenting with chest pain at a non-trauma emergency department

University hospital in Helsinki, Finland

Diagnosing chest pain

Seven pre-defined criteria are evaluated and were assigned as either typical or atypical

6 months

Prediction or exclusion of acute MI and major adverse coronary events (MACE) at six months

Seven pre-defined criteria are evaluated and were assigned as either typical or atypical: namely, location of chest pain (typical: left sided, atypical: right sided), character of pain (typical: crushing / sneezing / burning / tightness, atypical: stabbing / single spot / superficial), radiation (typical to the left or both arms, neck, back, atypical: not radiating), appearance of chest pain (typical: exercise induced / undulating / relieved with rest or nitroglycerin, atypical: inducible by pressure / abrupt palpitations / sustained / position dependent / respiration dependent / cough dependent), vegetative signs (typical dyspnea / nausea / diaphoresis atypical: absence of vegetative signs), history of coronary artery disease (typical: MI / PTCA / CABD, atypical: none) and risk factors for coronary artery disease namely: smoking, obesity, hypertension, diabetes, hyperlipidemia, and family history all typical, atypival was defined as absence or only one risk factor. The positive predictive value (PPV) and LR of typical and atypical criteria were evaluated for prediction or exclusion of acute MI and major adverse coronary events (MACE) at six months.

Thirteen percent (168 patients) of patients had an acute MI and 19% (240 patients) had a MACE (CVD, percutaneous coronary interventions, bypass surgery or MI) at six months follow up.

From the typical symptoms or history the likelihood ratios (LR) to predict an MI were: 1 typical symptom or history LR = 1.15; 2 typical symptoms and/or history LR = 1.32; 3 typical symptoms and/or history LR = 1.48; 4 typical symptoms and/or history LR = 1.77; 5 typical symptoms and/or history LR = 1.88; 6 typical symptoms and/or history LR = 1.85

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

See narrative for question 2; Table 1: Schillinger et al, 2004

From the atypical symptoms or history the LR to exclude an MI were: 1 atypical symptom or history LR = 1.05; 2 atypical symptoms and/or history LR = 1.25; 3 atypical symptoms and/or history LR = 1.76; 4 atypical symptoms and/or history LR = 2.22; 5 atypical symptoms and/or history LR = 3.19; 6 atypical symptoms and/or history LR = 3.00

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

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

Safety and adverse effects

None reported

Effect due to factor in study?

Yes

Consistency of results with other studies?

Consistent

Directly applicable to guideline population?

Correct population

Internal Validity

Well covered
Question: What is the diagnostic utility of pain relief with nitrates in the identification of patients with acute chest pain of cardiac origin.
Steele R;McNaughton T;McConahy M;Lam J;

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

Study Type  Diagnostic

Number of participant

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

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

Effect due to factor in study?

Consistency of results with other studies?

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

Internal Validity

Grading: 2++ High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
Grading: 2+  Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

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

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


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

Number of participant

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

The primary outcome of cardiac-related chest pain was found in 122 patients (18%), of which 68 had acute MI and 54 had unstable angina. An initial pain score of > 5 was documented in 478 patients (71%), and in this group the primary outcome of cardiac-related chest pain was found in 82 patients (17%). An initial pain score of equal to or less than 5 was documented in 186 patients (29%), and in this group the primary outcome of cardiac-related chest pain was found in 40 patients (17%).

In the total patient population, 125 (19%) patients had no change in pain, 206 (31%) patients had minimal pain reduction, 145 (22%) had moderate pain reduction, and 188 (28%) patients had significant or complete pain reduction. A change in the numeric descriptive scale score was not associated with a diagnosis of coronary artery disease in any of these 4 subgroups (using Pearson statistic = 1.0, P = 0.76). The study shows that nitroglycerin pain relief is not a useful diagnostic tool for identifying cardiac-related chest pain.

Effect due to factor in study?

Consistency of results with other studies?

15 May 2009  Page 30 of 196
Patient population directly applicable, patients with chest pain of suspected cardiac origin.

Internal Validity

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

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

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

Study Type Diagnostic

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

Number of participant

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/Test/
Factor being investigated

Comparisons

Length of Study/
Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

The study is directly applicable to the question of the utility of nitroglycerin pain relief in the diagnosis of chest pain of cardiac origin. The sensitivity and specificity of chest pain relief with nitroglycerin for the presence of active coronary artery disease were 35% and 58%, respectively. The positive and negative likelihood ratios were 0.85 and 1.4, respectively. Further analysis was conducted in 3 pre-specified subgroups for chest pain relief with nitroglycerin for the presence of active coronary artery disease. For troponin negative patients the sensitivity, specificity, positive likelihood ratio and negative likelihood ratio were 39%, 58%, 0.88 and 1.1, respectively. For patients with a history of coronary artery disease the sensitivity, specificity, positive likelihood ratio and negative likelihood ratio were 30%, 63%, 0.84 and 1.3, respectively. For patients with no history of coronary artery disease, the sensitivity, specificity, positive likelihood ratio and negative likelihoods were 40%, 56%, 0.87 and 1.1, respectively. ROC curves were constructed for chest pain relief by nitroglycerin and active coronary artery disease. For ROC curves of both reduction in pain intensity and absolute changes in pain intensity the plotted points closely approximated to a likelihood of 1.0. Hence regardless of which definition is used, either percentage chest pain reduction or absolute pain reduction, the test of chest pain with nitroglycerin has no value in determining the presence or absence of coronary artery disease.

Effect due to factor in study?

15 May 2009
Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Patient population directly applicable, patients with chest pain of suspected cardiac origin.
Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal*

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

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

Ref ID 7214 Am J Cardiol Pages 1264 to 1267 2002

Funding Not stated.

Patient population directly applicable, patients with chest pain of suspected cardiac origin.
Internal Validity
Question: Are the symptoms and description of the symptoms different in women presenting with acute chest pain of suspected cardiac origin compared with men
### Grading:

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

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

**Ref ID**: 25372

**Arch Intern Med**

**Pages**: 2405 to 2413

**Year**: 2007

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<table>
<thead>
<tr>
<th>Study Type</th>
<th>Systematic Review</th>
</tr>
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<tbody>
<tr>
<td>Number of participant</td>
<td>Cohort, Surveys, Registries.</td>
</tr>
<tr>
<td>Inclusion/Exclusion Criteria</td>
<td>Cohort, Surveys, Registries identified between 1970 to 2005</td>
</tr>
<tr>
<td>Patient Characteristics</td>
<td>Patients with ACS</td>
</tr>
<tr>
<td>Recruitment</td>
<td>Systematic review identified nine large cohort studies, and twenty smaller cohort or personal interview studies that provided information on ACS presentation with and without chest pain or discomfort according to sex</td>
</tr>
<tr>
<td>Setting</td>
<td>Emergency departments</td>
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<tr>
<td>Interventions/ Test/ Factor being investigated</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Comparisons</td>
<td>Signs and symptoms, men versus women</td>
</tr>
<tr>
<td>Length of Study/ Follow-up</td>
<td>Not applicable</td>
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<tr>
<td>Outcome measures studied</td>
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</table>

**Results**

Compared with men, 8 identified studies found that women are more likely to experience middle or upper back pain, 4 studies found that women are more likely to have neck pain, and 2 studies found that women are more likely to have jaw pain. Five studies found that women are more likely to have shortness of breath and five studies showed women are more likely to have nausea or vomiting. Loss of appetite, weakness and fatigue, and cough were identified as more common in women versus men in two studies each. Paroxysmal nocturnal dyspnea, indigestion and dizziness were reported as more common in women versus men in one study each. One study found that women appear to have a greater number of associated symptoms as part of their ACS presentation compared with men.

**Safety and adverse effects**

Not applicable

**Does the study answer the question?**

Yes. Women are significantly less likely to report chest pain or discomfort at presentation for ACS compared with men from accumulated data from 29 identified studies. The authors identified the following limitations of the review and other related studies; there is a lack of standardisation on data collection and reporting on women’s principal or associated ACS symptoms thus formal meta-analyses was not possible due to heterogeneity, a number of studies exclude patients that have ACS and no chest pain or discomfort, chest pain or discomfort is often lumped together with pain localised to other areas of the upper body in the absence of chest pain symptoms, hospital records are often very imprecise in characterising the presence of chest pain, as well as other associated symptoms, physician bias based on the patients pre-test probability in recording symptoms, survey bias when patients recollect symptoms retrospectively, the sensitivity of a particular symptom may be ascertained but the specificity of a symptom may not be considered, and the impact of potential association of co-morbid conditions (such as diabetes), with symptom...
presentation has not been examined in the review due to the lack of currently available data although this is likely to be important.

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

Fifteen studies were identified, four cohorts were in patients with all types of ACS and eleven cohorts were in patients with MI. The systematic review did not however provide a definition of ACS that was detailed in the selected studies.

Signs and symptoms

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

Ref: Am Heart J 2004 pg 27 to 33

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

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

Does the study answer the question? Cohort studies suggest that women exhibit different symptoms of ACS versus men, however, here was inconsistency in the gender-specific symptoms reported, in that no individual symptom was identified by all studies that examined the symptom. It is likely that the baseline characteristics of the populations varied, and the authors
stated that sex differences may disappear after controlling for variables such as age or co-morbid conditions. Some studies evaluated only a small number of symptoms, and may have missed other statistically significant symptoms.

<table>
<thead>
<tr>
<th>Effect due to factor in study?</th>
<th>Yes</th>
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<tbody>
<tr>
<td>Consistency of results with other studies?</td>
<td>Consistent</td>
</tr>
<tr>
<td>Directly applicable to guideline population?</td>
<td>Directly relevant to guideline population</td>
</tr>
<tr>
<td>Internal Validity</td>
<td>Adequately addressed</td>
</tr>
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</table>
### Gender differences on the risk evaluation of acute coronary syndromes: The CARDIO2000 study

**Ref ID**: 3520  
**Preventive Cardiology**: 71 to 77  
**2003**

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

Directly applicable to guideline population?  Not unselected chest pain population, however ACS I population is subset of this, therefore cohort is applicable as subset of the chest pain guideline population

Internal Validity  Well covered

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

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

Ref ID 25380 EUR J CARDIOVASC NURS PGS 152 to 158 2008

Study Type  Cohort  Funding  Norrbotten County Council provided funding for the myocardial registry

Number of participant  6342 patients (5072 men and 1470 women).

Inclusion/Exclusion Criteria  Patients with a diagnosis of MI according to standard WHO definition. Exclusion criteria were patients in the registry with incomplete data

Patient Characteristics  Patients with MI according to standard WHO definition

Recruitment  Not applicable

Setting  Northern Swedish registry survey

Interventions/Test/Factor being investigated  Symptom presentation and prehospital delay and risk stratification according to age and gender

Comparisons  Age and gender, with respect to symptoms of MI

Length of Study/Follow-up  Records over 15 years

Outcome measures studied  Signs and symptoms, hospital delay

Results  The study found that men were more likely to experience typical pain based on the MONICA criteria compared with women (86.3% versus 80.8%, respectively). Symptoms were also analysed with stratification for age and gender. A greater proportion of younger men (age group 25 to 34 years) had typical pain compared with older male age groups, and with increasing age a greater proportion of men experienced typical symptoms. For women, a lower proportion experienced typical symptoms compared with men in all age ranges, however in the age range 65 to 74 years the difference in proportion of men versus women with typical symptoms was less marked (79.8% versus 78.0%), hence in the oldest age group the frequency of atypical pain is similar in men and women.

The study analysed prehospital delay in seeking medial attention according to age and gender (from < 2 h to > 24 h). For the total male population compared with the female population, there was no difference in the proportions in time to hospital delay; < 2 h, 41.2% men versus 41.2% women, < 4 h, 20.2% men versus 19.8% women, < 4 to 24 h, 27.7% men versus 29.8% women, and < 24 h, 10.9% men versus 9.8% women. Analysis of prehospital delay by stratifying according to age and gender found that there was no consistent difference with gender, although for the oldest age group of 65 to 74 years the delay was greater for women compared with men, 25% of older men delayed for more than 4 h compared with 31% for women.

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

<table>
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<tr>
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<tr>
<td>Does the study answer the question?</td>
<td>Yes. Study found that women have atypical presentation of STEMI compared with men, and higher rates of hypertension, diabetes and hyperlipidaemia compared with men.</td>
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<tr>
<td>Effect due to factor in study?</td>
<td>Yes</td>
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<tr>
<td>Consistency of results with other studies?</td>
<td>Consistent</td>
</tr>
<tr>
<td>Directly applicable to guideline population?</td>
<td>Not unselected chest pain population, however STEMI population is subset of this, therefore cohort is applicable as subset of the chest pain guideline population</td>
</tr>
<tr>
<td>Internal Validity</td>
<td>Adequately addressed</td>
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</table>
Grading: 2-  Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal*

Are there gender differences in patients presenting with unstable angina?

Ref ID 1204 International journal of cardiology M/FS 281 to 286 2000

Study Type Cohort  Funding Not reported

Number of participant 313, 210 (67%) men, 103 (33%) women

Inclusion/Exclusion Criteria Patients transferred to St Georges Hospital London UK, with a view to coronary angiography and further management, during a 42 month period (January 1994-January 1997)

Patient Characteristics The mean age for men was 61.6±11 years, for women 63.5±10.5 years (P=0.14). 184 men were Caucasian, 23 were Asian (Indian subcontinent) and 3 had other ethnic origin. 83 women were Caucasian, 15 were Asian (Indian subcontinent) and 5 had other ethnic origin (P=0.4)

Recruitment Patients transferred to tertiary care unit

Setting St Georges Hospital, London, UK

Interventions/ Test/ Factor being investigated Gender differences in patients presenting with unstable angina

Comparisons Retrospective review of case notes of risk factors for men and women referred for coronary angiography and further care

Length of Study/ Follow-up Review of case notes

Outcome measures studied Differences in risk factors for men and women with unstable angina

Results The mean age was 61.6±11 years for men and 63.5±10.5 for women (P=0.14). 184 men were Caucasian, 23 were Asian (Indian subcontinent) and 3 had other ethnic origin. 83 women were Caucasian, 15 were Asian (Indian subcontinent) and 5 had other ethnic origin (P=0.4). 51% of men and 39% of women had a history of previous MI (P=0.06). 76% of men and 79% of women had angina pectoris (P=0.73). Time to seeking help: < 1 day - 23% men, 28% women; 1-7 days - 38% men, 33% women; > 1 week: 39% men, 39% women. 17% of men and 6% of women had a previous coronary artery bypass graft operation (P=0.013). 56% of men and 64% of women had hypercholesterolemia (P=0.23). The mean total serum cholesterol concentration was 6.4±1.6 mmol/l in men and 6.7±1.5 mmol/l in women (P=0.4). 42% of men and 49% of women had a family history of ischaemic heart disease (P=0.28). 11% of men and 23% of women had diabetes mellitus (P=0.007). 32% of men and 52% of women had a history of hypertension (P=0.001). 73% of men and 46% of women were current or previous smokers (P=0.00001). 25% of men and 40% of women were current smokers (P=0.06).

The study also considered the management of patients, a similar number of men and women underwent coronary artery bypass graft operation and coronary angioplasty.

Safety and adverse effects Not applicable

15 May 2009
The results found that more men than women with unstable angina were referred for coronary angiography reflecting the higher prevalence of ischaemic heart disease in men.

There was no significant difference between men and women in age, the ratio of Caucasian to non-Caucasian patients, past history of angina pectoris, the duration of time before seeking medical help, mean total serum cholesterol level, family history of ischaemic heart disease. The prevalence of hypercholesterolemia was higher in women but it was not significant. Women were more likely to have diabetes mellitus, a history of hypertension and to currently smoke. Men were more likely to have a history of previous MI, history of previous coronary artery bypass graft operation and a history of smoking.

The study also considered the subsequent management of patients, and showed that the subsequent management of patients was not influenced by their gender. A similar proportion of male and female patients underwent coronary artery bypass graft operation and coronary angioplasty.

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Highly selected population from a tertiary care centre and recruitment not detailed, and also retrospective therefore risk of bias.

Consistent

Not unselected chest pain population, however unstable angina population is subset of this, therefore cohort is applicable as subset of the chest pain guideline population

Not addressed
Question: Are the symptoms and description of the symptoms different in Black and Ethnic Minorities presenting with acute chest pain of suspected cardiac origin compared with Caucasians.
### Patient Characteristics

- **Inclusion/Exclusion Criteria**: Inclusion: patients presenting to the emergency department with a chief complaint of anterior, pericordial, or left lateral chest pain that could not be explained by obvious local trauma or abnormalities on a chest X ray. Patients that experienced cardiac arrest in the emergency department were excluded from the study. During the study period, 4173 potentially eligible patient visits occurred, and the final study population was 3031 after exclusions (11 due to incomplete data, 531 consent not obtained, 204 inadequate follow-up, 158 race not identified, and 238 as race was Asian or Hispanic).

- **Study Type**: Cohort

- **Recruitment**: Patients presenting to the emergency department with a chief complaint of anterior, pericordial, or left lateral chest pain that could not be explained by obvious local trauma or abnormalities on a chest X ray.

- **Setting**: Emergency department, USA, Dec 1983 to Oct 1988

- **Interventions/Test/Factor being investigated**: History, risk factors and signs and symptoms

- **Comparisons**: African Americans versus Caucasians with suspected acute MI

- **Length of Study/Follow-up**: Not applicable

- **Outcome measures studied**: History, risk factors and signs and symptoms

### Results

African American patients with a final diagnosis of acute MI had similar presenting signs and symptoms compared with the Caucasian patients. Comparing the two racial groups clinical characteristics of acute MI, the odds ratios were all greater than 1.0 for chest pain greater than or equal to 30 min, pressure type chest pain, radiation of pain to left arm, left shoulder, neck or jaw, diaphoresis and rales on physical examination for both racial groups but these were not statistically different between the groups. While it was found that African American patients were less likely to have a final diagnosis of acute MI (P < 0.0001), there was no longer a statistical association with race and acute MI after adjustments for race were made for presenting signs and symptoms using logistical regression analysis. The odds ratio for acute MI outcomes for African Americans compared with Caucasians was 0.77 (95% CI 0.54 to 1.1).
Yes, African Americans had a similar clinical presentation of acute MI compared with Caucasians.

Does the study answer the question?

Yes.

Effect due to factor in study?

Yes.

Consistency of results with other studies?

Consistent.

Directly applicable to guideline population?

Acute chest pain population therefore directly applicable.

Internal Validity

Adequately addressed.

Safety and adverse effects

Not applicable.

**Study Type**  
Cohort

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

**Number of participant**  
215 in total, 157 African American, 58 white

**Inclusion/Exclusion Criteria**  
Patients admitted with suspected acute MI. Patients were included if English was their primary language and they could recall pre-hospital events. Patients were excluded if they were of a race other than African American or Caucasian, were aged < 18 years, had known mental impairment, were pregnant, had a MI subsequent to admission, had a previous interview prior to admission, or had significant emergency data missing from their medical records.

**Patient Characteristics**  
Mean age - 59±14 years African American, 62±15 years white (P=0.13)  
Male – 46% African American, 57% white (P=0.15)

**Recruitment**  
Patients who were admitted with acute MI between April 1999 and August 1999 to the ED chest pain unit

**Setting**  
Secondary care, USA

**Interventions/ Test/ Factor being investigated**  
Comparison of Medical history and risk factors between African American and white patients with acute MI

**Comparisons**  
Medical history and risk factors of African American and white patients

**Length of Study/ Follow-up**  
Not reported

**Outcome measures studied**  
Medical history and risk factors

**Results**

Characteristics:

- Mean age - 59±14 years African American, 62±15 years white (P=0.13)
- Male – 46% African American, 57% white (P=0.15)
- Diabetes – 28% African American, 16% white (P=0.05)
- Hypertension – 67% African American, 55% white (P=0.12)
- Hypercholesterolemia – 28% African American, 34% white (P=0.5)
- Angina – 8% African American, 3% white (P=0.37)
- Heart attack – 27% African American, 16% white (P=0.06)
- Congestive heart failure – 12% African American, 12% white (P=0.99)

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Patients were interviewed from April 1999 to August 1999. Patients were identified through a floor census and screened ... no significant difference in the location of pain (above diaphragm, below diaphragm, both, other), the timing of the pain

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

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

There was no significant difference in the one worst reported symptom (respiratory, cardiac, gastrointestinal, other, unable to identify) between African American and white patients. There was also no significant difference in the location of pain (above diaphragm, below diaphragm, both, other), the timing of the pain (constant, intermittent, wax/wane) and the median discomfort and control of pain between African American and white patients.

Not applicable

Safety and adverse effects

Does the study answer the question?

Patients were interviewed from April 1999 to August 1999. Patients were identified through a floor census and screened through a brief review of their medical charts. Patients were approached to participate based on their medical record number. 215 met the inclusion criteria out of 588 who were approached.
A structured questionnaire was developed to assess the contextual, emotional and behavioural factors in patients seeking medical help. The questionnaire was adapted from existing questionnaires, after external validation by a group of experts it was piloted on 10 patients and altered accordingly.

Demographics and medical history:
27% were white and 73% were African American, there were no significant differences between the two groups’ age, sex and insurance status (suggestive of socioeconomic status).
African Americans were significantly more likely to have diabetes (P=0.05) and to be taking calcium-channel blockers (P=0.005), however white patients were more likely to have had coronary artery bypass surgery (P=0.01) and to have had a previous stomach complaint (P=0.03).

Symptoms at presentation:
Those who were diagnosis as not having an MI were more likely to have had stomach pain (P=0.03) and sweating (P=0.05) at presentation. No significant differences were found between African American and white patients in the objective symptoms. There was no significant difference in the one worst reported symptom (respiratory, cardiac, gastrointestinal, other, unable to identify) between African American and white patients. There was also no significant difference in the location of pain (above diaphragm, below diaphragm, both, other), the timing of the pain
African Americans were as likely as Caucasian patients to report typical objective symptoms but were marginally more likely to attribute their symptoms to a gastrointestinal source rather than a cardiac source (P = 0.05). Of 157 Caucasian patients, 11 patients were diagnosed as having had an MI (11%), while 27 out of 58 Caucasian patients (47%) were diagnosed with acute MI (P < 0.001). However of those patients with a final diagnosis of MI, 61% of African Americans attributed their symptoms to a gastrointestinal source and 11% to a cardiac source versus 26% and 33%, respectively for Caucasian patients.

Effect due to factor in study? Yes
Consistency of results with other studies? Consistent
Directly applicable to guideline population? Acute chest pain population therefore directly applicable
Internal Validity Not addressed

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

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

Ref ID 1424

Journal of the National Medical Association 665 to 671 1997

Study Type Cohort
Funding Agency for Health Care Policy and Research

Number of participant 10001, of which 3401 (34%) were African Americans, 6600 were white

Inclusion/Exclusion Criteria Included: aged greater or equal to 30 years presenting with chest or left arm pain, shortness of breath, or other symptoms suggestive of acute cardiac ischemia from 10 participating hospitals in east and midwest USA. Excluded: patients with chest pain/discomfort related to trauma, surgical emergencies, those with a clear non-cardiac cause, patients transferred from other hospitals

Patient Characteristics In the male group, the average age for African American patients was 52±14 years and 60±15 year for white patients (P<0.0001). The average time from symptom onset to emergency department arrival was 3 hours for African American patients and 2 hours for white patients (P=0.0006). 33% of African American men and 15% of white men were uninsured, 23% of African American men and 6% of white men had Medicaid, 28% of African Americans men and 44% of white men had Medicare; for all P <0.0001 (measure of socio economic status).

In the female group, the average age for African American patients was 55±15 years and 65±16 year for white patients (P <0.0001). The average time from symptom onset to emergency department arrival was 3.3 hours for African American patients and 3 hours for white patients (P=0.045). 26% of African Americans women and 12% of white women were uninsured, 24% of African Americans and 8% of white women had Medicaid, 33% of African Americans women and 56% of white women had Medicare; for all P <0.0001 (measure of socio economic status).

Recruitment Patients admitted to 10 hospitals in east and midwest USA

Setting Secondary care, USA

Interventions/ Test/ Factor being investigated If race is determinant in diagnosing acute MI or angina

Comparisons African Americans and white patients
Not reported

Signs and symptoms and risk factors to diagnose acute MI or angina

Medical History and Clinical Characteristics

Men
Ulcer – 16% African American, 16% white (P=0.74)
Hypertension – 57% African American, 44% white (P=<0.0001)
Angina – 29% African American, 42% white (P=<0.0001)
MI – 20% African American, 35% white (P=<0.0001)
Stroke – 9% African American, 8% white (P=0.47)
Diabetes – 20% African American, 20% white (P=0.88)
Current smoker – 56% African American, 30% white (P=<0.0001)
Cardiac medications – 47% African American, 59% white (P=<0.0001)
Chest pain – 77% African American, 75% white (P=0.20)
Chest pain as primary symptom – 69% African American, 70% white (P=0.49)
Shortness of breath – 62% African American, 51% white (P=<0.0001)
Abdominal pain – 20% African American, 12% white (P=<0.0001)
Nausea – 28% African American, 24% white (P=0.01)
Vomiting – 13% African American, 7% white (P=<0.0001)
Dizziness – 35% African American, 26% white (P=<0.0001)
Fainting – 8% African American, 7% white (P=0.32)
Rales – 19% African American, 20% white (P=0.14)
S3 sound – 4% African American, 3% white (P=0.013)
Congestive heart failure – 16% African American, 16% white (P=0.65)
Systolic blood pressure >160 – 21% African American, 23% white (P=0.29)
Diastolic blood pressure >90 – 36% African American, 28% white (P=<0.0001)

Women
Ulcer – 14% African American, 14% white (P=0.73)
Hypertension – 64% African American, 51% white (P=<0.0001)
Angina – 32% African American, 39% white (P=<0.0001)
MI – 18% African American, 26% white (P=<0.0001)
Stroke – 9% African American, 9% white (P=0.85)
Diabetes – 32% African American, 23% white (P=<0.0001)
Current smoker – 34% African American, 24% white (P=<0.0001)
Cardiac medications – 60% African American, 64% white (P=0.01)
Chest pain – 79% African American, 72% white (P=<0.0001)
Chest pain as primary symptom – 69% African American, 64% white (P=0.0002)
Shortness of breath – 61% African American, 55% white (P=<0.0001)
Abdominal pain – 17% African American, 13% white (P=0.0001)
Nausea – 35% African American, 29% white (P=0.0011)
Vomiting – 14% African American, 10% white (P=0.0001)
Dizziness – 33% African American, 26% white (P=<0.0001)
Fainting – 5% African American, 7% white (P=0.001)
Rales – 19% African American, 25% white (P=<0.0001)
S3 sound – 3% African American, 3% white (P=0.74)
Congestive heart failure – 15% African American, 18% white (P=0.019)
Systolic blood pressure >160 – 28% African American, 28% white (P=0.45)
Diastolic blood pressure >90 – 36% African American, 28% white (P=<0.0001)

Safety and adverse effects

Not applicable

Does the study answer the question?

The study found that there were differences in patients’ medical history dependant upon racial background. African Americans were more likely to smoke and have hypertension compared with Caucasians, and African American women were more likely to have diabetes than Caucasian women. Caucasian patients were more likely to have a history of angina or MI and to take cardiac medications. There was no difference in the number of African Americans and Caucasian male patients who had chest pain as a primary symptom. There were a higher number of African American female patients than Caucasian female patients who had chest pain as a primary symptom. African American patients were more likely to report additional symptoms of shortness of breath, abdominal pain, nausea, vomiting and dizziness. African Americans were more likely to have a diastolic blood pressure of > 90mmHg when admitted to hospital compared to Caucasian patients, and the authors stated that this is consistent with the finding of more previous systemic hypertension in African Americans.
Acute MI and angina was less likely to be diagnosed in African American men compared with Caucasian men (acute MI; 6% versus 12%, respectively; angina 8% compared to 20%). Non cardiac diagnoses were confirmed in almost half of African American men compared with one third of Caucasian men. Similarly only 4% of African American women had a final diagnosis of acute MI compared with 8% in Caucasian women, and angina was diagnosed in 12% of African American women compared with 17% of Caucasian women. Non cardiac diagnoses were confirmed in almost half of African American women compared with 39% of Caucasian women.

Logistic regression in 74% of the patients examined the racial differences in the diagnoses, using the following variables; medical history, sociodemographic factors, signs and symptoms, and the hospital the patient was admitted to. African American patients compared to Caucasian patients were half as less likely to develop acute MI (odds ratio 0.54, 95% CI 0.41 to 0.68).

Effect due to factor in study? Yes
Consistency of results with other studies? Consistent
Directly applicable to guideline population? Patients with chest pain, left arm pain, shortness of breath or symptoms suggestive of acute cardiac ischaemia, directly applicable.
Internal Validity Not addressed

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

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

Ref ID 25394 Heart pp 183 to 188 2007

Study Type Cohort
Number of participant 2905 patients, 604 (21%) were Asian and 2301 (79%) were Caucasian
Inclusion/Exclusion Criteria Consecutive patients requiring hospital admission for ACS recruited by a senior cardiac nurse. Patients of races other than Asian or Caucasian were excluded
Patient Characteristics Asians mean age 60.6 (SD 12.7) years, Caucasians 68.9 (SD 13.9) years (P < 0.001); Asians 66% male, Caucasians 62%
Recruitment Consecutive by nurse in emergency department
Setting Emergency department UK
Interventions/ Test/ Factor being investigated Signs and symptoms, risk factors
Comparisons Asians versus Caucasian
Length of Study/ Follow-up Not applicable
Outcome measures studied Signs and symptoms, risk factors
Results Frontal upper body discomfort was reported by 94% of Asian patients versus 89% of Caucasian patients (P < 0.001), while almost twice as many Asian patients reported pain on the rear of their body compared with Caucasian patients (46% versus 25%, respectively, P < 0.001). The character of the discomfort as described by the Asian patients was ‘weight’ (34%), followed by ‘squeezing’ (28%), and ‘ache’ (14%). For Caucasian patients the most common term was ‘weight’ (28%), followed by ‘ache’ (23%), and ‘squeezing’ (20%).
There was a small but statistically significant difference in the intensity of discomfort reported, with Asian patients reporting a median pain rating of 7.5 compared with 7.0 in Caucasian patients (P < 0.002). Twenty-four percent of Asian patients rated their discomfort at the maximum value of 10 compared with 19% of Caucasian patients. A smaller percentage of Asian patients (6%) reported feeling no discomfort at presentation (silent MI) compared with Caucasian patients (13%) (P = 0.002). These patients were identified by a combination of symptoms, including fatigue, shortness of breath, collapse and resuscitation following cardiac arrest. Logistic regression analysis was performed to determine which factors contributed to patients reporting a silent episode, and the most significant factor was a patient’s diabetic status; they were more than twice as likely to report that they felt no pain during presentation compared with non-diabetics (odds ratio 2.08, 95% CI 1.56 to 2.76). Analysis showed that Caucasian patients (odds ratio 1.61, 95% CI 1.08 to 1.10) were also more likely to feel no discomfort compared with Asian patients. Analysis with age as a continuous variable was also associated with silent episode.

Safety and adverse effects
Not applicable

Does the study answer the question?
Yes. Asian patients were younger, more likely to be diabetic and they tended to report greater intensity of pain over a greater area of the body, and more frequent discomfort over the rear of their upper thorax than Caucasian patients.

Effect due to factor in study?
Yes

Consistency of results with other studies?
Consistent

Directly applicable to guideline population?
Acute chest pain population therefore directly applicable

Internal Validity
Not addressed
Grading: 2-  Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal*

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

<table>
<thead>
<tr>
<th>Ref ID</th>
<th>Heart</th>
<th>pg.</th>
<th>276 to 279</th>
<th>2003</th>
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</table>

Funding: K. Barakat is supported by an MRC Clinical Training Fellowship

Study Type: Cohort

Number of participants: 371 patients, of which 108 were Bangladeshi and 263 were white

Inclusion/Exclusion Criteria: Patients who were white or Bangladeshi with acute MI. Inclusion criteria was acute MI as defined by the presence of cardiac chest pain with ST elevation > 1 mm in two consecutive leads, Q wave development, and a creatine kinase rise greater than twice the upper limit of normal (400 IU/ml).

Patient Characteristics: The mean age was 63±12 years in the Bangladeshi group and 68 ±19 years in the white group (P<0.0001). 87% of the Bangladeshi group were male compared to 70% of the white group (P<0.002). 1/3 of the Bangladeshi patients were fluent in English

Recruitment: Patients admitted to Royal London Hospital, UK, acute MI between May 1998 and April 2001

Setting: Royal London Hospital, UK

Interventions/ Test/ Factor being investigated: Bangladeshi patients compared to white patients with acute MI

Comparisons: Bangladeshi patients compared to white patients

Length of Study/ Follow-up: Not reported

Outcome measures studied: Risk factors, symptoms

Results: Baseline characteristics:

- Age (years) – Bangladeshi 63±12; Whites 68±19 (P<0.0001)
- Male sex – 87% Bangladeshi; 70% Whites (P=0.002)
- Smoking – 71.3% Bangladeshi; 70.3% Whites (P=0.85)
- Hypertension – 43.5% Bangladeshi; 38.4% Whites (P=0.36)
- Diabetes – 50% Bangladeshi; 15.2% Whites (P<0.0001)
- Family history of IHD – 13% Bangladeshi; 29.3% Whites (P=0.0005)
- Previous acute MI – 28.7% Bangladeshi; 48% Whites (P=0.0014)

Nature of chest pain and interpretation of symptoms by racial group: (Bangladeshi n=32, Whites n=31)
- Central pain – 40.6% Bangladeshi; 87.1% White (P=0.0006)
- Left sided pain – 34.4% Bangladeshi; 3.2% White (P=0.0006)
- Other pain – 25% Bangladeshi; 97% White (P=0.0006)
- Typical character of pain – 25% Bangladeshi, 58.1% White (P=0.0132)
- Non-classical character of pain – 75% Bangladeshi, 41.9% White (P=0.0132)
- Interpreted as acute MI – 46.9% Bangladeshi, 45.2% White (P=0.99)
- Interpreted as other – 53.1% Bangladeshi, 54.8% White (P=0.99)
- Initial response of sought health care advice – 46.9% Bangladeshi, 25.8% White (P=0.20)
- Initial response of sought family advice – 37.5% Bangladeshi, 61.3 White (P=0.20)
- Initial response of other – 15.6% Bangladeshi, 12.9% White (P=0.20)
Multivariate analysis of the likelihood of Bangladeshi patients to present with typical central chest pain compared with white patients:
Crude – (OR 0.11; 95% CI 0.03 to 0.38; P=0.0006)
Adjustment for age and sex – (OR 0.10; 95% CI 0.03 to 0.39; P=0.0007)
Adjustment for age, sex and diabetes – (OR 0.12; 95% CI 0.03 to 0.49; P=0.0031)
Adjustment for age, sex, diabetes, hypertension, smoking, family history of IHD and hypercholesterolemia – (OR 0.11; 95% CI 0.02 to 0.58; P=0.0094)
Adjustment for age, sex, diabetes, hypertension, smoking, family history of IHD, hypercholesterolemia and proficiency in English – (OR 0.10; 95% CI 0.01 to 0.79; P=0.0285)

Multivariate analysis of the likelihood of Bangladeshi patients to present with typical cardiac chest pain compared with white patients:
Crude – (OR 0.25; 95% CI 0.09 to 0.74; P=0.0118)
Adjustment for age and sex – (OR 0.25; 95% CI 0.08 to 0.77; P=0.0154)
Adjustment for age, sex and diabetes – (OR 0.19; 95% CI 0.05 to 0.70; P=0.0124)
Adjustment for age, sex, diabetes, hypertension, smoking, family history of IHD and hypercholesterolemia – (OR 0.13; 95% CI 0.03 to 0.63; P=0.0116)
Adjustment for age, sex, diabetes, hypertension, smoking, family history of IHD, hypercholesterolemia and proficiency in English – (OR 0.05; 95% CI 0.004 to 0.46; P=0.0091)

Safety and adverse effects
Not applicable

Does the study answer the question?
The baseline characteristics of the study showed that Bangladesis were younger, more often male and diabetic, and more likely to report a previous acute MI than Whites. However Bangladesis were less likely to report a family history of ischaemic heart disease than whites. 1/3 of the Bangladeshi patients were assessed to be fluent in English.

Bangladesis were significantly less likely to report central chest pain (OR 0.11; 95% CI 0.03 to 0.38; P=0.0006) than whites. This significant difference remained after adjustment for difference in age, sex, risk factor profiles and fluency in English. Bangladesis were also more likely to offer non-classic descriptions (sharp, stabbing, pinching, burning) and less likely to report classic descriptions of the character of pain (heaviness, tightness, weight, pressure, band-like, gripping) (OR 0.25; 95% CI 0.09 to 0.74; P=0.0118). These differences persisted after adjustment for difference in age, sex, risk factor profiles and fluency in English.

The study concluded that Bangladeshi patients with an acute MI were more likely to present with atypical symptoms compared to white patients. The Authors stated that this may lead to slower triage in the emergency department and delay in treatment, this factor needs recognition by emergency department staff in order to reduce mortality rates in this high risk group.

Effect due to factor in study?
Not certain- selected patients with chest pain, hence directness to question may be inappropriate as in that patients with atypical symptoms not necessary included

Consistency of results with other studies?
Consistent

Directly applicable to guideline population?
Selected patients with chest pain, hence directness to question may be inappropriate as in that patients with atypical symptoms not necessary included

Internal Validity
Not addressed
Question: What is the utility (incremental value) and cost effectiveness of the resting ECG in evaluation of individuals with acute chest pain of suspected cardiac origin?
Grading: 1++

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

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

Patient Characteristics

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

The presence of ST elevation (commonly defined as 1 mm in at least two contiguous limb leads or 2 mm in two contiguous precordial leads) was the most discriminating single ECG for ruling in a diagnosis of acute MI in patients with acute chest with a positive LR of 13.1 (95% CI 8.28 to 20.60, P < 0.001). A completely normal ECG was reasonably useful at ruling out a MI (LR+ 0.14, 95%CI 0.11 to 0.20, P = 0.007) in patients with acute chest pain. The two next best changes were the presence of Q waves (LR + 5.01, 95% 3.56 to 7.06) and ST depression (LR + 3.13, 95% 2.50 to 3.92). Reasonable discrimination of MI was possible when a number of features were combined, for example ST elevation, depression Q waves/ and or T waves (LR + 5.30 95% CI 3.66 to 7.70) (see Table 1). A completely normal ECG was reasonably useful at ruling out a MI (LR+ 0.14, 95%CI 0.11 to 0.20). It was stated that the summary results were difficult to interpret because of significant heterogeneity in the studies but that a single ECG was an important for diagnostic information in the evaluation of acute chest pain. A further number of studies were identified that examined ECG in addition to some or all of the following evaluations that had been used in the emergency department: signs, symptoms, and investigations. These were defined as 'black box' studies. There were fifteen studies evaluating real time decision making on the initial information available to physicians. Analysis of black box studies was divided into 4 subgroups: interpretation of admission ECG for MI and acute coronary syndrome, interpretation of clinical data other than ECG, A&E initial diagnosis for MI and acute coronary syndrome, and A&E decisions to admit for MI and acute coronary syndromes. Clinical interpretation of admission ECG studies showed that there was a very high LR+ (145 in the best quality paper) for ruling in an MI, however the sensitivity was low (LR- 0.58). The one study that examined the exclusive use of signs and symptoms in diagnosis found that clinical evaluation was not helpful. For the studies evaluating A&E initial diagnosis for MI gave a LR+ of 4.48 (95% CI 2.82 to 7.12) and a LR- of 0.29 (95% CI 0.18 to 0.49). For the category of A&E decisions to
<table>
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<tr>
<th>Safety and adverse effects</th>
<th>None reported</th>
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<td>Does the study answer the question?</td>
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<td>Effect due to factor in study?</td>
<td>Consistent</td>
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<td>Consistency of results with other studies?</td>
<td>Correct population</td>
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<td>Directly applicable to guideline population?</td>
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<td>Internal Validity</td>
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Accuracy and clinical effect of out-of-hospital electrocardiography in the diagnosis of acute cardiac ischemia: a meta-analysis

Ioannidis JP; Salem D; Chew PW; Lau J; Ref ID 198, Ann Emerg Med pgs. 461 to 470 2001

Study Type Systematic Review Funding Not reported
Number of participant 8 prospective and retrospective cohort studies

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

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

See Narrative question3; Table 4: Ioannidis et al. 2001
The studies identified found that out-of-hospital ECGs for AMI have a diagnostic odds ratio (OR) of 104 and 95% CI 48 to 224 and for ACI OR of 23 and 95% CI 6.3 to 85. The review reported that there was significant heterogeneity in the sensitivity and specificity results between the 8 studies which was possibly due to the difference in definition of an abnormal ECG. The review identified one study which compared computer interpreted ECG with physician interpreted ECG and showed the computer interpreted ECG had a better specificity (98% versus 95%) but a worse sensitivity (52% versus 66%) when compared to physician interpreted ECG. The review states that the diagnostic accuracy may be affected by the expertise interpreting the ECG but states that even experienced clinicians can miss a diagnosis.

The review concluded there was substantial data to show that out-of-hospital ECGs have similar diagnostic accuracy as standard ECGs for AMI and ACI. The authors suggest that an out-of-hospital ECG should be considered by paramedics in all chest pain patients.
Effect due to factor in study?
Consistency of results with other studies?
Directly applicable to guideline population?

Internal Validity

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

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

Ref ID 555 Acad Emerg Med  pgs 84 to 89  2006

Study Type Systematic Review  Funding Not stated
Number of participant Cohort studies best available evidence
Inclusion/Exclusion Criteria Included studies: advanced notification pre-hospital ECG comparisons with emergency room ECG as comparison.
Patient Characteristics Suspected acute MI.
Recruitment Systematic review: 5 studies cohort studies identified.
Setting Ambulance and emergency department.
Interventions/ Test/ Factor being investigated ECG
Comparisons Pre hospital ECG versus emergency department ECG.
Length of Study/ Follow-up One study reported mortality but this was not significant for pre hospital ECG versus emergency department ECG.
Outcome measures studied Door to treatment time.

Results The pre-hospital on scene time for acute MI was not significantly different when comparing these studies (total patient number of 519) (pooled weighted mean difference of 1.19 (95% CI –0.84 to 3.21). The door to treatment interval was compared for 181 patients and decreased with PHECG and advanced notification compared with no PHECG (mean weighted difference of 36.1 minutes (95% CI -63.0 to -9.327). However considered heterogeneity was found in these studies (Q statistic 10.9, P < 0.01). Only one study examined all cause mortality. There was no difference all cause mortality when PHECG was compared with no advanced notification for patients with acute MI (PHECG: 8.4% versus control: 15.5%, P < 0.22)

Safety and adverse effects

Does the study answer the question? Examines pre-hospital ECG recordings for accuracy with subsequent ECG in emergency department. Determines the accuracy of prehospital ECG in final diagnosis. Although not completely relevant to the ECG sensitivity / specificity in the diagnosis of coronary artery disease, informs on the setting of ECG.

Effect due to factor in study?
Consistency of results with other studies?

Directly applicable to guideline population?

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

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

Ref ID 1711 J Electrocardiol 329 to 339 2000

Study Type Cohort
Number of participant 1568 ECGs

Inclusion/Exclusion Criteria
The patients were aged over 18, who sought paramedic evaluation for chest pain which was non-traumatic or equivalent syndrome of presumed cardiac origin and who were classed as stable (a systolic blood pressure of 90 mmHg or more, absence of second- or third-degree heart block, ventricular fibrillation or ventricular tachycardia on initial examination). Patients were excluded if the paramedic thought a pre-hospital ECG would affect treatment, and if the ECG showed QRS duration, heart rate, atrial fibrillation or flutter, heat block, or fully paced rhythms

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

Recruitment
patients who had a prehospital ECG by paramedics

Setting
ambulance, USA

Interventions/ Test/ Factor being investigated
ECG diagnosis

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

Length of Study/ Follow-up

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

Results
See narrative question 3; tables 4, 5, 6, 7 Aufderheide et al., 2000
The study assessed the sensitivity and specificity of diagnosing AMI by assessment by both physicians of ST segment deviation, QT-end dispersion and QT-peak dispersion measurements independent of each other. The study showed the average sensitivity was 50.5% and specificity was 98%. The study went on to assess the sensitivity and specificity of diagnosing AMI by a computer through independent assessment of ST segment deviation, which showed a higher sensitivity of 90% but lower specificity of 56%. For independent assessment of QT-end and QT-peak dispersion the computer interpretation did not have a significant difference compared to the physicians' interpretation. The study went on to assess the sensitivity and specificity of diagnosing AMI when combining the information of QT-end and QT peak dispersions which showed that the physicians' significantly increased in sensitivity by 88% (90% versus 48%, P=<0.001), but decreased in specificity by 44% (55% vs. 99% P=<0.001) and PPV by 58% (40% vs. 95%, P=<0.001). The sensitivity and specificity were also assessed when ST segment deviation was included in the analysis, which showed this lead to the physicians' highest sensitivity 65% (compared to 48%, P=<0.001) and maintained specificity 97% (compared to 99%, P=<0.001)

The study continued to assess the sensitivity and specificity of diagnosing ACI; the physicians' had a lower sensitivity (38-40%). The study assessed the sensitivity and specificity by assessment by both physicians and the computer of ST segment deviation, QT-end dispersion and QT-peak dispersion measurements independent of...
The study assessed the sensitivity and specificity of diagnosing AMI by assessment of ST segment deviation, QT-end dispersion and QT-peak dispersion. The computer had a higher sensitivity (75%) but a lower specificity (66%). The study showed that for independent assessment of QT-end dispersion and QT-peak dispersion the computer had a higher sensitivity compared to the physicians (50-53% compared to 38-40%, P=<0.001), but the specificity, PPV and NPV were all comparable. The study went on to assess the sensitivity and specificity of diagnosing ACI when combining the information of QT-end and QT peak dispersions which showed that the physicians’ significantly increased in sensitivity by 70% (65-68% versus 6%, P=<0.001) and NPV by 19% (68%-69% versus 58%, P=<0.001), but decreased in specificity (80-81% vs. 92%, P=<0.001) and PPV (79% vs. 85%, P=<0.001). The sensitivity and specificity were also assessed when ST segment deviation was combined with QT-end dispersion, which showed this lead to the physicians’ highest sensitivity 62% (compared to 40%, P=<0.001) and NPV to 68% (compared to 58%, P=<0.001) and maintained specificity 90% (compared to 92%, P=<0.001) and PPV 87% (compared to 85%, P=<0.05)

Safety and adverse effects

None reported

Does the study answer the question?

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

Effect due to factor in study?

Yes

Consistency of results with other studies?

Consistent

Directly applicable to guideline population?

Patients had chest pain

Internal Validity

Well covered

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

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

Ref ID 926 American heart journal pp. 630 to 635 2002

Study Type Cohort

Funding Italian Ministry for Scientific and Technological Research

Number of participant 13 762 patients

Inclusion/Exclusion Criteria

Inclusion: over 18 years old, chest pain defined as pain in the thoracic region, independent of duration, radiation, or relation to exercise, occurring in the last 24 hours and lasting minutes to hours
The mean age was 65±18 years and 43% were women. Those who were categorised as being at high risk (21%) had a mean age of 63±10 years, 33% were female, 35% smoked, 25% had diabetes, 38% had hypertension, 13.4% died during the follow up.

Those who were categorised as being at intermediate risk (47%) had a mean age of 64±11 years, 38% were female, 33% smoked, 28% had diabetes, 41% had hypertension, 2.2% died during the follow up.

Those who were categorised as being at low risk (32%) had a mean age of 38±15 years, 66% were female, 12% smoked, 8% had diabetes, 22% had hypertension, 0.2% died during the follow up.

**Recruitment**
Admitted to emergency department with chest pain as described above

**Setting**
ED. Careggi General Hospital, Florence, Italy

**Interventions/ Test/ Factor being investigated**
Diagnosing chest pain

**Comparisons**
The chest pain score was based on: location of pain, radiation of pain, character of pain, history of angina

**Length of Study/ Follow-up**
6 months

**Outcome measures studied**
Effectiveness of chest pain score in diagnosing chest pain

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

The mean age was 65±18 years. Patients were classified into 1 of 4 groups.

1) Patients at low risk with obvious noncardiac causes of chest pain, chest pain score <4, normal ECG, and normal serum markers of cardiac injury obtained at least 6 hours from symptoms, were sent home and followed up. (2672 patients)
2) Patients at low risk with chest pain score ≥ 4, normal ECG, normal serum cardiac markers, independent of age or coexisting coronary risk factors, were not admitted and underwent a second-line evaluation and short-term observation in the CPU area, including chest radiography, serial 12-lead ECG, serial troponins and cardiac enzymes, echocardiography and arterial blood gas analysis. When at least one of these tests or procedure results was found to be suggestive of AMI, unstable angina or CAD or left ventricular failure was detected these patients were considered for angiography with no additional testing. After an observation period up to 6 hours patients without ongoing cardiovascular events underwent exercise tolerance test or SPECT or stress echocardiography. (1755 patients)
3) Patients at intermediate risk with clinical score ≥ 4 and abnormal ECG (ST-segment elevation <1mm or ST-segment depression <1mm at 60ms from J point) were admitted and managed in the CPU area.
4) Patients at high risk with ECG suggestive for AMI (defined as ST elevation ≥1 mm at 60ms from J point, ≥2 contiguous leads) were directly transferred to the coronary care unit and patients with suspected major cardiovascular disease, such as aortic arch dissection, pulmonary embolism, pneumothorax and acute pericarditis, were admitted and managed with arterial blood gas analysis, chest radiography, echocardiography, and thorax computed tomography if required by clinical assessment.

At six month follow up 0.2% of these patients were recognised as having nonfatal coronary artery disease, hence, the negative predictive value of a chest pain score of < 4 and normal ECG was > 99%

Of the patients with a chest pain score ≥ 4 and normal or non diagnostic electrocardiogram results (1755 patients, 40%), 20% of the low risk group with chest pain score < 4 (group 1) (885 patients) had documented coronary artery disease, 18% of which were by recurrent angina, delayed ECG changes, late rise in markers, the other 2% was by positive stress test.

There were 9335 intermediate and high risk patients, of which 2420 patients (26%) had an MI, 3764 patients (40%) had unstable angina, 129 (1.4%) had aortic
Of the patients with a chest pain score > 4 and normal electrocardiogram results, 20% (885 patients) had documented coronary artery disease. There were 9335 intermediate and high risk patients, of which 2420 patients (26%) had an MI, 3764 patients (40%) had unstable angina, 129 (1.4%) had aortic dissection and 408 (4%) had pulmonary embolism. Other multi-organ disease was found in 2256 patients.

The authors concluded that the chest pain score screening programme was effective and could significantly reduce admissions and optimise the care of those with an intermediate or high risk score. The authors also concluded that the screening programme could aid the diagnosis of alternative causes of chest pain in patients who do not have evidence of coronary artery disease.

Safety and adverse effects
None reported

Does the study answer the question?
Of the patients with a chest pain score > 4 and normal electrocardiogram results, 20% (885 patients) had documented coronary artery disease. There were 9335 intermediate and high risk patients, of which 2420 patients (26%) had an MI, 3764 patients (40%) had unstable angina, 129 (1.4%) had aortic dissection and 408 (4%) had pulmonary embolism. Other multi-organ disease was found in 2256 patients.

The authors concluded that the chest pain score screening programme was effective and could significantly reduce admissions and optimise the care of those with an intermediate or high risk score. The authors also concluded that the screening programme could aid the diagnosis of alternative causes of chest pain in patients who do not have evidence of coronary artery disease.

Effect due to factor in study?
Yes

Consistency of results with other studies?
Consistent

Directly applicable to guideline population?
Correct population

Internal Validity
Well covered

Fesmire FM;

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

Ref ID 6025 Am J Emerg Med 773 to 778 2000

Study Type Cohort
Funding Not reported

Number of participant 706 patients

Inclusion/Exclusion Criteria included: chest pain with suspected ACS

Patient Characteristics
The average age for category II was 57.3±11.3 years, 67.2% were men, 89.8% were Caucasian, 10.2% were African American, 62% had previous MI, 52.3% had previous PTCA/CABG. The average age for category III was 54.6±12.9 years, 61% were men, 76.6% were Caucasian, 22.8% were African American, 31.5% had previous MI, 25.2% had previous PTCA/CABG. The average age for category IV was 52.6±14.4 years, 49% were men, 67.9% were Caucasian, 29.8% were African American, 21.6% had previous MI, 15.4% had previous PTCA/CABG

Recruitment Patients presented with chest pain of suspected ACS to the emergency department between August 1995 and August 1998

Setting Emergency department, USA

Interventions/ Test/ Factor being investigated Continuous ST segment monitoring

Comparisons Sensitivity and specificity of serial ECG
Sensitivity and specificity of serial ECG

Results

Patients had an initial history, physical examination and ECG, and were subsequently classed in four different categories. Category I were patients with ACS with clinical and ECG criteria for emergency reperfusion therapy, category II were patients with probable ACS but without clinical and ECG criteria for emergency reperfusion therapy, category III were patients with possible ACS, category IV were patients with probable non-ACS chest pain but presence of pre-existing disease or significant risk factors for CAD. Category I were excluded from the study. The serial ECG was obtained at least every 10 minutes until the patient was taken for PTCA or for 2 hours.

See narrative question 3; Table 10, 11, 12, 13: Fesmire, 2000

28 patients were placed in category I, 137 patients were placed in category II, 333 patients were placed in category III and 208 patients were placed in category IV. Table 1, 2, 3 and 4 show the results of the study. Serial ECG for new injury or new/evolving ischemia had a sensitivity and specificity of 41.7% (95% CI 27.6 to 58.6) and 98.1% (95% CI 96.7 to 99) respectively for AMI and 15.5% (95% CI 10.6 to 21.5) and 94.4% (95% CI 98.2 to 99.9) for ACS. For AMI the serial ECG had a positive likelihood ratio (LR+) of 21.9 and negative likelihood (LR-) of 0.59 and for ACS a LR+ of 25.4 and LR- of 0.85. As a result of the serial ECG 26 patients had their treatment changed.

Safety and adverse effects

None reported

Does the study answer the question?

Serial ECG for new injury or new/evolving ischemia had a sensitivity and specificity of 41.7% (95% CI 27.6 to 58.6) and 98.1% (95% CI 96.7 to 99) respectively for AMI and 15.5% (95% CI 10.6 to 21.5) and 94.4% (95% CI 98.2 to 99.9) for ACS. For AMI the serial ECG had a positive likelihood ratio (LR+) of 21.9 and negative likelihood (LR-) of 0.59 and for ACS a LR+ of 25.4 and LR- of 0.85. As a result of the serial ECG 26 patients had their treatment changed.

Effect due to factor in study?

Yes

Consistency of results with other studies?

Consistent

Directly applicable to guideline population?

Patients had chest pain with suspected ACS

Internal Validity

Well covered

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

Usefulness of serial electrocardiograms for diagnosis of acute myocardial infarction

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

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

Number of participant  902 ECGs were reviewed, each ECG was also reviewed with a previous ECG for the same patient

Inclusion/Exclusion Criteria  ECG had to show an AMI, previous ECG had to be available from the clinical electrocardiographic database
The average age of the patients was 74±11 years, with 60.5% being men.

Usefulness of serial ECG versus single ECG, by a cardiologist, intern and computer accuracy of reading ECG

The study used ROC curves to evaluate the difference in interpretation and diagnosis of AMI when both ECGs were present compared to only the current ECG. The ROC curve showed that the neutral network performance was improved when both ECGs were present (area under ROC with current ECG = 0.85, area under ROC with both ECGs = 0.88; P = 0.02). The intern performed better when both ECGs were present (area under ROC with current ECG = 0.71, area under ROC with both ECGs = 0.78; P < 0.001) and diagnosed more AMI with both ECGs. The cardiologist performance did not have a statistically significant improve with both ECGs (area under ROC with current ECG = 0.79, area under ROC with both ECGs = 0.81; P = 0.36).

Safety and adverse effects
None reported

Consistency of results with other studies
Consistent

Effect due to factor in study?
Yes

Directly applicable to guideline population?
Patients had AMI

Internal Validity
Well covered

Sanchis J;Boyd Y;Llister A;Ntnez J;Consuegra L;Bosch M;Bertomeu V;Ruiz V;Chorro F;
The mean age was 64±12 years, 33% were women, 20% were current smokers, 59% had hypertension, 53% had hypercholesterolemia, 25% had diabetes, 44% had a history of IHD, 13% had a family history of IHD, 7% had had coronary surgery, 12% had ST depression, 9% had T wave inversion.

The chest pain score was based on: location, radiation, character, severity, what influenced the pain, associated symptoms, history of exertional angina. A clinical history, ECG and for those in the low risk group an early (<24 hours) exercise test was done.

### Inclusion/Exclusion Criteria
- **Inclusion**: Patients with chest pain of suspected cardiac origin as determined by a cardiologist on call with a negative troponin I concentration (measured at baseline, at 6, 8 and 12 hours). Exclusion: ST elevation, Left Bundle Branch Block, and heart failure, Killip > 1
- **Patient Characteristics**: The mean age was 64±12 years, 33% were women, 20% were current smokers, 59% had hypertension, 53% had hypercholesterolemia, 25% had diabetes, 44% had a history of IHD, 13% had a family history of IHD, 7% had had coronary surgery, 12% had ST depression, 9% had T wave inversion

### Recruitment
- Patients admitted to the emergency department in a teaching hospital in Spain

### Setting
- ED, teaching hospital in Spain

### Interventions/ Test/ Factor being investigated
- Diagnosing chest pain

### Comparisons
- The chest pain score was based on: location, radiation, character, severity, what influenced the pain, associated symptoms, history of exertional angina. A clinical history, ECG and for those in the low risk group an early (<24 hours) exercise test.

### Length of Study/ Follow-up
- 6 months

### Outcome measures studied
- Effectiveness of chest pain score in diagnosing chest pain

### Results
- An ECG was recorded in the emergency room and evaluated for ST segment depression (>1mm) and T wave inversion (peak inversion >1mm)
- Troponin I concentrations were taken at arrival, 6 hours (is patient arrived within 2 hours of onset of pain), 8 hours and 12 hours after pain onset. All patients had normal troponin concentrations at each measurement.
- Patients underwent a chest pain score assessment, an ECG, and for those in the low risk group an early (<24 hours) exercise test. The chest pain score was based on: location, radiation, character, severity, influenced by glyceryl trinitrate, stature, breathing, associated symptoms and history of exertional angina = +3. A clinical history was also taken.
- During a 6 month follow up, 25 patients (4.1%) had an acute MI, 9 (1.5%) died of cardiac causes and 29 (4.8%) had a major event (AMI or cardiac death).
- Those who could not have a negative exercise test had a very good prognosis compared to those who did not have a negative exercise test or those who could not exercise and do and exercise test.

See narrative for question 3; Table 16: Sanchis et al, 2005, Heart
See narrative for question 3; Table 17: Sanchis et al, 2005, Heart
For predictors of AMI the univariate and multivariate analysis showed: ST segment depression (univariate P = 0.004, multivariate P = 0.02, odds ratio (OR) 2.9, 95%CI 1.2 to 6.8), T-wave inversion (univariate P = 0.8, multivariate analysis could not be applied to T-wave inversion).
For predictors of a major event (AMI or cardiac death) the univariate and multivariate analysis showed: ST segment depression (univariate P = 0.003, multivariate P = 0.01, OR 2.8, 95%CI 1.3 to 6.3), T-wave inversion (univariate P = 0.7, multivariate analysis could not be applied to T-wave inversion).

The patients were stratified according to the four independent risk factors associated with a major event (AMI or cardiac death), these were chest pain score, diabetes, previous coronary surgery and ST-segment depression. The event rate increased with the number of risk factors: no risk factors 2.5% event rate, 1 risk factor 2.9% event rate, 2 risk factors 10.2% event rate, 3 or 4 risk factors 29.2% event rate. Three risk categories were defined: low risk: no or 1 risk factor 2.7% event rate,
During a 6 month follow up, 25 patients (4.1%) had an acute MI, 9 (1.5%) died of cardiac causes and 29 (4.8%) had a major event (AMI or cardiac death). Multivariate analysis found that ST segment depression was an independent factors in predicting an acute MI (univariate P = 0.004, multivariate P = 0.02, OR 2.9, 95% CI 1.2 to 6.8), and major events (AMI or cardiac death) (univariate P = 0.003, multivariate P = 0.01, OR 2.8, 95%CI 1.3 to 6.3).

Further analysis found that the event rate increased progressively with the progression of the number of independent risk factors, with the event rate increasing with the number of risk factors: no risk factors 2.5% event rate, 1 risk factor 2.9% event rate, 2 risk factors 10.2% event rate, 3 or 4 risk factors 29.2% event rate. From this 3 risk categories, low intermediate and high, were formed with the difference between each being significant.

NB there is overlap of patients included in this study and the study Sanchis et al 2005, JACC (New Risk Score for Patients with Acute Chest Pain, Non-ST-Segment Deviation, and Normal Troponin Concentrations).

**Safety and adverse effects**
None reported

**Does the study answer the question?**
During a 6 month follow up, 25 patients (4.1%) had an acute MI, 9 (1.5%) died of cardiac causes and 29 (4.8%) had a major event (AMI or cardiac death). Multivariate analysis found that ST segment depression was an independent factors in predicting an acute MI (univariate P = 0.004, multivariate P = 0.02, OR 2.9, 95% CI 1.2 to 6.8), and major events (AMI or cardiac death) (univariate P = 0.003, multivariate P = 0.01, OR 2.8, 95%CI 1.3 to 6.3).

Further analysis found that the event rate increased progressively with the progression of the number of independent risk factors, with the event rate increasing with the number of risk factors: no risk factors 2.5% event rate, 1 risk factor 2.9% event rate, 2 risk factors 10.2% event rate, 3 or 4 risk factors 29.2% event rate. From this 3 risk categories, low intermediate and high, were formed with the difference between each being significant.

NB there is overlap of patients included in this study and the study Sanchis et al 2005, JACC (New Risk Score for Patients with Acute Chest Pain, Non-ST-Segment Deviation, and Normal Troponin Concentrations).

**Effect due to factor in study?**
Yes

**Consistency of results with other studies?**
Consistent

**Directly applicable to guideline population?**
Correct population

**Internal Validity**
Well covered

Sanchis J; Bod Y V; N ez J; Bertomeu G; Gomez C; Bosch MJ; Consuegra L; Bosch X; Chorro FJ; Llercer A;...

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

**Study Type**
Cohort

**Number of participant**
646 patients

**Inclusion/Exclusion Criteria**
Inclusion criteria: acute chest pain of possible cardiac origin Exclusion: if the initial ECG showed ST-segment deviation (≥1mm elevation or depression) or if they had troponin I elevation

**Patient Characteristics**
The mean age was 64±12 years and 32% were women. 20% were smokers, 59% had hypertension, 53% had hypercholesterolemia, 26% had diabetes mellitus, 7% insulin dependant diabetes mellitus, 12% had a family history of IHD, 13% had at least 3 risk factors, 24% had prior coronary stenosis ≥ 50%, 43% had used aspirin in the previous 7 days, 25% had a prior MI, 9% had prior PTCA, 8% had prior CABG, 2% had a history of heart failure. On ECG 100% had T-wave inversion, 9% had confounding ECG

**Recruitment**
Patients admitted with acute chest pain to the emergency department in a teaching hospital in Spain during a 34 month period between 15th January 2001 and 30th November 2003

**Setting**
ED in a teaching hospital in Spain
Diagnosing chest pain

Comparisons
The chest pain score and other variables, described in results

Length of Study/ Follow-up
1 year

Outcome measures studied
The primary end point was all-cause mortality or nonfatal myocardial infarction, the secondary end point was all-cause mortality, nonfatal myocardial infarction or urgent revascularisation at 14 day follow up.

Results
Patients were excluded if they had ST-segment deviation (≥1mm elevation or depression) on the initial ECG or if they had troponin I elevation. All patients had T-wave inversion and 9% had confounding ECG (left branch bundle block of paced rhythm). An ECG was recorded in the emergency room.

Troponin I concentrations were taken at arrival, 6 hours (if patient arrived within 2 hours of onset of pain), 8 hours and 12 hours after pain onset. All patients had normal troponin concentrations at each measurement.

Patients underwent a chest pain score assessment based on: location, radiation, character, severity, influenced by glyceryl trinitrate, stature, breathing, associated symptoms and history of exertional angina. A clinical history and risk factor analysis was also taken.

At 1 year follow up, the primary end point (all-cause mortality or non-fatal MI) occurred in forty three patients (6.3%). At a 14 day follow up, the secondary end point (all-cause mortality or non-fatal myocardial infarction or urgent revascularisation) occurred in 35 patients (5.4%).

The univariate analysis showed that for: T-wave inversion (P = 0.4), confounding ECG (P = 0.09).

The multivariate analysis showed that for: confounding ECG (P = 0.3). The multivariate analysis did not give results for T-wave change or full results for confounding ECG.

The study showed from multivariate analysis ECG changes (T-wave inversion and confounding ECG) were not independent predictors of the primary end point.

Safety and adverse effects
None reported

Does the study answer the question?
Univariate analysis found that the following were independent factors in predicting all cause mortality or nonfatal myocardial infarction; t-wave inversion (P = 0.4), and confounding ECG (P= 0.09).
Multivariate analysis found that ECG changes were not independent factors in predicting all cause mortality or nonfatal myocardial infarction. Confounding ECG on multivariate analysis (P=0.3).

NB there is overlap of patients included in this study and the study Sanchis et al 2005, Heart J (Risk Stratification of Patients with Acute Chest Pain and Normal Troponin Concentrations).

Effect due to factor in study?
Yes

Consistency of results with other studies?
Consistent

Directly applicable to guideline population?
Correct population

Internal Validity
Well covered
Question: What is the utility (incremental value) and cost effectiveness of a chest X ray in evaluation of individuals with chest pain of suspected cardiac origin?
Grading: 2++
High-quality systematic reviews of case–control or cohort studies
High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

Estimating the likelihood of significant coronary artery disease

Ref ID: 10283
The American journal of medicine

Study Type: Cohort
Funding: Not reported

Number of participant: 3627 in training population, 1811 in test population

Inclusion/Exclusion Criteria: Patients with chest pain who were referred for cardiac catheterization at the Duke University Medical Center between November 1969 and January 1982

Patient Characteristics: Patient characteristics which were collected were:
- History: age, sex, chest pain history (pain type, severity, frequency, nocturnal, progressive, preinfarctional), duration of CAD, previous history of MI, congestive heart failure, history of vascular disease (Progressive chest pain - the frequency, severity or duration had increased in the 6 weeks prior to catheterisation; Preinfarctional chest pain - a very unstable pain pattern that resulted in admission to the coronary care unit for evaluation of the possible MI)
- Risk factors: smoking, hyperlipidaemia, hypertension, diabetes, family history
- Physical examination: ventricular gallop, systolic blood pressure
- ECG: ST-T wave changes, electrocardiographic premature ventricular contractions, Electrocardiographic Q waves
- Chest X-Ray: cardiomegaly

Recruitment: Patients admitted for cardiac catheterisation between November 1969 and January 1982

Setting: Secondary care, USA

Interventions/Test/Factor being investigated: Chest pain diagnosis

Comparisons: Patient characteristics which give a probability of disease

Length of Study/Follow-up: Not reported

Outcome measures studied: Probability of disease

Results: The study had a training population of 3627 patients who were seen between 1969 and January 1979, from these patients a stepwise logistic regression analysis was used to develop a model for predicting the probability of significant CAD. A test population of 1811 patients seen between January 1969 and January 1982, in this population the model developed in the test population was used to predict the probability of CAD for each patient.

The authors then tested the model in other populations (from CASS study) to estimate the prevalence of disease in subgroups of the patients in the literature (external validation)

Results from training population:
- Poor Clinical Predictors of Significant CAD and the Chi-squared: See narrative for question 4; Table 1; Pryor et al, 1983
- Cardiomegaly: 1.41
Progressive chest pain was described as chest pain when the frequency, severity or duration had increased in the 6 weeks prior to catheterisation. Preinfarctional chest pain was described as chest pain with a very unstable pain pattern that resulted in admission to the coronary care unit for evaluation of the possible MI.

The results from the training group show that cardiomegaly shown on chest x-ray was a poor predictor of significant coronary artery disease (chi-square = 1.41).

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

<table>
<thead>
<tr>
<th>Safety and adverse effects</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the study answer the question?</td>
<td>Yes</td>
</tr>
<tr>
<td>Consistency of results with other studies?</td>
<td>No similar studies</td>
</tr>
<tr>
<td>Directly applicable to guideline population?</td>
<td>Patients had chest pain</td>
</tr>
<tr>
<td>Internal Validity</td>
<td>Well covered</td>
</tr>
</tbody>
</table>
Grading: 2+

Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

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

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

Ref ID 1751

Annals of internal medicine 81 to 90 1993

Study Type Cohort

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

Number of participant

1030 patients, 168 had cardiac catheterization. At 3 years data for 973 patients (94%) was obtained.

Inclusion/Exclusion Criteria

Inclusion: Symptomatic patients, referred for non-invasive testing for suspected coronary artery disease

Exclusion: previous cardiac catheterization

Patient Characteristics

The mean age was 55, 37% were female, the mean pain frequency was 2 episodes a week, the mean durations of CAD symptoms was 12 months, 28% had typical angina symptoms, 52% atypical angina symptoms, 20% nonanginal pain, 18% progressive angina, 22% nocturnal angina, 44% smoked, 41% had a history of hypertension, 10% had diabetes, 11% had hyperlipidemia, 35% had ST-T wave changes on ECG, 18% had a history of MI, 8% had Q waves on ECG, 14% had a history of congestive heart failure, 0% had class IV congestive heart failure, 1% had ventricular gallop, 3% had peripheral vascular disease, 3% had cerebral vascular disease

Of the patients who went on to have a cardiac catheterization the mean age was 56, 31% were female, the mean pain frequency was 2 episodes a week, the mean durations of CAD symptoms was 7 months, 49% had typical angina symptoms, 47% atypical angina symptoms, 4% nonanginal pain, 24% progressive angina, 24% nocturnal angina, 53% smoked, 42% had a history of hypertension, 10% had diabetes, 13% had hyperlipidemia, 42% had ST-T wave changes on ECG, 33% had a history of MI, 11% had Q waves on ECG, 11% had a history of congestive heart failure, 0% had class IV congestive heart failure, 1% had ventricular gallop, 4% had peripheral vascular disease, 2% had cerebral vascular disease.

It can therefore be seen that those having a cardiac catheterization were more likely to be male, smoke, have a history of MI, have ST-T wave changes on ECG and to be suffering typical or progressive angina

At 3 years data for 973 patients (94%) was obtained. At the end of 3 years 844 patients were alive. 30 had died of cardiovascular causes, 19 had died of noncardiac causes, 18 had undergone angioplasty and 62 had had coronary artery bypass graft surgery.

Recruitment

Patients were referred for non-invasive testing for suspected coronary artery disease

Setting

Duke University Medical Centre USA

Interventions/ Test/ Factor being investigated

Physicians initial evaluation of patients with suspected CAD

Comparisons

The presence of significant coronary disease defined as any disease, severe disease, left main disease, predicting survival

Length of Study/ Follow-up

3 years

Outcome measures studied

Effectiveness of chest pain score to predict coronary artery disease and survival
Results

The three diagnostic outcomes were: the presence of significant coronary artery disease defined as ‘any disease’ (≥ 75% luminal diameter narrowing of at least one major coronary artery), presence of severe coronary artery disease defined as ‘severe disease’ (significant obstruction of all 3 main coronary arteries or the left main coronary artery) and the presence of significant left main artery obstruction defined as ‘left main disease’ (168 patients referred for cardiac catheterization). The prognostic outcome was survival at 3 years.

In the multivariable regression model used, chest x-ray to show cardiomegaly was not a significant predictor for any disease, severe disease or left main disease. However for cardiomegaly (shown on chest x-ray) was a significant predictor for survival at 3 years.

Safety and adverse effects

None reported

Does the study answer the question?

In the multivariable regression model used, chest x-ray which showed cardiomegaly was shown to be a significant predictor of survival. However it could not be used to predict coronary disease.

Effect due to factor in study?

Yes

Consistency of results with other studies?

No other similar studies

Directly applicable to guideline population?

Correct population

Internal Validity

Well covered
Question: In adults presenting with acute chest pain/discomfort of suspected cardiac origin, what is the clinical and cost effectiveness of giving oxygen compared with a placebo?
The routine use of oxygen in the treatment of myocardial infarction: systematic review

**Ref ID**: 24290

**Heart**

**Pages**: 1 to 15

**Year**: 2008

**Study Type**: Systematic Review

**Funding**: No specific funding was sought for this study.

**Number of participant**: Two RCTs

**Inclusion/Exclusion Criteria**

**Patient Characteristics**

**Recruitment**

**Setting**

**Interventions/ Test/ Factor being investigated**

**Comparisons**

**Length of Study/ Follow-up**

**Outcome measures studied**

**Results**

**Safety and adverse effects**

**Does the study answer the question?**

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

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

**Effect due to factor in study?**

**Consistency of results with other studies?**
A systematic review (SR) on the effectiveness of oxygen in reducing acute myocardial ischaemia identified 9 studies; 2 randomised controlled trials (RCT(s)) and 7 case control studies (Nicholson 2004). The intervention was oxygen of any flow rate or delivery method (excluding hyperbaric oxygen). The studies identified had a combined total of 463 patients, of which 93 were women and 37 which had no gender stated. Of the 7 studies that reported age, the ranges and the means were comparable. Seven out of 9 studies reported haemodynamic data. The data synthesis of the SR found that oxygen administration resulted in; an unchanged heart rate but a fall in stroke volume and cardiac volume, a rise in systemic vascular resistance, and either a slight rise or no change in arterial blood pressure (Nicholson 2004).

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

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

None of the studies reported any respiratory side effects, and only one study reported any side effect which was nausea as a reason for withdrawal from oxygen administration (Nicholson 2004).

The author of the SR concluded that there was a lack of strong evidence for using oxygen as a treatment of acute myocardial infarction (MI), although it was recognised that all patients with systemic hypoxaemia should have this corrected by oxygen administration (Nicholson 2004).

**Effect due to factor in study?**

**Consistency of results with other studies?**

**Directly applicable to guideline population?**

**Internal Validity**

Rawles JM; Kenmure AC;

Controlled trial of oxygen in uncomplicated myocardial infarction

<table>
<thead>
<tr>
<th>Ref ID</th>
<th>Br Med J</th>
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</thead>
<tbody>
<tr>
<td>2303</td>
<td>1121 to 1123 1976</td>
</tr>
</tbody>
</table>

**Study Type**  Randomised Controlled Trial

**Funding**  Not reported

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

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

**Patient Characteristics**  Those without confirmation of an MI:

Air group –
Number of patients  18
Number of men  17
Mean age  50.8 ± 2.4

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

Those with a confirmed MI:

Air group –
Number of patients  77
Number of men  61
Mean age  56.4 ± 0.8

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

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

**Setting**  Hospital - Coronary Care Unit
Oxygen or compressed air as given through an MC mask at a flow rate of 6 L/min for 24 hours.

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

Interventions/ Test/ Factor being investigated

Comparisons

Patients were followed up for 24 hours

Length of Study/ Follow-up

Outcome measures studied

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

Results

Those without confirmation of an MI:

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

Those with a confirmed MI:

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

Number of patients with arrhythmias after MI

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

Safety and adverse effects

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

Does the study answer the question?

The paper does start to address the key clinical question; it highlights several effects giving oxygen has to patients. The paper shows there is a significant increase in the sinus tachycardia for those who received oxygen compared to those who received air. The paper also showed that the serum aspartate aminotransferase level is significantly higher in the oxygen group than the air group. The paper shows that giving oxygen does not reduce to number arrhythmias, nor does it affect the number of mortalities or give rise to an improvement in left ventricular function.
The paper suggests that giving oxygen may be harmful and does not appear to give a beneficial effect. It suggests that oxygen should not be given routinely but instead should be given to those with obvious hypoxia.

**Effect due to factor in study?**

Patients were also able to receive diamorphine, which could have affect results, however it is likely that the intervention of oxygen was most likely to have caused the results of the study.

**Consistency of results with other studies?**

No other comparable studies

**Directly applicable to guideline population?**

Correct intervention and population

**Internal Validity**

Patients changed to oxygen were included in result

Wilson AT; Channer KS;

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

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

**Study Type** Randomised Controlled Trial

**Number of participant** 22 in group 1 receiving continuous oxygen post MI at 4 litres per minute by face mask; 20 in group 2 receiving no supplemental oxygen except for central cyanosis or respiratory distress.

**Inclusion/Exclusion Criteria**

50 consecutive patients with acute MI admitted to the coronary care unit at the Royal Hallamshire Hospital participate within six hours of the onset of thrombolytic therapy. Patients with central cyanosis, pulmonary disease requiring oxygen independent of the cardiac status or those in whom blood gas estimation showed a pCO-2 > 5.5 kPa and patients with left ventricular failure requiring inotrope support were excluded.

**Patient Characteristics**

There were 25 men and 17 women in the study. The two groups were comparable for the number of smokers (5 and 7 respectively), diabetics (2 and 2) and mean ages (64 and 65 years).

**Recruitment**

The subjects were consecutive patients with acute MI admitted to the coronary care unit at the Royal Hallamshire Hospital.

**Setting**

Royal Hallamshire Hospital, England

**Interventions/Test/Factor being investigated**

The incidence and degree of hypoxaemia in patients with acute MI was studied to assess the use of pulse oximetry and supplemental oxygen therapy in the first 24 hours after MI

**Comparisons**

A comparison is made between the use of continuous oxygen at 4 litres per minute and no oxygen therapy. All subjects were monitored with pulse oximetry through the first 24 hours post MI.

**Length of Study/Follow-up**

24 hours

**Outcome measures studied**

Oxygen saturation (SpO-2) and arrhythmias and ST segment changes were measured

**Results**

Twenty of the 42 (48%) patients had periods of at least moderate hypoxaemia (SpO-2 <90%) and 8 (19%) patients had severe hypoxaemia(SpO-2 <80%). Seven of the 8 severely hypoxaemic patients were in group 2 (p<0.05) which received no supplemental oxygen and were clinically undetected in all but one case (pO2 71%). There were no significant differences in the prescription of opiates between groups. There were no significant differences between groups in the incidence or type of arrhythmias (11 in each group) or ST segment changes (3 and 4 respectively).

The postal survey revealed the following: 105 units (51%) did not use routine oxygen yet 81 (77%) of these had a pulse oximeter. Only
This study demonstrates that hypoxaemia in the first 24 hours after an acute MI is a frequent and predictable occurrence and that this remains undetected by the medical and nursing staff unless a pulse oximeter is used.

Safety and adverse effects
None reported

Does the study answer the question?
This study demonstrates that hypoxaemia in the first 24 hours after an acute MI is a frequent and predictable occurrence and that this remains undetected by the medical and nursing staff unless a pulse oximeter is used.

Effect due to factor in study?
This study demonstrated no statistical correlation between hypoxaemic events and adverse cardiac events but the study was too small to assess this outcome effectively. Otherwise, the results of pulse oximetry appear to be accurate.

Consistency of results with other studies?
With regard to adverse cardiac events there is a lack of consistency.

Directly applicable to guideline population?
Yes

Internal Validity
No control arm and no allocation concealment
Question: In adults presenting with chest pain, what is the clinical and cost effectiveness of pain management (e.g. sublingual and buccal nitrates, diamorphine, morphine with anti-emetic) compared with active comparators?
Hayes MJ; Fraser AR; Hampton JR;

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

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

Study Type Randomised Controlled Trial

Funding Not reported

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

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

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

Diamorphine group - male:female ratio = 3.5:1, mean age 56 ± 10 years, mean duration of chest pain 7.9 ± 11.6 hours, previous analgesia (morphine, diamorphine or pethidine) 54%, admission heart rate 80 ± 23 beats per min, systolic blood pressure 127 ± 31 mm Hg, diastolic blood pressure 79 ± 24 mm Hg, mean AST 97 ± 68 IU/l, mean SHBD 544 ± 375 IU/l, ECG changes - anterior infarction 41%, other sites of infarction 2%, no changes of infarction 25%

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

Setting Secondary care, England

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

Comparisons intravenous buprenorphine, sublingual buprenorphine, diamorphine

Length of Study/ Follow-up 48 hours

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

Results The paper carried out 3 studies

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

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

Study 2
43 patients who required analgesia in the coronary care unit were given either injections of intravenous buprenorphine or sublingual tablets. 18 received a total of 20 tablets of sublingual buprenorphine 0.4 mg, and 25 received a total of 40 injections of intravenous buprenorphine 0.3 mg as and when they needed analgesia for chest pain. In this group only systemic blood pressure and heart rate were measured and the ECGs were continuously monitored. The degree of pain relief and more particularly the time of onset of pain relief were assessed subjectively by the medical and nursing staff.

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

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

Study 3
120 patients who were admitted to the CCU with chest pain due to suspected myocardial infarction and who required analgesia were randomly allocated in a double-blind fashion to receive either buprenorphine 0.3 mg intravenously or diamorphine 5 mg intravenously. There were no medical contraindications for inclusion in this trial. Patients were randomised in blocks of six, the trial ampoules being prepared and issued by the General Hospital pharmacy daily because of the instability of diamorphine when in solution. After entry into the trial records were kept of the time, dose, and frequency of subsequent analgesic administration. The time, degree, and duration of pain relief were monitored using an unmarked visual analogue scale, 3 which was scored by the patient. The scale was subsequently measured and pain relief expressed as a percentage of the original score. If the patients were asleep they were left undisturbed and considered to have complete pain relief. The incidence of nausea, vomiting, and other adverse reactions was also recorded.

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

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

Safety and adverse effects
None reported

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

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

Effect due to factor in study?
Yes

Consistency of results with other studies?
Consistent
Patients had chest pain due to suspected MI and required analgesia.

No report of concealment methods.

Hew E; Haq A; Strauss H;

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

Ref ID 3362

Current Therapeutic Research - Clinical and Experimental

394 to 402

1987

Study Type Randomised Controlled Trial

Funding not reported

Number of participants 24 patients received nalbuphine, 29 received morphine.

Inclusion/Exclusion Criteria

Inclusion: moderately severe to severe pain unresponsive to sublingual nitroglycerin and a suspected diagnosis of MI or unstable angina. Exclusion: heart rate less than 50 beats per minute, systolic blood pressure less than 90 mmHg, cardiac shock, acute or chronic renal failure, valvular heart disease, signs of right or left ventricular failure, pulmonary oedema, patient is a or suspected of being a drug user.

Patient Characteristics

In the nalbuphine group 3 were female, mean age was 60 years old. The mean pain was 5.5 ± 0.5, the mean systolic blood pressure was 134.5 ± 4.4 mmHg, diastolic blood pressure was 82.2 ± 2.8, the mean respiratory rate was 19.7 ± 0.6 breaths/min, the mean heart rate was 71.3 ± 3.9 beats/min, the concomitant of treatments were 7 patients had nitroglycerin infusion, 1 patient had antiarrhythmic, 1 patient had beta-blocker, 2 patients had calcium-channel blocker.

In the morphine group 9 were women, mean age 62.2 years old. The mean pain was 6.3 ± 0.4, the mean systolic blood pressure was 142.6 ± 5.3 mmHg, diastolic blood pressure was 80.1 ± 2.6, the mean respiratory rate was 20.7 ± 0.7 breaths/min, the mean heart rate was 74.1 ± 3.2 beats/min. The concomitant of treatments were 7 patients had nitroglycerin infusion, 2 patients had antiarrhythmic, 0 patients had beta-blocker, 0 patients had calcium-channel blocker.

Recruitment

Patients with ischemic chest pain admitted to 2 hospitals in Canada.

Setting

Secondary care (2 hospitals), Canada.

Interventions/ Test Factor being investigated

Comparisons

10 mg morphine or 20mg nalbuphine

Comparison

10 mg morphine or 20mg nalbuphine

Length of Study/ Follow-up

2 hours

Outcome measures studied

Pain relief

Results

Complete pain relief:
At 5 minutes – 21% on morphine, 42% on nalbuphine
At 15 minutes – 31% on morphine, 54% on nalbuphine
At 30 minutes – 34% on morphine, 54% on nalbuphine
At 60 minutes – 48% on morphine, 58% on nalbuphine
At 120 minutes – 55% on morphine, 67% on nalbuphine

The mean pain scores for nalbuphine group were consistently lower than for the morphine group. The difference in scores was greatest after 5 minutes (nalbuphine = 1.88, morphine = 3.48), however the difference was not significant (F = 3.07, P = 0.08). The mean pain relief scores and the sum of the pain relief scores consistently favoured nalbuphine with the greatest difference at 5 minutes but were not significantly different (F = 2.83, P = 0.10). Neither group had a significant change in either systolic or diastolic blood pressure (F = 1.45, P >0.21). The mean heart rate did not change significantly for either group (F = 1.82, P = 0.11).
Safety and adverse effects

There were 81 unpleasant or unusual side effects reported. In the morphine group 62% reported at least 1 side effect, compared to 75% in the nalbuphine group. The mean number of complaints in the morphine group was 1.5 and in the nalbuphine group was 1.6. There was no statistically significant difference in the incidence of any complaint, including drowsiness and dry mouth which was observed.

Adverse events: (number of patients)
- Drowsiness – 4 on morphine, 9 on nalbuphine
- Dizziness – 8 on morphine, 4 on nalbuphine
- Nausea – 5 on morphine, 6 on nalbuphine
- Dry mouth – 6 on morphine, 1 on nalbuphine
- Headache – 6 on morphine, 1 on nalbuphine
- Diaphoresis – 2 on morphine, 2 on nalbuphine
- Nervousness – 2 on morphine, 1 on nalbuphine
- Hypotension – 1 on morphine, 2 on nalbuphine
- Burning at injection site – 2 on morphine, 1 on nalbuphine
- Vomiting – 1 on morphine, 1 on nalbuphine
- Euphoria – 0 on morphine, 2 on nalbuphine
- Depressed – 1 on morphine, 1 on nalbuphine
- Urticaria – 1 on morphine, 1 on nalbuphine
- Bradycardia – 0 on morphine, 2 on nalbuphine
- Other – 4 on morphine, 4 on nalbuphine

Does the study answer the question?

None of the differences were statistically significant, the trend favoured nalbuphine. The greatest difference was seen at 5 minutes. The author states the ideal analgesic should provide prompt relief from pain and anxiety without adversely affecting hemodynamic or respiratory function, this study suggests that nalbuphine fulfils this and should be considered as an alternative to morphine.

Effect due to factor in study?

Yes

Consistency of results with other studies?

Consistent

Directly applicable to guideline population?

Patients had moderately severe to severe pain due to suspected MI or unstable angina and unresponsive to sublingual nitroglycerin

Internal Validity

Jamidar HA CSAA;

Nalbuphine versus diamorphine early in the course of suspected myocardial infarction

Ref ID 4222 Eur Heart J 597 to 602 1987

Study Type Randomised Controlled Trial

Funding Dr J Beets and Dupont supplied the Nalbuphine

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

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

Patient Characteristics

In the Nalbuphine group:
The mean age was 60.5 years, 41% were women. 43% smoked, 30% were ex-smokers. 2% had diabetes, 21% had previous hypertension. 13% had previous severe angina, 29% had previous moderate angina, 20% had previous mild angina. 8% had more than 2 previous MIs, 14% had 2 previous MIs, 29% had 1 previous MI, 49% had no previous MI.

In the Diamorphine group:
The mean age was 62.2 years, 34% were women. 35% smoked, 25% were ex-smokers. 9% had diabetes, 25% had previous hypertension. 16% had previous severe angina, 10% had previous moderate angina, 29% had previous mild angina. 8% had more than 2 previous MIs, 6% had 2 previous MIs, 26% had 1 previous MI, 60% had no previous MI. NOTE one person died before a full history could be taken (smoking and previous MI data missing)

15 May 2009   Page 86 of 196
Patients admitted with moderate or severe chest pain of a suspected acute MI

Royal Victoria Hospital, Belfast, Northern Ireland

≤ 20 mg nalbuphine or ≤ 5 mg diamorphine intravenously with 10 mg metoclopramide

between ≤ 20 mg nalbuphine or ≤ 5 mg diamorphine intravenously with 10 mg metoclopramide

2 hours

pain relief at set times

The results for pain relief for the nalbuphine group and the diamorphine group were similar with no statistically significant differences (P=>0.05). Pain was recorded at 10 minutes, 30 minutes, 60 minutes and 120 minutes. At 10 minutes 77% of the nalbuphine group and 68% of the diamorphine group had satisfactory pain relief; 44% of the nalbuphine group and 39% of the diamorphine group had complete pain relief. Satisfactory pain relief (grade 0 or 1 pain) was similar for both groups during each time assessment. So there was no significant difference between the two groups for total pain relief. The average pain score at each time interval was similar for both groups. The number of doses of each drug given over the 120 minutes were comparable (n 114 + SD 0-4, d 1-28±SD 0-5). Of those withdrawn from the trial (two doses of the test drug without satisfactory pain relief) 6 patients had received diamorphine and 11 nalbuphine. This difference was not statistically significant. Pain recurred after satisfactory pain relief in 2 patients who had received diamorphine and in 5 who had received nalbuphine.

There were no significant differences for heart rate, systolic and diastolic blood pressures between the two groups throughout the 120 minute observation period. Only one patient in the nalbuphine group and 3 in the diamorphine group required atropine and only 2 in the nalbuphine group and 2 in the diamorphine group received beta-blockers intravenously during the trial period. The numbers with cardiac failure initially and at 120 minutes showed no significant differences for the two groups. There were no significant differences between the two groups for mean peak CK, AST and LDH. Seven patients received streptokinase and their enzyme levels were excluded from analysis.

dizziness, nausea and vomiting was infrequent but occurred in both groups

In the Nalbuphine group: 16% had dizziness, 14% had nausea and vomiting, 10% had other side effects, 1% died (1 patient)
In the Diamorphine group: 17% had dizziness, 16% had nausea and vomiting, 7% had other side effects, 8% died (7 patients)

The results for pain relief for the nalbuphine group and the diamorphine group were similar with no statistically significant difference. The study showed that Nalbuphine is safe and is as effective as diamorphine, with the speed of pain relief and reoccurrence of pain being similar for both groups. Nalbuphine had no adverse events on infarct size nor deleterious heamodynamic side effects.

Yes

Consistent

The population was patients with moderate or severe chest pain of suspected MI

patients were withdrawn for further pain relief
Grading: 2++

High-quality systematic reviews of case–control or cohort studies
High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

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

Ref ID 2966 European Journal of Pain 115 to 125 1998

Study Type Cohort

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

Number of participant 2988

Inclusion/Exclusion Criteria Patients had chest pain or symptoms suggestive of AMI. Patients had to have a confirmed or suspected AMI or myocardial ischaemia and were hospitalised and stayed for more than 1 day.

Patient Characteristics The mean age was 69.3 ± 0.23 years (range 18-101 years), 40.2% were women. 921 patients developed an MI, 357 had a possible MI, 419 had myocardial ischaemia, 1291 had possible myocardial ischaemia

Recruitment patients with chest pain or symptoms suggestive of AMI admitted to CCU in Sweden

Setting Secondary care, Sweden

Interventions/ Test/ Factor being investigated 10mg morphine hydrochloride intravenously over one minute

Comparisons pain relief after being given 10mg morphine hydrochloride intravenously over one minute

Length of Study/ Follow-up 3 days

Outcome measures studied pain, morphine requirement

Results

The average pain intensity was 6.6±0.6 on the Numerical Rating Scale (NRS) before the morphine injection. There was rapid pain relief (6.9±11% after 20 minutes) after the morphine injection. After 20 minutes, a nadir was obtained where NRS ranged between 0 and 3 units. 7 out of 10 patients reported being pain free at one or more measurement point during the first 3 hours following morphine injection. However 3 patients needed supplementary analgesic treatment with meperidine and 1 patient was given metoprolol. 5 patients required diuretics but no patients were given thrombolysis or nitrates.

The patient characteristics which were associated with higher morphine requirements were: gender (female) P = <0.0455, history of angina pectoris P = <0.0001, previous CHF P = <0.0001, initial degree of suspicion of AMI P = <0.0001, presence of ST elevation on entry ECG P = <0.0001, presence of ST depression on entry ECG P = <0.0004, Q wave on entry ECG P = <0.0015.

The mean systolic/diastolic blood pressure at arrival at the CCU was 143±9/91±4.6mm Hg. After intravenous morphine administration there was a significant reduction in the diastolic blood pressure but a similar but non-significant trend in systolic blood pressure. Heart rate was 86±5.1 beats/minute on admission and tended to be reduced during the observation period after intravenous morphine. Respiratory frequency remained unchanged in all patients.
<table>
<thead>
<tr>
<th><strong>Safety and adverse effects</strong></th>
<th>None reported</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Does the study answer the question?</strong></td>
<td>The study showed that there was rapid pain relief 20 minutes after the morphine injection with 7 out of 10 patients reporting complete pain relief at 1 or more measurement points during the 3 hours observation. There were certain patient characteristics associated with higher morphine requirement: gender (female), history of angina pectoris, previous CHF, initial degree of suspicion of AMI, presence of ST elevation on entry ECG, presence of ST depression on entry ECG, Q wave on entry ECG.  The authors concluded that when intravenous morphine is given it has full effect after 20 minutes. The authors also concluded that the need for morphine administration in patients with confirmed or suspected AMI differed among subgroups, in particular those with a strongly suspected AMI required higher doses of morphine.</td>
</tr>
<tr>
<td><strong>Effect due to factor in study?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Consistency of results with other studies?</strong></td>
<td>Consistent</td>
</tr>
<tr>
<td><strong>Directly applicable to guideline population?</strong></td>
<td>Pains had chest pain or symptoms suggestive of AMI</td>
</tr>
<tr>
<td><strong>Internal Validity</strong></td>
<td>Well covered</td>
</tr>
</tbody>
</table>
Safety of pre-hospital therapy with morphine sulfate

Study Type  Cohort
Number of participant  84 patients
Inclusion/Exclusion Criteria  patients who received morphine sulphate in a prehospital setting
Patient Characteristics  the mean age was 68 years, 40 patients were male 39 were female and 5 patients did not have their sex documented
Recruitment  patients who the paramedics assessed as having ischaemic chest pain or pulmonary edema, which was agreed by a doctor at the base hospital were given intravenous morphine sulphate in 2mg increments along with other therapies according to treatment protocol
Setting  Paramedics, San Francisco, USA
Interventions/ Test/ Factor being investigated  safety of prehospital morphine sulphate use in an urban emergency medical system
Comparisons  The diagnosis by a paramedic and an emergency department doctor
Length of Study/ Follow-up  6 months
Outcome measures studied  1: Accuracy of paramedics diagnosis
2: Appropriate use of morphine sulphate
3: Side effects of appropriate and inappropriate use of morphine sulphate
Results  All patients who received morphine sulphate were included in the study. Patients who the paramedics assessed as having ischaemic chest pain or pulmonary oedema, paramedics phone through to the base hospital, where a mobile intensive care nurse and/or a doctor concurred the diagnosis. The paramedic then gave the patient intravenous morphine sulphate in 2mg increments along with other therapies according to treatment protocols. 3 private and 1 public paramedic provider agencies were included which took patients to 10 emergency departments. A total of 84 patients were given morphine sulphate.

The paramedics’ diagnosis was considered accurate in 77% of cases (65 out of 84) Paramedics diagnosed 40 patients with ischaemic chest pain, when patients were diagnosed in the emergency department - 30 had ischaemic chest pain, 4 had ischaemic chest pain and pulmonary oedema, 1 had a pulmonary oedema and 5 had another diagnosis. Paramedics diagnosed 31 patients with pulmonary oedema, when patients were diagnosed in the emergency department - 23 had pulmonary oedema, 4 had ischaemic chest pain and pulmonary oedema and 4 had another diagnosis. Paramedics diagnosed 13 patients with ischaemic chest pain and pulmonary oedema, when patients were diagnosed in the emergency department – 3 had ischaemic chest pain and pulmonary oedema, 9 had a pulmonary oedema and 1 had another diagnosis. (Other diagnosis included atypical chest pain, atypical chest pain and chronic heart failure, acute bronchospasm and pneumonia)

In the 9 cases where the paramedics miss diagnosed ischaemic chest pain or pulmonary oedema 5 patients were diagnosed as ischaemic chest pain but missed a
The study showed that the paramedics’ diagnosis was considered accurate in 77% of cases (65 out of 84). The appropriateness of morphine sulphate administration was assessed the 9 diagnosis which missed either ischaemic chest pain or pulmonary oedema were still treated correctly with morphine sulphate. The appropriateness use of morphine sulphate was 88%.

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

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

Does the study answer the question?
The study showed that the paramedics’ diagnosis was considered accurate in 77% of cases (65 out of 84). The appropriateness of morphine sulphate was 88%, and the overall side effects rate was 6%, the complication rate for inappropriate use of morphine sulphate was 10%.

The authors concluded that paramedics functioning with a system of base hospital direction can safely given morphine sulphate, with the inappropriate administration of morphine sulphate and complication rate being low.

Effect due to factor in study?
Yes

Consistency of results with other studies?
Consistent

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

Internal Validity
Well covered

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

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

Ref ID 1168 Clin Cardiol Pgs. 423 to 428 1986

Study Type Cohort

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

Number of participant 653 patients

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

Patient Characteristics The age range was 33-92 years with the median being 70 years. 38.3% were women, 47.1% were aged over 70 years, 39.2% had a previous infarction, 59.4% had angina pectoris, 36.2% had hypertension, 21.2% had congestive heart failure, 24.5% had furosemide before admission, 38.6% had beta blockers before admission,
10.2% had Ca antagonists before admission

Recruitment
Patients who were admitted to the CCU with suspected AMI were evaluated for inclusion

Setting
Patients home and hospital

Interventions/ Test/ Factor being investigated
Patients pain and analgesic requirement

Comparisons
Pain at home and in hospital

Length of Study/ Follow-up
3 days

Outcome measures studied
visual pain score, narcotic analgesic requirement

Results
The study recorded patient’s pain by a visual scale of 0-10 as reported by the patients (0 being no pain and 10 being worst pain imaginable). The pain scores recorded were the maximum pain at home (recorded once admitted to CCU) and every two hours for 6 hours after admission to CCU. If patients were asleep at the time of recording a score of 0 was reported. Patients were given morphine intravenously for severe pain and nitroglycerine sublingually for less severe pain interpreted as angina pectoris; where patients were given analgesics the pain score was increase by 2. MI was confirmed in 45% of patients and possible MI in 11.9%.

Mean maximum score at home
Patients with defined MI: 7.5
Patients with possible MI: 6.6
Patients with ischemia: 6.9
Patients with no ischemia: 5.9

Mean pain score during the first 6 hours (h) after arrival at CCU
Patients with defined MI: on arrival 2.3, after 2h 1.4, after 4h 1.1, after 6h 0.9
Patients with possible MI: on arrival 1.2, after 2h 0.7, after 4h 0.6, after 6h 0.4
Patients with ischemia: on arrival 1.4, after 2h 0.8, after 4h 0.6, after 6h 0.7
Patients with no ischemia: on arrival 1.6, after 2h 0.9, after 4h 0.6, after 6h 0.7

See narrative for question 17; table 1: Herlitz et al, 1986 and figure 1: Herlitz et al, 1986

Safety and adverse effects
None reported

Does the study answer the question?
The study showed that for pain at home there were small differences in the mean pain scores between the groups of patients. For those with an MI the maximum pain score was 7.5±0.2 where as for those without an MI the maximum pain score was 6.6±0.2 (P<0.001). The study showed that for pain in the CCU the maximum mean score had reduced to 1.8 for all patients compared to 7.0 maximum mean score for all patients at home. The study also showed that 98% of patients had chest pain at home, but only 51% had pain on arrival at the CCU. Figure 1 (see narrative for question 17; figure 1: Herlitz et al, 1986) shows the course of pain after arrival at the CCU

The authors commented that narcotic analgesics were given to 10% of patients after the end of recording pain scores and during the 3 day study 27.4% of patients were given nitroglycerine sublingually.

The authors of the study concluded that patients generally had worse pain at home than in the CCU. The mean pain score values show a trend of rapid decline in pain after arrival in the CCU, although there was variability in the intensity and duration of chest pain. The authors commented that there was a low difference in the pain scores between those having an MI and those who were not.

Effect due to factor in study?
Yes
**Consistency of results with other studies?**
No other studies compare at home to hospital pain management

**Directly applicable to guideline population?**
Patients had suspected MI

**Internal Validity**
Well covered

Scott ME; Orr R;

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

Ref ID 10272 Lancet pp. 1065 to 1067 1969

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Cohort</th>
<th>Funding</th>
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<tbody>
<tr>
<td>Number of participant</td>
<td>118 patients; 30 in diamorphine group, 31 in methadone group, 29 in morphine group and 25 in pentazocine group</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

**Inclusion/Exclusion Criteria**
Included: patients initially assessed to have moderate or severe pain due to suspected acute MI. Excluded: patients who had cardiac shock, cardiac failure, severe nausea, pronounced bradycardia, who have received a potent analgesic or an anti-emetic in previous 4 hours

**Patient Characteristics**
25% were women, the age range was 30-79 years old, with 79% of patients aged between 50-69 years old. 36% of the patients had acute myocardial ischaemia rather than definite infarction. There was no significant difference in the sex-distribution, age, previous history of MI among the 4 treatment groups.

**Recruitment**
Patients who were admitted to the cardiac department, Royal Victoria Hospital, Belfast, Northern Ireland, who were initially assessed to have moderate or severe pain due to suspected acute MI

**Setting**
Secondary care, Northern Ireland

**Interventions/ Test/ Factor being investigated**

**Comparisons**
5 mg diamorphine or 10 mg methadone, 10 mg morphine, 30 mg pentazocine

**Length of Study/ Follow-up**
2 hours

**Outcome measures studied**
Pain relief at 10, 30, 60 and 120 minutes

**Results**
For some degree of pain relief:
- At 10 minutes - 90% of patients on diamorphine, 90% on methadone, 93% on morphine, 85% on pentazocine.
- At 30 minutes - 87% of patients on diamorphine, 94% on methadone, 93% on morphine, 96% on pentazocine.
- At 60 minutes - 87% of patients on diamorphine, 89% on methadone, 90% on morphine, 82% on pentazocine.
- At 120 minutes - 90% of patients on diamorphine, 86% on methadone, 86% on morphine, 81% on pentazocine.

For complete of pain relief:
- At 10 minutes - 47% of patients on diamorphine, 32% on methadone, 17% on morphine, 19% on pentazocine.
- At 30 minutes - 43% of patients on diamorphine, 39% on methadone, 38% on morphine, 36% on pentazocine.
- At 60 minutes - 43% of patients on diamorphine, 50% on methadone, 45% on morphine, 27% on pentazocine.
- At 120 minutes - 34% of patients on diamorphine, 50% on methadone, 52% on morphine, 33% on pentazocine.
The results show equal pain relief by all 4 drugs. Diamorphine gave complete pain relief in 10 minutes to a higher number of patients, it was significantly higher compared to morphine and pentazocine but not significantly higher compared to methadone. At 30 minutes the pain relief is similar across all 4 drugs, however at 60 minutes patients on pentazocine had lower pain relief than the other 3 groups. The authors suggest that diamorphine is the drug of choice.

<table>
<thead>
<tr>
<th>Safety and adverse effects</th>
<th>Nausea and vomiting was similar across all groups (not statistically different). Morphine had an unexpected low number of patients with emetic sequelae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the study answer the question?</td>
<td>The results show equal pain relief by all 4 drugs. Diamorphine gave complete pain relief in 10 minutes to a higher number of patients, it was significantly higher compared to morphine and pentazocine but not significantly higher compared to methadone. At 30 minutes the pain relief is similar across all 4 drugs, however at 60 minutes patients on pentazocine had lower pain relief than the other 3 groups. The authors suggest that diamorphine is the drug of choice.</td>
</tr>
<tr>
<td>Effect due to factor in study?</td>
<td>Yes</td>
</tr>
<tr>
<td>Consistency of results with other studies?</td>
<td>Consistent</td>
</tr>
<tr>
<td>Directly applicable to guideline population?</td>
<td>Patients had moderate or severe pain due to suspected acute MI</td>
</tr>
<tr>
<td>Internal Validity</td>
<td>Well covered</td>
</tr>
</tbody>
</table>
Question: In adults presenting with chest pain/discomfort of acute suspected cardiac origin, what is the clinical and cost effectiveness of anti-platelet therapy (aspirin, clopidogrel alone or in combination) compared with a placebo?
Grading: 2+  Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

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

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

Ref ID 10246  Cardiology  Pgs. 141 to 147  2002

Study Type  Cohort  Funding  Not reported

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

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

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

Aspirin after admission to hospital
Mean age  64.5 ± 14
Patients
<59 years  224 (41%)
60-69 years  114 (20%)
>70 years  222 (39%)
Women  157 (27%)
Diabetes  184 (32%)
Hypertension  248 (43%)
Hyperlipidaemia  241 (42%)
Current smokers  222 (39%)
Prior MI  114 (20%)
Prior angina  154 (27%)
Prior heart failure  33 (6%)
Prior PTCA  51 (9%)
Prior CABG  11 (2%)
PVD  48 (8%)
History of stroke  51 (9%)
Gastrointestinal
disorder 74 (13%)  
Typical chest pain 469 (80%)  
MICU transport 90 (15%)  
Anterior MI 260 (45%)  
Spontaneous reperfusion 20 (3.4%)  

**Recruitment**  
Patients who were admitted to 26 coronary care units and 82 medicine wards in 26 hospitals  

**Setting**  
Hospital, ambulance & community in Israel  

**Interventions/ Test/ Factor being investigated**  
Aspirin administration - dose of >200mg chewable aspirin before or after admission to hospital  

**Comparisons**  
Aspirin being given before or after admission to hospital  

**Length of Study/ Follow-up**  
Follow up at 7 and 30 days  

**Outcome measures studied**  
Mortality, in-hospital complications, in-hospital treatments  

**Results**  
Aspirin given: before hospital after hospital P value  
All cause Mortality  
7 days 8 (2.4%) 42 (7.3%) 0.002  
30 days 16 (4.9%) 64 (11.1%) 0.001  
Re-hospitalisation  
Non-cardio 5 (13%) 23 (22%) 0.22  
Cardiovascular 59 (19%) 134 (27%) 0.02  

In-hospital complications  
Asystole 6 (2%) 39 (7%) < 0.001  
Resuscitation 12 (4%) 55 (9%) < 0.001  
Ventilation 17 (5%) 66 (11%) 0.001  

There was no significant difference in the following in-hospital complications recurrent MI, pulmonary oedema, sustained VT, primary VF, free wall rupture, ventricular septal defect, significant MR and cardiogenic shock  

In-hospital medications  
Ticlopidine  
/ clopidogrel 84 (25%) 75 (13%) < 0.001  
IB/IIa antagonists 97 (29%) 120 (21%) 0.005  
Heparin 301 (90%) 466 (80%) < 0.001  
Primary reperfusion 219 (65%) 299 (51%) < 0.001  

There was no significant difference in in-hospital management in the following drug therapies: aspirin, vasopressors, β-blockers, calcium blockers, nitrates, diuretics, ACE inhibitors, angiotensin-II antagonist, lipid lowering drugs and digitalis  

In-hospital procedures  
Coronary angiography 195 (58%) 252 (44%) < 0.001  
PTCA 136 (41%) 155 (27%) < 0.001  

There was no significant difference in in-hospital management in the following procedures: CABG, intra-aortic balloon pump, pulmonary artery catheter  

<table>
<thead>
<tr>
<th>Patients, n(%)</th>
<th>Primary reperfusion (n=518)</th>
<th>no primary reperfusion</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
<td>Late</td>
<td>p value</td>
</tr>
<tr>
<td>Age, years</td>
<td>59±12</td>
<td>60±12</td>
<td>0.1</td>
</tr>
<tr>
<td>Women</td>
<td>30(14%)</td>
<td>64(21%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Prior MI</td>
<td>54(25%)</td>
<td>53(18%)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

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Page 97 of 196
This study addresses the key clinical question of the effect of aspirin administration, however this is on patients who have an acute MI not those with undifferentiated chest pain. The study suggests that giving aspirin early results in lower mortality rates at 7 and 30 days and a lower rate of re-hospitalisation. This benefit was also seen in a sub-group analysis of patients who underwent reperfusion. The study showed that those who received aspirin before admission to hospital were more likely to be treated with heparin, ticlopidine / clopidogrel, IIb/IIIa antagonists. The paper states that the theoretical basis of early aspirin administration is due to the anti-platelet properties and its ability to aid reperfusion.

Safety and adverse effects

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

Does the study answer the question?

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

Effect due to factor in study?

Yes

Consistency of results with other studies?

Limited studies in this area, results appear consistent

Directly applicable to guideline population?

Population have a confirmed diagnosis of MI, intervention correct

Internal Validity

Well covered
Question: What is the utility and cost effectiveness of cardiac biomarkers in evaluation of individuals with acute chest pain of suspected cardiac origin?
Accuracy of biomarkers to diagnose acute cardiac ischemia in the emergency department: a meta-analysis

<table>
<thead>
<tr>
<th>Ref ID</th>
<th>Study Type</th>
<th>Funding</th>
</tr>
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<tbody>
<tr>
<td>215</td>
<td>Meta-analysis</td>
<td>Agency for Healthcare Research and Quality</td>
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</table>

<table>
<thead>
<tr>
<th>Number of participant</th>
<th>Inclusion/Exclusion Criteria</th>
<th>Patient Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>73 diagnostic studies searched from 1966 to December 1998</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions/Test/Factor being investigated</th>
<th>Comparisons</th>
<th>Length of Study/Follow-up</th>
<th>Outcome measures studied</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td>The meta-analysis evaluated the accuracy of biomarkers to diagnose acute cardiac ischemia in the emergency department. The analysis searched for papers examining the diagnostic performance of troponin I, troponin T, creatine kinase, CK-MB, myoglobin and CK-MB with myoglobin from 1966 to December 1998. The analysis considered 73 papers which considered the diagnosis of AMI. Where possible the authors only analyse papers which considered patients in emergency departments and the review took study quality into account when analysing the results. The study did not report the timing of the tests.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety and adverse effects</th>
<th>Does the study answer the question?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The analysis identified 7 studies which evaluated the diagnostic performance of single troponin I, the review reported the timing of the tests for two studies, one was at 2 hours from symptom onset and one was at 7 hours from onset of symptoms, but not for the other 5 studies. The prevalence of AMI ranged from 6%-39% in the studies with a total of 1149 patients included in the studies. The sensitivity ranged from 4% to 100% and the specificity ranged from 89% to 98% but 3 papers did not provide data for the specificity. The overall sensitivity was 39% and the specificity was 93%. For serial troponin I testing 2 studies were identified which had 6% and 9% prevalence of AMI and included 1393 patients. The review did not report the timing of the serial troponin I tests. The studies showed a sensitivity of 95% and specificity of 90% (sensitivity range 90%-100% and specificity range 83%-96%).</td>
</tr>
<tr>
<td></td>
<td>The analysis identified 8 studies which evaluated the diagnostic performance of single troponin T. The tests were conducted on admission to the emergency</td>
</tr>
</tbody>
</table>

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

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

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

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

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

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Ebell MH; Flewelling D; Flynn CA;

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

Ref ID 234 J Fam Pract 550 to 556 2000

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The systematic review evaluated troponin T and I for diagnosing AMI. The review searched for papers examining the diagnostic performance of troponin T and troponin I until December 1999. The review considered 19 papers which considered the diagnosis of AMI in patients with acute chest pain, presenting to an emergency department, that included the sensitivity or specificity for at least one biomarker at a set time.

The study identified 6 studies which evaluated the diagnostic value of troponin I in diagnosing AMI. The review did not report the prevalence of AMI in the test population but did report a meta-analysis of the sensitivity and specificity of troponin I at 1, 2, 3, 4, 5 and 6 hours from onset of pain. (See table in question 11 appendix for full results) The highest sensitivity occurred at 6 hours from onset of pain and was 90% and had a specificity of 95%.

The review identified 14 studies which evaluated the diagnostic value of troponin T in diagnosing AMI. Again the review did not report the prevalence of AMI in the test population but did report sensitivity and specificity for troponin T > 0.1 and for troponin T >0.2 at 1, 2, 3, 4, 6, 8 and 10 hours after onset of pain. (See table in question 11 appendix for full results). The highest sensitivity for troponin T > 0.1 occurred at 10 hours from onset of pain and was 93% and had a specificity of 80%, but had the highest specificity at 1 and 2 hours from onset which had a specificity of 87% but sensitivity of 47% and 53% respectively. The highest sensitivity for troponin T > 0.2 occurred at 8 and 10 hours from onset of pain and was 96% and had a specificity of 81% and 80% respectively, but had the highest specificity at 1 and 2 hours from onset which had a specificity of 87% but sensitivity of 14% and 33% respectively.
Directly applicable to guideline population?

Internal Validity

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

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

Ref ID 728

Study Type Economic Funding

Number of participant

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity
Grading: 2++
High-quality systematic reviews of case–control or cohort studies
High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

Guo X; Feng J; Guo H;

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

Ref ID 1321 Experimental and Clinical Cardiology pp. 298 to 301 2006

Study Type Diagnostic

Funding Science Research Fund of Guangzhou Red Cross Hospital

Number of participant 502 patients
Patients were included if they had chest pain of suspected AMI, patients were admitted to the cardiac department or CCU

89.1% had AMI (86.9% had TnT+ and 2.2% had TnT-)

Inclusion/Exclusion Criteria

Patient Characteristics Diagnosing AMI

Recruitment

Setting

Interventions/Test/Factor being investigated Troponin T at admission and 6 and 12 hours after admission

Comparisons No comparison

Length of Study/Follow-up

Outcome measures studied

Results For results see Table 1 in Question 11 appendix

Safety and adverse effects

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Kost GJ; Kirk JD; Omand K;

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Diagnosing AMI

Troponin T, troponin I, CK-MB and myoglobin at presentation and 3, 6 and 12 hours after admission

Biomarkers were compared to each other

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

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Diagnostic</th>
</tr>
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<tbody>
<tr>
<td>Number of participant</td>
<td>97 patients</td>
</tr>
<tr>
<td>Inclusion/Exclusion Criteria</td>
<td>Patients were included if they had acute chest pain which was possible AMI, presenting to the emergency department</td>
</tr>
<tr>
<td>28% had AMI</td>
<td></td>
</tr>
<tr>
<td>Patient Characteristics</td>
<td>Diagnosing AMI</td>
</tr>
<tr>
<td>Recruitment</td>
<td></td>
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<tr>
<td>Setting</td>
<td></td>
</tr>
<tr>
<td>Interventions/ Test/ Factor being investigated</td>
<td>Troponin T, troponin I, CK-MB and myoglobin at presentation and 3, 6 and 12 hours after admission</td>
</tr>
<tr>
<td>Comparisons</td>
<td>Biomarkers were compared to each other</td>
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<tr>
<td>Length of Study/ Follow-up</td>
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<tr>
<td>Outcome measures studied</td>
<td></td>
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<tr>
<td>Results</td>
<td>For results see Table 1 in Question 11 appendix</td>
</tr>
<tr>
<td>Safety and adverse effects</td>
<td></td>
</tr>
<tr>
<td>Does the study answer the question?</td>
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</tr>
<tr>
<td>Effect due to factor in study?</td>
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<td>Consistency of results with other studies?</td>
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<tr>
<td>Directly applicable to guideline population?</td>
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</tr>
<tr>
<td>Internal Validity</td>
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</tbody>
</table>

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Grading: 2+

Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

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

![Image: Journal Citation]

Ref ID 780

Number of participants: 397 patients

Patients were included if they were aged over 18 years old, had acute chest pain of possible cardiac origin admitted to the CCU. Patients were excluded if evidence of ST elevation on admission ECG, evidence of MI in previous 2 weeks, inability to provide informed consent.

28% had AMI

Inclusion/Exclusion Criteria:

Diagnosing chest pain

Recruitment

Setting

Interventions/Test

Factor being investigated:

Troponin I at 6 hours from onset of worst symptoms or from presentation if timing of symptoms was unclear

Comparisons:

Standard management (CK, AST and ECG)

Length of Study/Follow-up

Outcome measures studied

Results:

For results see Table 1 in Question 11 appendix

Safety and adverse effects

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

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

15 May 2009
Confirming a diagnosis of AMI

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

Ref ID 10340 OJM - Monthly Journal of the Association of Physicians pgs. 711 to 718 1999

Study Type Diagnostic Funding Not reported

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

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

Inclusion/Exclusion Criteria

Patient Characteristics Confirming a diagnosis of AMI

Recruitment

Setting

Interventions/ Test/ Factor being investigated CK-MB, troponin I, myoglobin, triple test (troponin I, myoglobin and CK-MB) at a mean of 4.89 hours over 72 hours from onset of pain

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

Length of Study/ Follow-up

Outcome measures studied

Results For results see Table 1 in Question 11 appendix

Safety and adverse effects

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Eggers KM; Oldgren J; Nordenskjöld A; Lindahl B;

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

Ref ID 608 Am Heart J pgs. 81 2004

Study Type Diagnostic Funding Dade Behring Inc. and Cardiological Decision Support Uppsala AB,
Excluding an AMI diagnosis

Troponin I, CK-MB at presentation at 6 and 12 hours after presentation

In Uppsala, Sweden

Number of participant
197 consecutive patients with chest pain and a non diagnostic ECG
Patients were included if they had had chest pain for longer than 15 minutes within the last 24 hours which was suspected to be unstable angina or AMI and admitted to the CCU
Patients were excluded if they had pathological ST-segment elevation on the admission ECG leading to immediate reperfusion

22% had AMI

Inclusion/Exclusion Criteria
Patient Characteristics
Excluding an AMI diagnosis

Recruitment

Setting

Interventions/ Test/ Factor being investigated
Myoglobin with troponin I, CK-MB at presentation at 6 and 12 hours after presentation

Comparisons
Troponin I

Length of Study/ Follow-up

Outcome measures studied

Results

For results see Table 1 in Question 11 appendix

Safety and adverse effects

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

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

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

Ref ID 1983 Am Heart J pg 332 to 337 1999

Study Type Diagnostic

Number of participant 327 consecutive patients over a 3 month period were evaluated for AMI. Patients were excluded if less than 2 blood samples were taken. The study was conducted at the Hennepin county Medical centre, Minneapolis, USA

19% had a final diagnosis of AMI (of which 79% had a diagnostic ECG and 21% had a non diagnostic ECG)

15 May 2009 Page 108 of 196
The diagnosis of AMI

All patients had CK, CK-MB and CTnI tested every 6-8 hours from admission for 24-48 hours. The tests were compared to each other and the AMI diagnosis was based on the WHO diminution.

Inclusion/Exclusion Criteria

Patient Characteristics

The diagnosis of AMI

Recruitment

Setting

Interventions/Test/Factor being investigated

All patients had CK, CK-MB and CTnI tested every 6-8 hours from admission for 24-48 hours.

Comparisons

The tests were compared to each other and the AMI diagnosis was based on the WHO diminution.

Length of Study/Follow-up

Outcome measures studied

Results

For results see Table 1 in Question 11 appendix

Safety and adverse effects

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

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

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

Ref ID: 629

Ann Emerg Med

12 to 19

2004

Study Type: Diagnostic

Funding: Phillips Medical Systems, Millennium Pharmaceuticals Inc, Bristol-Myers Squibb Medical Imaging and EmCare Inc.

Number of participants

975 patients

Patients were included if they had a baseline troponin level of 1.0 ng/ml or less and an initial non-diagnostic ECG, presenting to a University hospital, USA

4.5% had AMI

Inclusion/Exclusion Criteria

Patient Characteristics: Diagnosing AMI

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Recruitment

Setting

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

Comparisons
no comparison

Length of Study/Follow-up

Outcome measures studied

Results
For results see Table 1 in Question 11 appendix

Safety and adverse effects

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Recruitment Setting

Patient Characteristics


Study Type Diagnostic

Funding Not reported

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

24% had AMI

Inclusion/Exclusion Criteria

Patient Characteristics Diagnosing AMI

Recruitment

Setting

Interventions/Test/Factor being investigated
Troponin T

Comparisons
no comparison
**Length of Study/ Follow-up**

**Outcome measures studied**

**Results**

For results see Table 1 in Question 11 appendix

**Safety and adverse effects**

**Does the study answer the question?**

**Effect due to factor in study?**

**Consistency of results with other studies?**

**Directly applicable to guideline population?**

**Internal Validity**

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

The diagnostic value of troponin T testing in the community setting

**Study Type** Diagnostic

**Funding** Kits were provided by DYN Diagnostics, Israel

**Number of participant** 349 patients

Patients were included if they were aged over 30 years, with at least 20 consecutive minutes of chest pain beginning at least 8 hours before presentation and occurring within the last 6 days

Patients were excluded if they had renal failure, ST elevation on ECG, had a diagnosis of ACS or had undergone revascularization

Patients were recruited from 44 community clinics in Jerusalem, Israel

1.7% had AMI

**Inclusion/Exclusion Criteria**

**Patient Characteristics** Diagnosing AMI

**Recruitment**

**Setting**

**Interventions/ Test/ Factor being investigated** Troponin T

**Comparisons** No comparison

**Length of Study/ Follow-up**

**Outcome measures studied**

**Results**

For results see Table 1 in Question 11 appendix

15 May 2009
### Safety and adverse effects

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

### Internal Validity

Zarich S; Bradley K; Seymour J; Ghali W; Traboulsi A; Mayall ID; Bernstein L;

Impact of troponin T determinations on hospital resource utilization and costs in the evaluation of patients with suspected myocardial ischemia

<table>
<thead>
<tr>
<th>ID</th>
<th>Ref</th>
<th>Study Type</th>
<th>Patient Characteristics</th>
<th>Setting</th>
<th>Interventions/ Test/ Factor being investigated</th>
<th>Comparisons</th>
<th>Length of Study/ Follow-up</th>
<th>Outcome measures studied</th>
<th>Results</th>
<th>Safety and adverse effects</th>
<th>Does the study answer the question?</th>
<th>Effect due to factor in study?</th>
<th>Consistency of results with other studies?</th>
</tr>
</thead>
<tbody>
<tr>
<td>10352</td>
<td></td>
<td>Economic</td>
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Impact of troponin T determinations on hospital resource utilization and costs in the evaluation of patients with suspected myocardial ischemia

Ref ID 10352 Am J Cardiol pgs. 732 to 736 2001
Directly applicable to guideline population?

Internal Validity

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

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

Ref ID: 731 Clin Chim Acta 185 to 192 2002

Study Type Diagnostic    Funding Not reported

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

32% had AMI or unstable angina

Inclusion/Exclusion Criteria

Patient Characteristics: Diagnosing AMI

Recruitment

Setting

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

Comparisons: Compared to each other

Length of Study/ Follow-up

Outcome measures studied

Results: For results see Table 1 in Question 11 appendix

Safety and adverse effects

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

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

Ref ID: 748

Medical Principles and Practice

2002

18 to 22

Grading: 2-

Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal*

Patient Characteristics

Number of participants: 124 patients (group 1 = 86 patients, group 2 = 38 patients)

Patients were included in group 1 if they had a diagnosis of ACS, group 2 were healthy age-matched patients with no history of cardiovascular disease or any other chronic disease.

Group 1 patients were admitted to the CCU. 59% had AMI, 41% had unstable angina.

Inclusion/Exclusion Criteria

Patient Characteristics

Diagnosing AMI and unstable angina

Recruitment

Setting

Interventions/Test/Factor being investigated

Troponin I at presentation and 8 and 16 hours from presentation

Comparisons

no comparison

Length of Study/Follow-up

Outcome measures studied

Results

For results see Table 1 in Question 11 appendix

Safety and adverse effects

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Vatansever S; Akkaya V; Erk O; Oztürk S; Karan MA; Salmayenli N; Taşpılıoglu C; Gölker K;

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

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Diagnosing AMI

TroponinT and myoglobin at 2 hours from presentation

Not reported

Internal Validity

Patient Characteristics

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

For results see Table 1 in Question 11 appendix

Safety and adverse effects

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

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

Diagnostic marker cooperative study for the diagnosis of myocardial infarction

Funding

Boehringer Mannheim Corporation, Dade International, Helena Laboratories, Spectral Diagnostics, Inc, and NHLBI
Diagnosing AMI

Biomarkers were compared with each other

<table>
<thead>
<tr>
<th>Number of participant</th>
<th>955 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients were included if aged over 21 years old with chest pain lasting for 15 minutes or longer suspected to be myocardial in origin and occurring within 24 hours of presentation.</td>
<td></td>
</tr>
<tr>
<td>Patients presented to hospitals in Texas, USA</td>
<td></td>
</tr>
<tr>
<td>100% had AMI</td>
<td></td>
</tr>
</tbody>
</table>

**Inclusion/Exclusion Criteria**

**Patient Characteristics**

**Recruitment**

**Setting**

**Interventions/ Test/ Factor being investigated**

CK-MB, troponin I, troponin T, myoglobin at 2, 4, 6, 8, 10, 18 and 22 hours after presentation

**Comparisons**

Biomarkers were compared with each other

**Length of Study/ Follow-up**

**Outcome measures studied**

**Results**

For results see Table 1 in Question 11 appendix

**Safety and adverse effects**

**Does the study answer the question?**

**Effect due to factor in study?**

**Consistency of results with other studies?**

**Directly applicable to guideline population?**

**Internal Validity**
Question: What is the incremental benefit and cost effectiveness of a clinical history, risk factors and physical examination in evaluation of individuals with stable chest pain of suspected cardiac origin?
Bedside diagnosis of coronary artery disease: a systematic review

**Study Type**
Systematic Review

**Funding**
Not reported

**Number of participant**
64 studies

**Inclusion/Exclusion Criteria**

**Patient Characteristics**

**Recruitment**

**Setting**

**Interventions/ Test/Factor being investigated**

**Comparisons**

**Length of Study/Follow-up**

**Outcome measures studied**

**Results**

**Safety and adverse effects**

**Does the study answer the question?**

Most of the papers reviewed were of patients presenting with stable intermittent chest pain who were then referred for coronary angiography. Most of the studies had excluded patients with valvular heart disease or nonischemic cardiomyopathy. The studies used either >50% stenosis or 70-75% stenosis off any epicardial vessel as the diagnostic standard.

The study showed that for diagnosing CAD over all the physical examination gave little additional diagnostic information (see narrative for question 27; Table 1: Chun and McGee, 2004). The presence of an ear lobe crease gave a small increase to the probability of CAD (likelihood ratio (LR)=2.3). Arcus senilis and an ankle-brachial index <0.9 had no statistical significance, and the presence of chest wall tenderness was also diagnostically unhelpful.

The review calculated the LR by pooling the data from the included studies which used 2 diagnostic criteria for CAD (>50% stenosis and >70% to 75% stenosis). The study also analysed the data separately (>50% stenosis and >70-75% stenosis) which showed the pooled LR remained the same. In studies which used > 50% stenosis the pooled LR were 5.6 for typical angina, 1.1 for atypical angina, and 0.1 for nonanginal chest pain. The review calculated LRs including data from studies that combined patients with a history of MI with those without; the LRs were the same if only those studies excluding prior MI were analysed. In studies of patients without a history of MI the pooled likelihood ratios were 5.8 for typical angina, 1.3 for atypical angina and 0.1 for nonanginal chest pain.

The study showed that for the diagnosing MI, (see narrative for question 27; Table 2: Chun AA; McGee SR;...
Chun and McGee, 2004 and Table 3: Chun and McGee, 2004) the ECG was more useful in diagnosing MI, however systolic blood pressure <100 mmHg (LR=3.6), diaphoresis on examination (LR=2.9), diastolic blood pressure <60 mmHg (LR=2.5), and presence of jugular venous distention (LR=2.4) were also helpful in diagnosing MI. A normal ECG was most useful in ruling out a diagnosis of MI but the patient having chest wall tenderness was also helpful for ruling out the diagnosis.

**Effect due to factor in study?**
Yes

**Consistency of results with other studies?**
Consistent

**Directly applicable to guideline population?**
Correct population

**Internal Validity**

Chun AA; McGee SR;

Bedside diagnosis of coronary artery disease: a systematic review

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

**Study Type** Systematic Review

**Number of participant** 64 studies

**Inclusion/Exclusion Criteria**

**Patient Characteristics**

**Recruitment**

**Setting**

**Interventions/ Test/ Factor being investigated**

**Comparisons**

**Length of Study/ Follow-up**

**Outcome measures studied**

**Results**

**Safety and adverse effects**

**Does the study answer the question?**

Most of the papers reviewed were of patients presenting with stable intermittent chest pain who were then referred for coronary angiography. Most of the studies had excluded patients with valvular heart disease or nonischemic cardiomyopathy. The studies used either >50% stenosis or 70-75% stenosis off any epicardial vessel as the diagnostic standard. The study showed that for diagnosing CAD over all the physical examination gave little additional diagnostic information (see narrative for question 26; Table 1: Chun and McGee, 2004). The presence of an ear lobe crease gave a small increase to the probability of CAD (likelihood ratio (LR)=2.3). Arcus senilis and an ankle-brachial index <0.9 had no statistical significance, and the presence of chest wall tenderness was also diagnostically unhelpful.

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The review calculated the LR by pooling the data from the included studies which used 2 diagnostic criteria for CAD (>50% stenosis and >70% to 75% stenosis). The study also analysed the data separately (>50% stenosis and >70-75% stenosis) which showed the pooled LRs remained the same. In studies which used > 50% stenosis the pooled LRs were 5.6 for typical angina, 1.1 for atypical angina, and 0.1 for nonanginal chest pain. The review calculated LRs including data from studies that combined patients with a history of MI with those without; the LRs were the same if only those studies excluding prior MI were analysed. In studies of patients without a history of MI the pooled likelihood ratios were 5.8 for typical angina, 1.3 for atypical angina and 0.1 for nonanginal chest pain.

The study showed that for the diagnosing MI, (see narrative for question 26; Table 3: Chun and McGee, 2004 and Table 4: Chun and McGee, 2004) the ECG was more useful in diagnosing MI, however systolic blood pressure <100 mmHg (LR=3.6), diaphoresis on examination (LR=2.9), diastolic blood pressure <60 mmHg (LR=2.5), and presence of jugular venous distention (LR=2.4) were also helpful in diagnosing MI. A normal ECG was most useful in ruling out a diagnosis of MI but the patient having chest wall tenderness was also helpful for ruling out the diagnosis.

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

**Internal Validity**

Chun AA; McGee SR;

Bedside diagnosis of coronary artery disease: a systematic review

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

**Study Type** Systematic Review

**Number of participant** 64 studies

**Inclusion/Exclusion Criteria**

**Patient Characteristics**

**Recruitment**

**Setting**

**Interventions/Test/Factor being investigated**

**Comparisons**

**Length of Study/Follow-up**

**Outcome measures studied**

**Results**

**Safety and adverse effects**

15 May 2009
Most of the papers reviewed were of patients presenting with stable intermittent chest pain who were then referred for coronary angiography. Most of the studies had excluded patients with valvular heart disease or nonischemic cardiomyopathy. The studies used either >50% stenosis or 70-75% stenosis off any epicardial vessel as the diagnostic standard.

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**Does the study answer the question?**
Yes

**Effect due to factor in study?**
Consistent

**Consistency of results with other studies?**
Correct population

**Directly applicable to guideline population?**

**Internal Validity**
Grading: 2++
High-quality systematic reviews of case–control or cohort studies
High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

Diamond GA; Forrester JS;

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

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

Study Type Cohort

Funding Not reported

Number of participant 4952 had coronary angiography, 23,996 autopsy (autopsy patients had died from other causes e.g. trauma and non-cardiac related diseases)

Inclusion/Exclusion Criteria Not applicable

Patient Characteristics

- Patients were considered to have typical angina if they had substernal discomfort brought on by physical exertion and was relieved within 10 minutes through rest or nitroglycerin.
- Patients were considered to have atypical angina if they had discomfort which was either not substernal or was not bought on by exertion or not relieved after 10 minutes by rest or nitroglycerin.
- Patients were considered to have non-anginal discomfort if they did not have 1 or more of the above characteristics.

Recruitment Not applicable

Setting Secondary care, USA

Interventions/ Test/ Factor being investigated Prevalence of CAD based on age, sex and symptoms

Comparisons Coronary angiography in symptomatic patients and autopsy

Length of Study/ Follow-up Not applicable

Outcome measures studied Prevalence of CAD based on age, sex and symptoms

Results

See narrative for question 27; Table 4a: Diamond and Forrester, 1979, Table 4b: Diamond and Forrester, 1979 and Table 4c: Diamond and Forrester, 1979 (autopsy patients had died from other causes e.g. trauma and non-cardiac related diseases)

See narrative for question 27; Table 4a: Diamond and Forrester, 1979 and Table: 4b: Diamond and Forrester, 1979

Table 4a shows the prevalence of CAD confirmed by coronary angiography in patients described as having “typical angina”, “atypical angina” and “nonanginal chest pain” from 4952 patients. From the table it can be seen that the prevalence of disease in persons with typical angina is about 90%, where as atypical angina shows a 50% prevalence (P<0.001) and nonanginal chest pain a 16% prevalence (P<0.001). Table 4b summarises pathological data obtained from 23,996 autopsies, showing the mean prevalence of CAD to be 4.5%. The prevalence of CAD observed at autopsy is similar to that in asymptomatic patients confirmed by coronary angiography. Table 4b also shows that there are significant differences (P<0.001) in disease prevalence when patients are grouped by age and sex.

From table 4a and 4b giving data of the estimate of disease likelihood when the patient’s age and sex are known and a second estimate when the presence or absence of symptoms are known. The pre-test likelihood of disease for any patients
The study reviewed the literature to estimate the pre-test likelihood of disease (defined by age, sex and symptoms), the results were analysed through Bayes’ theorem of conditional probability. The studied described how the probability of CAD can be determined in a patient before testing from information readily obtained from clinical evaluation.

The study showed that combining data of the estimate of disease likelihood when the patient’s age and sex are known and a second estimate when the presence or absence of symptoms are known. The pre-test likelihood of disease for any patients based on any combination of age, sex and symptoms can be determined by conditional-probability analysis. The results of this analysis can be seen in table 3 which shows the results of all combinations of age, sex and symptoms, which shows a wide range of pre-test likelihoods.

Safety and adverse effects

Does the study answer the question?

The study reviewed the literature to estimate the pre-test likelihood of disease (defined by age, sex and symptoms), the results were analysed through Bayes’ theorem of conditional probability. The studied described how the probability of CAD can be determined in a patient before testing from information readily obtained from clinical evaluation.

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Effect due to factor in study?

Yes

Consistency of results with other studies?

Consistent

Directly applicable to guideline population?

Patients had chest pain

Internal Validity

Well covered

Diamond GA; Forrester JS;

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

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

Study Type Cohort

Funding Not reported

Number of participant

4952 had coronary angiography, 23,996 autopsy (autopsy patients had died from other causes e.g. trauma and non-cardiac related diseases)

Inclusion/Exclusion Criteria

Not applicable

Patient Characteristics

Not applicable

Patients were considered to have typical angina if they had substernal discomfort brought on by physical exertion and was relieved within 10 minutes through rest or nitroglycerin.

Patients were considered to have atypical angina if they had discomfort which was either not substernal or was not bought on by exertion or not relieved after 10 minutes by rest or nitroglycerin.

Patients were considered to have non-anginal discomfort if they did not have 1 or more of the above characteristics.

Recruitment

Not applicable

Setting Secondary care, USA

Interventions/ Test/ Factor being investigated

Prevalence of CAD based on age, sex and symptoms

Comparisons

Coronary angiography in symptomatic patients and autopsy

15 May 2009 Page 123 of 196
Prevalence of CAD based on age, sex and symptoms

The study reviewed the literature to estimate the pre-test likelihood of disease (defined by age, sex and symptoms), the results were analysed through Bayes' theorem of conditional probability. The study described how the probability of CAD can be determined in a patient before testing from information readily obtained from clinical evaluation. The study showed that combining data of the estimate of disease likelihood when the patient's age and sex are known and a second estimate when the presence or absence of symptoms are known. The pre-test likelihood of disease for any patients based on any combination of age, sex and symptoms can be determined by conditional-probability analysis. The results of this analysis can be seen in table 3 which shows the results of all combinations of age, sex and symptoms, which shows a wide range of pre-test likelihoods. See narrative for question 26; Table 4c: Diamond and Forrester, 1979

Table 4a shows the prevalence of CAD confirmed by coronary angiography in patients described as having "typical angina", "atypical angina" and "nonanginal chest pain" from 4952 patients. From the table it can be seen that the prevalence of disease in persons with typical angina is about 90%, where as atypical angina shows a 50% prevalence (P<0.001) and nonanginal chest pain a 16% prevalence (P<0.001). Table 4b summarises pathological data obtained from 23 996 autopsies, showing the mean prevalence of CAD to be 4.5%. The prevalence of CAD observed at autopsy is similar to that in asymptomatic patients confirmed by coronary angiography. Table 4b also shows that there are significant differences (P<0.001) in disease prevalence when patients are grouped by age and sex.

From table 4a and 4b giving data of the estimate of disease likelihood when the patient's age and sex are known and a second estimate when the presence or absence of symptoms are known. The pre-test likelihood of disease for any patients (according to any combination of age, sex and symptoms) was determined by conditional-probability analysis. The results of this analysis can be seen in table 4c which shows the results of all combinations of age, sex and symptoms, which shows a wide range of pre-test likelihoods. See narrative for question 26; Table 4c: Diamond and Forrester, 1979

Safety and adverse effects

None

Does the study answer the question?

The study reviewed the literature to estimate the pre-test likelihood of disease (defined by age, sex and symptoms), the results were analysed through Bayes' theorem of conditional probability. The study described how the probability of CAD can be determined in a patient before testing from information readily obtained from clinical evaluation. The study showed that combining data of the estimate of disease likelihood when the patient's age and sex are known and a second estimate when the presence or absence of symptoms are known. The pre-test likelihood of disease for any patients based on any combination of age, sex and symptoms can be determined by conditional-probability analysis. The results of this analysis can be seen in table 3 which shows the results of all combinations of age, sex and symptoms, which shows a wide range of pre-test likelihoods

Effect due to factor in study?

Yes

Consistency of results with other studies?

Consistent

Directly applicable to guideline population?

Patients had chest pain

Internal Validity

Well covered

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

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

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

Study Type  Cohort  Funding  Not reported

15 May 2009  Page 124 of 196
Number of participant 1097, 70% men, 30% women

Inclusion/Exclusion Criteria

Inclusion: referred for non invasive testing for suspected CAD without previous MI or coronary bypass surgery

Patient Characteristics

Mean age 56±11 years
Patients were considered to have typical angina if they had substernal discomfort brought on by physical exertion and was relieved within 10 minutes through rest or nitroglycerin.
Patients were considered to have atypical angina if they had discomfort which was either not substernal or was not bought on by exertion or not relieved after 10 minutes by rest or nitroglycerin.
Patients were considered to have non-anginal discomfort if they did not have 1 or more of the above characteristics.

Recruitment

Patients who were referred for noninvasive testing for suspected CAD at the Cedars-Sinai Medical Center Cardiac Stress Laboratories, USA, between 1st January 1979 and 15th November 1980

Setting

Secondary care, USA

Interventions/ Test Factor being investigated

Risk factors for diagnosing CAD

Comparisons

Risk factors for diagnosing CAD

Length of Study/ Follow-up

Not reported

Outcome measures studied

Diagnosis of CAD

Results

46 patients had 0 diseased vessels, 21 patients had 1 diseased vessel, 46 patients had 2 diseased vessels, 57 patients had 3 diseased vessels, and 124 patients had 1 + 2 + 3 diseased vessels

See narrative for question 26; Table 5: Diamond et al, 1983
CAD probability and angiography (diseased vessels = d.v.)

Estimates before testing
Mean probability: 0.291 d.v.=0, 0.595 d.v=1, 0.623 d.v=2, 0.660 d.v=3, 0.635 d.v.=1+2+3
Standard deviation: 0.259 d.v.=0, 0.342 d.v=1, 0.334 d.v=2, 0.327 d.v=3, 0.332 d.v.=1+2+3

Estimates before angiography
Mean probability: 0.253 d.v.=0, 0.745 d.v=1, 0.772 d.v=2, 0.843 d.v=3, 0.800 d.v.=1+2+3
Standard deviation: 0.322 d.v.=0, 0.387 d.v=1, 0.321 d.v=2, 0.284 d.v=3, 0.315 d.v.=1+2+3

All estimates
Test combinations: 500 d.v.=0, 316 d.v=1, 640 d.v=2, 724 d.v=3, 1680 d.v.=1+2+3
Mean probability: 0.304 d.v.=0, 0.557 d.v=1, 0.730 d.v=2, 0.746 d.v=3, 0.704 d.v.=1+2+3
Standard deviation: 0.321 d.v.=0, 0.377 d.v=1, 0.323 d.v=2, 0.331 d.v=3, 0.322 d.v.=1+2+3

Safety and adverse effects

None

Does the study answer the question?

The study considered the probability of CAD and the disease prevalence. This showed that there was no significant difference between the predicted probability and the probability shown on angiography if probability was based on the age and sex of the patient, within the difference symptom classes. This, the authors states, shows the importance of clinical history as a diagnostic test.

The study stated that the probability of CAD in each symptom class was consistently slightly higher in the patients with CAD compared to those without CAD, which the authors suggest shows that the Framingham risk factors were “modest discriminators
for CAD independent of symptom classification”. The data the study gained was assessed based on the age, sex, symptoms and risk factors before diagnostic testing, and based on all the data gained before catheterization and again with all the data after every test had been carried out. For each assessment the probability of disease increased in proportion to the number of diseased vessels, however there were large standard deviations.

The study showed that the mean probability for CAD increased from 30% for the patients in the normal group to 56% for the patients with 1 vessel disease, and increased to 75% for patients with 3 vessel disease. There was overlap between data sets especially for those with 2 and 3 vessel disease, which showed no significant difference. This, the study stated, led to 8% of the probability estimates for the normal patients being in excess of 90%, and for 9.7% of the probability estimates for the patients with disease shown on angiography to be 10% under. There was a 3.4% difference between predicted probability and actually probability of CAD from the estimate based on sex, age, symptoms and risk factors. The study used graphs to determine relationships between the variables and disease prevalence, and showed that the calculated probability of CAD accurately reflected the actual angiographic disease prevalence. See narrative for question 26; Figure 1: Diamond et al, 1983 and Figure 2 Diamond et al, 1983

The study also assessed the probability of CAD and extent of disease. This showed that when the patient had a probability of below ‘25% when disease was present single vessel disease was slightly more prevalent than multi-vessel disease, while above a probability of 75% multi-vessel disease predominated. At a probability of 100% multi-vessel disease accounted for 89% of all angiographic disease”. The significance of these differences varied, however it shows that it does indicate that disease probability also acted as a quantitative measure of anatomic severity.

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

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

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

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

Study Type Cohort
Number of participant 1097, 70% men, 30% women
Inclusion/Exclusion Criteria
Inclusion: referred for non invasive testing for suspected CAD without previous MI or coronary bypass surgery
Patient Characteristics Mean age 56±11 years
Patients were considered to have typical angina if they had substernal discomfort brought on by physical exertion and was relieved within 10 minutes through rest or nitroglycerin.
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Recruitment Patients who were referred for noninvasive testing for suspected CAD at the Cedars-Sinai Medical Center Cardiac Stress Laboratories, USA, between 1st January1979 and 15th November 1980

15 May 2009 Page 126 of 196
Setting
Secondary care, USA

Interventions/ Test/ Factor being investigated
Risk factors for diagnosing CAD

Comparisons
Risk factors for diagnosing CAD

Length of Study/ Follow-up
Not reported

Outcome measures studied
Diagnosis of CAD

Results

46 patients had 0 diseased vessels, 21 patients had 1 diseased vessel, 46 patients had 2 diseased vessels, 57 patients had 3 diseased vessels, and 124 patients had 1+2+3 diseased vessels

See narrative for question 27; Table 5: Diamond et al, 1983
CAD probability and angiography (diseased vessels = d.v.)

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All estimates
Test combinations: 500 d.v.=0, 316 d.v.=1, 640 d.v.=2, 724 d.v.=3, 1680 d.v.=1+2+3
Mean probability: 0.304 d.v.=0, 0.557 d.v.=1, 0.730 d.v.=2, 0.746 d.v.=3, 0.704 d.v.=1+2+3
Standard deviation: 0.321 d.v.=0, 0.377 d.v.=1, 0.323 d.v.=2, 0.331 d.v.=3, 0.322 d.v.=1+2+3

Safety and adverse effects
None

Does the study answer the question?
The study considered the probability of CAD and the disease prevalence. This showed that there was no significant difference between the predicted probability and the probability shown on angiography if probability was based on the age and sex of the patient, within the disease symptom classes. This, the authors states, shows the importance of clinical history as a diagnostic test.

The study stated that the probability of CAD in each symptom class was consistently slightly higher in the patients with CAD compared to those without CAD, which the authors suggest shows that the Framingham risk factors were “modest discriminators for CAD independent of symptom classification”. The data the study gained was assessed based on the age, sex, symptoms and risk factors before diagnostic testing, and based on all the data gained before catheterization and again with all the data after every test had been carried out. For each assessment the probability of disease increased in proportion to the number of diseased vessels, however there were large standard deviations.

The study showed that the mean probability for CAD increased from 30% for the patients in the normal group to 56% for the patients with 1 vessel disease, and increased to 75% for patients with 3 vessel disease. There was overlap between data sets especially for those with 2 and 3 vessel disease, which showed no significant difference. This, the study stated, led to 8% of the probability estimates for the normal patients being in excess of 90%, and for 9.7% of the probability estimates for the patients with disease shown on angiography to be 10% under. There was a 3.4% difference between predicted probability and actually probability of CAD from the estimate based on sex, age, symptoms and risk factors. The study used graphs to determine relationships between the variables and disease prevalence, and showed that the calculated probability of CAD accurately reflected the actual angiographic disease prevalence. See narrative for question 27; Figure 1: Diamond et al, 1983 and
The study also assessed the probability of CAD and extent of disease. This showed that when the patient had a probability of below 25% when disease was present single vessel disease was slightly more prevalent than multi-vessel disease, while above a probability of 75% multi-vessel disease predominated. At a probability of 100% multi-vessel disease accounted for 89% of all angiographic disease*. The significance of these differences varied, however it shows that it does indicate that disease probability also acted as a quantitative measure of anatomic severity.

**Effect due to factor in study?**
Yes

**Consistency of results with other studies?**
Consistent

**Directly applicable to guideline population?**
Patients had suspected CAD

**Internal Validity**
Well covered

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

Estimating the likelihood of significant coronary artery disease

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

**Study Type** Cohort

**Number of participant**
3627 in training population, 1811 in test population

**Inclusion/Exclusion Criteria**
Patients with chest pain who were referred for cardiac catheterization at the Duke University Medical Center between November 1969 and January 1982

**Patient Characteristics**
Patient characteristics which were collected were:

- History: age, sex, chest pain history (pain type, severity, frequency, nocturnal, progressive, preinfarctional), duration of CAD, previous history of MI, congestive heart failure, history of vascular disease (Progressive chest pain - the frequency, severity or duration had increased in the 6 weeks prior to catheterisation; Preinfarctional chest pain - a very unstable pain pattern that resulted in admission to the coronary care unit for evaluation of the possible MI)

- Risk factors: smoking, hyperlipidaemia, hypertension, diabetes, family history

- Physical examination: ventricular gallop, systolic blood pressure

- ECG: ST-T wave changes, electrocardiographic premature ventricular contractions, Electrocardiographic Q waves

- Chest X-Ray: cardiomegaly

**Recruitment**
Patients admitted for cardiac catheterisation between November 1969 and January 1982

**Setting**
Secondary care, USA

**Interventions/ Test/ Factor being investigated**
Chest pain diagnosis

**Comparisons**
Patient characteristics which give a probability of disease
Outcome measures studied

Results

The study had a training population of 3627 patients who were seen between 1969 and January 1979, from these patients a stepwise logistic regression analysis was used to develop a model for predicting the probability of significant CAD. A test population of 1811 patients seen between January 1969 and January 1982, in this population the model developed in the test population was used to predict the probability of CAD for each patient. The authors then tested the model in other populations (from CASS study) to estimate the prevalence of disease in subgroups of the patients in the literature (external validation).

Results from training population: See narrative for question 26; Table 6: Pryor et al, 1983
Clinically Important Characteristics and the Chi-squared:
- Pain type (typical, atypical or nonanginal): 1091
- Previous MI: 511
- Sex: 187
- Age: 119
- Smoking: 79
- Hyperlipidaemia: 26
- ST-T wave changes: 28
- Diabetes: 12

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

Poor Clinical Predictors of Significant CAD and the Chi-squared: See narrative for question 26; Table 7: Pryor et al, 1983
- Chest pain severity: 0.96
- Chest pain frequency: 8.57
- Nocturnal chest pain: 2.22
- Progressive chest pain: 2.54
- Preinfarction angina: 9.70
- Vascular disease: 0.40
- Duration of CAD: 9.16
- Congestive heart failure: 0.59
- Hypertension: 5.19
- Family history: 6.39
- Ventricular gallop: 1.06
- Cardiomegaly: 1.41
- Electrocardiographic premature ventricular contractions: 0.46

The results from the training group are shown under “Clinically Important Characteristics and the Chi-squared” in the order of their importance (chi-squared added to the model by the parameter, adjusting for the characteristics that precede it). The type of chest pain (typical, atypical or nonanginal) was the most important characteristic followed by previous MI, sex, age, smoking, hyperlipidaemia, ST-T wave changes on ECG, diabetes. The results above show the 4 significant interactions which were found.

The study also showed that in men the effect of an increasing age was more important than in women, smoking was more important for women than men, and that smoking and hyperlipidaemia were more important at younger ages. The results for the other characteristics which were found to have small or nonsignificant effects on the prevalence of disease are shown under “Poor Clinical Predictors of Significant CAD and the Chi-squared”

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

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

Safety and adverse effects

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

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

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

Effect due to factor in study?

Yes

Consistency of results with other studies?

Consistent

Directly applicable to guideline population?

Patients had chest pain

Internal Validity

Well covered

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

Estimating the likelihood of significant coronary artery disease

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

Study Type Cohort

Number of participants

3627 in training population, 1811 in test population

Inclusion/Exclusion Criteria

Patients with chest pain who were referred for cardiac catheterization at the Duke University Medical Center between November 1969 and January 1982

Patient Characteristics

Patient characteristics which were collected were:

History: age, sex, chest pain history (pain type, severity, frequency, nocturnal, progressive, preinfarctional), duration of CAD, previous history of MI, congestive heart failure, history of vascular disease (Progressive chest pain - the frequency, severity or duration had increased in the 6 weeks prior to catheterisation;
Preinfarctional chest pain - a very unstable pain pattern that resulted in admission to the coronary care unit for evaluation of the possible MI

Risk factors: smoking, hyperlipidaemia, hypertension, diabetes, family history

Physical examination: ventricular gallop, systolic blood pressure

ECG: ST-T wave changes, electrocardiographic premature ventricular contractions, Electrocardiographic Q waves
Chest X-Ray: cardiomegaly

### Recruitment

Patients admitted for cardiac catheterisation between November 1969 and January 1982

### Setting

Secondary care, USA

### Interventions/ Test/
Factor being investigated

Chest pain diagnosis

### Comparisons

Patient characteristics which give a probability of disease

### Length of Study/
Follow-up

Probability of disease

### Results

The study had a training population of 3627 patients who were seen between 1969 and January 1979, from these patients a stepwise logistic regression analysis was used to develop a model for predicting the probability of significant CAD. A test population of 1811 patients seen between January 1969 and January 1982, in this population the model developed in the test population was used to predict the probability of CAD for each patient. The authors then tested the model in other populations (from CASS study) to estimate the prevalence of disease in subgroups of the patients in the literature (external validation)

Results from training population: See narrative for question 28; Table 4: Pryor et al, 1983

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

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

Poor Clinical Predictors of Significant CAD and the Chi-squared: See narrative for question 28; Table 5: Pryor et al, 1983
- Chest pain severity: 0.96
- Chest pain frequency: 8.57
- Nocturnal chest pain: 2.22
- Progressive chest pain: 2.54
- Preinfarction angina: 9.70
- Vascular disease: 0.40
- Duration of CAD: 9.16
- Congestive heart failure: 0.59
- Hypertension: 5.19
- Family history: 6.39
- Ventricular gallop: 1.06
- Cardiomegaly: 1.41
Progressive chest pain was described as being chest pain when the frequency, severity or duration had increased in the 6... greatest difference in predicted disease compared to observed disease was seen in patients with nonanginal chest pain.

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

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

None

Electrocardiographic premature ventricular contractions: 0.46

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

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

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

None

Safety and adverse effects

Does the study answer the question?

Yes

Consistency of results with other studies?

Consistent
Directly applicable to guideline population? Patients had chest pain

Internal Validity Well covered

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

Estimating the likelihood of significant coronary artery disease

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

Study Type Cohort Funding Not reported

Number of participant 3627 in training population, 1811 in test population

Inclusion/Exclusion Criteria Patients with chest pain who were referred for cardiac catheterization at the Duke University Medical Center between November 1969 and January 1982

Patient Characteristics Patient characteristics which were collected were:
- History: age, sex, chest pain history (pain type, severity, frequency, nocturnal, progressive, preinfarctional), duration of CAD, previous history of MI, congestive heart failure, history of vascular disease (Progressive chest pain - the frequency, severity or duration had increased in the 6 weeks prior to catheterisation; Preinfarctional chest pain - a very unstable pain pattern that resulted in admission to the coronary care unit for evaluation of the possible MI)
- Risk factors: smoking, hyperlipidaemia, hypertension, diabetes, family history
- Physical examination: ventricular gallop, systolic blood pressure
- ECG: ST-T wave changes, electrocardiographic premature ventricular contractions, Electrocardiographic Q waves
- Chest X-Ray: cardiomegaly

Recruitment Patients admitted for cardiac catheterisation between 1969 and 1982

Setting Secondary care, USA

Interventions/ Test/ Factor being investigated Chest pain diagnosis

Comparisons Patient characteristics which give a probability of disease

Length of Study/ Follow-up

Outcome measures studied Probability of disease

Results The study had a training population of 3627 patients who were seen between 1969 and January 1979, from these patients a stepwise logistic regression analysis was used to develop a model for predicting the probability of significant CAD. A test population of 1811 patients seen between January 1969 and January 1982, in this population the model developed in the test population was used to predict the probability of CAD for each patient.

The authors then tested the model in other populations (from CASS study) to estimate the prevalence of disease in subgroups of the patients in the literature (external validation)

Results from training population: See narrative for question 27; Table 6: Pryor et al, 1983

Clinically Important Characteristics and the Chi-squared:
Pain type (typical, atypical or nonanginal): 1091
Previous MI: 511
Sex: 187
Age: 119
The results from the training population showed the type of chest pain (typical, atypical or nonanginal) was the most important characteristic followed by previous MI, sex, age, smoking, hyperlipidaemia, ST-T wave changes on ECG, diabetes. The results above show the 4 significant interactions which were found. The study also showed that in men the effect of an increasing age was more important than in women, smoking was more important for women than men, and that smoking and hyperlipidaemia were more important at younger ages. The results for the other characteristics which were found to have small or nonsignificant effects on the prevalence of disease are shown under "Poor Clinical Predictors of Significant CAD and the Chi-squared".

The authors then validated the model in the test population which showed that the predicted probability of disease is nearly identical to the observed prevalence. This was with the exception of the group with predicted estimates of 0.475 to 0.525 (this group 6 out of 34 patients, with significant disease). The median prediction for patients with disease was 94% compared with a median prediction of 33% for patients without disease. A predicted probability of significant disease > 0.83 was found in 75% of patients with disease and in less than 10% of patients with disease. A probability of significant disease < 0.33 was found in nearly 50% of patients without disease and in less than 5% of patients with disease.

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

Safety and adverse effects

None

Does the study answer the question?

The results from the training population showed the type of chest pain (typical, atypical or nonanginal) was the most important characteristic followed by previous MI, sex, age, smoking, hyperlipidaemia, ST-T wave changes on ECG, diabetes. The study also showed that in men the effect of an increasing age was more important than in women, smoking was more important for women than men, and that smoking and hyperlipidaemia were more important at younger ages. The study also found some characteristics to have small or nonsignificant effects on the prevalence of disease.
The authors then validated the model in the test population which showed that the predicted probability of disease is nearly identical to the observed prevalence. When comparing the model to an external population the study showed that the predicted estimates from the model were nearly equal to the observed prevalence of disease. The predicted estimates from the model of the probability of significant disease were nearly identical to the observed prevalence for subgroups based on “age, sex and history of MI” or “age, sex and pain type”. However the greatest difference in predicted disease compared to observed disease was seen in patients with nonanginal chest pain.

| Effect due to factor in study? | Yes |
| Consistency of results with other studies? | Consistent |
| Directly applicable to guideline population? | Patients had chest pain |
| Internal Validity | Well covered |
Value of the history and physical in identifying patients at increased risk for coronary artery disease

**Grading:** 2+

Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

**Study Type**  
Cohort

**Number of participants**  
1030 patients, 168 had cardiac catheterization

**Inclusion/Exclusion Criteria**

**Inclusion:** Symptomatic patients, referred for non-invasive testing for suspected coronary artery disease

**Exclusion:** previous cardiac catheterization

**Patient Characteristics**

The mean age was 55, 37% were female, the mean pain frequency was 2 episodes a week, the mean durations of CAD symptoms was 12 months, 28% had typical angina symptoms, 52% atypical angina symptoms, 20% nonanginal pain, 18% progressive angina, 22% nocturnal angina, 44% smoked, 41% had a history of hypertension, 10% had diabetes, 11% had hyperlipidemia, 35% had ST-T wave changes on ECG, 18% had a history of MI, 8% had Q waves on ECG, 14% had a history of congestive heart failure, 0% had class IV congestive heart failure, 1% had ventricular gallop, 3% had peripheral vascular disease, 3% had cerebral vascular disease.

Of the patients who went on to have a cardiac catheterization the mean age was 56, 31% were female, the mean pain frequency was 2 episodes a week, the mean durations of CAD symptoms was 7 months, 49% had typical angina symptoms, 47% atypical angina symptoms, 4% nonanginal pain, 24% progressive angina, 24% nocturnal angina, 53% smoked, 42% had a history of hypertension, 10% had diabetes, 13% had hyperlipidemia, 42% had ST-T wave changes on ECG, 33% had a history of MI, 11% had Q waves on ECG, 11% had a history of congestive heart failure, 0% had class IV congestive heart failure, 1% had ventricular gallop, 4% had peripheral vascular disease, 2% had cerebral vascular disease.

It can therefore be seen that those having a cardiac catheterization were more likely to be male, smoke, have a history of MI, have ST-T wave changes on ECG and to be suffering typical or progressive angina.

**Recruitment**

Patients were referred for non-invasive testing for suspected coronary artery disease

**Setting**

Duke University Medical Centre USA

**Interventions/ Test/ Factor being investigated**

Physicians initial evaluation of patients with suspected CAD predicts coronary anatomy

**Comparisons**

The presence of significant coronary disease defined as any disease, severe disease, left main disease

**Length of Study/ Follow-up**

90 days

**Outcome measures studied**

Effectiveness of chest pain score to predict coronary artery disease

**Results**

The three diagnostic outcomes were; the presence of significant coronary artery disease defined as ‘any disease’ (≥ 75% luminal diameter narrowing of at least one major coronary artery), presence of severe coronary artery disease defined as ‘severe disease’ (significant obstruction of all 3 main coronary arteries or the left main coronary artery) and the presence of significant left main artery obstruction defined as ‘left main disease’ (168 patients referred for cardiac catheterization). The

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Pryor DB; Shaw L; McCants CB; Lee KL; Mark DB; Harrell FE; Muhlbaiyer LH; Califf RM;
In the multivariable regression model used, the following variables were significant predictors for any disease; age, gender, chest pain (type), diabetes, smoking, hyperlipidaemia, previous history of myocardial infarction, and significant Q waves and ST-T wave changes. For severe disease, the following variables were significant predictors; age, gender, chest pain (type, frequency, course, nocturnal, length of time present), diabetes, smoking, hyperlipidaemia, hypertension, peripheral or cerebral artery disease, carotid bruit, previous history of myocardial infarction, and significant Q waves and ST-T wave changes. For left main disease, the following variables were significant predictors; age, gender, chest pain (type), diabetes, peripheral or cerebral artery disease and carotid bruit. For survival at 3 years the following variables were significant predictors; age, gender, chest pain (frequency, course, nocturnal), peripheral or cerebral artery disease, carotid bruit, ventricular gallop, previous history of myocardial infarction, significant Q waves and ST-T wave changes, conduction abnormalities, premature ventricular contractions and cardiomegaly. The likelihood of any disease, severe coronary disease, left main disease and survival was predicted from the initial history, physical examination, electrocardiogram and chest X ray (these tests were defined as the ‘initial evaluation’). The models which were used were based on mathematical models in a previous study (Pryor, 1983 – see extraction).

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

Safety and adverse effects

None reported

Does the study answer the question?

Yes

Effect due to factor in study?

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

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

Directly applicable to guideline population?  Correct population

Internal Validity  Well covered

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

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

Ref ID 1751  Annals of internal medicine  pp. 81 to 90  1993

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

Number of participants 1030 patients, 168 had cardiac catheterization

Inclusion/Exclusion Criteria

Inclusion: Symptomatic patients, referred for non-invasive testing for suspected coronary artery disease

Exclusion: previous cardiac catheterization

Patient Characteristics

The mean age was 55, 37% were female, the mean pain frequency was 2 episodes a week, the mean durations of CAD symptoms was 12 months, 28% had typical angina symptoms, 52% atypical angina symptoms, 20% nonanginal pain, 18% progressive angina, 22% nocturnal angina, 44% smoked, 41% had a history of hypertension, 10% had diabetes, 11% had hyperlipidemia, 35% had ST-T wave changes on ECG, 18% had a history of MI, 8% had Q waves on ECG, 14% had a history of congestive heart failure, 0% had class IV congestive heart failure, 1% had ventricular gallop, 3% had peripheral vascular disease, 3% had cerebral vascular disease

Of the patients who went on to have a cardiac catheterization the mean age was 56, 31% were female, the mean pain frequency was 2 episodes a week, the mean durations of CAD symptoms was 7 months, 49% had typical angina symptoms, 47% atypical angina symptoms, 4% nonanginal pain, 24% progressive angina, 24% nocturnal angina, 53% smoked, 42% had a history of hypertension, 10% had diabetes, 13% had hyperlipidemia, 42% had ST-T wave changes on ECG, 33% had a history of MI, 11% had Q waves on ECG, 11% had a history of congestive heart failure, 0% had class IV congestive heart failure, 1% had ventricular gallop, 4% had peripheral vascular disease, 2% had cerebral vascular disease.

It can therefore be seen that those having a cardiac catheterization were more likely to be male, smoke, have a history of MI, have ST-T wave changes on ECG and to be suffering typical or progressive angina

Recruitment

Patients were referred for non-invasive testing for suspected coronary artery disease

Setting

Duke University Medical Centre USA

Interventions/Test/Factor being investigated

Physicians initial evaluation of patients with suspected CAD predicts coronary anatomy

Comparisons

The presence of significant coronary disease defined as any disease, severe disease, left main disease

Length of Study/Follow-up

90 days

Outcome measures studied

Effectiveness of chest pain score to predict coronary artery disease

15 May 2009  Page 138 of 196
In the multivariable regression model used, the following variables were significant predictors for any disease; age, gender, chest pain (type), diabetes, smoking, hyperlipidaemia, previous history of myocardial infarction, and significant Q waves and ST-T wave changes. For severe disease, the following variables were significant predictors; age, gender, chest pain (type, frequency, course, nocturnal, length of time present), diabetes, smoking, hyperlipidaemia, hypertension, peripheral or cerebral artery disease, carotid bruit, previous history of myocardial infarction, and significant Q waves and ST-T wave changes. For left main disease, the following variables were significant predictors; age, gender, chest pain (type), diabetes, peripheral or cerebral artery disease and carotid bruit. For survival at 3 years the following variables were significant predictors; age, gender, chest pain (frequency, course, nocturnal), peripheral or cerebral artery disease, carotid bruit, ventricular gallop, previous history of myocardial infarction, significant Q waves and ST-T wave changes, conduction abnormalities, premature ventricular contractions and cardiomegaly. The likelihood of any disease, severe coronary disease, left main disease and survival was predicted from the initial history, physical examination, electrocardiogram and chest X ray (these tests were defined as the ‘initial evaluation’). The models which were used were based on mathematical models in a previous study (Pryor, 1983 – see extraction).

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

Safety and adverse effects

None reported

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

Predicted coronary artery endpoints and survival based on the initial evaluation closely corresponded to actual findings. Predictions using the initial evaluation were then compared with predictions based on the treadmill exercise test. The initial evaluation was slightly better at distinguishing patients with and without coronary artery disease compared with the treadmill exercise test. The initial evaluation and the treadmill exercise test had similar discriminatory performances for patients with and without severe disease and risk of death at 3 years, while for left main disease, while the treadmill exercise test was slightly better for identify patients with left main disease. The models which were used were based on mathematical models in a previous study (Pryor, 1983 – see extraction).

During the study a chest X-ray was also performed, the results did not help in predicting coronary disease, however they could be used to predict survival.
Effect due to factor in study? Yes
Consistency of results with other studies? Consistent
Directly applicable to guideline population? Correct population
Internal Validity Well covered

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

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

Number of participant 1074 patients
Inclusion/Exclusion Criteria Inclusion: had at least 2 episodes of chest pain that led to the index visit. Exclusion: patients whose index visit led to a diagnosis of acute MI were excluded

Patient Characteristics
Recruitment Patients admitted to Stanford University Medical Centre, or seen at Palo Alto VA Medical Center and Kaiser-Permanente Medical Center, Santa Medical Centre, USA
Setting Primary and Secondary care USA
Interventions/ Test/ Factor being investigated Diagnosing coronary artery disease
Comparisons Age, men, pain brought on by exertion, having to stop all activities when pain occurs, history of MI, pain relieved within 3 minutes of taking nitroglycerin, and ≥ 20 pack years of smoking
Length of Study/ Follow-up Median follow up 11 months
Outcome measures studied Effectiveness of chest pain score to predict coronary artery disease

Results Seven clinical characteristics were identified as independent predictors of significant coronary stenosis; age > 60 years, pain brought on by exertion, patient having to stop all activities when pain occurs, history of myocardial infarction, pain relieved within 3 minutes of taking nitroglycerin, at least 20 pack years of smoking, and male gender. The following were not independent predictors of disease status, location and radiation of pain, character of pain, history of hypertension, history of hypercholesterolaemia, history of angina pectoris, pain worsened by cough, deep breathing, movement of torso, or movement of arm. The chest pain score was used to test the probability of coronary artery disease (CAD) in patients from two primary care practices (997 patients) and one angiography referral practice (166 patients).

Distribution of patients among Chest Pain Score Subgroups: See narrative for
question 27; Table 9: Sox et al, 1990
1980 Arteriography Training Set:
Score 0-4: 1 had significant CAD, 9 had insignificant CAD and the prevalence of CAD was 0.10
Score 5-9: 13 had significant CAD, 20 had insignificant CAD and the prevalence of CAD was 0.39
Score 10-14: 33 had significant CAD, 16 had insignificant CAD and the prevalence of CAD was 0.67
Score 15-19: 77 had significant CAD, 8 had insignificant CAD and the prevalence of CAD was 0.91
Score 20-25: 34 had significant CAD, 0 had insignificant CAD and the prevalence of CAD was 1.00
The total number of patients was: 158 with significant CAD, 53 had insignificant CAD and the prevalence of CAD was 0.76

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

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

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

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

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

The authors concluded that health care professionals should take in to account the
Safety and adverse effects

The chest pain score was used to test the probability of coronary artery disease in patients from two primary care practices (997 patients) and one angiography referral practice (166 patients). Although the patients in the primary and secondary settings had similar chest pain scores derived from the clinical history, the prevalence of coronary artery disease in the primary care patients was lower than the angiography patients across the first four score bands compared with the angiography patients, while the prevalence at the highest score band was similar in both the primary and secondary settings. The authors concluded that health care professionals should take into account the clinical setting when using the patient's history to estimate the probability of disease.

Does the study answer the question?

Yes

Effect due to factor in study?

Consistent

Consistency of results with other studies?

Correct population

Directly applicable to guideline population?

Well covered

Internal Validity

Safety and adverse effects

None reported

Does the study answer the question?

Yes

Effect due to factor in study?

Consistent

Consistency of results with other studies?

Correct population

Directly applicable to guideline population?

Well covered

Internal Validity

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

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

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

Study Type Cohort

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

Number of participant 1074 patients

Inclusion/Exclusion Criteria Inclusion: had at least 2 episodes of chest pain that led to the index visit. Exclusion: patients whose index visit led to a diagnosis of acute MI were excluded

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Setting Primary and Secondary care USA

Interventions/ Test/Factor being investigated Diagnosing coronary artery disease

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Seven clinical characteristics were identified as independent predictors of significant coronary stenosis; age > 60 years, pain brought on by exertion, patient having to stop all activities when pain occurs, history of myocardial infarction, pain relieved within 3 minutes of taking nitroglycerin, at least 20 pack years of smoking, and male gender. The following were not independent predictors of disease status: location and radiation of pain, character of pain, history of hypertension, history of hypercholesterolaemia, history of angina pectoris, pain worsened by cough, deep breathing, movement of torso, or movement of arm. The chest pain score was used to test the probability of coronary artery disease (CAD) in patients from two primary care practices (997 patients) and one angiography referral practice (166 patients).

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

Safety and adverse effects
None reported

Does the study answer the question?
The chest pain score was used to test the probability of coronary artery disease in patients from two primary care practices (997 patients) and one angiography referral practice (166 patients). Although the patients in the primary and secondary settings had similar chest pain scores derived from the clinical history, the prevalence of coronary artery disease in the primary care patients was lower than the angiography patients across the first four scores bands compared with the angiography patients, while the prevalence at the highest score band was similar in both the primary and secondary settings. The authors concluded that health care professionals should take in to account the clinical setting when using the patient’s history to estimate the probability of disease

Effect due to factor in study? Yes

Consistency of results with other studies? Consistent

Directly applicable to guideline population? Correct population

Internal Validity
Well covered

Wu EB; Hodson F; Chambers JB;

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

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

Study Type Cohort

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

Number of participant
404 patients recruited from 363 consecutive patients seen as out-patients, and 829 consecutive patients undergoing day-case coronary angiography. 155 of the 404 had an exercise test

Inclusion/Exclusion Criteria
Inclusion: chest pain for > 1 month without a previous history of MI, coronary angiography, angioplasty or coronary artery bypass grafting
Exclusion: ECG showed pathological Q waves or regional wall motion abnormalities on echocardiogram

Patient Characteristics
The mean age was 60.6±9.5 years. 66% (268) were males, the mean age for males 60.5±9.1 years; 34% (137) were females, the mean ages for females was 60.8±10.2 years. Of all the patients 60% (244) had significant coronary artery disease; 40% (161) had normal coronary anatomy

Recruitment
Patients who met criteria recruited from out patients at Cardiothoracic Centre, Guy's and St Thomas' Hospital, London, UK

15 May 2009  Page 144 of 196
Diagnosing chest pain

The chest pain score was based on: description of pain, clinical history, medication, clinical examination, stigmata of risk, resting ECG.

Multivariant Poisson regression analysis showed that gender (P < 0.001), age (P < 0.001), relief with rest (P=0.046), dizziness (P=0.030), smoking (P=0.006), hypertension (P=0.016), hypercholesterolemia (P=0.214), diabetes (P=0.016) and chest pain score (P = 0.009) were independently differentiated those patients with and without CAD. A secondary analysis was conducted to relate the chest pain score to the Framingham and Duke Scores. The Duke Score is a weighted index based on ST-segment deviation, treadmill time and exercised-induced angina (Duke Treadmill Score = Exercise time – [5xSTdeviation] – [4xTreadmill angina]). The chest pain score was found to have a sensitivity of 91.4% and a specificity of 28%, compared to the Duke score’s sensitivity of 82.4% and specificity of 31%. The study found that the combination of the chest pain score with Framingham and the Duke score had additive predictive value for risk of coronary artery disease.

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Safety and adverse effects

None reported

Does the study answer the question?

Yes

Effect due to factor in study?

Yes

Setting

Guy's and St Thomas' Hospital, London, UK

Interventions/ Test/ Factor being investigated

Diagnosing chest pain

Comparisons

The chest pain score was based on: description of pain, clinical history, medication, clinical examination, stigmata of risk, resting ECG.

Length of Study/ Follow-up

Not reported

Outcome measures studied

Diagnosis of coronary artery disease, or exclusion of diagnosis of coronary artery disease

Results

The chest pain score was based on the following: localisation of pain, radiation, quality of pain, duration, length of pain episode, frequency, associated features (breathlessness, digital paraesthesiae, palpation, light-headedness), precipitation (exercise, rest, any time, neck or back movement, carrying, swallowing, lying flat/stooping, emotional stress, particular situations), exacerbating / relieving factors (inspiration, GNT, genuine relief < 5 minutes) relief with (milk/antacids, belching, local massage rest). A medical history was also taken of: hypertension, hypercholesterolemia, diabetes, smoking and number of cigarettes per day, previous MI, alcohol intake per week, medication being used (aspirin, statins, beta blockers, calcium antagonists, nitrates, heart, the patients weight, height, heart rhythm, systolic, diastolic, heart rate, apex position and character, intercostal space, heart murmurs, heart sounds stigmata of risk (arcus, xanthelasmas, xanthomata, ear lobe crease) and a resting ECG. This chest pain score was based on a modification of the Master Questionnaire with 3 additional questions to define the exercise score, the rest and duration score.

1) if you go up a hill on 10 separate occasions how many do you experience chest pain; 2) if you have chest pain 10 times in a row how many happen when you are sitting or resting; 3) how long does the pain last for. For question 1 10/10 was described as “typical” and 1-9/10 was “atypical”; for question 2 a rest index of 0 or 1 was “typical” and 2 or more was “atypical”; for question 3 pain lasting less than 5 minutes was “typical” and pain last more than 5 minutes was “atypical”.
### Consistency of results with other studies?
Consistent

### Directly applicable to guideline population?
Correct population

### Internal Validity
Well covered

Wu EB; Hodson F; Chambers JB;

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

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

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15 May 2009 Page 146 of 196
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Safety and adverse effects
None reported

Does the study answer the question?
Yes

Consistency of results with other studies?
Consistent

Directly applicable to guideline population?
Correct population

Internal Validity
Well covered

The mean age was 60.6±9.5 years. 66% (268) were males, the mean age for males 60.5±9.1 years; 34% (137) were females, the mean ages for females was 60.8±10.2 years. Of all the patients 60% (244) had significant coronary artery disease; 40% (161) had normal coronary anatomy.
Diagnosing chest pain

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Multivariate Poisson Regression Analysis, (see narrative for question 28; Table 6: Wu et al, 2005) showed that gender (P < 0.001), age (P < 0.001), relief with rest (P=0.046), dizziness (P=0.030), smoking (P=0.006), hypertension (P=0.016), hypercholesterolemia (P=0.214), diabetes (P=0.016) and chest pain score (P = 0.009) were independently differentiated those patients with and without CAD. A secondary analysis was conducted to relate the chest pain score to the Framingham and Duke Scores. The Duke Score is a weighted index based on ST-segment deviation, treadmill time and exercised-induced angina (Duke Treadmill Score = Exercise time – [5xSTdeviation] – [4xtreadmill angina]). The chest pain score was found to have a sensitivity of 91.4% and a specificity of 28%, compared to the Duke score’s sensitivity of 82.4% and specificity of 31%. The study found that the combination of the chest pain score with Framingham and the Duke score had additive predictive value for risk of coronary artery disease.

Safety and adverse effects

None reported

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Effect due to factor in study?

Yes
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### Grading: 2-

Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal*

---

**Cook DG; Shaper AG;**

Breathlessness, angina pectoris and coronary artery disease

**Ref ID 10282**

The American journal of cardiology 1989 pg 921 to 924

**Study Type**

Cohort

**Funding**

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

**Number of participant**

7735 men

**Inclusion/Exclusion Criteria**

Random selection of men from different GP practices, patients were excluded if they had severe mental or physical disability

**Patient Characteristics**

Not reported

**Recruitment**

Random selection of men from different GP practices, patients were excluded if they had severe mental or physical disability

**Setting**

Primary care, UK

**Interventions/Test/Factor being investigated**

Breathlessness affecting Angina

**Comparisons**

Breathlessness and other risk factors

**Length of Study/Follow-up**

5 years

**Outcome measures studied**

Prevalence of Angina after 5 years

**Results**

See methodology at start of "results summary" below

See narrative for question 26; Table 9: Cook and Shaper, 2004

Age-standardised prevalence rates of CAD by breathlessness grade:

- **None:** 6394 men, 3.5% recall, 6.5% ECG, 7% possible MI, 4.4% angina
- **Mild:** 697 men, 8.7% recall, 9.1% ECG, 12.6% possible MI, 15.5% angina
- **Moderate:** 358 men, 17.7% recall, 14.6% ECG, 21.6% possible MI, 28.8% angina
- **Severe:** 273 men, 27.6% recall, 18.5% ECG, 33.3% possible MI, 40.9% angina

All: 7722 men, 5.5% recall, 7.6% ECG, 9.1% possible MI, 7.9% angina

See narrative for question 26; Table 10: Cook and Shaper, 2004

Prevalence of angina by breathlessness grade:

- **None:** 89% none, 7% mild, 3% moderate, 1% severe
- **Nonexertional pain:** 79% none, 11% mild, 5% moderate, 4% severe
- **Possible angina**
  - **Grade 1:** 51% none, 18% mild, 16% moderate, 15% severe
  - **Grade 2:** 31% none, 9% mild, 17% moderate, 43% severe
- **Definite angina**
  - **Grade 1:** 45% none, 22% mild, 19% moderate, 14% severe

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

The study applied logistic models to find the age standardised prevalence and incidence rates of angina with age being the continuous variable. The study considered the relationship between breathlessness and chest pain, with the result of men with breathlessness being more likely to have angina than those with chest pain or with non-exertional chest pain. Breathlessness was also more common in those with grade 2 angina than those with grade 1 angina (however the study states that grade 1 angina only had 95 men and was too small to be used in evaluation).

The study also considered the effect of smoking, which showed that smoking was not strongly related to breathlessness in men, with the rate of angina increasing dependent upon the breathlessness grade but not with smokers. This can be seen as men who had smoked had only a 39% higher rate of angina compared to those who

Safety and adverse effects

See narrative for question 26; Table 12: Cook and Shaper, 2004
Age-standardised prevalence rate of angina in % by breathlessness grade and smoking:
None: 4.5% never smoked, 4.5% ex-smoker, 4.3% current smoker
Mild: 18.5% never smoked, 18.2% ex-smoker, 12.6% current smoker
Moderate: 25.7% never smoked, 26.7% ex-smoker, 30% current smoker
Severe: 25.5% never smoked, 36.5% ex-smoker, 45.9% current smoker
All: 6.2% never smoked, 7.9% ex-smoker, 8.6% current smoker

See narrative for question 26; Table 13: Cook and Shaper, 2004
Age-standardised prevalence rate of angina in % 5 years after initial screening:
None: 5.8% no angina, 47.1% angina
Mild: 13% no angina, 44.9% angina
Moderate: 24.6% no angina, 58.6% angina
Severe: 28.2% no angina, 74.4% angina

See narrative for question 26; Table 14: Cook and Shaper, 2004
Relation of breathlessness grade at screening to outcome at 5 years in men with no evidence of CAD:
None: 5228 men, 91.9% alive with no CAD, 4% alive with angina, 1.6% nonfatal MI, 0.9% dead from MI, 1.6% dead from non CAD cause
Mild: 471 men, 82.6% alive with no CAD, 10% alive with angina, 2.3% nonfatal MI, 0.8% dead from MI, 4.3% dead from non CAD cause
Moderate: 177 men, 72.7% alive with no CAD, 20.9% alive with angina, 2.1% nonfatal MI, 0.9% dead from MI, 3.4% dead from non CAD cause
Severe: 100 men, 62.8% alive with no CAD, 25.4% alive with angina, 2.7% nonfatal MI, 2.4% dead from MI, 6.7% dead from non CAD cause

Does the study answer the question?

See narrative for question 26; Table 11: Cook and Shaper, 2004
Mean levels of risk factors for CAD by breathlessness grade:
None: 49.9 years old, 39% smokers, 25.4 kg/m2 BMI, 144.9 mmHg systolic blood pressure, 6.30 mmol/l serum total cholesterol
Mild: 51.1 years old, 53% smokers, 26.1 kg/m2 BMI, 146.4 mmHg systolic blood pressure, 6.27 mmol/l serum total cholesterol
Moderate: 52.6 years old, 53% smokers, 26.2 kg/m2 BMI, 145.4 mmHg systolic blood pressure, 6.31 mmol/l serum total cholesterol
Severe: 53.5 years old, 52% smokers, 25.7 kg/m2 BMI, 143.4 mmHg systolic blood pressure, 6.24 mmol/l serum total cholesterol

Grade 2: 30% none, 2% mild, 20% moderate, 48% severe
had never smoked. The authors concluded that smoking was not an important risk factor for angina. However breathlessness was strongly related to angina (men with grade 2 or 3 breathlessness were 5 times as likely to develop angina after 5 years as those with graded 0 or 1). There was also a strong relationship between breathlessness and the presence of signs and symptoms of CAD.

Effect due to factor in study? Yes
Consistency of results with other studies? Yes

Directly applicable to guideline population? Mixed population, selected from GP practices
Internal Validity Well covered
Question: Are the symptoms and description of the symptoms different in women presenting with stable chest pain of suspected cardiac origin compared with men.
Grading: 2++ High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

Diamond GA; Forrester JS;

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

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

Study Type Cohort Funding Not reported.

Number of participant Two separate cohorts assessed: 4952 patients referred for coronary angiography, 23 996 autopsies

Inclusion/Exclusion Criteria Not applicable

Patient Characteristics

Suspected stable angina in 1 cohort (patients referred for angiogram)
Patients were considered to have typical angina if they had substernal discomfort brought on by physical exertion and was relieved within 10 minutes through rest or nitroglycerin.
Patients were considered to have atypical angina if they had discomfort which was either not substernal or was not bought on by exertion or not relieved after 10 minutes by rest or nitroglycerin. Patients were considered to have non-anginal discomfort if they did not have 1 or more of the above characteristics.

Autopsy: general population

Recruitment Patients referred for angiography

Setting Secondary care, USA

Interventions/ Test/ Factor being investigated Prevalence of coronary artery disease based on age, sex and symptoms.

Comparisons Coronary angiography in 1 cohort, evidence of stenosis in 2 cohort at autopsy.

Length of Study/ Follow-up Not applicable

Outcome measures studied Prevalence of coronary artery disease based on age, sex and symptoms.

Results

In 4953 patients with stable chest pain referred for angiogram; the prevalence of disease in patients with typical angina symptoms was about 90%, whereas for atypical angina patients was a 50% prevalence (P < 0.001) and non-cardiac chest pain patients was 16% (P < 0.001). The prevalence of CAD observed at autopsy is similar to that in asymptomatic patients confirmed by coronary angiography.

Significant differences in disease prevalence occurred when patients were classified according to age and sex. For women the differences range from 0.3% for women aged 30 years to 39 years of age, to 7% for women aged 60 years to 69 years. Women in all age ranges had a lower prevalence compared with the respective age ranges in men. The pre-test likelihood of disease for any patients (according to any combination of age, sex and symptoms) was determined by conditional-probability analysis. There are a wide range of pre-test likelihoods according to sex, gender and symptoms. For example a women with atypical symptoms and aged 35% has a pre-test likelihoods of 4% compared with 92% for a man aged 55 years with typical symptoms.

The authors noted that the approach used in the study was a mathematical formalisation of the intuition of the physicians reviewing the literature, or the use of
past experience to assess a patients’ pre-test likelihoods. Both of these approaches relied upon the use of data from specific populations, but that they do provide reliable estimates of the probability of coronary artery disease based on the patients age, symptoms and gender.

Safety and adverse effects
Not reported

Does the study answer the question?
Yes. The study reviewed the literature to estimate the pre-test likelihood of disease (defined by age, sex and symptoms), and the results were analysed through Bayes’ theorem of conditional probability. The study described how the probability of CAD can be determined in a patient before testing from information readily obtained from clinical evaluation. The study showed that combining data of the estimate of disease likelihood when the patient’s age and sex are known and a second estimate when the presence or absence of symptoms are known provides an estimate of the pre-test likelihood of disease for any patients based on any combination of age, sex and symptoms can be determined by conditional-probability analysis. For example, the likelihood of a woman having CAD at age ranges less than 59 years and with typical angina symptoms will be lower than a man with in the comparable age ranges.

Effect due to factor in study?
Yes

Consistency of results with other studies?
Consistent

Directly applicable to guideline population?
Patients in cohort used to develop theoretical pre-test likelihoods had stable chest pain, directly applicable to the guideline.

Internal Validity
Well covered

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

Presentation of stable angina pectoris among women and South Asian people.[see comment]2008


Study Type Cohort

Funding In part, British Heart Foundation for primary author

Number of participant Of 11,082 patients seen at the rapid chest pain access clinic the following patients were excluded; 579 previous CAD, 246 patients diagnosed with ACS on day of visit, 448 prior visit to the unit during study period, 291 no chest pain, 501 due to missing data, 83 pain not diagnosed with angina, 40 not tracked by the Office for National Statistics, 968 excluded as other ethnic background (not Caucasian or Asian). Thus of the final number of people identified (7,794), 2,676 were Caucasian women, 2,929 were Caucasian men, 980 were South Asian women, and 1,209 were South Asian men

Inclusion/Exclusion Criteria Inclusion: suspected angina, recent onset chest pain

Patient Characteristics Women South Asian median age 57.6 years (49 to 67 years), Women Caucasian median age 50.6 years (42 to 58 years) (P < 0.001), Men South Asian median age 49.8 years (41 to 69 years), Men Caucasian median age 54.7 years (45 to 65 years) (P < 0.001). South Asian versus Caucasian women more likely to have diabetes and hypertension, less likely to smoke. South Asian versus Caucasian men more likely to have hypertension, less likely to smoke.

Recruitment Consecutive recent onset chest pain from 6 rapid access chest pain clinics

Setting UK rapid access chest pain clinics
Gender and race presentation atypical versus typical pain

Comparisons

Gender and race presentation atypical versus typical pain, outcomes of death from ACS and hospital admission due to ACS (coded according to ICD-10 classification) determined up to 3 years of clinic visit.

Length of Study/Follow-up

3 years from clinic visit

Outcome measures studied

Outcomes of death from ACS and hospital admission due to ACS (coded according to ICD-10 classification)

Results

More women than men reported atypical chest pain symptoms (56.5% versus 54.5%, respectively P = 0.054). Cardiologists were more likely to describe the symptoms of women as atypical compared with men (73.3% agreement between cardiologist summary and the symptom score, kappa statistic 0.43). With respect to symptoms and diagnosis, sex did not modify the association between exercise echocardiography results and receiving a diagnosis of angina, and after excluding patients with a positive exercise test result, cardiologist and typical symptom scores both remained predictive of a diagnosis of angina. With respect to symptoms and diagnosis, using cardiologist summaries typical symptoms in women were more strongly associated with coronary death or ACS (hazard ratio 3.74, 95% CI 2.80 to 5.01) than among men (hazard ratio 1.51, 95% CI 1.16 to 1.97, P < 0.001). This finding was also true for symptom scores (women; hazard ratio 2.30, 95% CI 1.70 to 3.11, men; hazard ratio 1.23, 95% CI 0.96 to 1.57, P < 0.002). According to cardiologist summaries and symptom scores, women with typical symptoms were more likely than men to have coronary outcomes (cardiologist summaries for women hazard ratio 1.49, 95% CI 1.09 to 2.04, and symptom score for women hazard ratio 1.39, 95% CI 1.06 to 1.84).

The authors stated that compared to those with atypical chest pain, women with typical symptoms had worse clinical outcomes. More South Asians compared with Caucasians reported atypical chest pain symptoms (59.9% versus 52.5%, respectively P < 0.001), and the cardiologist described more South Asians as having atypical presentation compared with Caucasians. South Asians were also more likely to report pain that was not associated with exercise. With respect to symptoms and diagnosis, ethnicity did not modify the association between exercise echocardiography results and receiving a diagnosis of angina, and after excluding patients with a positive exercise test result, cardiologist and typical symptom scores both remained predictive of a diagnosis of angina. According to cardiologist summaries and symptom scores, South Asians with typical symptoms were as likely as Caucasians with typical symptoms to have a coronary outcome for cardiologist summaries (hazard ratio 1.27, 95% CI 0.89 to 1.81), and more likely with symptom scores (hazard ratio 1.41, 95% CI 1.04 to 1.91). Among South Asians with atypical symptoms, the symptom score was associated with coronary outcomes (unadjusted log rank test P = 0.30), although adjusted Cox regression ratios showed that atypical pain had similar prognostic value for coronary outcomes across ethnic background.

Safety and adverse effects

Not applicable

Does the study answer the question?

The authors stated that compared to those with atypical chest pain, women with typical symptoms had worse clinical outcomes, with atypical chest pain, South Asians with typical symptoms had worse clinical outcomes.

Effect due to factor in study?

Yes

Consistency of results with other studies?

Consistent

Directly applicable to guideline population?

Chest pain patients with suspected angina, directly relevant to guideline
Internal Validity

Well covered
Question: What is the utility (incremental value) and cost effectiveness of the resting ECG in evaluation of individuals with stable chest pain of suspected cardiac origin?
The paper reviewed both studies of acute patients and stable patients. The review considered patients with acute chest pain of suspected cardiac origin, ECG changes were found to be the most discriminating criteria for the diagnosis of acute MI compared with signs and symptoms and risk factors. For a normal ECG the sensitivity was 1 to 13%, specificity was 48 to 77%, LR+ 0.20 (95% CI 0.1 to 0.3) and LR- 1.4 (95% CI 1.4 to 1.6). For ST-T wave abnormalities the sensitivity was 5 to 7%, specificity was 47 to 74%, LR+ 0.20 (95% CI 0.1 to 0.6) and LR- 1.5 (95% CI 0.9 to 2.6). For ST elevation the sensitivity was 31 to 49%, specificity was 97 to 100%, LR+ 22 (95% CI 16 to 30) and LR- 0.6 (95% CI 0.6 to 0.6). For ST depression the sensitivity was 20 to 62%, specificity was 88 to 96%, LR+ 4.5 (95% CI 3.6 to 5.6) and LR- 0.8 (95% CI 0.7 to 0.9). Q wave had a sensitivity of 10 to 34% and a specificity of 96 to 100%, LR+ 22 (95% CI 7.6 to 62) and LR- 0.8 (95% CI 0.8 to 0.9). T wave inversion had a sensitivity of 9 to 39%, and a specificity of 84 to 94%, LR+ 2.2 (95% CI 1.8 to 2.6) and LR- 0.9 (95% CI 0.8 to 1.0)

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

Stable patients:
Most studies, in patients presenting with stable intermittent chest pain were then referred for coronary angiography. The majority of these studies excluded patients
with valvular heart disease or non-ischaemic cardiomyopathy. The studies used either > 50% stenosis or 70-75% stenosis off any epicardial vessel as the diagnostic standard (see narrative for question 3; Table 1: Chun and McGee, 2004 and Table 2: Chun and McGee, 2004). Patients presenting with acute MI were hospitalised for further monitoring and testing.

The review found that for diagnosing coronary artery disease the ECG gave little additional diagnostic information. A normal ECG gave a sensitivity of 23 to 33%, a specificity of 50-69%, LR+ 0.7 (95%CI 0.3 to 1.6) and a LR- 1.2 (95%CI 0.8 to 1.9). For ST-T wave abnormalities the sensitivity was 14 to 44%, specificity was 73 to 93%, LR+ 1.4 (95%CI 1.0 to 1.9) and LR- 0.9 (95% CI 0.9 to 1.0) (see narrative for question 3; Table 3: Chun and McGee, 2004).

**Effect due to factor in study?**
Yes

**Consistency of results with other studies?**
Consistent

**Directly applicable to guideline population?**
Correct population

**Internal Validity**
**Grading:** 2++  
High-quality systematic reviews of case–control or cohort studies  
High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

**Estimating the likelihood of significant coronary artery disease**

<table>
<thead>
<tr>
<th>Ref ID</th>
<th>The American journal of medicine</th>
<th>Pages: 771 to 780</th>
<th>1983</th>
</tr>
</thead>
</table>

**Study Type**  
Cohort

**Funding**  
Not reported

**Number of participants**  
3627 in training population, 1811 in test population

**Inclusion/Exclusion Criteria**  
Patients with chest pain who were referred for cardiac catheterization at the Duke University Medical Center between November 1969 and January 1982

**Patient Characteristics**  
Patient characteristics which were collected were:  
History: age, sex, chest pain history (pain type, severity, frequency, nocturnal, progressive, preinfarctional), duration of CAD, previous history of MI, congestive heart failure, history of vascular disease (Progressive chest pain - the frequency, severity or duration had increased in the 6 weeks prior to catheterisation; Preinfarctional chest pain - a very unstable pain pattern that resulted in admission to the coronary care unit for evaluation of the possible MI)  
Risk factors: smoking, hyperlipidaemia, hypertension, diabetes, family history  
Physical examination: ventricular gallop, systolic blood pressure  
ECG: ST-T wave changes, electrocardiographic premature ventricular contractions, Electrocardiographic Q waves  
Chest X-Ray: cardiomegaly

**Recruitment**  
Patients admitted for cardiac catheterisation between November 1969 and January 1982

**Setting**  
Secondary care, USA

**Interventions/ Test/ Factor being investigated**  
Chest pain diagnosis

**Comparisons**  
Patient characteristics which give a probability of disease

**Length of Study/ Follow-up**  
Outcome measures studied

**Results**  
The study had a training population of 3627 patients who were seen between 1969 and January 1979, from these patients a stepwise logistic regression analysis was used to develop a model for predicting the probability of significant CAD. A test population of 1811 patients seen between January 1969 and January 1982, in this population the model developed in the test population was used to predict the probability of CAD for each patient.  
The authors then tested the model in other populations (from CASS study) to estimate the prevalence of disease in subgroups of the patients in the literature (external validation)

Results from training population: See narrative for question 3; Table 14:Pryor et al, 1983  
Clinically Important Characteristics and the Chi-squared:  
Pain type (typical, atypical or nonanginal): 1091  
Previous MI: 511
Progressive chest pain was described as being chest pain when the frequency, severity or duration had increased in the 6 weeks prior to catheterisation. ST-T wave changes was shown to be a clinically important characteristic in predicting significant CAD, as were the type of chest pain (typical, atypical or nonanginal) was the most important characteristic followed by previous MI, sex, age, smoking, hyperlipidaemia and diabetes. Electrocardiographic premature ventricular contractions were shown to be poor predictors of significant CAD.

The authors then validated the model in the test population which showed that the predicted probability of disease is nearly identical to the observed prevalence. The authors then externally validated using the population from the CASS study. There was disagreement on patients classified as having nonanginal chest pain (where the greatest difference in predicted disease compared to observed disease was seen), but the predicted estimates from the model were nearly equal to the observed prevalence of disease.

Safety and adverse effects
None

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

The results from the training population showed the ST-T wave changes was an most important characteristic for predicting significant CAD, but electrocardiographic premature ventricular contractions were shown to be a poor predictor of significant CAD.

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

Effect due to factor in study?
Yes

Consistency of results with other studies?
Consistent

Directly applicable to guideline population?
Patients had chest pain

Internal Validity
Well covered
The mean age was 55, 37% were female, the mean pain frequency was 2 episodes a week, the mean durations of CAD symptoms was 12 months, 28% had typical angina symptoms, 52% atypical angina symptoms, 20% nonanginal pain, 18% progressive angina, 22% nocturnal angina, 44% smoked, 41% had a history of hypertension, 10% had diabetes, 11% had hyperlipidemia, 35% had ST-T wave changes on ECG, 18% had a history of MI, 8% had Q waves on ECG, 14% had a history of congestive heart failure, 0% had class IV congestive heart failure, 1% had ventricular gallop, 3% had peripheral vascular disease, 3% had cerebral vascular disease

Of the patients who went on to have a cardiac catheterization the mean age was 56, 31% were female, the mean pain frequency was 2 episodes a week, the mean durations of CAD symptoms was 7 months, 49% had typical angina symptoms, 47% atypical angina symptoms, 4% nonanginal pain, 24% progressive angina, 24% nocturnal angina, 53% smoked, 42% had a history of hypertension, 10% had diabetes, 13% had hyperlipidemia, 42% had ST-T wave changes on ECG, 33% had a history of MI, 11% had Q waves on ECG, 11% had a history of congestive heart failure, 0% had class IV congestive heart failure, 1% had ventricular gallop, 4% had peripheral vascular disease, 2% had cerebral vascular disease.

It can therefore be seen that those having a cardiac catheterization were more likely to be male, smoke, have a history of MI, have ST-T wave changes on ECG and to be suffering typical or progressive angina.

Recruitment
Patients were referred for non-invasive testing for suspected coronary artery disease

Setting
Duke University Medical Centre USA

Interventions/ Test/ Factor being investigated
Physicians initial evaluation of patients with suspected CAD predicts coronary anatomy

Comparisons
The presence of significant coronary disease defined as any disease, severe disease, left main disease

Length of Study/ Follow-up
90 days

Outcome measures studied
Effectiveness of chest pain score to predict coronary artery disease

Results
The three diagnostic outcomes were; the presence of significant coronary artery disease defined as ‘any disease’ (≥ 75% luminal diameter narrowing of at least one major coronary artery), presence of severe coronary artery disease defined as ‘severe disease’ (significant obstruction of all 3 main coronary arteries or the left main coronary artery) and the presence of significant left main artery obstruction defined as ‘left main disease’ (168 patients referred for cardiac catheterization). The prognostic outcome was survival at 3 years.

In the multivariable regression model used, the following variables were significant predictors for any disease; significant Q waves and ST-T wave changes (as well as age, gender, chest pain (type), diabetes, smoking, hyperlipidaemia and previous history of myocardial infarction). For severe disease, the following variables were
In the multivariable regression model used, the following variables were significant predictors for any disease; significant Q waves and ST-T wave changes (as well as age, gender, chest pain (type, frequency, course, nocturnal, length of time present), diabetes, smoking, hyperlipidaemia, hypertension, peripheral or cerebral artery disease, carotid bruit and previous history of myocardial infarction). For left main disease ECG changes were not significant predictors. For survival at 3 years the following variables were significant predictors; significant Q waves and ST-T wave changes, conduction abnormalities, (as well as age, gender, chest pain (frequency, course, nocturnal), peripheral or cerebral artery disease, carotid bruit, ventricular gallop, previous history of myocardial infarction, premature ventricular contractions and cardiomegaly).

The likelihood of any disease, severe coronary disease, left main disease and survival was predicted from the initial history, physical examination, electrocardiogram and chest X ray (these tests were defined as the 'initial evaluation'). The models which were used were based on mathematical models in a previous study (Pryor, 1983 – see extraction).

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

Safety and adverse effects

None reported

Does the study answer the question?

In the multivariable regression model used, the following variables were significant predictors for any disease; significant Q waves and ST-T wave changes. For severe disease, the following variables were significant predictors; significant Q waves and ST-T wave changes. For left main disease ECG results were not significant predictors. For survival at 3 years the following variables were significant predictors; significant Q waves and ST-T wave changes. The likelihood of any disease, severe coronary disease, left main disease and survival was predicted from the initial history, physical examination, electrocardiogram and chest X ray (these tests were defined as the 'initial evaluation').

Predicted coronary artery endpoints and survival based on the initial evaluation closely corresponded to actual findings. Predictions using the initial evaluation were then compared with predictions based on the treadmill exercise test. The initial evaluation was slightly better at distinguishing patients with and without coronary artery disease compared with the treadmill exercise test. The initial evaluation and the treadmill exercise test had similar discriminatory performances for patients with and without severe disease and risk of death at 3 years, while for left main disease, the treadmill exercise test was slightly better for identify patients with left main disease. The models which were used were based on mathematical models in a previous study (Pryor, 1983 – see extraction).

Effect due to factor in study?

Yes

Consistency of results with other studies?

Consistent

Directly applicable to guideline population?

Correct population

Internal Validity

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

<table>
<thead>
<tr>
<th>Ref ID</th>
<th>Annals of internal medicine</th>
<th>1993</th>
</tr>
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</table>

#### Study Type
- **Cohort**

#### Number of participant
- 1030 patients, 168 had cardiac catheterization

#### Inclusion/Exclusion Criteria
- **Inclusion:** Symptomatic patients, referred for non-invasive testing for suspected coronary artery disease
- **Exclusion:** previous cardiac catheterization

#### Patient Characteristics
- The mean age was 55, 37% were female, the mean pain frequency was 2 episodes a week, the mean durations of CAD symptoms was 12 months, 28% had typical angina symptoms, 52% atypical angina symptoms, 20% nonanginal pain, 18% progressive angina, 22% nocturnal angina, 44% smoked, 41% had a history of hypertension, 10% had diabetes, 11% had hyperlipidemia, 35% had ST-T wave changes on ECG, 18% had a history of MI, 8% had Q waves on ECG, 14% had a history of congestive heart failure, 0% had class IV congestive heart failure, 1% had ventricular gallop, 3% had peripheral vascular disease, 3% had cerebral vascular disease
- Of the patients who went on to have a cardiac catheterization the mean age was 56, 31% were female, the mean pain frequency was 2 episodes a week, the mean durations of CAD symptoms was 7 months, 49% had typical angina symptoms, 47% atypical angina symptoms, 4% nonanginal pain, 24% progressive angina, 24% nocturnal angina, 53% smoked, 42% had a history of hypertension, 10% had diabetes, 13% had hyperlipidemia, 42% had ST-T wave changes on ECG, 33% had a history of MI, 11% had Q waves on ECG, 11% had a history of congestive heart failure, 0% had class IV congestive heart failure, 1% had ventricular gallop, 4% had peripheral vascular disease, 2% had cerebral vascular disease.
- It can therefore be seen that those having a cardiac catheterization were more likely to be male, smoke, have a history of MI, have ST-T wave changes on ECG and to be suffering typical or progressive angina

#### Recruitment
- Patients were referred for non-invasive testing for suspected coronary artery disease

#### Setting
- Duke University Medical Centre USA

#### Interventions/ Test/ Factor being investigated
- Physicians initial evaluation of patients with suspected CAD predicts coronary anatomy

#### Comparisons
- The presence of significant coronary disease defined as any disease, severe disease, left main disease

#### Length of Study/ Follow-up
- 90 days

#### Outcome measures studied
- Effectiveness of chest pain score to predict coronary artery disease

#### Results
- The three diagnostic outcomes were; the presence of significant coronary artery disease defined as ‘any disease’ (≥ 75% luminal diameter narrowing of at least one major coronary artery), presence of severe coronary artery disease defined as ‘severe disease’ (significant obstruction of all 3 main coronary arteries or the left main coronary artery) and the presence of significant left main artery obstruction defined as ‘left main disease’ (168 patients referred for cardiac catheterization). The
prognostic outcome was survival at 3 years. In the multivariable regression model used, the following variables were significant predictors for any disease; age, gender, chest pain (type), diabetes, smoking, hyperlipidaemia, previous history of myocardial infarction, and significant Q waves and ST-T wave changes. For severe disease, the following variables were significant predictors; age, gender, chest pain (type, frequency, course, nocturnal, length of time present), diabetes, smoking, hyperlipidaemia, hypertension, peripheral or cerebral artery disease, carotid bruit, previous history of myocardial infarction, and significant Q waves and ST-T wave changes. For left main disease, the following variables were significant predictors; age, gender, chest pain (type), diabetes, peripheral or cerebral artery disease and carotid bruit. For survival at 3 years the following variables were significant predictors; age, gender, chest pain (frequency, course, nocturnal), peripheral or cerebral artery disease, carotid bruit, ventricular gallop, previous history of myocardial infarction, significant Q waves and ST-T wave changes, conduction abnormalities, premature ventricular contractions and cardiomegaly. The likelihood of any disease, severe coronary disease, left main disease and survival was predicted from the initial history, physical examination, electrocardiogram and chest X ray (these tests were defined as the ‘initial evaluation’). The models which were used were based on mathematical models in a previous study (Pryor, 1983 – see extraction).

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

Safety and adverse effects

None reported

Effect due to factor in study?

Yes
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<table>
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<tbody>
<tr>
<td><strong>Consistency of results with other studies?</strong></td>
<td>Consistent</td>
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<tr>
<td><strong>Directly applicable to guideline population?</strong></td>
<td>Correct population</td>
</tr>
<tr>
<td><strong>Internal Validity</strong></td>
<td>Well covered</td>
</tr>
</tbody>
</table>
Question: What is the diagnostic utility of calcium scoring for the evaluation of patients with stable chest pain of cardiac origin.
Grading: 2++  High-quality systematic reviews of case–control or cohort studies. High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal.

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

Ref ID 11854 Eur Radiol 620 to 624 1999

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

Funding  Not reported.

Study Type  Diagnostic

Number of participant

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/Test/Factor being investigated

Comparisons

Length of Study/Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

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

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

The results are directly applicable.

Internal Validity

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

15 May 2009  Page 169 of 196
Continuous probabilistic prediction of angiographically significant coronary artery disease using electron beam tomography

Ref ID: 9143 Circulation Pgs: 1791 to 1796 2002

Study Type: Diagnostic

Number of participants: 1851

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/Test/ Factor being investigated

Comparisons

Length of Study/Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

The results are directly applicable.

Internal Validity


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

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

15 May 2009 Page 170 of 196
Men had higher calcium compared with women, increasing age was associated with higher scores, and calcium scores in patients with coronary artery disease were higher than those patients without coronary artery disease. No calcium was detected in 128 (23.7%) of 540 men and in 116 (40.8%) of 284 women without significant coronary artery disease, as compared with 5 (0.7%) of 685 men and 0 of 255 women with coronary stenoses greater than or equal to 50%. Thus, exclusion of coronary calcification was associated with an extremely low probability of stenoses greater than or equal to 50% in men and women. At various score ranges. The sensitivities for calcium scores were higher than their respective specificities and this was especially marked for a score > 0 (any calcium detected) (sensitivities; 99% in men and 100% in women, specificities; 23% in men and 40% in women).

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

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

Ref ID 6184 Am J Cardiol Pages 1150 to 1152 2004

Study Type Diagnostic Funding Not reported

Number of participant

15 May 2009 Page 171 of 196
Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/Test/Factor being investigated

Comparisons

Length of Study/Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

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

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

The results are directly applicable.

Internal Validity

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

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

<table>
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Study Type Diagnostic

Number of participant

Funding Not reported.

Inclusion/Exclusion Criteria

Patient Characteristics

15 May 2009 Page 172 of 196
340 patients had mean calcium score $271 \pm 606$ (range 0 to 7002). 92 patients had score of 0 / 248 patients > 0. 162 patients (48%) no significant angiographic lesions. Mean calcium scores increased with coronary artery disease severity, and the calcium score mean differences were significant comparing patients without coronary stenosis, and patients with vessel disease, respectively (P < 0.001). Patients with > 70% stenosis and three-vessel disease had median score of 3740 (range 2635 to 4716, 3 patients). For calcium score greater or equal to 56 sensitivity 86% and specificity 85%. PPV 86% and NPV 84%. 92 patients (27%) had calcium scores of 0: 44 women and 48 men. In 44 women coronary angiography no stenosis. In 6 men (6.5%) with calcium scores of 0, coronary angiography found stenoses; single vessel disease in 3 men, 2 vessel disease in 2 men, and 3 vessel disease in 1 man.
Setting

Interventions/ Test/
Factor being investigated

Comparisons

Length of Study/
Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

41 patients 16 slice-CT and 60 patients 64-slice CT. 16-slice MSCT: coronary angiography detected obstructive coronary lesions in 18 (44%) patients, and overall calcium score sensitivity and specificity values 89% and 87%. 64-slice MSCT: coronary angiography detected obstructive coronary lesions in 32 (53%) patients, and the overall sensitivity and specificity values 91% and 96%. There was little difference in the diagnostic accuracy of 16- and 64-slice MSCT between the four Agatston groups (0 to 100, 101 to 400, > 400 and > 100) Patients with > 70% stenosis and only single vessel involvement had a median score of 482 (range 23 to 2450, 12 patients).

Effect due to factor in study?
Consistency of results with other studies?

Directly applicable to guideline population?

The results are directly applicable.

Internal Validity

15 May 2009
Grading: 2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal.

Herzog C; Britten M; Balzer JO; Mack MG; Zangos S; Ackermann H; Schaechinger V; Schaller S; Flohr T; Vogl TJ; Kitamura A; Kobayashi T; Ueda K; Okada T; Awata N; Sato S; Shimamoto T;

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

Ref ID 6464 Eur Radiol pp. 169 to 177 2004

Study Type Diagnostic

Number of participant

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

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

Effect due to factor in study?

Consistency of results with other studies?

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

Internal Validity

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

15 May 2009
Evaluation of coronary artery calcification by multi-detector row computed tomography for the detection of coronary artery stenosis in Japanese patients

Ref ID 4238 J Epidemiol 187 to 193 2005

Study Type Diagnostic Funding Not reported.

Number of participant

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

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

Effect due to factor in study?

Consistency of results with other studies?

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

Internal Validity

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

Coronary artery stenoses: detection with calcium scoring, CT angiography, and both methods combined

Ref ID 4898 Radiology 415 to 422 2005

Study Type Diagnostic Funding Departments of Cardiology and Radiology, Concord

15 May 2009 Page 176 of 196
Number of participant

50 consecutive patients. Coronary stenosis greater 50% present in 30 (60%) of 50 patients. 14 patients had single vessel disease 16 sixteen patients had multivessel disease. Sensitivity and specificity varied according to calcium score thresholds. Mean calcium scores were higher in patients with stenosis compared with patients without stenosis: 700±541 versus 99±140 (P < 0.001). Calcium score to discriminate between the presence or absence of stenosis greater for patients than for individual vessels and segments as demonstrated by ROC curve analysis (area under ROC curve 0.88, 0.84 and 0.74, respectively).

Safety and adverse effects

Does the study answer the question?
The results are directly applicable.

Effect due to factor in study?

Consistency of results with other studies?

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

Internal Validity

Raff GL;Gallagher MJ;O’Neill WW;Goldstein JA;

Diagnostic accuracy of noninvasive coronary angiography using 64-slice spiral computed tomography.

Ref ID 4496 J Am Coll Cardiol pgs. 552 to 557 2005

Study Type Diagnostic Funding Ministrelli Cardiovascular Research Fund.

Number of participant
70 consecutive patients. The mean calcium score in patients was 326±472. 35 patients: scores from 0 to 100 / 17 patients scores of 101 to 400, and 18 out of 70 had scores of 401 to 1804. When a calcium score was low (0 to 100), sensitivity, specificity, and positive and negative predictive values for the presence of significant stenosis (stenosis > 50%) were 94%, 95%, 94% and 95%. Diagnostic accuracy was also good for score 101 to 400, however, with extreme calcification the specificity and negative predictive values were reduced (both 67%).
Setting

Interventions/ Test/
Factor being
investigated

Comparisons

Length of Study/
Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

231 low to intermediate risk CAD based on calcium score calcium score patients. Obstructive CAD (greater than 50%) in 9 patients (7%) with calcium score = 0. In patients with a low calcium score (1 to 100) obstructive CAD in 18 patients. Highly significant correlation between calcium score and degree of CAD. Patients with no signs of atherosclerosis from coronary angiography (20 patients) mean total scores of 104 (range 0 to 1459).

The results are directly applicable.
Question: What is the diagnostic utility of non-invasive and invasive tests for the evaluation of patients with stable chest pain of suspected cardiac origin.
Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial. [Review] [207 refs]

Ref ID 527  Health Technol Assess  1 to 115  2007

Study Type Diagnostic

Number of participants

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

The aim of the study was to demonstrate equivalence in exercise time between those randomised to functional tests (SPECT, MRI, stress echo) compared with angiography. The clinical outcome measure was exercise time (Modified Bruce protocol) at 18 months. After initial testing, there were unequivocal results for 98% of angiography, 94% of SPECT (P = 0.05), 78% of MRI (P < 0.001) and 90% of stress echocardiography patients (P < 0.001). Twenty two percent of SPECT patients, 20% of MRI patients and 25% of stress echo patients were not subsequently referred for an angiogram. Positive functional tests were confirmed by positive angiography in 83% of SPECT patients, 89% of MRI patients and 84% of stress echo patients. Negative functional tests were performed in 31% of SPECT patients, 52% of MRI patients and 48% of stress echo patients tested. Coronary artery bypass graft surgery was performed in 10% of the angiography group, 11% in the MRI group and 13% in both the SPECT and stress echo group. Percutaneous coronary artery intervention was performed in 25% of the angiography group, 18% in the SPECT group and 23% in both the MRI and stress echo group.

At 18 months, there was no clinical difference in total exercise time comparing SPECT and stress echo with angiography. The MRI group had significantly shorter mean total exercise time compared with the angiography group (mean 35 seconds less (P < 0.05) with an upper limit of the CI 1.14 minutes less than in the angiography group). It was concluded that between 20 to 25% patients can avoid invasive testing using functional testing as a gateway to angiography without substantial effects on
outcome. MRI had the largest number of test failures and in this study had the least practical use in screening patients with suspected CAD, although it had similar outcomes to stress echo.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

The results are directly applicable to the guideline.

Internal Validity
Grading: 2++

High-quality systematic reviews of case–control or cohort studies
High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

Danias PG; Roussakis A; Ioannidis JP;

Diagnostic performance of coronary magnetic resonance angiography as compared against conventional X-ray angiography: a meta-analysis. [Review] [60 refs]

Ref ID 5534 J Am Coll Cardiol pgs. 1867 to 1876 2004

Study Type Diagnostic

Funding Not stated.

Number of participant

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

The SR examined magnetic resonance angiography diagnostic performance at the segment, vessel and patient level, and meta-analysis found that in evaluable segments of native coronary arteries, coronary magnetic resonance angiography has moderately high sensitivity for detecting significant proximal stenosis

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

The results of the SR are directly applicable to the guideline.

Internal Validity

Heijenbrok-Kal MH; Fleischmann KE; Hunink MG;

Stress echocardiography, stress single-photon-emission computed tomography and electron beam computed tomography for the assessment of coronary artery disease: a meta-analysis of diagnostic performance

15 May 2009
### Study identifies the sensitivities and specificities of imaging technologies enabling an assessment of diagnostic performance and hence provides appropriate information for the guideline.

**Study Type**  
Diagnostic

**Funding**  
Netherlands Organisation for Scientific Research (program grant 904-66-09) and grant from American Society of Echocardiology

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<th>Directly applicable to guideline population?</th>
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<tr>
<td>The results are directly applicable to the guideline.</td>
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### Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease

**Study Type**  
Diagnostic

**Funding**  
HTA NHS R&D programme.
This SR and meta-analysis aimed to assess the diagnostic value of 64-slice CT in CAD when compared to conventional CA. Methodology was clearly described. Twenty-one diagnostic studies (n=1286 patients) were included. Levels of analysis included patient (n=18), segment (n=17), left main artery (n=5), left anterior descending (LAD) overall (n=7), LAD proximal (n=5), left circumflex overall (n=7), right coronary artery overall (n=7), stents (n=6) and CABGs (n=4). The median prevalence of CAD across the 21 studies was 58%. A separate SROC curve was derived for each level of analysis e.g. one for patient-level and another for segment level. Sensitivity, specificity, PPV and NPV for patient-based evaluation were 99%, 89%, 93%, and 100%, respectively. For segment-based analysis results were 90%, 97%, 76% and 99%, respectively. The studies were heterogeneous in terms of their participants. In some studies the participants were all suspected CAD, in others they were all known CAD or a mixture of both, or with previous CABG or had LBBB.

The results of the study are broadly applicable to the guideline, although up to 75% of included studies were not on stable chest pain patients.

Mowatt G; Vale L; Brazzelli M; Hernandez R; Murray A; Scott N; Fraser C; McKenzie L; Gemmell H; Hillis G; Metcalfe M;

Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction

Ref ID: 786

Health Technol Assess

ii to 89 2004

Study Type: Diagnostic

Number of participant

Inclusion/Exclusion Criteria

Funding: HTA NHS R&D programme.
**Patient Characteristics**

**Recruitment**

**Setting**

**Interventions/ Test/ Factor being investigated**

**Comparisons**

**Length of Study/ Follow-up**

**Outcome measures studied**

**Results**

**Safety and adverse effects**

**Does the study answer the question?**

For diagnostic studies the interventions included were SPECT vs. stress ECG, with CA as the reference standard test. In situations where CA would be an inappropriate reference standard, clinical follow-up was accepted as the reference standard. For prognostic studies, strategies involving SPECT were compared with strategies that did not. These included:

- Stress ECG-SPECT-CA vs Stress ECG-CA
- Stress ECG-SPECT vs stress ECG alone
- SPECT-CA vs CA alone
- Stress ECG vs SPECT vs CA
- SPECT vs CA
- Stress ECG vs SPECT

Sensitivity: For studies excluding patients with previous MI: SPECT (n=4) median range 0.92 (0.76-0.93); Stress ECG (n=4) median range 0.66 (0.42-0.85). For studies including patients with previous MI: SPECT (n=10) median range 0.76 (0.63-0.93); Stress ECG (n=10) median range 0.63 (0.44-0.92). Due to heterogeneity among studies no weighted averages were conducted for either SPECT or stress ECG.

Specificity: For studies excluding patients with previous MI: SPECT (n=4) median range 0.74 (0.54-0.90); Stress ECG (n=4) median range 0.77 (0.58-0.88). For studies including patients with previous MI: SPECT (n=10) median range 0.65 (0.10-0.80); Stress ECG (n=10) median range 0.77 (0.41-0.80). Due to heterogeneity among studies no weighted averages were conducted for either SPECT or stress ECG.

Positive LRs: the range of positive LRs was 0.95-8.99 (median 2.33) for SPECT and 1.14-5.60 (median 2.06) for stress ECG. All positive LRs were <10 in both tests. LRs for both tests were calculated for 12 of the 16 studies. For both tests there was significant heterogeneity among positive LRs (p<0.001).

Negative LRs: Negative LRs ranged from 0.09 to 1.12 (median 0.29) for SPECT and from 0.18 to 0.91 (median 0.57) for stress ECG. Values varied considerably among studies. Two studies showed negative LR for SPECT <0.1 (0.09) and LRs for SPECT were smaller than those for stress ECG.

**Effect due to factor in study?**

**Consistency of results with other studies?**

**Directly applicable to guideline population?**

High quality SR. Heterogeneity of studies was taken into consideration in analysis. Prospective and retrospective primary studies of SPECT MPS.
Diagnostic performance of stress cardiac magnetic resonance imaging in the detection of coronary artery disease: a meta-analysis. [Review] [44 refs]

Ref ID 1118 J Am Coll Cardiol pgs. 1343 to 1353 2007

Study Type Diagnostic
Funding Not stated.

Number of participant

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question? The SR determines the diagnostic utility of cardiac magnetic resonance imaging in the detection of CAD. The SR found that the tests have good sensitivity and specificities, however, the disease prevalence in the identified is studies high, and the performance of the test may not be as sensitive or specific in lower prevalence populations.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population? The included studies were determining the performance of the test to determine CAD hence the population is directly applicable to the guideline.

Internal Validity

Vanhoenacker PK; Heijenbrok-Kal MH; Van HR; Decramer I; Van-Hoe LR; Wijns W; Hunink MM;

Diagnostic performance of multidetector CT angiography for assessment of coronary artery disease: meta-analysis

Ref ID 10274 Radiology pgs. 419 to 428 2007

15 May 2009 Page 187 of 196
This review assessed the diagnostic performance of CT angiography using 4, 16, and 64-slice detectors. Six studies of 64-slice CT were included. The study concluded that the newer generation scanners significantly reduced the proportion of non-assessable coronary artery segments. Combined with reduction of the heart rate through the use of beta-blockers, practically all coronary artery segments are assessable.

Also, as one increases the size of the unit analysed from coronary arterial segments, to vessels, and to patients, the sensitivity increase, the specificity decreases, and the overall diagnostic performance decreases.

Prevalence of CAD was relatively high in the source populations. The results of this study may therefore not be generalizable to low-prevalence populations.

The results are directly applicable to the guideline.
Grading: 2+  
Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

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Abdulla J; Abildstrom SZ; Gotzsche O; Christensen E; Kober L; Torp-Pedersen C;

64-Multislice detector computed tomography coronary angiography as potential alternative to conventional coronary angiography: A systematic review and meta-analysis

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**Funding**  
Not reported.

**Study Type**  
Diagnostic

**Number of participant**  
Type of study not specified.

**Inclusion/Exclusion Criteria**

**Patient Characteristics**

**Recruitment**

**Setting**

**Interventions/ Test/ Factor being investigated**

**Comparisons**

**Length of Study/ Follow-up**

**Outcome measures studied**

**Results**

**Safety and adverse effects**

**Does the study answer the question?**  
This meta-analyses found that there were differences in sensitivity and specificity values in per-segment vs. per-patient analysis due to calculated higher prevalence of CAD in per-patient data. Sensitivity in per-patient data was 97.5% vs. 86 in per-segment data, in analysis of native coronary arteries. And specificity was 91% vs. 96%, in per-patient and per-segment, respectively.

In general CT demonstrated high accuracy particularly by its high negative predictive values. The accuracy was highest in assessing CABG (96.5) and lowest in stented segments (92%).

**Effect due to factor in study?**

**Consistency of results with other studies?**

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

**Internal Validity**

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15 May 2009  
Page 189 of 196
The aim of the SR was to examine the diagnostic accuracy of dobutaine stress echocardiography in women. For the detection of coronary artery disease in women, dobutamine stress echocardiography has reasonable sensitivity and good specificity. Similar sensitivities and specificities were found in studies comparing diagnostic performance in men versus women. Dobutamine stress echocardiology is at least as sensitive as SPECT for the detection of coronary artery disease in women.

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<td>Funding</td>
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The study is directly applicable to the guideline.
The SR reports that there are wide variabilities in the sensitivities and the specificities in the identified 147 diagnostic studies (mean sensitivity, 68%; range, 23-100%; SD, 16%; and mean specificity, 77%; range, 17-100%; SD, 17%). These differences cannot be explained by publication year, but lower sensitivities are reported in studies with consider additional tests in conjunction with exercise ECG.

### Patient Characteristics

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<td>62.8 11.7</td>
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<td>Women</td>
<td>64.1 11.8</td>
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Gender differences in pain characteristics of chronic stable angina and perceived physical limitation in patients with coronary artery disease

### Study Type

- **Cohort**

### Number of Participant

- 89 men and 39 women. Patients ranged in age from 35 to 86 years, there were 89 men and 39 women, with a mean age of 62.8 SD 11.7 years and 64.1 SD 11.8 years, respectively (not significant)

### Inclusion/Exclusion Criteria

Patients with a history of CAD, currently stable disease and angina documented by cardiologists from 3 outpatient cardiology clinics. All patients had experienced an episode of chronic stable angina within the previous week. Patients were excluded if they had experienced acute MI, or coronary revascularisation in the previous 6 months. Patients were also exclude if they screened negative on the supplemented Rose questionnaire, or had any active exacerbation of gastrointestinal symptoms

### Patient Characteristics

- Angina patients
<table>
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<tr>
<td>Setting</td>
<td>Outpatient coronary care units</td>
</tr>
<tr>
<td>Interventions/Test/Factor being investigated</td>
<td>Descriptors of pain and pain intensity</td>
</tr>
<tr>
<td>Comparisons</td>
<td>Men versus women</td>
</tr>
<tr>
<td>Length of Study/Follow-up</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>Outcome measures studied</td>
<td>Results from pain questionnaires.</td>
</tr>
</tbody>
</table>

### Results

Men had been diagnosed with coronary artery disease for longer than women with a mean of 12.9 SD 9.6 years versus 8.8 SD 9.8 (P = 0.030). There was a greater proportion of African American women compared with African American men (43.6% versus 13.5%, respectively, P = 0.001), more men had a history of acute MI than women (79.8% versus 58.0%, respectively P = 0.014) and more men had a history of coronary artery bypass graft compared with women (70.8% versus 28.2%, respectively P = 0.001). There was no difference between men and women in the history of the following; diabetes, hyperlipidaemia, hypertension, acute MI, percutaneous transluminal coronary angioplasty, GI problems. The was no difference in family history of coronary artery disease and current smoking between men and women.

Twelve percent of men and 10% of women reported one episode in the previous 7 days, and completed the SF-MPQ based on recall of that episode. Those patients experiencing more than 1 episode chose one specific episode to recall, the most commonly reported reason for choice of episode was that it was the most recent (52.9% men, 36.4% women), and the second reason was that it was the most painful (14.7% men, 18.2% women). The was no difference in the frequency of angina chest pain within in the previous 7 days comparing men with women (mean number of episodes 6.58 SD 7.95 for men and 2.23 SD 3.34). Men reported a mean of 1.7 SD 1.8 days since their last pain episode and women reported a mean of 1.9 SD 1.7 days. For men the most frequent words chosen to describe their angina were aching (74.2%), heavy (70.2%), tiring-exhausting (70.8%) and sharp (56.2%). For women the most frequent words were aching (76.9%), tiring-exhausting (76.9%), heavy (66.7%), hot-burning (61.5%), sharp (53.8%), and fearful (51.3%). Others descriptors that were chosen less frequently (<35%) were; throbbing, shooting, stabbing, gnawing, splitting and punishing-cruel. Chi square analysis found that women were more likely to describe their angina as hot-burning (P = 0.001) and tender (P = 0.007) compared with men. Women reported significantly higher overall pain intensity as measured by VAS (on a range of 0 to 10 women 6.08 SD 2.7 versus men 5.03 SD 2.4, P = 0.036). No gender differences were found for total sensory or affective intensity scores, or the number of pain words chosen.

<table>
<thead>
<tr>
<th>Safety and adverse effects</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the study answer the question?</td>
<td>Somewhat, study identifies that women describe angina pain differently to men.</td>
</tr>
<tr>
<td>Effect due to factor in study?</td>
<td>Validated pain questionnaires used so results are likely to be consistent and appropriate descriptors</td>
</tr>
<tr>
<td>Consistency of results with other studies?</td>
<td>Consistent</td>
</tr>
<tr>
<td>Directly applicable to guideline population?</td>
<td>Stable angina population as defined as screening positive on the supplemented Rose questionnaire, hence directness somewhat limited as chest pain population in guideline.</td>
</tr>
<tr>
<td>Internal Validity</td>
<td>Well covered</td>
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</tbody>
</table>
The study found that the exercise ECG for women had lower accuracy compared with men, sensitivity 61% versus 70% and specificity 70% versus 77%. There was wide variability in the sensitivities for exercise ECG in women (27% to 91%) and also specificity (46% to 86%). The variability was not associated with the exclusion of patients with baseline ECG changes. Sensitivity and specificity were highly correlated suggesting that investigators may have different threshold for the identification for interpreting a test as positive, despite using the same threshold for interpreting a test as positive. Exercise thallium scanning in women had a higher sensitivity but a lower specificity compared with exercise ECG in women, but the differences were not clinically relevant. Although data was limited in this study exercise echocardiography has higher sensitivities and specificities compared with the other 2 tests.

No information was given on heterogeneity.

The results are directly applicable to the guideline.
The SR the summary odds ratio for an abnormal multislice CT was elevated 16.9 fols (95% CI 11.0 to 26.1) indicating that an abnormal segment had a 16.9 fold increased odds of significant CAD at cardiac catheterization. In contrast the summary odds ratio was increased 6.4 fold (95% CI 5.0 to 8.3) for MRI. An inverse relationship between diagnostic specificity and CAD prevalence for multislice CT was observed, which remained consistent when controlling for average age and the frequency of men enrolled in each study. No relationship was found for MRI. The authors concluded that MSCT has a significantly better diagnostic accuracy in the detection of CAD compared with MRI.

The results of the SR are directly applicable to the guideline.
This review answers the question it set out to answer. That is, it provides an estimate of the diagnostic value of 64-slice CT when compared to coronary angiography (CA). It included patients with known CAD and those with suspected CAD (those presenting with chest pain) and as such is useful for our question. However, it would have been even more useful if separate results had been presented for those groups separately.

Very little information on the type of studies included was reported. E.g. number of RCTs, cohort studies etc. And no details of the number of patients included in the sensitivity/specificity calculations were reported. However, sensitivity/specificity was reported at patient, vessel and segment level.

The results of this SR are directly applicable to the guideline.
Grading: 2- Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal*

A systematic review on diagnostic accuracy of CT-based detection of significant coronary artery disease. [Review] [60 refs]

Ref ID 177 Eur J Radiol pages 449 to 461 2008 Mar

Study Type Diagnostic

Funding Not stated.

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

This study assessed the diagnostic accuracy of multislice CT (4-8-16- and 64-slice), although only 5 studies were 64 slice and study sizes ranged from 35 to 84 patients. The main conclusion is that with 64 slice scanners, diagnostic accuracy is high on a per segment basis. Per patient however, this accuracy may be lower in patients with multivessel disease, which may limit the utility of CT in populations at high risk for CAD. Apart from selection bias, this study highlights the fact that most of the studies used two independent investigators to read the scans which might differ from routine clinical practice, and which consequently could limit the applicability of the findings.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

The results of the study may not be applicable to the guideline as it was poorly conducted. Very little information is given on the type of studies included (RCTs, cohorts). No details of the number of patients included in the meta-analysis are given.

Internal Validity