



Clinical Epidemiology and Health Service Evaluation Unit

Evidence Report

Excluding acute cardiac ischaemic events in patients presenting to emergency departments with chest pain

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LIST OF ABBREVIATIONS

AHRQ	Agency for Healthcare Research and Quality
ACEP	American College of Emergency Physicians
SRPC	Society of Rural Physicians of Canada
ED	Emergency Department
LOS	Length of stay
WHO	World Health Organisation
AMI or MI	Acute Myocardial Infarction or Myocardial Infarction
ACI	Acute Cardiac Ischaemia
cTnI	Cardiac Troponin I
cTnT	Cardiac Troponin T
CK	Creatine Kinase
CK-MB	Creatine kinase MB isoenzyme
ESE	Exercise stress echocardiography
ECG	Electrocardiogram
SECG	Serial electrocardiograms
LBBB	Left bundle branch block
EBCT	Electron-beam computed tomography
^{99m} Tc-GLA	Technetium-99m labelled D - Glucaric Acid

SUMMARY

Task

The Clinical Epidemiology & Health Service Evaluation Unit was asked to review the research literature on the best practice in excluding an acute ischemic event when patients present to an emergency department with chest pain.

Conclusions and recommendations

This literature review identified 4 guidelines relevant to this topic. A summary of each of these guidelines can be found in Appendix 1. The latest guideline published in 2000 by the American College of Emergency Physicians (ACEP) provides a very good summary of evidence concerning diagnosis of AMI and practical diagnostic regimens for use in patients presenting to ED with chest pain.

In 1998, ACEP produced a document outlining all possible causes of chest pain. ED staff are likely to find this document most useful as a reference for making a differential diagnosis when faced with ambiguous chest pain symptoms. The other two guidelines are of interest but are not as up to date as the ACEP 2000 clinical policy incorporating guidelines for patient management.

The AHRQ health technology assessment (AHRQ 2001) considered the accuracy of technologies for diagnosing chest pain in the ED. It reviewed their clinical impact when used in this setting and contains rigorous meta-analytic overviews of both the accuracy of the technology and its clinical impact. The information from this review is directly relevant to the management of chest pain in ED (*see Appendix 2*).

A critical appraisal of the primary publications from 1999 - 2001 in this area did not add a great deal to that already identified, especially by the AHRQ review (*see Appendix 3*). However it did add further weight to the recommendations from the AHRQ about the use of serial biomarker measurement providing an opportunity for the development of effective timed myocardial infarction “rule-out” protocols.

Feasibility

Suitable material for informing a best practice approach to excluding an acute ischemic event when patients present to an emergency department with chest pain was presented in the AHRQ 2001 report and ACEP 2000 clinical policy.

METHODOLOGY

Search Strategy

The Clinical Epidemiology & Health Service Evaluation Unit defines best available evidence as that research we can identify that is least susceptible to bias. This was determined through applying the predefined NHMRC criteria (*see Appendix 4*).

The search commenced with systematic reviews, evidence-based clinical guidelines or health technology assessments and randomised controlled trials. If sound relevant material of this type is identified then the search ceased. Otherwise the search

strategy is broadened to include studies which are more prone to bias making them less generalisable. Case-control and longitudinal cohort studies are included in our critical appraisal reports. Other studies, which have less methodical rigour, are included but not critically appraised.

Resources Searched

We searched the following databases and Internet websites:

- Cochrane Library CD-ROM
- Medline (OVID)
- CINAHL (OVID)
- SumSearch <http://sumsearch.uthscsa.edu/searchform4.htm>
- National Guidelines Clearinghouse (<http://www.guidelines.gov>), and other evidence-based sites known to store guidelines
- NHS Centre for Reviews and Dissemination (NHS CRD) http://www.nelh.nhs.uk/guidelines_database.asp.
- Agency for Healthcare Research and Quality (<http://www.ahrq.gov>)

Refinements, Searching & Reporting Constraints

We only included articles published since 1999, and applied the following inclusion and exclusion criteria:

Inclusion Criteria

- Focus on all patients with chest pain in the emergency department;
- Published primary studies;
- Published clinical practice guidelines (whether generated through evidence-based methods or through consensus)

Exclusion Criteria

- Study examined less than five patients;
- Study was published in a language other than English;
- Study presented data included in another published report;
- Study examined long term therapy not possible to implement in ED.

CLINICAL PRACTICE GUIDELINES

A total of four guidelines were identified that addressed treatment of all chest pain. The descriptive characteristics of these guidelines are shown in Table 1. Where available, we include a brief summary of cited guidelines in Appendix 1.

Table 1. Description of guidelines cited

Characteristic	ACEP, 2000
Developers	American College of Emergency of Physicians
Title	Clinical Policy: Clinical issues in the evaluation and management of adult patients presenting with suspected acute myocardial infarction or unstable angina.
Outcomes Considered for ED	ECG eligibility, role of angioplasty, use of serum markers, serial 12 lead ECG, chest pain evaluation units.
Methods to Collect Evidence	MEDLINE search between 1993-1998
Methods to Analyse Evidence	Review by expert subcommittee
Length	26 pages
URL	http://www.acep.org/library/files/pdf/cp402120.pdf
Comments	Excellent summary of evidence concerning diagnosis of AMI, and practical diagnostic regime.

Characteristic	ACEP, 1998
Developers	American College of Emergency Physicians
Title	Chest Pain: Clinical Decision-Making
Outcomes Considered for ED	Not stated
Methods to Collect Evidence	Not stated
Methods to Analyse Evidence	Not stated
Length	13 pages
URL	http://cqhane.netfirms.com/chest%20pain.pdf
Comments	Limited referencing, but good source of information for all possible conditions that may cause chest pain

Characteristic	ACEP, 1995
Developers	American College of Emergency Physicians
Title	Clinical Policy for the initial approach to adults presenting with a chief complaint of chest pain, with no history of trauma
Target Population	Adult population, presenting with chest pain. Does not include patients, with history of proximate trauma, or visible lesions in chest area, individuals with very brief periods of pain
Outcomes Considered for ED	Correct diagnosis of chest pain
Methods to Collect Evidence	Not stated
Methods to Analyse Evidence	Expert panel
Length	26 pages
URL	http://www.acep.org/library/files/pdf/cp402050.pdf or Ann Emerg Med, 1995; 25: 274-299
Comments	This document is a number of years old now, but has a very useful quick reference form attached for diagnosis and treatment of chest pain. Includes conditions other than AMI.

Characteristic	SRPC, 1999
Developers	Society of Rural Physicians of Canada
Title	Chest pain guideline and continuous quality improvement system for Canadian rural emergency health care facilities
Target Population	Adult population, presenting with chest pain to a rural hospital setting.
Outcomes Considered for ED	Rapid identification and initial management of patients with possible acute coronary ischemic syndromes and acute myocardial infarction.
Methods to Collect Evidence	MEDLINE searches
Methods to Analyse Evidence	Expert panel
Length	1 page flow chart with an 11 page supporting document
URL	http://www.cma.ca/cjrm/vol-4/issue-1/0009.htm Or Canadian Journal of Rural Medicine, 1999; 4(1) 9-19Ann
Comments	Only recommends ECG and clinical symptoms for diagnosis of AMI or ACI.

HEALTH TECHNOLOGY ASSESSMENT

A comprehensive health technology assessment report published in 2001, by the Agency for Healthcare Research and Quality (AHRQ) was identified. This report considered the accuracy of technologies for diagnosing chest pain in the ED and their clinical impact when used in this setting. In addition, the report also conducted decision and cost-effectiveness (CE) analyses to investigate the interactions between technologies' diagnostic performances and costs, populations and outcomes. An extensive summary of the report is presented in Appendix 2.

Characteristic	AHRQ, 2001
Developers	Agency for Healthcare Research and Quality
Title	<i>Evaluation of Technologies for Identifying Acute Cardiac Ischemia in Emergency Departments</i> . Evidence Report/Technology Assessment Number 26. AHRQ Publication No. 01-E006, May 2001
Target Population	Studies examining the diagnostic value of technologies in assessing risk of ACI, AMI, and UAP, in the Emergency Department
Outcomes Considered for ED	Unnecessary hospitalisations; test sensitivity and specificity.
Methods to Collect Evidence	MEDLINE search for articles published between 1966 and December 1998.
Methods to Analyse Evidence	Meta analysis and systematic review
Length	315 pages
URL	http://www.ahrq.gov/clinic/aciscinv.htm
Comments	Excellent summary of the technologies used to diagnose AMI and ACI, and the evidence support for them.

Published Primary Literature

An update of evidence was conducted for new original articles, using a modified version of the search strategy employed by Ioannidis, et al. (AHRQ, 2001), in the MEDLINE database.

MEDLINE Search Strategy Used

Setting (any of)

Emergency medical service communication systems/or Emergency medical services/or Transportation of patients/
Exp mobile health units/or “prehospital”.mp.
Exp telecommunications/
Exp transportation of patients/
Exp emergency medical technicians/
Exp Emergency service, hospital/
Emergenc\$.tw.

Disease (any of)

Exp myocardial ischemia/di [Diagnosis]
Exp chest pain/di [Diagnosis]
(chest pain or myocardial infarction or myocardial ischem\$).tw

Technology

Exp “sensitivity and specificity”/

Population

Limit to human

Limits (all of)

Yr 1999 – 2001

Limit to English language

Not review

Not letter

Not editorial

Outcome of the Search

The search lead to 101 documents being identified. Abstracts were reviewed for all and 42 documents met the inclusion criteria and full articles were sought. Of these, one was not in English, four were review articles (despite the search strategy used) and one could not be located prior to the review being completed. Therefore 36 articles were reviewed. Critical appraisal of the individual articles is located in the following pages. A composite summary of the findings is included below and citations and abstracts can be found in Appendix 3.

The conclusion from the critical appraisal of these articles is that the evidence for the use of serial measurements of biomarkers in ED rather than single sample measurement is becoming stronger. It is pointing towards the development of an accurate and efficacious “rule out” protocol for myocardial infarction within 6 hours of presentation at ED (see Herren et al, 2001). However more work is required over a longer time period before the recommendations made by Herren and colleagues could be adopted.

Primary Publications Summary

Non-standard Lead ECG

Practically all of the cited articles have used ECG measurements to some degree. However, only Aufderheide, et al (2000) have recently focused on a part of ECG as the primary focus of analysis. This well conducted prospective cohort study supports the use of computerised detection of QT- dispersion and ST-segment deviations, instead of manual interpretation of ECG findings.

Exercise Stress Testing

Five articles were cited for exercise stress testing. As a group, the quality was not high. As all studies selected only very low risk groups, the prevalence of coronary events was very low. Unfortunately, sample sizes were not high enough to record sufficient coronary events for any confidence to make conclusions about the effectiveness of this technology. All studies showed no adverse effects associated with this technique. However, it is yet to be shown that this technique provides any additional diagnostic value for very low risk patients. These results further support the AHRQ (2001) findings.

Biomarkers

Considerable research has been conducted into the utility of biomarkers in predicting AMI and ACI. As most of these papers examine a number of markers

simultaneously, these papers have been divided into single sample, or serial measurements, and not test specific groups.

Single sample measures

To find a biomarker that can identify AMI or ACI at admission is an ideal. Three papers cited have explored the utility of various biomarkers in this role. The biomarkers examined were cTnI and cTnT, CK, and CK-MB, Myoglobin. The quality of these studies was generally good.

The sensitivity of individual markers was poor (highest value reported was for cTnI at 53% sensitivity, with 91% specificity, Porela et al, 2000) indicating inadequate predictive value for a rule out protocol. However, when combined with ECG and a combination of markers, this value was shown to jump considerably. For example, Porela, et al, (2000) found a combination of ECG, CK-MB or cTnI could give a sensitivity of 90%, but with only a specificity of 54%. As such, using such a test could identify 90% of all AMI cases, 46% of positive cases being incorrectly identified. The use of combined measurements at initial evaluation is a relatively new development, with only one study cited by AHRQ (2001) doing so.

Serial Measurements

There has been a substantial volume of work produced on the serial measurement of markers, with the aim of improving test performance. The quality of this work is heterogeneous, as are the results.

Some of the heterogeneity can be explained by the time frame over which the repeated tests were taken. The work by Zimmerman, et al (1999) helps explain this, as it characterises the variation in sensitivity and specificity of all the main biomarkers over a 22-hour period following onset of chest pain. This work shows that CK-MB subforms, myoglobin, cTnT, cTnI all have a maximal sensitivity at around 10 hours after onset of pain. CK-MB and CK-MB mass increase sensitivity with time, plateauing at around 10 hours.

Other studies have shown sensitivities of 91 and 94% (specificity 91.4 and 94% respectively) within 2 hours, for measurement of change in CK-MB or change in CK-MB and cTnI (Fesmire, 2000a, Fesmire, 2000b). These are very promising results, as they suggest a very prompt rule out decision.

There are also other promising 'rule out protocols' that take longer to reach a decision. This is an important area of development since the studies reviewed by AHRQ (2001).

Technetium-99m Sestamibi Myocardial Perfusion Imaging

Four new studies examined myocardial perfusion imaging as a diagnostic tool, but only two could be used to report the sensitivity of this test. These well-conducted studies showed very good performance (sensitivity of 92, and 100%, with specificities of 67 and 86% respectively, Kontos, et al, 1999 & Paventi, 2001). These reported specificities would still lead to a high number of patients being admitted unnecessarily. These results are consistent with those of the AHRQ (2001) document.

Electron beam computed tomography

One study reported results from this new potential diagnostic tool for AMI (Laudon, et al, 1999). This small study showed excellent sensitivity (100%) for AMI, there was a relatively poor specificity (63%). This technique may need more development. There were no studies reported in the AHRQ (2001) results that used this technique.

Goldman Chest Pain Protocol

The two studies reporting on the use of the Goldman protocol did not provide strong support for the diagnostic tool, with information being very difficult to extract. In the one study where sensitivity could be calculated, a value of 76.7% for AMI was achieved with a specificity of 52.3%. The AHRQ (2001) cites stronger evidence for this protocol.

Other Computer-Based Decision Aids

Aase (1999) reported on a new computer aided decision protocol. This program had good results, with 84% sensitivity and 75% specificity for diagnosing AMI.

Left bundle-branch blocks (LBBB) sub-population specific studies

Two studies specifically studied a sub-population who presented to the ED with LBBB. These studies both found that the ECG results had very low sensitivities in this group for detecting AMI. ECG combined with CK-MB measurement did increase the sensitivity of the diagnosis, but only to 63%. As such, patients with LBBB should be treated with increased caution.

ORIGINAL ARTICLES REVIEWED

Non-standard Lead ECG

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Aufderheide, et al, 2000	Computerised 12-lead ECGs with QT-dispersion and ST-segment deviations combined with physician consensus	Country: USA Median age:62 Age range: Not stated Enrolled: 1568 Evaluation: 1161 male (%): 54.7 Race: 79.6% White	Age >18 Stable condition. Chest pain	Trauma	WHO criteria; appropriate 12-lead ECG changes CK-MB, Troponin T or I results based on established criteria in hospital labs.	AMI 24.6
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	Computerised classification based on achieving >85% specificity for detecting ACI and AMI. QT end threshold value was >45ms. QT-peak threshold was >55ms	AMI 65 ACI 62	AMI 97 ACI 80	This study supports a potential clinical role for automated QT dispersion when combined with other diagnostic methods for detecting AMI and ACI. Physician consensus alone has higher specificity (99%), but lower sensitivity (48%)	Not stated	

Exercise Stress Testing

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria ²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Buchsbaum, et al, 2001	Exercise stress echocardiography at approximately 6 hrs	Country: USA Mean age: Not stated Age range: Not stated Enrolled: 149 Evaluation: 148 male (%):Not stated Race: Not stated	Low-risk patients: Age ≥ 30 years Normal CK-MB isoenzyme Normal or non-diagnostic ECG No history of cardiac disease	Not stated	30 and 60-day telephone follow up to determine if MI, cardiac death, or cardiac revascularization had occurred. Medical records used to confirm events.	Cardiac event: 2.7
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	New wall motion abnormalities observed on post-exercise images (≥1mm of ST depression observed at 80ms from J point)	75	97.1	Exercise stress echocardiography (ESE) can be used to evaluate low-risk chest pain patients in the ED. Patients with a normal ESE may be considered for discharge with minimal risk of sequelae.	Only four adverse events observed. Small number of events will result in unstable estimates of sensitivity.	Small number of events observed. The sample was selected at the discretion of an attending physician, with poor description of criteria used.

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria ²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Geleijnse, et al, 2000	Early dobutamine-atropine stress echocardiography if CK and ECG results were negative	Country: Europe Mean age:58 Age range: 22-83 Enrolled:102 Evaluation: male (%): 66 Race: Not stated	Chest pain<12hrs	Trauma or other explanations for chest pain. Initial CK level and ECG results indicative of myocardial infarction or unstable angina. Known tachyarrhythmias. Uncontrolled hypertension (≥ 180/110 mmHg). Significant heart disease. Known coronary artery disease.	No definition of AMI. Follow up for 6 months	AMI:4

	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	New or worsening wall thickening abnormalities.	0	54	Early dobutamine-atropine stress echocardiography may safely distinguish between low-and high risk subsets for subsequent cardiac events in patients with spontaneous chest pain and non-diagnostic ECG.	90% of patients had interpretable conditions.	Only one AMI observed for the study population. Small numbers prevent clear conclusions being drawn.

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Krasuski, et al, 1999	Exercise testing using standard and modified Bruce protocols	Country: USA Mean age:56.5 Age range: 25-90 Enrolled: 195 Evaluation: 133 male (%): 55.8 Race: ND	Patients scheduled for weekend exercise testing	Not stated	30 day follow up: need for ED visits and hospitalisation, 6 month follow up: (MI, cardiac catheterisation, PTCA, CABG) and survival.	ND
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	Intermediate: ECG changes 1mm horizontal or down-sloping ST depression, or chest pain during exercise or if patient unable to achieve adequate workload Positive: at least 2mm horizontal or down-sloping ST depression or a 1mm ST depression in conjunction with typical chest pain, with a fall in blood pressure	Unavailable	Unavailable	Weekend and Holiday exercise testing is a safe and effective means of risk stratification prior to hospital discharge for patients with chest pain. It also reduces length of stay and is cost saving	95.9% (187/195) patients follow up at 6 months	Insufficient reporting of data for sensitivity and specificity calculations

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Lewis, et al, 1999	Immediate exercise treadmill testing using modified Bruce protocol	Country: USA Mean age:58 Age range:30-85 Enrolled:100 Evaluation:100 male (%):64 Race: Not stated	Patients with confirmed coronary artery disease. Low risk patients determined by ECG and clinical findings	ECGs diagnostic of AMI or ACI. ST-segment and T-wave changes that would prevent accurate interpretation of exercise ECG. Patients with pulmonary or vascular disease. Heart failure. Suspicious aortic dissection. chest pain believed to be from non-cardiac origin.	Presence of chest pain and either abnormal serial ECG changes of AMI or cardiac isoenzymes.	Coronary event: 10
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	≥1mm horizontal or down-sloping ST-segment depression or elevation 80 ms after the J point, significant arrhythmia, systolic blood pressure decrease of ≥10mm Hg or significant symptoms	Not performed	Not performed	Immediate exercise treadmill testing of low risk patients with chest pain and known CAD is effective in further stratifying this group into patients who can be safely discharged and those who require hospital admission.	Poor description of reference criteria. Poor description of follow up procedures	Insufficient reporting to determine sensitivity and specificity of the test results

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Sarullo, et al, 2000	Immediate exercise treadmill testing using Bruce protocol	Country: Europe Mean age: 57 Age range: ND Enrolled: ND Evaluation: 190 male (%): 66.8 Race: Not stated	Age >30 Anterior, precordial, or left later chest pain	Trauma X-ray abnormalities	Follow up for 12 months. Chart review, and telephone interviews. Endpoints included ED visits, cardiac events (AMI, death, PTCA, or CABG). No definitions provided.	AMI: 1.1

	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	ECG ≥1mm horizontal or down-sloping ST-segment depression or elevation 80ms after J point. Or significant arrhythmia, systolic BP decrease >10mmHg, or significant symptoms. Non diagnostic test classed as peak heart rate <85% of predicted	84	92.5	Immediate exercise treadmill testing of low-risk patients with chest pain who are at sufficient risk to be designated for hospital admission is effective in further stratifying this group into those who can be safely discharged immediately and those who require hospitalisation.	No reported loss to follow up.	Poorly defined criteria for diagnosis.

Biomarkers

Single sample measures of CK, CK-MB, cTnI, cTnT, and myoglobin

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Huggon, et al, 2001	Biochemical markers measured at presentation to ED	Country: UK Mean age: Incomplete Age range: Not stated Enrolled:323 Evaluation:227 male (%): Incomplete Race: Not stated	Chest Pain or history of MI	Not Stated	Retrospective examination of medical records - History of typical chest pain, serial ECG showing evolutionary changes, serial CK values rising above twice the upper limit of normal.	AMI 22.0 (50/227)

	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	Initial ECG - ST segment elevation ≤ 2 mm in two contiguous chest leads, or ST segment elevation of 1mm in two contiguous limb leads. Troponin T - 0.1ng/ml Myoglobin - 90ng/ml Total CK - 170 U/L women, 190 U/L males CKMB activity 24U/L -CKMB mass - 5ng/mL then 7.5ng/ml	ECG 70 Troponin T 40 Myoglobin 44 Total CK 40 CKMB activity 33 CKMB mass 52	ECG 99 Troponin T 90 Myoglobin 86 Total CK 86 CKMB activity 90 CKMB mass 88	The ECG is of more diagnostic use than biochemical markers in the first six hours after the onset of pain, but biochemical markers give additional positive diagnostic information in patients presenting later than this. The negative predictive accuracy of biochemical markers is too low for a single sample to be useful for excluding myocardial infarction in the first six hours after onset of symptoms.	29.7 % (996/3230) of patients lost to follow up	Questions over the number and quality of patients enrolled, as doctors were requested to take extra blood samples from possible AMI patients. Difficult to determine adherence and the population from which the study sample was drawn.

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Ooi, et al, 2000	Initial ECG, CK-MB, Troponin-T rapid assay (cTnT) singly or combined	Country: Asia Median age: 62 Age range: 27-95 Enrolled:165 Evaluation:152 male (%):67.1 Race:63.8% Chinese	Age ≥ 20 Typical chest pain Atypical chest pain in whom AMI cannot be excluded with out further observation. No chest pain but with clinical presentation suggestive of AMI.	Known MI, or treatment for MI in last 2 weeks. Non-cardiac chest pain Chest trauma. Cardiac compression or defibrillation done prior to blood samples taken. Recent IM injection Uraemia clinically or with raised serum creatine $> 150\mu\text{mol/L}$.	WHO criteria: (1) clinical history of chest discomfort >30 min, (2) appropriate 12-lead ECG changes; (3) rise and fall of serum cardiac enzymes.	AMI: 50

	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	cTnT > 0.2ng/mL CK-MB mass > 6ng/mL Relative index ≥5%	ECG: 76.3 cTnT: 31.6 CK-MB mass: 38.2 Combined scores: 89.4	ECG: 79.7 cTnT: 100 CK-MB mass: 97.4 Combined scores: 78.3	The first ECG was the most sensitive test while the combination of chest pain, ECG, cardiac enzymes and cTnT gave the best results in the initial diagnosis of AMI. If the first ECG, CK-MB mass and cTnT are all negative, the probability of having an AMI is 12%.	4.6% (7/152) patients lost to follow up.	Very high rate of AMI and hospital admission (97%). Serial measurements may have given more accurate results.

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Porela, et al, 2000	ECG, CK-MB, cTnI at admission	Country: Finland Mean age:68 Age range: Not stated Enrolled: 311 Evaluation:301 male (%):Not stated Race: Not stated	Chest pain, dyspnoea, or arrhythmia suggestive of acute myocardial ischaemia	Trauma or operation	CK-MB level ≥ 11µg/L	
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	ECG: modified Aldrich score greater ≥ 10, or horizontal or down sloping ST depression ≥ 1mm CK-MB mass ≥5µg/L cTnI ≥0.1µg/L	ECG: 66 CK-MB: 60 cTnI: 53 ECG or CK-MB or cTnI: 90	ECG: 65 CK-MB: 92 cTnI: 91 ECG or CK-MB or cTnI: 54	The commonly available biochemical and ECG criteria allow risk stratification of patients with a suspected acute ischemic event. The data analysis can easily be automated and is independent of patient delay.		

Serial Measurements of CK, CK-MB, cTnI, cTnT, and myoglobin

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria ²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Bock, et al, 1999	Serial total CK-MB, and isoform analysis, at 0, 1, & 3 hours post presentation with chest pain,	Country: USA Mean age:58.2 Age range:17-92 Enrolled: 231 Evaluation:231 male (%):65.4 Race: Not stated	Chest pain or other cardiac symptoms not more than 12 hours prior to presenting to ED.	Patients immediately starting thrombolytic therapy.	WHO criteria, using ECG and CK-MB mass at 0, 8 and 16hr after presentation.	AMI: 16.8
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	Total CK-MB : 6IU/L, or CK-MB2 >2.0IU/L or MB2/MB1 ratio > 1.7, for any sample	68	92	Analysis of CK-MB by high-voltage electrophoresis is an effective method for rapid diagnosis of MI with the isoform analysis enhancing early sensitivity.		Isoform data not available until 1 week post admission. This study raises questions concerning the feasibility of using this technique within ED setting.

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria ²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Bholasingh, et al, 2001	CK-MB mass sampling at admission, 5,7, & 10 hours post onset of symptoms.	Country: Europe Mean age:62 Age range: 24-96 Enrolled: 1109 Evaluation: 653 male (%): 56.8 Race: Not stated	Chest pain with typical cardiac chest pain.	Patients transferred to CCU (eg evidence of myocardial damage, unstable angina). Patients discharge from ED with atypical or non-cardiac chest pain.	Follow at 30 days, six months and 24 months by telephone interview, with patient or associated person. Medical records examined for cardiac events using WHO criteria to define AMI.	ND: Data reported only patients that were initially excluded from an AMI diagnosis.
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	CK-MB mass limit set at 7µg/L for 1996 cohort. CK-MB mass limit set at 8.0 U/L for 1994 cohort.	Not Relevant: clinical impact study	Not Relevant: clinical impact study	Using a rule-out AMI protocol with a rapid and sensitive CK-MB mass assay and serial sampling, the LOS of patients with chest pain in the cardiac ED can be reduced without compromising safety.		Compares two samples over two different time periods. Potential for historic events to bias results.

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria ²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Fesmire, 2000a	CK-MB and cTnI at baseline, and 2hr delta CK-MB and delta cTnI.	Country: USA Mean age:54.7 Age range: Not stated Enrolled: Not Relevant Evaluation: 578 male (%):57.8 Race: 74.2 Caucasian	Chest pain. Baseline CK-MB ≥ 12 ng/mL and cTnI ≥ 3 ng/mL a second CK-MB and cTnI at approximately 2hrs	Recent cocaine use. Tachyarrhythmia. Pulmonary edema.	WHO criteria: chest pain ≥ 30 minutes, and any of the following: serial rise of CK-MB ≥ 12 ng/mL and CK-MB index $\geq 4\%$, a serial rise in cTnI ≥ 3 ng/mL; new Q wave formation in two contiguous leads: patient death.	AMI: 9.9
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	Retrospective analysis based on ROC data. 2hr cTnI ≥ 0.9 ng/mL 2hr Ck-MB ≥ 6.4 ng/mL Delta CK-MB: ≥ 1.5 ng/mL Delta cTnI ≥ 0.2 ng/mL	Both 2hr delta CK-MB and delta cTnI had sensitivities of 91.2	Both 2hr delta CK-MB and delta cTnI had specificities: 91.4	Patients with either a rise in CK-MB of ≥ 1.5 ng/mL or a rise in cTnI ≥ 0.2 ng/mL in two hours should receive consideration for aggressive anti-ischaemic therapy and further diagnostic testing before making an exclusionary diagnosis of non-ischaemic chest pain.		Retrospective analysis..

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria ²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Fesmire, 2000b	Continuous 12 lead ST segment monitoring with automated serial ECG monitoring (SECG) with change in CK-MB from presentation to ED, and 2hrs later.	Country: USA Mean age: 54.5 Age range: Not stated Enrolled: 706 Evaluation: 706 male (%): 58.6 Race: 77% Caucasian	Chest pain, with suspected ischaemic heart disease	Recent cocaine use. Tachyarrhythmia. Demand pacemaker. Pulmonary oedema.	WHO criteria: chest pain ≥ 30 minutes, and any of the following: serial rise of CK-MB ≥ 12 ng/mL and CK-MB index $\geq 4\%$, a serial rise in cTnI ≥ 3 ng/mL; new Q wave formation in two contiguous leads: patient death.	AMI: 10.8

	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	<p>Base line CK-MB >6ng/mL cTnI >1.5ng/mL Increase of CK-MB of 1.5 ng/mL from initial to 2hr test.</p> <p>ECG: if evaluating physician interpreted the ECG as revealing new injury or new ischemia.</p>	<p>Initial ECG: 39.8 Plus baseline CK-MB: 55.4 Plus SECG: 74.7 Plus delta 2hr CK-MB: 94.0</p>	<p>Initial ECG: 98.7 Plus baseline CK-MB: 98.6 Plus SECG: 97 Plus delta 2hr CK-MB: 93.6</p>	<p>SECG monitoring in conjunction with the 2 hour delta CK-MB allows for early identification and exclusion of MI, and can assist the ED physician in making appropriate treatment and disposition decisions.</p>		<p>Very promising results</p>

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Herren, 2001	<p>Serial measurements of CK-MB mass at 3 and 6 hours post onset of chest pain, and continuous ST segment monitoring (12 lead) for six hours</p>	<p>Country: UK Mean age: Not stated Age range: Not stated Enrolled: 383 Evaluation: 292 male (%):Not stated Race: Not stated</p>	<p>Chest pain for less than 12 hours Age>25</p>	<p>Trauma Other medical cause of chest pain ECG evidence of AMI or MI Hypertensive or arrhythmia</p>	<p>48 hours post admission, either troponin T concentration (positive if 0.1µg/l), or screening for MI using WHO criteria.</p>	<p>AMI: 12.3 (36/292)</p>
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	<p>Change in ST segment ≥2mm in any one lead, or 1mm in any three leads, Or Absolute CK-MB mass concentration > 5µg/l or ↑ of 3µg/l on consecutive samples</p>	<p>97.2</p>	<p>93</p>	<p>The six-hour rule-out protocol for MI is accurate and efficacious. It can be used in patients presenting to ED with chest pain indicating low to moderate risk of MI.</p>	<p>23.8% total loss to follow up, due to refusal to participate, violation of protocol or inadequate follow up.</p>	<p>Important study. Questions over appropriateness of gold standard (longer time frame?) and large proportion lost to follow up.</p>

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Peacock, et al, 2001	Serial CK and MB fractions measured on arrival to ED then 8 and 16 hrs post presentation. A composite outcome for the index visit and at 6 months was developed. The composite outcome was defined as either death, Q-wave MI, or a revascularisation procedure (either PTCA or CABG)	Country: USA Mean age:62.1 Age range: Not stated Enrolled: 698 Evaluation: 698 male (%):58.3 Race:57.8 Caucasian	Suspicion of acute coronary syndrome, based on emergency physician based assessment of history, ECG and physical examination. Age >18	Unable to obtain informed consent. thrombolytic therapy, coronary revascularization, or MI within 3 weeks of presentation, cardiopulmonary resuscitation within 7 days of presentation, major surgical procedure within 7 days, need for blood pressure support, transfer from another hospital, symptoms present for more than 12 hours prior to ED admission, chronic dialysis, or baseline creatine of >2.0 mg/dL.	WHO criteria; chest pain consistent with cardiac origin and new Q-waves > 0.04 ms.	acute coronary syndrome: 24.9
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	CK < 220U/L or CK-MB < 8.8ng/mL	Acute 34.5 6 months 32	Acute 88.7 6 months 84	The adverse event rate for patients with suspected acute coronary syndromes and elevated MB is the same whether or not the total CK is elevated. These patients should be considered as having had an acute coronary syndrome.	No data on loss to follow up.	No data on loss to follow up. Low sensitivity values.

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Johnson, et al, 1999	Two or more measures of cTnI during first 24 hrs of presentation to ED, as well as CK-MB	Country: USA Mean age: 61 Age range: Not stated Enrolled: 1477 Evaluation: 1303 male (%): 52 Race: white 65%, black 24%	Anterior, precordial or left lateral chest pain	Trauma. Abnormalities on chest radiography. Less than 2 measurements of cTnT in first 24 hrs post presentation to ED	CK-MB >5% or total CK showing typical rise or fall. CK-MB mass >5ng/mL ECG with pathologic Q-wave. Thrombolytic therapy over next day required if new ST elevation evolved, or occlusion of infarct related artery	11
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	Total CK activity ≥5% CK-MB mass ≥5ng/mL cTnT > 0.1ng/mL	Total CK activity: 64 CK-MB mass: 98 cTnT: 99	Total CK activity: 98 CK-MB mass: 97 cTnT: 85	In a heterogeneous patient population seen in the ED with acute chest pain, cTnT was similar to CK-MB (activity and mass assays) for detection of AMI and superior to the CK-MB mass assay as a marker for major cardiac events early in the hospital stay among those who were ruled out for an AMI.		Further study is required to determine how to use this assay to provide more appropriate, cost effective care.

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria ²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Peacock, et al, 2000	cTnI levels measured at baseline 4,8 and 16 hrs post admission.	Country: USA Mean age: 59.8 Age range: Not stated Enrolled: 266 Evaluation: 266 male (%): 47.7 Race: 48.1% white. 47 % black	Age >18 years Suspected acute coronary syndrome	Thrombolytic therapy, coronary revascularization, or MI within past 3 weeks. Major surgical procedure in past 7 days. Vasopressors or beta-blockers, calcium channel blockers, angiotension-converting enzyme inhibitors, or nitrates. Symptoms > 12 hrs. Long term dialysis or CK >176.8µg/L.	WHO criteria; chest pain consistent with cardiac origin and new Q-waves > 0.04 ms.	Adverse event: 7.9 AMI: 1
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	cTnT > 0.2µg/L	For adverse event at index visit: 9.5 For adverse event at 6 months: 0	For adverse event at index visit: 99.2 For adverse event at 6 months: 98.4	Determination of troponin T levels has a low sensitivity and high specificity for predicting outcomes in low-risk patients evaluated for suspected acute coronary syndromes. Study does not support a strategy of relying solely on troponin testing for disposition decisions.		Very low incidence of AMI in sample.

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria ²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Van Lente, et al, 1999	Measurement of troponin T & I and CK-MB in patients with suspected acute coronary syndrome, at presentation and at 4, 8,16 hrs thereafter	Country: USA Mean age:65 Age range: Not stated Enrolled: 255 Evaluation: 255 male (%):58 Race: Not stated	Suspected acute coronary syndromes, with renal disease. Two cohorts from a larger database used to match Troponin T, and Troponin I.	Cardiopulmonary resuscitation within 7days, angiography or thrombolytic therapy within 3 weeks, or were given vasodepressors.	WHO criteria, with at least two of: chest pain consistent with cardiac origin, appropriate 12-lead ECG changes or characteristic changes in CK and CK-MB (total CK ≥220 U/L and RI 4%) ascertained retrospectively.	AMI 18.7

	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	Not stated. Study design set to determine utility of tests in sub-population.	Range of values provided	Range of values provided	The ability of cardiac troponin T & I to predict risk for subsequent adverse outcomes in patients presenting with acute coronary syndromes is reduced in the presence of renal insufficiency.	Case matched study.	Not a prospective study. Results should only be assessed in terms of utility of troponin T & I and CK-MB in patients with or without renal disease.

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Wilcox, et al, 2001	Prediction of outcome based on CK and CK-MB, and troponin I levels, and clinical symptoms.	Country: Australia Mean age:67.1 Age range:16-93 Enrolled:434 Evaluation:424 male (%):55 Race: Not stated	Consecutive patients where CK-MB was requested.	Not stated	Cardiac and all cause mortality within 30 days of presentation	Not relevant
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	Not relevant as a predictive value study	Not relevant	Not relevant	Compared with CK-MB, cardiac troponin I more accurately predicts 30-day mortality rates in patients presenting to the ED. Moreover, troponin I levels identify additional groups of patients at increased risk of death not so identified by measuring CK-MB values.	10/424 patients lost to follow up.	Not directly related to diagnosing AMI

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Green, et al, 2000	Single-sample myoglobin, CK-MB, cTnT, physical examination	Country: USA Mean age:60.3 Age range: Enrolled: 470 Evaluation:396 male (%): 49.5 Race:62% white	Males \geq 30, and Females \geq 40, with any of chest pain, epigastric pain, unexplained shortness of breath, new onset of CHF, acute pulmonary oedema, dysrhythmia, ECG change; Or any age with known coronary artery disease, diabetes hyperlipidemia, cocaine use within 72 hrs.	Non cardiac aetiology clearly documented by radiography or other technical assessment, symptoms temporally related to direct trauma, inability to consent.	Telephone follow up at 14 days following admission to ED. If not contactable, a letter was sent out. Medical records examined. Death records searched for those patients that could not be followed up. MI defined by WHO criteria.	AMI: 9.6
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	Myoglobin \geq 110ng/mL CK-MB \geq 10IU/L cTnT \geq .2ng/mL	Myoglobin: 28.9 CK-MB: 23.7 cTnT: 23.7	Myoglobin: 91.3 CK-MB: 98.3 cTnT: 94.7	The early prognostic sensitivity of myoglobin may allow identification of some high-risk patients missed by physician judgment, CK-MB, and cTnT. Myoglobin should be considered for use in the ED based on both diagnostic and prognostic abilities.	15.7% of patients excluded from analysis (59 patients excluded due to insufficient sera and 15 due to loss to follow up).	

Other Biomarkers

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria ²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Bayes-Genis, et al, 2000	D-Dimer levels measured at admission to ED. thrombin-anti-thrombin complexes, prothrombin fragment 1+2, activated factor VII, and fibrinogen were measured.	Country: Europe Mean age: 56.9 Age range: Not stated Enrolled: 300 Evaluation: 257 male (%): 62 Race: Not stated	Age > 25. Chief complaint: chest pain (central or left sided) <6hrs.	Coronary revascularization within 6 months. Presence of D-dimer altering conditions. Conditions known to alter activity of coagulation system. Non consenting.	Prolonged chest pain occurring at rest accompanied by ST-segment elevation or depression evolving into pathological Q-wave or T-wave inversion confirmed by CK levels >180U/L and CK-MB fraction of more than twice upper limit.	AMI: 14
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	Exploratory analysis. D-dimer limit of 500 µg/L. 1. "Conventional criteria": Presence of radiating CP. 2. Positive ECG (new Q-waves, ST-segment elevation ≥0.1mV; ST-segment depression ≥0.1mV; T-wave inversion if deviation ≥0.1mV from baseline in 2 or more contiguous leads. Deviations 80ms after J point in intervals of 0.5mm. T-wave deviation 3. Initial CK>180U/L.	D-dimer: 65 D-dimer & conventional criteria: 92	D-dimer: 85 D-dimer & conventional criteria: 97	D-Dimer, an expression of ongoing thrombus formation and lysis, is a marker of substantial incremental value for the early diagnosis of acute coronary syndromes presenting with chest pain. It adds independent information to traditional assessment for myocardial infarction. D-Dimer can be incorporated into clinical decision models in the ED.	14% (257/300) lost to follow up	Very promising

Combination of biomarkers

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria ²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Jurlander, et al, 2000	Serum myoglobin, CK-MB mass, and Troponin-T, every 6 hours	Country: Europe Mean age: 63 Age range:28-88 Enrolled:155 Evaluation:150 male (%):68 Race: Not stated	Suspected AMI. Chest pain at rest for > 30 min, but < 2 hrs.	No serum samples or 12 lead ECG on admission to ED	WHO criteria. Typical history, typical chest pain, transient elevation of CK-MB ≥ 15 IU/L.	AMI: 53.5
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	ECG: ST-segment elevation ≥ 0.1 mV in two limb leads or ≥ 0.2 mV in two precordial leads. Propose diagnostic strategy using cTnT and CK-MB mass (no limits defined)	86.7	61	Analysis of biochemical tests in the emergency department prior to hospital admission could accurately identify approximately 20% additional acute myocardial infarction patients. The prognosis of these patients is poor, and they may be a target for primary PTCA or new early initiated aggressive medical therapies.	3.2% (5/155) lost to follow up. No clear definition of biomarker limits on the diagnostic strategy proposed	Retrospective analysis.

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Polanczyk, et al, 1999	CK-MB mass alone, CK-MB mass with cTnI if CK value normal, CK-MB mass followed by cTnI if CK-MB value is normal and ECG shows ischemic changes; both CK-MB mass and cTnI; cTnI alone; all the above in combination with early exercise testing.	Country: USA Mean age: Not stated Age range: Not stated Enrolled:4145 Evaluation: 4145 male (%): Race: Not stated	acute chest pain	Not Stated	Not stated	11.8
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	CK-MB mass > 5ng/mL, cTnI >0.4ng/mL	CK-MB mass: 68 cTnI: 55 CK-MB mass and cTnI: 71	CK-MB mass: 98 cTnI: 93 CK-MB mass and cTnI: 92	Measurement of CK-MB mass plus early exercise testing is a cost-effective initial strategy for younger patients and those with a low to moderate probability of myocardial infarction. Troponin I measurement can be a cost effective second test in higher-risk subsets of patients if the CK-MB level is normal and early exercise testing is not an option.	No definitions of AMI.	Retrospective analysis. Important data on costs associated with various testing options for detecting AMI.

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria ²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Wu, et al, 1999	Reflex algorithm, based on myoglobin, total CK, CK-MB isoenzyme, cTnI, at initial, 4, 8, 12 hrs post presentation	Country: USA Mean age: Not stated Age range: Not stated Enrolled: 101 Evaluation: 101 male (%): Not stated Race: Not stated	Chest pain. ECG normal on non-diagnostic	Not Stated	WHO criteria at discharge	33.6
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	Complicated diagnostic protocol	100	92.5	Compared to performing four tests on all patient samples, the reflex algorithm would have reduced the number of necessary tests from 442 to 130 (71% reduction) for AMI patients, and 871 to 469 (46% reduction) for non-MI patients, if prospectively implemented.		Retrospective evaluation.

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria ²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Zimmerman, et al, 1999	Serial sampling of CK-MB subforms, myoglobin, total CK-MB, cTnT and cTnI, at 2, 4, 6, 10, 14, 18, 22 hrs after presentation.	Country: USA Mean age: 55.3 Age range: Not stated Enrolled: 955 Evaluation: 955 male (%): 59.8 Race: Not stated	Age >21 years Chest pain ≥ 15 minutes, of suspected myocardial origin, occurring within 24 hrs of presentation.	Not stated	CK-MB mass ≥ 7ng/mL and CK-MB index ≥2.5%.	AMI: 12.5

	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	CK-MB mass ≥7ng/mL CK-MB >9IU/L. Myoglobin >85ng/mL cTnT >01.ng/mL cTnI >1.5ng/mL	Based on best result over 22 hr period. CK-MB subforms: 96.2, 10 hrs CK-MB mass: 95.7, 22 hrs CK-MB: 98.1, 14 hrs Myoglobin: 86.5, 10 hrs cTnT: 86.5, 10 hrs cTnI: 95.7, 18 hrs	Based on specificity at the time of most sensitive results. CK-MB subforms: 90.2, 10 hrs CK-MB mass: 99.6, 22 hrs CK-MB: 96.1, 14 hrs Myoglobin: 90.2, 10 hrs cTnT: 96.4, 10 hrs cTnI: 93, 18 hrs	The CK-MB subform assay alone or in combination with troponin reliably triages patients with chest pain and should lead to improved therapy and reduced cost.	Use of related test criteria for a reference criterion.	Outlines the changes in sensitivity and specificity of biomarkers over time following admission to ED.

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Grzybowski, et al, 2000	Prediction of death within 7 days in patients with suspected AMI (retrospective study). Key predictors were: female gender, over 65 years, and high SBP.	Country: USA Mean age:66.6 Age range: Not stated Enrolled: 291 Evaluation: 244 male (%): 58.6 Race: 58.6% white	Chief complaints: chest pain or shortness of breath. Age >18	Only patients with outcome data were analysed.	Examination of medical records for death within 7 days of ED arrival, MI, unstable angina, and cardiac arrest.	AMI - 96%
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	Not stated	86	53	A triage rule based on multivariate model can identify the group at high risk of early cardiac death. This decision rule needs to be prospectively validated.		Retrospective study. Predictor variables need to be accessed prospectively.

Technetium-99m Sestamibi Myocardial Perfusion Imaging

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria ²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Kontos, et al, 1999	CT Sestamibi imaging and serial myocardial marker measurement of CK-MB, total CK activity, cTnI over 8 hrs.	Country: USA Mean age:56 Age range: Not stated Enrolled: 721 Evaluation: 620 male (%):47 Race: Not stated	Suggestive symptoms of myocardial ischemia.	Patients at high risk of coronary disease. Patients who had had a PCTA within previous 6 months.	MI within one week of admission, performance of revascularization, or significant coronary disease on angiography within 6 weeks.	MI: 9
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	Discrete perfusion defect with associated abnormalities in wall motion and/or thickening, or Serial cTnI ≥ 2.0 ng/mL, or Serial cTnI ≥ 1 ng/mL	Perfusion imaging: 92 Serial cTnI ≥ 2.0 ng/mL: 90 Serial cTnI ≥ 1 ng/mL: 97	Perfusion imaging: 67 Serial cTnI ≥ 2.0 ng/mL:96 Serial cTnI ≥ 1 ng/mL: 94	Early perfusion imaging and serial cTnI have comparable sensitivities for identifying myocardial infarction. Perfusion imaging identified more patients who underwent revascularization or who had significant coronary disease, but had lower specificity. The two tests can provide complementary information for identifying patients at risk for ACS.	3 patients had uninterpretable images. No description of follow up techniques used to confirm diagnosis.	Unclear follow up procedures.

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Kosnik, et al, 2001	Technetium-99m sestamibi imaging within 2hrs of onset of pain, in conjunction with ECGs, cardiac enzymes, standard cardiac rhythm monitoring.	Country: USA Mean age:56 Age range: Not stated Enrolled: 69 Evaluation: 69 male (%): 43 Race: 26% white	Age≥18 years Non diagnostic ECG	Trauma; Arrhythmia Heart failure; Shock Pain resolved under 2hrs Pregnancy; Previous MI; Current cardiac complications; Diagnostic ECG (≥ 1mm ST segment elevation or depression or Q waves).	Not stated	Not stated
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	Interpretation by expert physician (EP) as positive, negative, or equivocal.	Not relevant as clinical impact study	Not relevant as clinical impact study	Sestamibi scanning results appropriately affected the EP's estimates of the probability of AMI and UA and improved disposition decisions. Scanning all low-risk patients would be likely to have increased costs.	No reporting on how follow up was achieved to determine if a cardiac event occurred.	Low sample size.

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Mariani, et al, 1999	99mTc-GLA injection, and imaging 3 hrs latter, serial CPK levels on at least 5 occasions.	Country: Europe Mean age:62 Age range: ND Enrolled: 28 Evaluation: 28 male (%): 79 Race: Not stated	Highly suggestive symptoms of AMI. (Prolonged chest pain unresponsive to nitrates, associated with persistent ST segment changes on ECG.	Not stated	Review of cardiologist, based on serial ECGs, presence of wall motion abnormalities on Echocardiogram and on serial CPK values.	AMI 82
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	Independent evaluation by 3 physicians, who were unaware of other diagnostic information.	Not performed	Not performed	99mTc-GLA localises in zones of acute myocardial necrosis when injected within 9 hrs of onset of infarction.		Small number of subjects. Diagnostic test characteristics need to be determined.

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Paventi, et al, 2001	Echocardiography, myocardial marker analysis, and myocardial perfusion imaging with 99mT sestamibi at 4 hrs post presentation.	Country: Italy Mean age: Not stated Age range: Not stated Enrolled: 555 Evaluation: 555 male (%): Not stated Race: Not stated	Patients with moderate risk of myocardial ischemia (typical symptoms lasting >30 minutes). Patients with low risk of Myocardial ischemia (typical symptoms lasting <30 minutes, or longer atypical symptoms).	Inadequate echocardiographic views.	WHO criteria: at least two of: symptoms consistent with myocardial ischemia for >30 minutes; evolving diagnostic ECG changes; CK-MB by mass assay >8.0ng/dL with RI >4. Long term follow up via telephone interviews, and death certificate records.	Not stated
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	Echocardiography: hypokinesis or akinesis of 2 or more contiguous segments, abnormal wall motion of one segment visible in 2 different views, or global hypokinesis with moderate to severe systolic dysfunction (ejection fraction >40%) without segmental wall motion abnormalities. Perfusion imaging: Discrete perfusion defect with an associated abnormality in wall motion or thickening.	Echocardiography: 100 Perfusion imaging: 100	Echocardiography: 84 Perfusion imaging: 86	Myocardial perfusion imaging and two-dimensional echocardiography are highly concordant when performed on patients initially considered at low or moderate risk for MI or ischemia. When combined with the clinical characteristics, both imaging techniques could help accurately identify the patient at high risk who requires admission and the patient at low risk who could undergo early stress testing to be safely discharged from the ED.	No clear reporting of follow up data on coronary events.	

Electron beam computed tomography

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria ²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Laudon, et al, 1999	Electron-beam computed tomography (EBCT) of coronary arteries plus other cardiac tests	Country: USA Mean age: 47.9 Age range:30-65 Enrolled: 105 Evaluation: 100 male (%):54 Race:93% white	Men <55, Female < 65 Normal initial cardiac enzyme values, and normal or indeterminate initial ECG.	Known coronary artery disease, known AMI, hemodynamic instability, pregnancy	Treadmill exercise test, radionuclide stress test, exercise echocardiogram interpreted as positive by cardiologist	AMI:14
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	Review by cardiovascular radiologist with the aid of automated software to identify coronary artery calcification.	100	63	EBCT is a rapid and efficient screening tool for patients admitted to the ED with angina-like chest pain, normal cardiac enzyme concentrations, indeterminate ECG findings and no history of coronary artery disease. Such patients with negative EBCT results may be safely discharged from the ED without further testing or observation.		Small numbers tested, but very promising results

Goldman Chest Pain Protocol

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria ²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Durairaj, et al, 2001	Goldman prediction rule	Country: USA Mean age:57.5 Age range:17-98 Enrolled:1061 Evaluation: 1033 male (%):48.7 Race:27% African American	Chest pain, and non chest pain with indicators of cardiac origin of symptoms.	Patients admitted from outpatients, transfers from inpatient services or other hospitals were excluded.	Cited previous work.	2.9%

	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	Not stated, cited previous work	Based on ruling out very low risk patients only: 76.7.	Based on ruling out very low risk patients only: 52.3.	The prediction rule accurately identified patients with or without chest pain who were at very low risk of major complications, identifying a subset from whom cardiac monitoring could be withheld safely.	2.6% (28/1061) Patients lost to follow up.	Follow up only over 72 hour period.

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Reilly, et al, 1999	Goldman prediction rule	Country: USA Mean age: Not stated Age range: Not stated Enrolled: 215 Evaluation: 207 male (%): 45 Race: not stated	Suspected acute ischaemic heart disease. Age > 18 years.	Not stated	Not stated	Major cardiac complications: 4.3
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	ECG suspicious for AMI, ECG suspicious for acute ischemic, systolic blood pressure < 100 mm Hg, rales bilaterally above the lung bases, known history of unstable ischemic heart disease.	Not performed.	Not performed.	This independent validation of the prediction rule suggests that it can improve triage decisions for patients admitted with suspected acute ischemic heart disease. Additional studies are needed to test prospectively the performance of the prediction rule in actual decision making, its acceptance by clinicians and its cost effectiveness.		Unclear how independent diagnosis was achieved, or the method of follow up undertaken. As such, results are very difficult to interpret.

Other Computer-Based Decision Aids

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria ²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Aase, 1999	Decision support computer program (DSP) in addition to clinical judgements, and ECG findings	Country: Norway Mean age: Not stated Age range: Not stated Enrolled: 493 Evaluation: 493 male (%):64.3 Race: Not stated	Chest pain	Not stated	Not stated	AMI: 36.1
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	Decision made by a computer program using Bayes' theorem	84.3	75.2	Use of DSP in the emergency room on easily available anamnestic and clinical variables may improve referrals to the CCU, optimise therapy and resource use.	No information on how follow up and final diagnosis was determined.	

Left bundle-branch blocks sub-population specific studies

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria ²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Kontos, et al, 2001a	Clinical histories, ECG and serial CK measurement in ED of patients with left bundle-branch block.	Country: USA Mean age:66 Age range: Not stated Enrolled: 7725 Evaluation:182 male (%):30.2 Race: Not stated	Left bundle-branch block (LBBB)	Not stated	CK-MB \geq 8.0 ng/mL and Relative index = 4.0 and characteristic increase and decrease in markers.	AMI: 13

	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	Retrospective analysis of records	New LBBB: 42 Combined ST-segment and CK-MB: 63	New LBBB: 42 Combined ST-segment and CK-MB: 99	ECG criteria for identifying patients with AMI and LBBB identify only a small minority of patients with AMI. Treating all patients with LBBB and chest pain with fibrinolytics would result in treatment of a significant number of patients without AMI.	ND	Unclear how follow up was achieved. Important work on evaluating AMI in a sub-population.

Study, year,	Diagnostic protocol	Location, population	Inclusion criteria²	Exclusion criteria	Reference criteria	Prevalence of disease (%)
Shlipak et al., 1999	Retrospective analysis of initial ECG data to predict AMI in patients with LBBB.	Country: USA Mean age: ND Age range: ND Enrolled: 83 Evaluation: 103 admissions male (%): ND Race: ND	Age > 18 years. Acute cardiopulmonary symptoms and complete LBBB on initial 12-lead ECG.	No measure of CK or troponin I within 12 hrs of initial ECG.	MI: characteristic clinical presentation and troponin I ≥ 1.5 mg/L or CK-MB fraction ≥ 7 U/L	AMI: 30
	Test criteria for AMI	Sensitivity (%)	Specificity (%)	Study conclusions	Potential verification bias	Limitations/comments
	Any 3 ST-segment abnormalities	23	82	The ECG is a poor predictor of MI in a community-based cohort of patients with LBBB and acute cardiopulmonary symptoms. Acute thrombolytic therapy should be considered for all patients with LBBB who have symptoms consistent with MI.	Multiple admissions into the study were allowed. The authors analysed the possible effects of this, and found that the results did not change when the subsequent admissions were omitted.	Questionable use of readmitting the same patient on multiple ED admissions.

Appendix 1: Summary of guidelines concerning AMI

Summary 1

**American College of Emergency Physicians. Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting with Suspected Acute Myocardial Infarction or Unstable Angina
Ann Emerg Med. May 2000;35:521-544.**

This clinical policy focuses on critical issues in the evaluation and management of patients with acute myocardial infarction or unstable angina. A MEDLINE search for articles published between January 1993 and December 1998 was performed using combinations of the key words chest pain, acute myocardial infarction, unstable angina, thrombolytics, primary angioplasty, 12-lead ECG, ST-segment monitoring, cardiac serum markers, and chest pain centers. Subcommittee members and expert peer reviewers also supplied articles with direct bearing on the policy.

This policy focuses on 5 areas of current interest and/or controversy: (1) ECG eligibility criteria for fibrinolytic therapy, (2) role of primary angioplasty in patients with acute myocardial infarction, (3) use of serum markers to diagnose acute myocardial infarction, (4) serial 12-lead ECGs during the initial evaluation, and (5) chest pain evaluation units. Recommendations for patient management are provided for each of these 5 topics based on strength of evidence (Standards, Guidelines, Options). *Standards* represent patient management principles that reflect a high degree of clinical certainty; *Guidelines* represent patient management principles that reflect moderate clinical certainty; and *Options* represent other patient management strategies based on preliminary, inconclusive, or conflicting evidence, or based on panel consensus. This guideline is intended for physicians working in hospital-based emergency departments or chest pain evaluation units.

Methodology

This clinical policy was created after careful review and critical analysis of the peer-reviewed literature. A MED-LINE search for articles published between January 1993 and December 1998 was performed using combinations of the key words chest pain, AMI, unstable angina, and thrombolytics. Abstracts were reviewed by subcommittee members, who then selected the following topics on which to focus this policy: (1) ECG eligibility criteria for fibrinolytic therapy, (2) role of primary angioplasty in patients with AMI, (3) use of serum markers to diagnose AMI, (4) serial 12-lead ECGs during the initial evaluation, and (5) chest pain evaluation units. Additional MEDLINE searches were performed using the key words 12-lead ECG, ST-segment monitoring, cardiac serum markers, and chest pain centers. Pertinent articles were selected from the reviewed abstracts and from bibliographies of initially selected papers. Committee members and expert reviewers also supplied papers from their own knowledge base. All publications were stratified by at least 2 of the subcommittee members into 1 of 3 categories of strength of evidence, and some were down-graded 1 or more levels as necessary based on a standardized formula that graded papers on size, methodology, validity of conclusions, and potential sources of bias.

This policy is not intended to be a complete manual on the initial evaluation and management of patients with AMI and unstable angina. Some areas suggested by expert peer reviewers for

addition of further discussion included utilization of serum markers to risk stratify unstable angina patients, use of combinations of serum markers to exclude AMI, risk stratification tools such as the acute time-insensitive predictive instrument (ACI-TIPI) and Goldman criteria for predicting need of intensive care admission, and discussion of multiple technologies for identifying acute coronary syndromes (ACS). These areas have been discussed to some degree in other clinical policies and represent areas that ACEP may address in future updates of this current policy. The reasons for developing clinical policies in emergency medicine and the approaches used in their development have been enumerated.

This policy is a product of the ACEP clinical policy development process, including expert review, and is based on the existing literature; where literature was not available, consensus of emergency physicians was used. Expert review comments were received from emergency physicians, physicians from other specialties, such as cardiologists, and specialty societies including members of the American Academy of Family Physicians, American Association for Clinical Chemistry, and the American Society of Nuclear Cardiologists. Their responses were used to further refine and enhance this policy. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology or the practice environment changes significantly. During the review process, all papers were given a baseline “strength of evidence” by the subcommittee members, according to the following criteria:

Strength of evidence A—Interventional studies including clinical trials, observational studies including prospective cohort studies, aggregate studies including meta-analyses of randomized clinical trials only.

Strength of evidence B—Observational studies including retrospective cohort studies, case-controlled studies, aggregate studies including other meta-analyses.

Strength of evidence C—Descriptive cross-sectional studies, observational reports including case series, case reports; consensual studies including published panel consensus by acknowledged groups of experts. Strength of Evidence A and B papers were then rated on elements the committee believed were most important in creating a quality work. A and B papers with significant flaws or design bias were downgraded from 1 to 3 levels based on a set formula. Strength of Evidence C articles were downgraded 1 level if they demonstrated significant flaws or bias. Articles downgraded below a “C” strength of evidence were given an “X” rating and were not used in formulating this policy. Clinical findings and strength of recommendations regarding patient management were then made according to the following criteria:

Evidence-based standards. Generally accepted principles for patient management that reflect a high degree of clinical certainty (ie, based on “strength of evidence A” or overwhelming evidence from “strength of evidence B” studies that directly address all the issues).

Guidelines. Recommendations for patient management that may identify a particular strategy or range of management strategies that reflect moderate clinical certainty (ie, based on “strength of evidence B” that directly addresses the issue, decision analysis that directly addresses the issue, or strong consensus of “strength of evidence C”).

Options. Other strategies for patient management based on preliminary, inconclusive, or conflicting evidence, or, in the absence of any published literature, based on panel consensus.

Scope of Application

This guideline is intended for physicians working in hospital-based emergency departments or chest pain center evaluation units.

Patient management recommendations

1. ECG eligibility criteria for emergent reperfusion therapy

Evidence-based standards. Assess for fibrinolytic therapy in patients presenting within 12 hours of symptom onset if ECG reveals:

1. ST-segment elevations greater than 0.1 mV in 2 or more contiguous leads that are not characteristic of early repolarization or pericarditis, nor of a repolarization abnormality from LVH or BBB in patients with clinical presentation suggestive of AMI.
2. Any type of BBB (right, left, paced, and atypical— new or old) in patients with clinical presentation suggestive of AMI.

Guidelines. Assess for fibrinolytic therapy if ECG reveals LBBB and ST-segment deviations of 1 mm or more toward the major QRS deflection or 5 mm or more away from the major QRS deflection in 2 or more contiguous leads in patients with atypical presentation of AMI.

Options. Assess for fibrinolytic therapy if ECG reveals:

1. ST-segment depressions of 1 mm or more with upright T waves in 2 or more contiguous anterior precordial leads in patients with clinical presentation suggestive of posterior AMI.
2. ST elevations of 1 mm or more in 2 or more contiguous nonstandard leads (V 4 R through V 6 R, V 7 through V 9) in patients with clinical presentation suggestive of isolated right ventricular or posterior AMI.
3. RBBB, atypical BBB, or paced BBB and ST-segment deviations of 1 mm or more toward the major QRS deflection or of 5 mm or more away from the major QRS deflection in 2 or more contiguous leads in patients with atypical presentation of AMI.

2. Role of primary angioplasty in patients with AMI

Evidence-based standards. Primary coronary angioplasty when performed by experienced personnel within 90 minutes of diagnosis of AMI is as effective as fibrinolytic therapy in AMI patients meeting standard criteria for emergency reperfusion therapy.

Guidelines. If resources are available, consider primary coronary angioplasty as an alternative to fibrinolytic therapy in AMI patients meeting standard criteria for emergent reperfusion therapy providing it can be performed within 90 minutes of diagnosis of AMI.

Options. None specified.

3. Serum marker analysis in AMI

Evidence-based standards. No single determination of one serum biochemical marker of myocardial necrosis *reliably identifies** or *reliably excludes*** AMI less than 6 hours of symptom onset. No serum biochemical marker identifies or excludes unstable angina at any time after symptom onset.

Guidelines. In patients presenting with acute chest pain and a negative baseline serum marker

level, consider repeat serum marker testing at the following time intervals from symptom onset ‡ before making an exclusionary diagnosis of non-AMI chest pain:

- CK-MB activity 8–12 hours
- CK-MB mass 6–10 hours
- CK-MB subforms 6–10 hours
- cTnT 8–12 hours
- cTnI 8–12 hours

The exact timing of the repeat determination of the serum marker value should take into account the sensitivity, precision, and institutional norms of the assay being used, as well as the release kinetics of the marker being measured. CK-MB activity, CK-MB mass, cTnT, and cTnI all reliably identify and exclude AMI 12 to 24 hours after symptom onset. Because of its rapid release kinetics, myoglobin alone does not reliably identify or exclude AMI at any time interval after symptom onset and is best used in conjunction with the other common serum markers. cTnT and cTnI are the preferred serum markers in patients presenting greater than 24 hours after symptom onset.

Options. Consider repeat determination of CK-MB mass 2 to 3 hours after baseline or repeat myoglobin at 1 to 2 hours after baseline for utilization of the .CK-MB or .myoglobin when the repeat serum marker level is drawn at a time interval before the time intervals discussed in the Guidelines recommendation above.

*Reliably identifies = sensitivity $\geq 90\%$ with positive likelihood ratio ≥ 10

**Reliably excludes = specificity $\geq 90\%$ with negative likelihood ratio ≤ 0.1

4. Serial 12-lead ECGs in the ED

Evidence-based standards. Performing SECG or repeat ECGs at select time intervals after presentation results in an incremental increase in identification of injury or ischemia in patients with AMI and unstable angina compared with the baseline ECG. Its greatest value appears to be when it is used in patients with intermediate or high clinical likelihood of AMI or unstable angina who are spending at least 1 hour in the ED or in identification of successful reperfusion from fibrinolytic treatment.

Guidelines. Perform repeat ECG at a set time interval after presentation or automated SECG monitoring during the ED evaluation of patients in whom the initial ECG is non-diagnostic for injury and who have symptoms consistent with ongoing or recurrent ischemic chest pain.

Options. Perform repeat ECG at a set time interval after presentation or automated SECG monitoring during the ED evaluation of patients with a low suspicion of AMI or unstable angina.

5. Chest pain evaluation units

Evidence-based standards. Chest pain evaluation units are a safe and effective alternative to routine admission for evaluation of low- to intermediate-risk chest pain patients. Further investigation needs to be performed to determine the most cost-effective and efficient utilization of available diagnostic modalities.

Guidelines. As an alternative to admission, consider use of a CPEU protocol consisting of serial serum marker determinations, serial ECGs, and selective stress testing for evaluation and risk stratification of patients at low- to intermediate-risk for AMI and ACS.

Options. None stated.

Summary 2

'CHEST PAIN: CLINICAL DECISION-MAKING' **American College of Emergency Physicians,** **1998 Scientific Assembly**

This document provides a guide to all causes of chest pain and to the diagnostic tools which are appropriate for use with each of the causes identified.

A Diseases You Can't Afford to Miss

1. Myocardial infarction

WHO Criteria: At least 2 of the following:

- (1) Ischemic chest discomfort > 30 min
- (2) ECG evolution: ST waves, Q waves
- (3) Serum cardiac marker changes

2. Unstable Angina

Presentation

- (1) New onset of chest pain > 20 mins
- (2) Chest pain at rest > 20 mins
- (3) Chest pain at previously tolerated levels of activity
- (4) Chest pain not relieved by previously effective dose of nitroglycerin

3. Aortic Dissection

Presentation

- (1) Sudden, excruciating chest pain
- (2) Often "tearing" and radiating to back
- (3) May have neurologic abnormalities, CHF, syncope
- (4) May have BP differential between arms
- (5) May have murmur of AI

4. Pericarditis

Presentation

- (1) Sharp, central chest pain
- (2) Pain worse recumbent; better leaning forward
- (3) Pericardial friction rub is pathognomonic (LLSB)
- (4) ECG findings
 - (a) Diffuse concave-upward ST segment elevation
 - (b) Sometimes PR-segment depression

5. Cardiac Tamponade

Presentation

- (1) Chest pressure/discomfort with SOB
- (2) May see elevated JVP, hypotension, tachypnea, narrow pulse pressure, pulsus paradoxus
- (3) May see electrical alternans on ECG
- (4) Echocardiography is diagnostic (ED or formal US)

6. Pulmonary Embolus

1. Presentation

- (1) 96% will have either dyspnea, pleuritic pain or tachycardia

- (2) Sx: Chest pain (88%), dyspnea (84%), apprehension/anxiety (59%), syncope (13%)
- (3) Findings: RR > 16 (92%) [but who counts, anyway], rales (58%), HR > 100 (44%), Temp > 37.8 (43%)

2. Diagnostic Modalities:

- (1) CXR - Usually non-contributory
- (2) ECG - May see sinus tachycardia or rarely S1-Q3-T3
- (3) V/Q Scan - 85% Sensitive. Must interpret in light of your pre-test probability.
- (4) Pulmonary angiogram - Still the gold standard: 96-98% sensitive and specific
- (5) Helical CT - Becoming more popular. Sensitivity close to V/Q. Will it replace it?
- (6) MRI - Under evaluation. May prove quite useful.
- (7) Lower extremity doppler ultrasound - Helpful if positive. Not helpful if negative.
- (8) D-Dimer - Degradation product of fibrin. Disagreement about utility at this time.
- (9) ABG - 10-15% have normal A-a gradient. Little utility unless pre-test probability is very low.

7. Pneumothorax

8. Acute Chest Syndrome of Sickle Cell Disease

Adult presentation

- (1) Chest pain: 84% (Severe, 44%)
- (2) Fever: 64%
- (3) Cough: 63%
- (4) Shortness of breath: 47%
- (5) Chills: 39%
- (6) Diagnosis made by new infiltrate on CXR

9. Esophageal Rupture

Presentation

- (1) Severe chest pain, usually pleuritic
- (2) Dyspnea, SOB, cyanosis
- (3) Odonophagia
- (4) Pain on neck flexion
- (5) Pale, diaphoretic, severely ill appearing
- (6) Subcutaneous emphysema
- (7) Hamman's crunch
- (8) CXR: May see pneumo-mediastinum, pleural effusion, pneumothorax, widened mediastinum

If undiagnosed, is uniformly fatal

B. Diseases You Would Like Not to Miss

- 1. Pneumonia
- 2. Esophageal Disease (Spasm, Reflux, Inflammation)
- 3. Peptic or Gastric Ulcer (with or without perforation)
- 4. Cholecystitis
- 5. Early Disseminated Lyme Disease
May present with chest pain, syncope, dizziness, SOB, A-V block

C. Benign Diagnoses (Relatively)

1. Panic Disorder
 - (1) Intense fear accompanied by chest pain, dyspnea, nausea
 - (2) Seen in 30-50% of patients with chest pain and normal coronary arteries
 2. Depression
 3. Herpes Zoster
 4. Hyperventilation
 5. Chest Wall Pain / Costochondritis
-

D. Making the Diagnosis of Myocardial Infarction

1. History
 - (1) Worry more: males, older, h/o MI, pain > 1 hour, diaphoresis
 - (2) Worry less: "sharp" pain, age < 40
2. Physical Examination
 - (1) Worry more: rales
3. ECG
 - (1) (1) 50-60% of AMI patients will have diagnostic changes
 - (2) Normal or non-diagnostic ECG -> low risk patients
 - (3) Comparison with old ECG may not change admission decision, but may change level of acuity
 - (4) Abnormalities:
 - ST-T elevation > 1mm in standard pattern
 - Q waves (.04 sec, 1/3 height of R wave) (except in III)
 - T wave inversion (unless only in III or V1)
 - Hyper-acute T waves in 2 or more leads
 - LBBB (even if old), in light of ischemic pain should be treated aggressively
 - Suspect RV infarction with distended neck veins & clear lungs:
ST-T elevation of >1mm in V4R is diagnostic
 - (5) Increased sensitivity through automated serial 12-lead ECG
4. Serum Markers
 - (1) CK - not used by itself
 - (2) CK-MB total activity (IU/ml)
 - (3) CK-MB mass (ng/ml) - The current gold standard CK-MB Index (CK-MB mass / CK total activity)
 - (4) CK-MB Subforms - In development
 - (5) Myoglobin - Sensitive but not specific; narrow window
 - (6) Troponin-T - Very sensitive; may help risk-stratify unstable angina
 - a. Troponin-I - Most specific for cardiac injury
 - b. Combining markers, eg myoglobin/CK-MB mass
 - c. Delta measurements: Ongoing work to evaluate utility of rise in marker value while still in normal range
2. Problems with comparing serum marker studies
 - (1) Assay under evaluation often used as dx criterion of AMI
 - (2) Inconsistencies in cut-off values used for marker
 - (3) Wide variation in populations studied
 - (4) Few studies are outcome-based
5. Neural Networks
 1. Network is trained

2. Network establishes its own decision basis
3. Feedback over time can improve decision process
4. Significant potential
5. Shortcomings:
 - (1) Individual diagnosis based
 - (2) Each system a different interface
 - (3) Feedback of local data probably required
6. Ancillary Studies
 1. Exercise Tolerance Test (ETT)
 - (1) Least expensive
 - (2) Most available
 - (3) Can be utilized as part of a "rapid r/o" protocol
 - (4) Only 65-70% sensitivity for CAD
 2. Stress Echocardiography
 - (1) Intermediate expense
 - (2) Operator dependent
 - (3) About 80% sensitive for CAD
 - (4) Availability?
 3. Thallium Perfusion Scan
 - (1) Short window due to rapid wash-out
 4. Sestamibi
 - (1) Better image, 1-2 hour window
 - (2) May be as sensitive as stress echo but needs more study
7. Special Cases
 1. The Elderly
 2. Cocaine-Chest Pain

E. Management Plan for Cardiac Chest Pain

- A. Risk Stratification
 1. High Risk
 - (1) Ischemic or new ECG findings
 - (2) Ongoing chest pain
 - (3) Abnormal vital signs
 - (4) Rales
 2. Moderate Risk
 - (1) Nondiagnostic ECG
 - (2) Symptoms > 20-30 minutes, now resolved
 3. Low Risk
 - (1) Normal ECG
 - (2) Symptoms < 20-30 minutes, now resolved
- B. Evaluation, including ECG must be prompt
- C. Infarcting
 1. Have a standard procedure
 2. Lytics: Fair evidence: up to 6 hrs, delay increases infarct size
 3. Angioplasty
- D. Who to admit where?
 1. High risk: CCU
 2. Medium/Low risk:
 - Telemetry/Chest Pain Observation

- (1) Immediate Exercise Testing in Low Risk Patients
 - (2) Immediate Myocardial Perfusion Imaging in Low Risk Patients
- E. ED Chest Pain Evaluation Units
- 1. Pros
 - (1) More rapid throughput of low risk chest pain patients
 - (2) More cost-effective evaluation of same
 - (3) An additional alternative to admission or discharge
 - (4) Additional service line for ED
 - (5) Potential for improved patient satisfaction
 - 2. Cons
 - (1) Additional responsibility and effort for emergency physicians
 - (2) Potential for lost revenue for hospital
 - (3) Potential for higher charges for patients admitted to hospital
 - (4) After evaluation unit stay
 - (5) Potential requirement for capital improvement and increased
 - (6) Staffing
 - (7) Potential for inappropriate use as disposition
 - 3. Requirements
 - (1) Interdisciplinary planning
 - (2) Location, monitoring & resuscitation equipment
 - (3) Appropriate staffing
 - (4) Protocol driven

F. Documentation of the Chest Pain Visit

- A. The Minimum (ACEP, 1995)
 - 1. Character of pain
 - 2. Age
 - 3. Associated symptoms
 - 4. Past history
 - 5. Vital signs
 - 6. Cardiovascular exam
 - 7. Pulmonary exam
- B. When MI is in the Differential
 - 1. Pain: Quality, onset/duration, location, radiation, made worse by, made better by
 - 2. Associated symptoms: Diaphoresis, nausea/vomiting, SOB/DOE, fatigue, syncope
 - 3. Past cardiac history, risk factors
 - 4. Vital signs
 - 5. Cardiovascular exam: JVD, heart (rhythm, murmurs, gallops)
 - 6. Pulmonary exam (rales, wheezes)
 - 7. Extremities: peripheral edema
 - 8. ECG, CXR
- C. Other additional documentation based on diagnostic suspicion
- D. The Discharged Chest Pain Patient
 - 1. Are your discharge instructions adequate?
 - 2. Is your record completed at the time of discharge?
 - 3. Re-read your record in your head from the witness stand
 - (1) Is your record consistent with the chief complaint, the triage note and the nurses notes?
 - (2) Does your record support your diagnosis and disposition?

- (4) "Not documented, not done"
 - a. Does your record address those things we can't afford to miss?
 - b. If you don't think it's cardiac (or other problems you can't afford to miss), say so
 - 4. How does your ED deal with patient phone calls?
 - 5. We lose the most \$ on the youngest MI's
 - E. Discharge against medical advice (AMA) patients require special care and documentation
 - 1. Don't get into an ego-duel
 - 2. Provide the best treatment and follow-up you can
 - 3. Explain the life threat
 - 4. Carefully document the refusal of care
 - 5. If you have an AMA form, fill it out **completely**
 - 6. Use a second person witness; family member is best
 - 7. Always offer future care
-

Summary 3

Clinical policy for the initial approach to adults presenting with a chief complaint of chest pain, with no history of trauma American College of Emergency Physicians, 1995

Chest pain is one of the most common and complex symptoms for which patients seek emergency medical care. For these reasons the chief complaint of chest pain was selected as the focus for the first clinical policy by the American College of Emergency Physicians. The original policy, published in 1990, was primarily a consensus document based on standard textbooks, review articles, and clinical practice experience. There was at that time little scientific evidence in the medical literature to support specific historical or clinical findings or therapeutic modalities. The original policy was therefore intentionally nondirective on many issues of specific diagnostic methods and therapy.

Since 1990 there has been an explosion of research and publication activity relating to the diagnosis and treatment of disorders causing chest pain. Among these are multinational, multicenter and independent investigator studies on the use of specific therapeutic agents and diagnostic modalities in coronary artery disease, myocardial infarction, and thromboembolic disease.

This clinical policy was developed by the ACEP Clinical Policies Committee and went through ACEP's clinical policy development process, including expert review and field testing. Expert reviewers included emergency physicians, physicians from other specialties, and various specialty societies. Comments were received from members of the American Academy of Family Physicians, the American College of Cardiology, the American Heart Association, the Internal Medicine Center to Advance Research and Education (IMCARE) Practice Guidelines Network, and the Emergency Nurses Association. Field test volunteers represented varied geographic areas, practice settings, and patient populations. All of the expert review and field test comments and recommendations were given careful consideration by the Clinical Policies Committee as they made decisions about the policy.

The revised clinical policy on chest pain, like the original in format and tone, concentrates on identification of situations associated with high morbidity and mortality. There has been an ongoing effort to balance guidelines between the needs of the emergency physician practicing in a small hospital and those of the attending emergency physician at a large academic center. This revision places a greater emphasis on identification of risk factors for specific diseases and is more directive regarding specific diagnostics and therapies that are no longer controversial and have been accepted as efficacious. ACEP, however, clearly recognizes the ultimate importance of the individual clinician's judgment, and that there are variations in practice.

There remain many evolving issues in diagnosis and therapy awaiting further research before firm recommendations can be made.

From this policy document the following form has been taken as a good example of all the factors needing consideration when a patient presents at ED with chest pain.

Quick Reference Form: Chest Pain Revision

For adults with chest pain and no history of trauma. This policy does *not* include history of proximate trauma; or visible lesions; or isolated breast disease; or pain of very brief duration (lasting for seconds only).

Circle line number if yes. **Bolded actions are rules.** Actions not bolded are guidelines.

Chief Complaint

Chest pain with no history of trauma

History

Pain

1. Ongoing *and* severe *and* crushing *and* substernal *or* same as previous pain diagnosed as MI
IV access, supplemental oxygen, cardiac monitor, ECG, aspirin, nitrates, management of ongoing pain, admit, serum cardiac markers (eg, CKMB), CXR, anticoagulation
2. Severe *or* pressure *or* substernal *or* exertional *or* radiating to jaw, neck, shoulder, or arm
ECG, IV access, supplemental oxygen, cardiac monitor, serum cardiac markers (eg, CKMB), CXR, nitrates, management of ongoing pain, admit
3. Tearing, severe, and radiating to back
large-bore IV access, supplemental oxygen, cardiac monitor, CXR, ECG, differential upper extremity blood pressures, aortic imaging, management of ongoing pain, admit
4. Similar to that of previous pulmonary embolus
IV access, supplemental oxygen, cardiac monitor, ABG/oximetry, anticoagulation/pulmonary vascular imaging, ECG, CXR, admit
5. Indigestion or burning epigastric
ECG
6. Pleuritic
CXR, ECG
7. Age (male>33 years, female>40 years)
ECG

Associated Symptoms

8. Syncope or near-syncope
ECG, cardiac monitor, Hct
9. SOB, DOE, PND, or orthopnea
ECG, ABG/oximetry, CXR
10. Significant hemoptysis
CXR, respiratory isolation, ABG/oximetry
11. Nausea/vomiting
ECG
12. Productive or chronic cough
respiratory isolation, CXR
13. Palpitations
cardiac monitor, ECG
14. Significant weight change
CXR
15. Diaphoresis
ECG

Past Medical History

16. Previous MI
ECG
17. Coronary artery bypass graft/angioplasty
ECG
18. Cocaine use within last 96 hours
ECG
19. Previous positive cardiac diagnostic studies
ECG
20. Cardiac medications
serum drug levels, ECG
21. Diuretics
potassium level, magnesium level
22. IV drug abuse
ABG/oximetry, CXR, ECG
23. major risk factors for coronary artery disease (see Appendix A)
ECG
24. major risk factors for pulmonary embolism (see Appendix A)
ABG/oximetry, CXR, pulmonary vascular imaging, venous imaging, ECG
25. major risk factors for thoracic aortic aneurysm/dissection (see Appendix A)
CXR, aortic imaging, ECG
26. major risk factors for pericarditis/myocarditis (see Appendix A)
serum cardiac markers, CXR, echocardiography, ECG
27. major risk factors for pneumothorax (see Appendix A)
oximetry, CXR
28. major risk factors for pneumonia (see Appendix A)
ABG/oximetry, CXR

Physical Examination

Vital Signs

29. Irregular pulse
rhythm strip/cardiac monitor, ECG
30. Tachypnea (RR>24)
ABG/oximetry, CXR, ECG
31. Fever (>38°C/100.4°F)
CXR
32. Hypertension (>160/110)
CXR, ECG
33. Tachycardia (>100)
ABG/oximetry, ECG
34. Bradycardia (<60)
IV access, ECG

Appearance

35. Cyanosis with respiratory distress
IV access, supplemental oxygen, cardiac monitor, ABG, CXR, ECG, methemoglobin level, pulmonary vascular imaging, intubation, admit
36. Diaphoresis
ECG, IV access, ABG/oximetry, serum cardiac markers, CXR, admit

Cardiovascular

37. Significant differential upper extremity blood pressures
large-bore IV access, CXR, ECG, supplemental oxygen, cardiac monitor, aortic imaging
38. New murmur
ECG, CXR, echocardiography
39. Pericardial rub
ECG, serum cardiac markers, CXR, echocardiography
40. Irregular rhythm .
rhythm strip/cardiac monitor, ECG
41. JVD
1 CXR, ECG
42. S₃ gallop
CXR, ECG

Pulmonary

43. Unilateral diminished breath sounds
CXR, ABG/oximetry
44. Localized dullness to percussion
CXR
45. Pleural rub
ABG/oximetry, CXR, ECG
46. Unilateral rales
supplemental oxygen, ABG/oximetry, CXR
47. Bilateral rales
IV access, supplemental oxygen, ABG/oximetry, CXR, ECG
48. Wheezing
supplemental oxygen, cardiac monitor, ABG/oximetry, FEV₁ /PEF, CXR, ECG, bronchodilators

Extremities

49. Signs of DVT: leg swelling, pain, tenderness, warmth, or erythema
ABG/oximetry, CXR, pulmonary vascular imaging, venous imaging, ECG
50. Bilateral edema
CXR, ECG

Diagnostic Testing

51. cardiac monitor/ECG: new dysrhythmia
cardiac monitor, IV access, supplemental oxygen, potassium level, magnesium level, serum cardiac markers, ECG, antidysrhythmic therapy
52. ECG: new injury
IV access, supplemental oxygen, cardiac monitor, assess for thrombolytic therapy (see Appendix B) or other reperfusion techniques, anticoagulation, aspirin, nitrates, management of ongoing pain, admit, serial serum cardiac markers, CXR, cardiac imaging, serial ECGs, magnesium therapy if not given thrombolytics, b-blockers
53. ECG: new ischemic changes
IV access, supplemental oxygen, cardiac monitor, anticoagulation, aspirin, nitrates, management of ongoing pain, admit, comparison with previous ECG if available, serial serum cardiac markers, CXR, serial ECGs, b-blockers
54. ECG: nondiagnostic ECG
comparison with previous ECG if available, IV access, supplemental oxygen, cardiac monitor, serial serum cardiac markers, CXR, serial ECGs, nitrates, management of ongoing pain
55. CXR: acute pulmonary edema

- IV access, supplemental oxygen, cardiac monitor, ABG/oximetry, ECG, preload/afterload reduction (eg, diuretics/nitrates),** serum cardiac markers, management of ongoing pain, inotropic support, admit
56. CXR: wide mediastinum (new)
large-bore IV access, aortic imaging, differential upper extremity blood pressure, supplemental oxygen, cardiac monitor, blood type and crossmatch, surgical consult
57. CXR: large pneumothorax
re-expansion, IV access, supplemental oxygen, ABG/oximetry, admit
58. CXR: small pneumothorax
 IV access, ABG/oximetry, serial CXRs, re-expansion, consult
59. CXR: new infiltrate
 respiratory isolation, supplemental oxygen, ABG/oximetry, appropriate cultures, sputum for Gram stain, antibiotics, admit
60. CXR: new mass
 ABG/oximetry
61. CXR: new effusion
 ABG/oximetry, thoracentesis
62. ABG: new significant A–a gradient or new significant reduction in PO₂
Supplemental oxygen, CXR, IV access, cardiac monitor, pulmonary vascular imaging, ECG, admit
63. VQ scan: high probability of pulmonary embolus
IV access, supplemental oxygen, cardiac monitor, ABG/oximetry, anticoagulation, admit, assess for thrombolytic therapy (see Appendix B), ECG
64. VQ scan: intermediate, low, and normal in presence of high clinical suspicion
 IV access, supplemental oxygen, cardiac monitor, venous imaging, pulmonary angiography, anticoagulation, admit

Assessment

65. Unstable angina: new-onset exertional
ECG, aspirin, IV access, supplemental oxygen, cardiac monitor, nitrates, consult/admit
66. Unstable angina: ongoing or recurrent ischemia
IV access, supplemental oxygen, cardiac monitor, ECG, anticoagulation, aspirin, nitrates, management of ongoing pain, admit, serial serum cardiac markers, CXR, cardiac imaging, serial ECGs, b–blockers
67. High clinical suspicion of MI with nondiagnostic ECG
IV access, supplemental oxygen, cardiac monitor, anticoagulation, aspirin, nitrates, management of ongoing pain, admit, serial serum cardiac markers, .CXR, cardiac imaging, serial ECGs, magnesium therapy, b–blockers
68. High clinical suspicion of MI with bundle branch block
IV access, supplemental oxygen, cardiac monitor, assessment for thrombolytic therapy (see Appendix B) or other reperfusion techniques, anticoagulation, aspirin, nitrates, management of ongoing pain, admit, serial serum cardiac markers, CXR, cardiac imaging, serial ECGs, magnesium therapy if not given thrombolytics, b–blockers
69. Low clinical suspicion of MI with nondiagnostic ECG .
 IV access, supplemental oxygen, cardiac monitor, serial serum cardiac markers, CXR, cardiac imaging, serial ECGs, anticoagulation, b–blockers, aspirin, nitrates, management of ongoing pain, admit
70. Acute MI with diagnostic ECG
IV access, supplemental oxygen, cardiac monitor, assessment for thrombolytic therapy (see Appendix B) or other reperfusion techniques, anticoagulation, aspirin, nitrates, management of ongoing pain, admit, serial serum cardiac markers, CXR, cardiac imaging, serial ECGs, magnesium therapy if not given thrombolytics , b–blockers

71. Aortic dissection
large-bore IV access, supplemental oxygen, cardiac monitor, blood type and crossmatch, ECG, management of blood pressure/cardiac contractility, management of ongoing pain, immediate surgical consultation, admit, aortic imaging
72. Pericarditis/myocarditis
ECG, serum cardiac markers, CXR, echocardiography, consult/admit
73. Pneumonia
CXR, ABG/oximetry, appropriate cultures, sputum for Gram stain, antibiotics
74. Pulmonary embolus
IV access, supplemental oxygen, cardiac monitor, ABG/oximetry, CXR, ECG, anticoagulation, admit, assessment for thrombolytic therapy (see Appendix B), venous imaging, consultation for filter placement if history of recurrent pulmonary embolus
75. Pneumothorax
CXR, IV access, supplemental oxygen, ABG/oximetry, serial CXRs, re-expansion, consult/admit
76. Acute pulmonary edema
IV access, supplemental oxygen, cardiac monitor, ABG/oximetry, CXR, ECG, preload/afterload reduction (eg, diuretics/nitrates), serum cardiac markers, management of ongoing pain, inotropic support, admit

Disposition

77. Admission
transfer care to accepting physician
78. Transfer
follow ACEP and other applicable transfer policies
79. Discharge
provide referral for follow-up care, provide instructions regarding treatment and circumstances that require return to emergency department

Notes:

Abbreviations

- A-a gradient=arterial to alveolar oxygen gradient
 ABG=arterial blood gas
 CXR=chest x-ray
 DVT=deep vein thrombosis
 DOE=dyspnea on exertion
 ECG=electrocardiogram
 FEV 1 /PEF=forced expiratory volume 1-second /peak expiratory flow
 IV=intravenous
 JVD=jugular venous distension
 MI=myocardial infarction
 PND=paroxysmal nocturnal dyspnea
 SOB=shortness of breath

APPENDIX A: RISK FACTORS

Coronary Artery Disease

Family history of coronary artery disease
Men, age > 33; Women, age > 40
Diabetes mellitus
Hypertension
Cigarette use
Left ventricular hypertrophy
Elevated cholesterol blood levels (High LDL/Low HDL/Cholesterol levels)
History of chronic cocaine use

Pulmonary Embolism

Prolonged immobilization
Surgery lasting >30 minutes within the last 3 months
History of DVT or pulmonary embolus
Malignancy
Pregnancy or recent pregnancy
History of pelvis or lower extremity trauma
Oral contraceptive use combined with cigarette smoking
Congestive heart failure
Chronic obstructive pulmonary disease
Obesity
Hypercoagulability (Antithrombin III deficiency, etc)

Thoracic Aortic Aneurysm/Dissection

Hypertension
Congenital disease of ascending aorta or aortic valve
Inflammatory disease of aorta
Connective tissue disease
Pregnancy
Arteriosclerosis
Cigarette use

Pericarditis/Myocarditis

Infection (eg, tuberculosis, viral)
Autoimmune/systemic disease (eg, lupus erythematosus)
Acute rheumatic fever (autoimmune)
Recent myocardial infarction or cardiac surgery
Malignancy
Radiation therapy to mediastinum
Uremia
Drugs (Procainamide, Hydralazine, INH, etc)
History of a prior episode of pericarditis

Pneumothorax

History of previous pneumothorax
Valsalva manoeuvre
Lung disease (obstructive, cancer, infection, connective tissue disease)
Cigarette use

Pneumonia

Chronic lung disease
Altered consciousness/impaired gag reflex
Neuromuscular disease
Thoracic cage deformity
Cigarette use
Preceding viral respiratory infection
Immunodeficiency

APPENDIX B: CONTRAINDICATIONS TO THROMBOLYTIC THERAPY

Major Contraindications

Active internal bleeding
Severe uncontrollable hypertension
History of hemorrhagic CVA
Known intracranial aneurysm, AV malformation, or neo-plasm
Intracranial or spinal surgery within the last 6 weeks
Significant cranial or spinal trauma within the last 6 weeks

Other Contraindications

History of poorly controlled severe hypertension
History of nonhemorrhagic CVA
Major surgery within the last 6 weeks
Significant trauma within the last 6 weeks (including prolonged CPR)
Gastrointestinal bleeding within the last 6 weeks
Pregnancy
Diabetic proliferative retinopathy
Likelihood of left heart thrombus (eg, mitral stenosis with atrial fibrillation)
Recent puncture of noncompressible vessel
Age >75
Acute pericarditis

*It is important for the treating physician to realize that the above list of contraindications to thrombolytic therapy has evolved primarily as a result of historical recommendations, with almost no supporting scientific data. The decision to use thrombolytic therapy entails an assessment of potential adverse risks versus anticipated benefits. Subgroup analysis of existing studies has demonstrated that select subsets of patients traditionally excluded from thrombolytic therapy receive benefits from thrombolytic therapy which outweigh the risks.

Summary 4

Chest pain guideline and continuous quality improvement system for Canadian rural emergency health care facilities

Society of Rural Physicians of Canada, 1999

Jim Thompson, MD, Charlottetown, PEI; Nick Balfour, MD, Vernon, BC; Peter Butt, MD, Saskatoon, Sask.; Graham Dodd, MD, Salmon Arm, BC; Valerie Krym, MD, Edmonton, Alta.; Chris Loreto, MD, Timmins, Ont.; Keith MacLellan, MD, Shawville, Que.; Jock Murray, MD, New Glasgow, NS; Tom O'Neill, MB BCh, Shawville, Que; Mark Quigg, MD, Collingwood, Ont.; James Rourke, MD, Goderich, Ont.; Michael Shuster, MD, Banff, Alta.; Paul Turner, MD, Perth, Ont. *CJRM* 1999;4(1):9-19

Guideline overview

The guideline is divided into 4 clinical phases: "prefacility," "waiting room," "triage nurse" and "physician". These phases are shown sequentially but can overlap. The fifth phase, "continuous quality assurance," includes a CQI mechanism to promote self-evaluation for identifying sources of delays that might be unique to individual REHCFs. ACIS and AMI must always be considered in any patient presenting to an emergency department with chest discomfort. The guideline emphasizes these disorders but does not preclude other entities in the differential diagnosis of chest pain or discomfort.

Prefacility phase

The inability of patients to recognize symptoms of AMI is a well-known cause for delay in treatment. Health system managers can have a variable but generally positive effect on reducing thrombolysis times, and therefore morbidity and mortality, by promoting adequate public education.

A significant proportion of rural patients with AMI arrive at REHCFs in private vehicles rather than by ambulance, the latter being the usual form of transport for urban patients. Ambulance transport, even at the basic life support level has many theoretical advantages over private transport: a supply of oxygen, transport in a semi-Fowler's position, administration of acetylsalicylic acid (ASA) and earlier notification of the REHCF staff.

However, no research has been done to support a recommendation regarding ambulance use in rural settings. Some research from urban settings suggests that calling an ambulance can result in delayed arrival at the emergency department and that the risk of cardiac arrest in patients who travel by private vehicle is very low. On the other hand, there is evidence that the presence of trained nurses and paramedics working in the prehospital environment can improve significantly the recognition of AMI and subsequently early thrombolysis.

Waiting room phase

Large-volume, urban emergency departments often employ a triage nurse, who interviews all patients as soon as they enter the waiting room to determine their priority. This level of staffing is not practical in many REHCFs, where special solutions are required for the waiting room phase. Participation in the CQI process can heighten the awareness of all staff who interact with patients in the waiting room or lobby.

Nursing phase (triage and initial management)

The guideline reminds nursing staff about key issues in triaging patients with chest pain and managing those with suspected ACIS and AMI.

Cummings found that a team of at least 3 professionals at the bedside was required to speed response (A, II-3, R-III). In many REHCFs the triage nurse often has multiple roles, including caring for inpatients and maternity patients. A single nurse might cover the REHCF, particularly in low-volume periods. In these situations the nurse should be able to call other nurses for assistance, since many nursing functions should be carried out simultaneously. In many, and perhaps most, REHCFs the triage nurse will also be one of the nurses treating a patient with AMI; hence, we placed the triage and nursing management phases together.

Patients who might have coronary ischemia or infarction should be triaged to a very high urgency level owing to the risk that the patient will become unstable, the need for prompt thrombolysis, and the need to call in additional nurses, the on-call physician and the laboratory technician.

There is insufficient evidence to recommend a preferred sequence for nursing tasks when limited numbers of nurses are available to assist. The sequence we show is based on the Advanced Cardiac Life Support principle of managing the airway first, then breathing (oxygen) and then circulation (cardiac monitor and intravenous line). The importance of a cardiac monitor and intravenous line for patients with AMI in rural hospitals has been indirectly demonstrated by Hindle and associates. They documented a moderate rate of complications, such as hypotension and arrhythmia, in rural patients treated with thrombolysis. An electrocardiogram must be obtained and interpreted as soon as possible because it is critically important for diagnosing ACIS and AMI and for determining whether thrombolysis is indicated. Electrocardiography should be done by a registered nurse when a laboratory technician is not immediately available (A, III, R-III). The initial ECG should be shown or faxed to the on-call physician very early in the triage phase.

The dosage of oxygen in chest pain is controversial. There appear to be benefits from supplemental oxygen because hypoxemia can be associated with ongoing pain, ischemia, arrhythmia and myocardial dysfunction. However, there is also animal evidence that oxygen-free radicals can exacerbate both infarction and reperfusion injury. No direct connection has been made between administered oxygen dose and oxygen toxicity. The recommendation of the American Heart Association in *Advanced Cardiac Life Support 1997-99* is to start oxygen at a rate of only 4 L/min by nasal cannula. Therefore the practice of administering high-dose oxygen (10 to 15 L/min) to patients with chest pain but no other indication cannot be supported (D, II-2, R-III), but the administration of, at the least, low-dose oxygen can be (B, II-2, R-III).

Early administration of ASA is as effective as thrombolysis alone: together they produce added benefit, but how "early" ASA must be given has not been determined. For practical reasons, and because it seems logical to initiate ASA administration as early as possible, we recommend that ASA be given as soon as the patient is suspected of suffering an AMI, before the physician confirms the diagnosis. The precise timing deserves further research. Emergency department use of ASA is an established recommendation for AMI and unstable angina (A, I, R-III).

The role of sublingual nitroglycerin is controversial. Although it can relieve ischemia and pain in patients with angina and is widely used, its use in AMI has not been well studied. In fact until 2 decades ago nitroglycerin was contraindicated in AMI. There is some evidence of beneficial hemodynamic effects of sublingual nitroglycerin in AMI comparable to intravenous nitroglycerin, although this comes with a significant increase in heart rate and decrease in systolic blood pressure. Sublingual nitroglycerin can cause profound hypotension in patients with AMI, particularly inferior AMI, but the precise frequency of this complication is not well documented. One prehospital study found that sublingual nitroglycerin was associated with profound hypotensive bradycardia, hypotension or apnea/asystole in 4 of 300 cases. Patients with inferior AMI and ST elevation in lead V4R on a 15-lead ECG often present with hypotension. In one study, 11% of such patients had cardiogenic shock. Sublingual nitroglycerin can cause profound hypotension in these patients, although the precise risk has not been measured. Hindle and associates¹⁵ found that significant hypotension was present at some point in 23.1% of patients who received thrombolysis in rural Alberta. Although it is not known how many of those patients had hypotension as a result of right ventricular infarction, clearly the risk is present. Therefore sublingual nitroglycerin should be withheld, or used with caution, if right ventricular infarction is suspected (D, II-2, R-III). Certainly it should be withheld if the patient is hypotensive or bradycardic (E, II-1, R-III). The on-call physician might not be present when the decision to give or withhold nitroglycerin has to be made. This creates a conundrum for rural nurses who must manage a patient with chest pain before a physician can confirm the diagnosis. Further research is needed to determine the true risk of complications induced by the use of sublingual nitroglycerin in rural settings.

Physician phase (diagnosis and definitive treatment)

The guideline encourages early physician attendance and reminds physicians about key issues in assessing patients with chest pain with a view to ruling out or diagnosing ACIS and AMI and initiating appropriate treatment for AMI.

CAEP recommends that the decision to initiate thrombolysis should be made only on the advice of a qualified physician. This does not preclude thrombolysis in level 1 or 2 REHCFs if they are appropriately staffed with trained, qualified and experienced registered nurses and paramedics, and if a clear consultation process to a physician is established (A, II-2, R-III).

The short time objectives for initiating thrombolysis are controversial and have not been verified with appropriate outcome research in any setting, either rural or urban. Although myocardial rescue is clearly time-dependent, the degree of improved outcome by shortening the objective is not clear from the literature. A number of rural physicians have reported during Internet discussions and teleconferences that these objectives seem unrealistic in REHCFs staffed by physicians on call-back rather than in-house, or in REHCFs where there are no physicians in the community. It has been emphasized, however, that the time frames are objectives, not standards of care.

We therefore recommend that the objectives for door-to-drug time should be 30 minutes for classic AMI presentations when the physician is immediately available in the REHCF (B, I, R-III). It should be 60 minutes when the AMI presentation is not classic, complications are present, or when the physician has to be called back to attend the patient (B, III, R-III). Missed opportunities for coronary thrombolysis in rural facilities have not been studied, but they undoubtedly occur and the rate could be improved in some facilities. AMI diagnosis can be difficult when symptoms and the ECG are atypical, and atypical presentations of AMI are

common. About 50% of initial ECGs are not diagnostic of AMI. The rural nurse and physician can improve diagnosis and the rate of AMI recognition in these situations by re-evaluating the patient often, obtaining serial ECGs, using the 15-lead ECG and consulting with colleagues. When specialist physicians are not available in the rural community then specialist consultation should be available promptly by telephone and facsimile.

The guideline reminds physicians of important concepts in the recognition and management of AMI. Hindle and associates found that adjunctive therapies with proven benefit in the management of AMI were used variably in REHCFs. ASA was given in 96.7%, but beta-blockers in only 59.8% of cases. The American Heart Association recommends nitroglycerin intravenously with thrombolysis. There is some evidence that intravenous nitroglycerin is beneficial in both AMI and unstable angina, although its precise role remains unclear. There is insufficient published information to provide practice standards for rate of use of these adjunctive therapies.

Continuous quality improvement phase

The guideline encourages REHCF nonclinical and clinical staff to identify causes of delay soon after each case and to capture that information on a data-entry form. This approach has proven effective in urban settings. However, urban solutions appear to be too labour intensive for many REHCFs, so the Committee devised a shorter dataset, which includes physician call-back and interfacility transfer. The CQI process requires that this information be entered into the CMM software. Both nurses and physicians should fill in a data collection form during and soon after the episode to ensure that accurate, complete information is collected. The CMM reporting module makes it easy for local managers to print tailored reports for prompt feedback to staff and managers.

The CMM software can be installed on a computer in each REHCF and data entered either by the emergency nurse or health records staff. All patients who are considered for the diagnosis of AMI in either the emergency department or in-patient wards should be entered. REHCFs should set up regular in-services to ensure that all hospital staff remain current and understand the guideline (A, II-2, R-III). The CMM software reports can be used during in-services to improve guideline compliance.

Implementation of the guideline and continuous quality improvement program in Canada

The summary wall poster and CMM software are being distributed to all Canadian rural hospitals with 24-hour emergency departments. The rural chest pain guideline was designed to be as generic as possible. However, so many variations exist in the staffing, inventory and layout of REHCFs and in the geography of rural communities in Canada, that some institutions will need to modify the guideline to suit their circumstances. This can be done by developing a chest pain care map. It can be inserted as part of the patient chart to remind staff about optimal care options and to record actual patient care for each individual.

Further work

Obviously much research needs to be done in many areas of managing AMI and ACIS in rural settings. A chest pain care map should be devised for REHCFs. Research should be conducted to determine the effectiveness of our guideline and CQI program in REHCFs. The guideline will require modification, as new evidence becomes available regarding both the

effectiveness of specific interventions in the management of AMI and the organization, function and staffing of REHCFs. Data collected with the CMM software can be pooled to study AMI management by REHCFs over a wide area and to identify causes of delay. Since the same nurses and physician who cover the emergency department in many REHCFs also cover the in-patient wards, this chest pain guideline and CQI system can also be used to manage in-patients. We did not explore special issues that might need to be considered when using this system for in-patients. Evidence-based guidelines should be developed for the continued management of AMI and ACIS in REHCFs after initial emergency care, including guidelines for inpatient management and interfacility transfer.

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Appendix 2: Summary of AHRQ Evidence Report No. 26

Evidence Report/Technology Assessment: Number 26

Evaluation of Technologies for Identifying Acute Cardiac Ischemia in Emergency Departments

Under its Evidence-based Practice Program, the Agency for Healthcare Research and Quality (AHRQ) is developing scientific information for other agencies and organizations on which to base clinical guidelines, performance measures, and other quality improvement tools. Contractor institutions review all relevant scientific literature on assigned clinical care topics and produce evidence reports and technology assessments, conduct research on methodologies and the effectiveness of their implementation, and participate in technical assistance activities.

Introduction

Acute myocardial infarction (AMI) is the leading cause of death in the United States. Investigating the causes, progression, and treatment of AMI continues to be a national research priority. In clinical medicine, much research has focused on the early diagnosis and treatment of acute cardiac ischemia (ACI), which includes both unstable angina pectoris (UAP) and AMI. In 1991, the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health initiated the National Heart Attack Alert Program (NHAAP) to study the issues related to rapid recognition and response to patients with signs and symptoms of ACI in emergency department (ED) settings, the point at which most of these patients enter the health care system. This ongoing effort brings together scientists, clinicians, and NHLBI staff with a Coordinating Committee that includes representatives of 40 professional organizations.

In 1994, the NHAAP Working Group on Evaluation of Technologies for Identifying Acute Cardiac Ischemia in the Emergency Department was formed to assess the technologies for diagnosing ACI and AMI in the ED. Members of the Working Group had expertise in the areas of cardiology, emergency medicine, general internal medicine, family practice, and nursing, as well as in the specific disciplines of meta-analysis and health services research. The Working Group reviewed all technologies for diagnosing ACI in the ED. The assessments of these technologies in actual use in EDs, and the nature, extent, and quality of the evidence on which the assessments were based, are presented in the Working Group's final 1997 report, *An Evaluation of Technologies for Identifying Acute Cardiac Ischemia in the Emergency Department*.

Reporting the Evidence

In 1998, the Agency for Healthcare Research and Quality (AHRQ, formerly the Agency for Health Care Policy and Research [AHCPR]), working as a partner for the NHLBI's NHAAP, contracted with the New England Medical Center's Evidence-based Practice Center (EPC) to update the 1997 NHAAP report. The EPC was charged with evaluating the evidence on these diagnostic technologies published since October 1994.

As before, the purpose of the review was to assess the accuracy of technologies for diagnosing ACI in the emergency department and their clinical impact when used in this

setting. However, the original 1997 report did not provide quantitative estimates of the test performance or clinical impact of the diagnostic technologies. To address this, we conducted meta-analyses where possible in which we reexamined all the studies reviewed in the original report, abstracted the necessary data, and combined these data with more recently published studies. We also conducted decision and cost-effectiveness (CE) analyses to investigate the interactions between technologies' diagnostic performances and costs, populations, and outcomes, and to provide an evidence-based framework on which to base recommendations. NHAAP Working Group members help frame some of the study issues but they were not involved in the evaluation of evidence or in the writing of the report.

Methods

We conducted a systematic and comprehensive search of the English-language literature published between 1966 and December 1998. Literature was retrieved from a computer MEDLINE search, references cited in the 1997 Working Group report, review of references of retrieved articles, and assistance from domain experts. Search terms included those related to the diagnosis of ACI, AMI, and UAP in the ED and to the following technologies:

- Prehospital electrocardiography (ECG).
- Continuous/serial ECG.
- Non-standard leads ECG.
- Exercise stress ECG.
- The ACI Time-Insensitive Predictive Instrument (ACI-TIPI).
- The Goldman chest pain protocol.
- Biochemical tests and biomarkers (e.g., creatine kinase [CK] or its subunit [CK-MB], troponin T, etc.).
- Sestamibi myocardial perfusion imaging.
- Echocardiography.
- Computer-based decision aids.

Inclusion Criteria

We followed the general approach for selecting studies taken by the Working Group in its report. We considered reports if they came from work done in the ED setting; results coming from other settings (e.g., the cardiac care unit) were used only if little or no ED-based data were available. Data from non-ED settings were used with the understanding that they suggest potential utility but do not directly apply to the emergency setting.

We accepted prospective and retrospective studies that evaluated one or more of the technologies considered in this evidence report and included patients 18 years and older who presented to the ED with symptoms suggestive of ACI. We placed no restrictions on patients' gender or ethnicity. In general, ED testing consists of either a single test performed within the initial 4-hour period after presentation to the ED, or repeated testing up to 14 hours after the patient's presentation to the ED. We accepted studies with minor deviations from this standard.

Data were abstracted according to a written protocol and were summarized in evidence tables.

Grading of the Evidence

The evidence-grading scheme we used assesses four dimensions that are important for the proper interpretation of the evidence:

- Size of the study (weight of the evidence).
- Applicability (population category and prevalence of disease).

- Diagnostic performance or magnitude of clinical impact.
- Methodological quality (internal validity).

Applicability. We grouped the populations and settings of the studies using a four-category scale to help interpret the results. We also collected data about the prevalence of ACI or AMI to assist the interpretation. The four defined population categories are:

- **Category I**—Studies that included all patients with signs and symptoms suggestive of ACI, such as chest pain, shortness of breath, jaw pain, acute pulmonary edema, and so forth. This is the most inclusive category. Few studies met Category I criteria.
- **Category II**—Studies that used chest pain as the inclusion criteria. Most studies belong to this group. Category II is a subset of Category I.
- **Category III**—Studies that included patients with chest pain but excluded those with clinical or ECG findings of AMI. Many studies, especially studies of stress cardiac imaging or testing, belong to this group. Category III is a subset of Category II.
- **Category IV**—Studies in which all patients were hospitalized or which used additional criteria that enrolled highly selected subpopulations. We also placed retrospective studies in this category.

Test performance studies. When there were sufficient data for a technology, we used three complementary methods of synthesizing data across several studies to report on its test performance:

1. Summary receiver operating characteristics (SROC) analysis.
2. Separately combined sensitivity and specificity values using a random effects model.
3. The summary diagnostic odds ratios using a random effects model.

We defined a three-level methodological quality scale for test performance studies graded as follows:

- **A (least bias)**—Such as a study that adheres to the traditionally held concepts of high quality diagnostic evaluation, including:
 - Clear descriptions of the population and setting.
 - Clear descriptions of the reference standard, the test under investigation, and the diagnostic criteria.
 - Masked interpretation of the reference test and the test under investigation.
 - Verification of the diagnoses in all or most of the patients with negative results.
 - No significant reporting errors that are likely to result in substantial bias.
- **B (susceptible to some bias)**—A study that does not meet all the criteria in category A, but its deficiencies are unlikely to cause major bias.
- **C (likely to have significant bias)**—A study with significant design or reporting flaws that cannot preclude major bias. This category includes studies in which verification bias could be a major issue and studies that have significant amounts of missing information or discrepancies in their reporting.

Clinical impact studies. In the few instances where there are sufficient data reported by clinical impact studies, dichotomous outcomes expressed as risk ratio or continuous outcomes were combined using a random effects model.

We defined a three-level methodological quality scale for clinical impact studies graded as follows:

- **A (least biased)**—Such as prospective controlled trials.
- **B (susceptible to some bias)**—Such as prospective cohort studies.
- **C (likely to have significant bias)**—Other designs or studies with significant conduct or reporting problems that could lead to large bias.

Findings

General Observations

The MEDLINE literature search identified 6,667 titles, a third of which were published from 1994 onward, indicating increased research activities on this topic over the past 5 years compared to the previous 27 years. From these abstracts, 407 full articles were retrieved for review, 106 of which are included in the analysis.

A diverse array of technologies with varying degrees of diagnostic accuracy is available for use in general or selected populations to diagnose ACI in the ED. About half the studies analyzed were in population category II and about 30 percent in category III. Prevalence of AMI across studies, even within population categories and in similar settings, varied widely with little indication that similarly reported inclusion criteria among studies resulted in similar levels of AMI prevalence.

Despite this, there is some indication that overall, studies that included all patients with chest pain (population category II) have higher prevalence of AMI than either studies that included all patients with symptoms suggestive of ACI (population category I) or studies that excluded patients with diagnostic ECGs (population category III). In addition, though differences in AMI prevalence among different settings are not statistically significant, there is evidence that studies that analyzed only admitted ED patients have higher prevalence of AMI than those that included all ED patients. Thus, these two populations may truly be different.

Specific Findings

Most studies evaluated the accuracy of the technologies; only a few evaluated the clinical impact of routine use. To summarize:

- Prehospital 12-lead ECG has moderate sensitivity (76 percent) and specificity (88 percent) for diagnosis of ACI. It has demonstrated a reduction of the mean time to thrombolysis by 33 minutes and short-term overall mortality in randomized trials.
- In the general ED setting, only ACI-TIPI has demonstrated, in a large multicenter clinical trial, a reduction in unnecessary hospitalizations without decreasing the rate of appropriate admission for patients with ACI.
- The Goldman chest pain protocol has good sensitivity (about 90 percent) for AMI but has not been shown to result in any differences in hospitalization rate, length of stay or estimated costs, in the single clinical impact study performed. Its applicability to patients with UAP has not been evaluated.
- Single measurement of biomarkers at presentation to the ED has poor sensitivity for AMI although most biomarkers have high specificity (over 90 percent). Serial measurements can greatly increase the sensitivity for AMI while maintaining their excellent specificity. Biomarkers cannot identify most patients with UAP.
- Diagnostic technologies to evaluate ACI in selected populations, such as echocardiography, sestamibi perfusion imaging, and stress ECG, may have very good to excellent sensitivity; however, they have not been sufficiently studied.

Results of Decision and Cost-Effectiveness Analyses

Decision and cost-effectiveness analyses were performed for 17 technologies and 4 combinations of technologies that have been evaluated in the literature and this report. The cost analysis is from the payers' perspective (e.g. health insurance companies); patient outcomes are either appropriate triage or 30-day survival of patients with ACI.

As not all technologies can be applied to all patients in the ED (such as stress ECG), two different ED populations were used for the analysis:

- A general population model, which includes all patients in the ED.
- A subgroup model, in which high-risk patients are excluded.

Stress tests, sestamibi imaging, and serial and continuous ECG were evaluated only in the subgroup population.

As expected, technologies with the best diagnostic accuracy for AMI and UAP have the highest values for appropriate triage for patients with ACI. Technologies that are more effective (greater number of patients with ACI appropriately triaged) tend to have higher total costs, with the exception of ACI-TIPI. The biomarkers are least costly and have the lowest values for appropriate triage. Algorithms, combination technologies, and echocardiography are the next most effective technologies, in that order. Sestamibi imaging and exercise ECG are more expensive than other technologies but have excellent diagnostic performance for ACI.

Based on data using only the diagnostic performance data of technologies, the combination technology of troponin T and echocardiography has the best CE among all technologies applicable to the general population model. If results from clinical impact studies are incorporated, ACI-TIPI has the best CE because of its very high triage accuracy and low cost.

The incremental CE of troponin T and echocardiography is about \$7,670 per additional appropriate triage for a patient with ACI compared with serial or combination biomarkers. The incremental CE of the next most effective technology, the artificial neural network, is approximately \$10,560. Given the economic ramifications and the effects on the patient of a missed ACI diagnosis, this incremental CE for troponin T and echocardiography is minimal. Because the estimates for detection of UAP are based on sparse data, we also evaluated the triage accuracy and cost-effectiveness of technologies for appropriate triage for patients with AMI only. The relative CE rankings do not change compared with the rankings for patients with ACI. There are few but important differences, however, in triage accuracy:

1. The Goldman protocol improves significantly.
2. Serial CK-MB improves slightly.
3. The combination of troponin T and echocardiography is slightly better than ACI-TIPI (a difference of one patient with AMI appropriately triaged).

The combination of troponin T and echocardiography is the most cost-effective, followed by the artificial neural network. The incremental CE between these two technologies is much larger than in the general ACI model: approximately \$137,000 per additional appropriately triaged patient with AMI.

In the low-risk patient subgroup model, ACI-TIPI is again the most cost-effective technology if data from clinical impact studies are incorporated. Sestamibi stress imaging has the best diagnostic performance (detects 82 percent of patients with ACI), followed by sestamibi rest scanning, and exercise ECG. The costs of exercise ECG and stress sestamibi are nearly the same. The incremental CE between the two technologies is a mere \$364 per appropriately triaged patient, reflecting the higher effectiveness of stress sestamibi for its cost relative to exercise ECG.

The incremental CE between stress sestamibi imaging and the next cost-effective technology, the combination of troponin T and echocardiography, is much greater: \$12,757. However, given that stress sestamibi imaging results in the appropriate triage of 37 additional patients

with ACI (per 1,000 ED patients) compared with troponin T and echocardiography, it appears to be a very cost-effective technology.

If data from the ACI-TIPI trial are used, the incremental CE of using ACI-TIPI compared with troponin T and echocardiography is only \$1,502 per additional appropriate triage for a patient with ACI, a truly negligible increase for improved triage accuracy.

Considering only triage accuracy for patients with AMI, the combination of troponin T and echocardiography is the most cost-effective. Exercise ECG and stress sestamibi imaging also have excellent triage accuracy; however, the per ED patient costs of these two technologies is about \$500 more than that of troponin T and echocardiography.

Future Research

- Most studies evaluated the performance of a technology in diagnosing AMI; future studies should also evaluate a technology's performance in diagnosing UAP.
- Some technologies (e.g., echocardiography, sestamibi imaging, exercise ECG, serial biomarkers, and new biomarkers such as P-selectin and fatty acid binding proteins) remain under-evaluated.
- To date, most studies have evaluated the application of a single technology on patients. Research is needed to determine whether combinations of tests, such as a panel of biomarkers, or of multiple modalities, such as ECG with serial CK-MB measurements, perform better than the component tests alone.
- Because good test performance, in isolation, does not automatically translate to appropriate utilization or desired outcomes, clinical impact studies are needed to evaluate the clinical outcomes of the actual use of the test.
- The prevalence of ACI among the studies varies widely and may be explained only partially by differences in patient populations. The wide variation of prevalence has an unknown effect on test performance and interpretation of the results, and may indicate incomplete reporting of study biases. We need to understand the reason for the heterogeneity of the prevalence among studies with seemingly similar patient populations.
- The methodological quality and the reporting of the diagnostic performance studies on this topic varies widely and could be improved substantially.

Availability of Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality by the New England Medical Center under contract No. 290-97-0019. Printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 1-800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 26, *Evaluation of Technologies for Identifying Acute Cardiac Ischemia in Emergency Departments* (AHRQ Publication No. 01-E006).

The Evidence Report can also be downloaded as a zipped file online at:

<http://www.ahrq.gov/clinic/evrptfiles.htm>.

AHRQ Publication No. 00-E031

Current as of September 2000

Appendix 3 Abstracts of all primary publications which were critically appraised

Prehospital 12-Lead Electrocardiography

No new data.

Continuous/Serial 12-Lead ECG

No new data specifically on this area

Nonstandard Lead ECG

Aufderheide TP, Xue Q, Dhala AA, Reddy S, Kuhn EM. The added diagnostic value of automated QT-dispersion measurements and automated ST-segment deviations in the electrocardiographic diagnosis of acute cardiac ischemia. *Journal of Electrocardiology* 2000;**33**(4):329-39.

The purpose of this study was to determine the added value of automated QT dispersion and ST-segment measurements to physician interpretation of 12-lead electrocardiograms (ECGs) in patients with chest pain. To date, poor reproducibility of manual measurements and lack of shown added value have limited the clinical use of QT dispersion. Twelve-lead ECGs (n = 1,161) from the Milwaukee Prehospital Chest Pain Database were independently classified by 2 physicians into 3 groups (acute myocardial infarction (AMI), acute cardiac ischemia (ACI), or nonischemic), and their consensus was obtained. QT-end and QT-peak dispersions were measured by a computerized system. The computer also identified ST-segment deviations. Sensitivity, specificity, and positive predictive values (PPVs) and negative predictive values (NPV) for AMI and ACI were evaluated independently and in combinations. For AMI, physicians' consensus classification was remarkably good (sensitivity, 48%, specificity, 99%). Independent classification by QT-end and QT-peak dispersions or ST deviations was not superior to the physicians' consensus. Optimal classification occurred by combining automated QT-end dispersion and ST deviations with physicians' consensus. This combination increased sensitivity for the diagnoses of AMI by 35% (65% vs 48%, P < .001) and ACI by 55% (62% vs 40%, P < .001) compared with physicians' consensus, while maintaining comparable specificity. This study supports a potential clinical role for automated QT dispersion when combined with other diagnostic methods for detecting AMI and ACI.

Exercise Stress Testing

Buchsbaum M, Marshall E, Levine B, et al. Emergency department evaluation of chest pain using exercise stress echocardiography. *Academic Emergency Medicine* 2001;**8**(2):196-9.

OBJECTIVE: Patients with a low risk of coronary artery disease (CAD) presenting to the emergency department (ED) with chest pain pose a diagnostic dilemma because a small percentage will suffer an acute myocardial infarction (MI) and sudden death. The authors conducted this study to determine whether exercise stress echocardiography (ESE) could be used to further support the safe discharge of these low-risk patients. **METHODS:** A convenience sample of patients > or =30 years of age without a prior cardiac history who presented to an academic community hospital with chest pain, normal initial creatine kinase, and electrocardiography without ischemic changes underwent ESE within 6 +/- 1.7 hours (mean +/- SD). Abnormal ESE was defined as regional wall motion abnormality at rest or after exercise. The ED disposition and three- and six-month follow-up for cardiac events were recorded. This was a prospective observational cohort study. **RESULTS:** Of a total of 149 eligible patients, 145 completed the study. The mean age (+/-SD) was 47 +/- 9 years; 56% were male. No adverse events were noted during ESE. Seven patients (5%) had abnormal ESE (2 with rest wall motion abnormalities and 5 with exercise-induced wall motion abnormalities). Five of the seven underwent cardiac catheterization; three had CAD. All patients received telephone follow-up at three months and six months. Of the 138 patients with a normal ESE, all were free of cardiac events at three months. One

patient had a non-Q-wave MI at six months (negative predictive value = 99.3%, 95% CI = 97.8% to 100%).
CONCLUSIONS: Exercise stress echocardiography can be used to evaluate low-risk chest pain patients in the ED. Patients with a normal ESE may be considered for discharge with minimal risk of sequelae.

Geleijnse ML, Elhendy A, Kasprzak JD, et al. Safety and prognostic value of early dobutamine-atropine stress echocardiography in patients with spontaneous chest pain and a non-diagnostic electrocardiogram. *European Heart Journal* 2000;**21**(5):397-406.

AIMS: To risk stratify and shorten hospital stay in patients with spontaneous (resting) chest pain and a non-diagnostic electrocardiogram (ECG). METHODS AND RESULTS: The study comprised 102 patients (mean age 58+/-12 years, 67 men) with spontaneous chest pain and a non-diagnostic ECG. Forty-three patients had suspected coronary artery disease and 59 had known (but of unknown actual significance) coronary artery disease. All patients underwent serial creatine kinase enzyme measurements, continuous ECG monitoring for at least 12 h and early dobutamine-atropine stress echocardiography in patients with negative creatine kinase enzymes and normal findings at ECG monitoring. Dobutamine-atropine stress echocardiography was considered positive in patients with new or worsening wall thickening abnormalities. Patients with negative dobutamine-atropine stress echocardiography were discharged after the test. In-hospital and 6 month follow-up events noted were cardiac death, non-fatal myocardial infarction, unstable angina, and coronary artery bypass surgery or angioplasty. Thirteen patients had evidence of evolving myocardial infarction by elevated creatine kinase enzymes, or unstable angina by ECG monitoring. In the remaining 89 patients, dobutamine-atropine stress echocardiography was performed after a median observation period of 31 h (range 12-68 h). During dobutamine-atropine stress echocardiography no serious complications (death, non-fatal myocardial infarction, sustained ventricular tachycardia or ventricular fibrillation) occurred. Dobutamine-atropine stress echocardiography results were of poor quality in three, non-diagnostic in six, negative in 44 and positive in 36 patients. In the 80 patients with diagnostic dobutamine-atropine stress echocardiography, variables associated with in-hospital events (n=7) were history of exertional angina (P<0.005), chest pain score (P<0.005), stress-induced angina (P<0.001) and positive dobutamine-atropine stress echocardiography (P<0.005). Variables associated with follow-up events (n=11) were history of exertional angina (P<0.05), chest pain score (P<0.001), stress-induced angina (P<0.01) and positive dobutamine-atropine stress echocardiography (P<0.01). At multivariate analysis the only significant predictor of events was positive dobutamine-atropine stress echocardiography (P<0.01). CONCLUSION: Early dobutamine-atropine stress echocardiography may safely distinguish between low- and high-risk subsets for subsequent cardiac events in patients with spontaneous chest pain and a non-diagnostic ECG. Copyright 2000 The European Society of Cardiology.

Krasuski RA, Hartley LH, Lee TH, Polanczyk CA, Fleischmann KE. Weekend and holiday exercise testing in patients with chest pain. *Journal of General Internal Medicine* 1999;**14**(1):10-4.

OBJECTIVE: To determine the outcome, safety, and possible cost savings of patients undergoing weekend or holiday exercise treadmill testing. DESIGN: Medical records of all 195 patients scheduled for weekend and holiday exercise testing were reviewed, and 77.9% of patients were contacted by telephone to ascertain medical outcomes and need for further emergency department or inpatient care. Costs were calculated from estimates of days of hospitalization saved and incremental costs incurred in conjunction with weekend or holiday testing. SETTING: Urban tertiary care academic medical center. PATIENTS: A total of 195 patients were scheduled for testing, and 181 tests were performed. Over three quarters (75.1%) of patients underwent testing for assessment of chest pain. Other indications included risk stratification after myocardial infarction or coronary angioplasty or prior to noncardiac surgery, or evaluation for arrhythmias, dyspnea, or syncope. MEASUREMENTS AND MAIN RESULTS: Outcomes included results and complications of testing, hospital course after testing, subsequent emergency department visits and readmissions, myocardial infarction, need for cardiac catheterization or revascularization, and mortality. No complications were noted during testing. In 136 patients tested for the indication of chest pain, 90 (66.2%) had negative tests, 39 (28.7%) were intermediate, and 6 (4.4%) were positive for ischemia. Same day discharge occurred in 115 (84.6%) of the patients, saving an estimated 185 days of hospitalization (\$316.83 per patient tested). Event rates over the 6 months following discharge were low. CONCLUSIONS: Weekend and holiday exercise testing is a safe and effective means of risk stratification prior to hospital discharge for patients with chest pain. It also reduces length of stay and is cost saving.

Lewis WR, Amsterdam EA, Turnipseed S, Kirk JD. Immediate exercise testing of low risk patients with known coronary artery disease presenting to the emergency department with chest pain. *Journal of the American College of Cardiology* 1999;**33**(7):1843-7.

OBJECTIVES: The purpose of this study was to demonstrate the safety and utility of immediate exercise treadmill testing (IETT) of low risk patients presenting to the emergency department with known coronary artery disease (CAD). BACKGROUND: More than 70% of the two million patients admitted to U.S. hospitals annually for suspected acute myocardial infarction (AMI) are found not to have had a cardiac event. We have previously demonstrated the safety and efficacy of IETT of selected low risk patients without known CAD presenting to the emergency department with chest pain. This study extends this approach to selected patients with a history of CAD. METHODS: One hundred patients evaluated by the chest pain emergency room to rule out AMI underwent IETT using a modified Bruce protocol upon admission to the hospital (median time <1 h). RESULTS: Twenty-three patients (23%) had positive exercise electrocardiograms (ExECGs); an uncomplicated non-Q wave AMI was diagnosed in two patients. Thirty-eight patients (38%) had negative ExECGs and 39 patients (39%) had nondiagnostic ExECGs. Of these 100 patients, 64 were discharged immediately after IETT, 19 were discharged in less than 24 h after negative serial cardiac enzymes and stable electrocardiograms and 17 were discharged after further evaluation and treatment. There were no complications from exercise testing and no late deaths or AMI during six-month follow-up. CONCLUSIONS: Immediate exercise treadmill testing of low risk patients with chest pain and known CAD is effective in further stratifying this group into patients who can be safely discharged and those who require hospital admission.

Sarullo FM, Di Pasquale P, Orlando G, et al. Utility and safety of immediate exercise testing of low-risk patients admitted to the hospital with acute chest pain. *International Journal of Cardiology* 2000;**75**(2-3):239-43.

It is common practice to hospitalize patients with chest pain for a period of observation and to perform further diagnostic evaluation such as exercise treadmill testing (ETT) once acute myocardial infarction (AMI) has been excluded. This study evaluates the safety and efficacy of immediate ETT for patients admitted to the hospital with acute chest pain. One hundred and ninety non-consecutive low-risk patients admitted to the hospital from emergency department with acute chest pain underwent ETT using Bruce protocol immediately on admission to the hospital (median time 165+30 min). Fifty-seven (30%) patients had positive exercise electrocardiograms, 44 (77.2%) of whom had significant coronary narrowing by angiography. An uncomplicated anterior non-Q-wave AMI was diagnosed in one patient. One hundred and eleven (58.4%) patients had negative and 22 (11.6%) patients had non-diagnostic exercise electrocardiograms. Of these 133 patients, 86 (64.7%) were discharged immediately after ETT, 19 (14.3%) were discharged within 24 h, and 28 (21%) were discharged after 24 h of observation. There were no complications from ETT. During the 17+/-6 months follow-up no patients died, and only eight (7.2%) patients with negative ETT experienced a major cardiac event (one AMI and seven angina). In conclusion, our results suggest that immediate ETT of low-risk patients with chest pain who are at sufficient risk to be designated for hospital admission, is effective in further stratifying this group into those who can be safely discharged immediately and those who require hospitalization.

Biomarkers

Creatine Kinase (CK), Single and Serial Measurements

Bock JL, Brogan GX, Jr., McCuskey CF, Thode HC, Jr., Hollander JE, Gunther T.

Evaluation of CK-MB isoform analysis for early diagnosis of myocardial infarction. *Journal of Emergency Medicine* 1999;**17**(1):75-9.

Measurement of CK-MB and its isoforms by high-voltage electrophoresis has been proposed as a sensitive test for early detection of myocardial infarction (MI). We performed a prospective study of this test in 231 patients presenting to the Emergency Department with symptoms consistent with ischemic chest pain. Blood specimens were obtained at 0, 1, and 3 h following presentation, and plasma was immediately frozen and analyzed within 1 week by high-voltage electrophoresis for total CK-MB and isoforms. The test was considered positive whenever total CK-MB was elevated (>6 U/L) or the cardiac isoform MB2 was relatively increased (MB2 > 2 U/L and MB2/MB1 > 1.7). This test had a sensitivity of 68% overall and 55% for specimens collected within 3 h of symptom onset. It was positive within 3 h of presentation in 36/39 (92%) of patients with confirmed MI. Specificity was 92% overall and did not vary with time after symptoms. The CK-MB alone, at the cutoff of 6 U/L, had lower sensitivity overall (56%; p = 0.01) and within 3 h of onset (39%; p = 0.03), and higher

specificity overall (98%; $p < 0.001$). Lowering the cutoff for CK-MB alone to match the sensitivity of the isoform test caused a greater loss of specificity. It is concluded that analysis of CK-MB by high-voltage electrophoresis is an effective method for rapid diagnosis of MI, with the isoform analysis enhancing early sensitivity.

Creatine Kinase Subunit (CK-MB), Single and Serial Measurements

Bholasingh R, de Winter RJ, Fischer JC, Koster RW, Peters RJ, Sanders GT. Safe discharge from the cardiac emergency room with a rapid rule-out myocardial infarction protocol using serial CK-MB(mass). *Heart* 2001;**85**(2):143-8.

OBJECTIVE: To determine whether a new protocol, using a rapid and sensitive CK-MB(mass) assay and serial sampling, can rule out myocardial infarction in patients with chest pain and decrease their length of stay in the cardiac emergency room without increasing risk. **DESIGN:** The combined incidence of cardiac death and acute myocardial infarction at 30 days, six months, and 24 months of follow up were compared between patients discharged home from the cardiac emergency room after ruling out myocardial infarction with a CK-MB(activity) assay in 1994 and those discharged home after a rapid CK-MB(mass) assay in 1996. **SETTING:** Cardiac emergency room of a large university hospital. **PATIENTS:** In 1994 and 1996, 230 and 423 chest pain patients, respectively, were discharged home from the cardiac emergency room with a normal CK-MB and an uneventful observation period. **RESULTS:** The median length of stay in the cardiac emergency room was significantly reduced, from 16.0 hours in 1994 to 9.0 hours in 1996 ($p < 0.0001$). Mean event rates in patients from the 1994 and 1996 cohorts, respectively, were 0.9% (95% confidence interval (CI) -0.3% to 2.1%) v 0.7% (95% CI -0.1% to 1.5%) at 30 days, 3.0% (95% CI 0.8% to 5.2%) v 2.8% (95% CI 1.2% to 4.4%) at six months, and 7.0% (95% CI 3.7% to 10.3%) v 5.7% (95% CI 3.5% to 7.9%) at 24 months. Kaplan-Meier survival analysis showed no difference in mean event-free survival at 30 days, six months, and 24 months of follow up. **CONCLUSIONS:** Using a rule-out myocardial infarction protocol with a rapid and sensitive CK-MB(mass) assay and serial sampling, the length of stay of patients with chest pain in the cardiac emergency room can be reduced without compromising safety.

Fesmire FM. A rapid protocol to identify and exclude acute myocardial infarction: continuous 12-lead ECG monitoring with 2-hour delta CK-MB. *American Journal of Emergency Medicine* 2000;**18**(6):698-702.

A prospective observational study was performed in 706 chest pain patients who underwent our chest pain evaluation protocol which consists of continuous 12-lead ST-segment monitoring with automated serial ECG (SECG) and a 2-hour delta (delta) CK-MB level determination before ED physician making final disposition decision to determine the incremental value of our 2-hour protocol for identifying myocardial infarction (MI) as compared with the initial ECG in combination with a baseline CK-MB. The initial ECG was obtained on presentation and considered positive if it revealed injury or ischemia. SECGs were obtained at least every 10 minutes and considered positive if it revealed new injury or ischemia. The baseline CK-MB value was considered positive if it was ≥ 12 ng/mL and index $\geq 4\%$. Δ CK-MB was defined as a difference between the 2 hour and baseline CK-MB and was considered positive if the value was $\geq +1.5$ ng/mL. MI was defined as acute myocardial infarction (AMI) or recent AMI (ie, AMI patients presenting on falling curve of CK-MB). The incremental value of the 2 hour protocol (ie, SECG in conjunction with Δ CK-MB) was more sensitive for identification of MI than the baseline protocol (ie, initial ECG in conjunction with the baseline CK-MB) (94.0% versus 55.4%; $P < .0001$) and reliably both identified (+LR = 14.6) and excluded MI (-LR = 0.06). SECG monitoring in conjunction with the 2 hour Δ CK-MB allows for early identification and exclusion of MI, and can assist the ED physician in making appropriate treatment and disposition decisions.

Fesmire FM. Delta CK-MB outperforms delta troponin I at 2 hours during the ED rule out of acute myocardial infarction. *American Journal of Emergency Medicine* 2000; **18**(1):1-8.

It has been shown that a rise in creatine kinase MB bank (CK-MB) of $\geq +1.6$ ng/mL in 2 hours is more sensitive and equally specific for detection of acute myocardial infarction (AMI) as compared with a 2-hour CK-MB ≥ 6 ng/mL during the emergency department (ED) evaluation of chest pain. Because cardiac specific troponin I (cTnI) is thought to have similar early release kinetics as compared with CK-MB mass, we undertook a retrospective cohort study in 578 chest pain patients whose baseline CK-MB and cTnI was less than two times the hospital's upper limits of normal and who underwent a 2-hour CK-MB and cTnI to compare sensitivities and specificities of the 2-hour delta CK-MB (Δ CK-MB) and delta cTnI (Δ cTnI) for AMI and

30-day Adverse Outcome (AO). Thirty day AO was defined as AMI, life-threatening complication, death, or percutaneous transluminal coronary angioplasty (PTCA)/coronary artery bypass graft (CABG) within 30 days of ED presentation. Optimum delta values were determined by choosing the smallest cutoff value greater than the assay precision where the deltaCK-MB and delta cTnI had a positive likelihood ratio for 30-day AO of $>$ or $=$ 15. A deltaCK-MB $>$ or $=$ +1.5 ng/mL was more sensitive than a deltaTnI $>$ or $=$ +0.2 ng/mL for AMI (87.7% versus 61.4%; $P < .0005$) and 30-day AO (56.7% versus 42.3%; $P < .005$). There were no differences in specificities for AMI and 30-day AO. Combining the two tests (MBdelta $>$ or $=$ +1.5 ng/mL and/or a deltaTnI $>$ or $=$ +0.2 ng/mL) resulted in an incremental increase in sensitivity of 89.5% for AMI and 61.9% for AO ($P < .005$). Patients with either a rise in CK-MB of $>$ or $=$ +1.5 ng/mL or rise in cTnI of $>$ or $=$ +0.2 ng/mL in 2 hours should receive consideration for aggressive antiischemic therapy and further diagnostic testing before making an exclusionary diagnosis of nonischemic chest pain.

Green GB, Dehlinger E, McGrievy TS, et al. CK-MB isoforms for early risk stratification of emergency department patients. *Clinica Chimica Acta* 2000;**300**(1-2):57-73.

The potential clinical utility of single sample CK-MB isoforms measurement for early risk stratification of Emergency Department (ED) patients with possible myocardial ischemia was evaluated among 405 patients presenting to two urban EDs. Clinical and serologic data were prospectively collected and the occurrence of adverse events (AEs) and myocardial infarction (MI) during the 14-day outcome period was recorded and utilized to calculate and compare relative risks (RR) and predictive values of isoforms and CK-MB alone. Among the 405 patients, 67 accrued 105 AEs. Both isoforms and CK-MB alone were predictive of AEs with RR of 3.32 (2.09, 5.27) and 6.28 (4.64, 8.52), respectively. Isoforms had higher sensitivity for AEs compared to CK-MB (65.7% [54.3, 77.0] vs. 14.9% [6.4, 23.5]; $p < .01$) but lower specificity (69.2% [64.3, 74.2] vs. 99.7% [99.1, 100.0]; $p < .01$). Isoforms' superior sensitivity allowed identification of many high risk patients missed by CK-MB alone. Further, for the prediction of MI, isoforms had superior diagnostic sensitivity and equivalent specificity. This investigation supports the emergency department use of early, single sample CK-MB isoform testing.

Herren KR, Mackway-Jones K, Richards CR, Seneviratne CJ, France MW, Cotter L. Is it possible to exclude a diagnosis of myocardial damage within six hours of admission to an emergency department? Diagnostic cohort study. *BMJ* 2001;**323**(7309):18.

Objective: To assess the clinical efficacy and accuracy of an emergency department based six hour rule-out protocol for myocardial damage. Design: Diagnostic cohort study. Setting: Emergency department of an inner city university hospital. Participants: 383 consecutive patients aged over 25 years with chest pain of less than 12 hours' duration who were at low to moderate risk of acute myocardial infarction. Intervention: Serial measurements of creatine kinase MB mass and continuous ST segment monitoring for six hours with 12 leads. Main outcome measure: Performance of the diagnostic test against a gold standard consisting of either a 48 hour measurement of troponin T concentration or screening for myocardial infarction according to the World Health Organization's criteria. Results: Outcome of the gold standard test was available for 292 patients. On the diagnostic test for the protocol, 53 patients had positive results and 239 patients had negative results. There were 18 false positive results and one false negative result. Sensitivity was 97.2% (95% confidence interval 95.0% to 99.0%), specificity 93.0% (90.0% to 96.0%), the negative predictive value 99.6%, and the positive predictive value 66.0%. The positive likelihood ratio was 13.9 and the negative likelihood ratio 0.03. Conclusions: The six hour rule-out protocol for myocardial infarction is accurate and efficacious. It can be used in patients presenting to emergency departments with chest pain indicating a low to moderate risk of myocardial infarction.

Peacock WF, Emerman CL, McErlean ES, et al. Normal CK, elevated MB predicts complications in acute coronary syndromes. *Journal of Emergency Medicine* 2001;**20**(4):385-90.

The implications of an elevated Creatine kinase (CK)-MB isoenzyme (MB) in suspected acute coronary syndromes, with a normal total CK, is not well established. Despite many guidelines on managing patients with acute coronary ischemia, none indicates strategies for patients with elevated MB and with a normal CK. The outcome consequence of this result is not firmly established. Our objective was to prospectively evaluate outcomes in patients with suspected acute coronary syndromes, normal initial total CK, and increased MB. All Emergency Department patients with suspected acute coronary syndromes and creatinine $<$ 2.0 mg/dL were eligible for study entry. Serial CK and MB fractions were measured on arrival in the Emergency Department, then 8 and 16 h postpresentation. A composite outcome of death, Q-wave myocardial infarction, or revascularization was defined at the index visit and 6 months later. Outcomes were determined by blinded record review and by telephone contact. In the 698 patients entered, the acute composite outcome rate was 25%

(175) and 6.3% (44) at 6 months. Acute and 6 month adverse outcome rates were statistically the same for all patients with an elevated MB fraction, regardless of the total CK level. An elevated MB conferred a higher event rate than did a normal MB. We conclude that the adverse event rate for patients with suspected acute coronary syndromes and an elevated MB is the same whether or not the total CK is elevated. These patients should be considered as having had an acute coronary syndrome.

Troponin T and Troponin I

Johnson PA, Goldman L, Sacks DB, et al. Cardiac troponin T as a marker for myocardial ischemia in patients seen at the emergency department for acute chest pain. *American Heart Journal* 1999;**137**(6):1137-44.

BACKGROUND: Identification of patients with acute chest pain at high risk for cardiovascular complications is a common and difficult challenge for clinicians and must be based initially on data from the history, physical examination, electrocardiogram, and chest radiograph. Some data suggest that elevations in cardiac troponin T (cTnT) may be useful for detection of less severe degrees of myocardial injury that may occur in some patients with unstable angina. Therefore we designed a prospective follow-up study to assess the diagnostic performance and prognostic value of cTnT in a population of patients presenting to the emergency department with acute chest pain. **METHODS:** The patient population included all 1477 admitted patients aged 30 years or more who presented to the emergency department of an urban teaching hospital from October 1992, through February 1994, with a chief symptom of acute chest pain not explained by trauma or chest radiograph abnormalities. The 1303 patients (88%) who had 2 or more measurements of cTnT during the first 24 hours after presentation comprised the final study population. Sensitivity, specificity, positive predictive value, negative predictive value, and receiver operator characteristics curve (ROC) were determined for cTnT and creatine kinase-MB (CK-MB) (measured using activity and mass assays) data from the first 24 hours after admission for the outcomes of acute myocardial infarction (AMI) and major cardiac events during the first 72 hours of hospitalization. **RESULTS:** The sensitivity and specificity of cTnT (threshold of 0.1 ng/mL) for detecting AMI during the first 24 hours after presentation were 99% and 86%, respectively. The CK-MB activity and mass assays had diagnostic performance for detecting AMI similar to cTnT. Among patients who did not meet study criteria for AMI, cTnT was elevated during the first 24 hours in 31% of patients who had major complications, compared with a 17% rate for the CK-MB activity assay and a 3% rate for the CK-MB mass assay. In these patients, the cTnT assay had superior diagnostic performance compared with the CK-MB mass assay as a marker for cardiac complications as assessed with ROC analysis ($P < .0004$). **CONCLUSIONS:** In a heterogeneous population of patients seen in the emergency department with acute chest pain, cTnT was similar to CK-MB (activity and mass assays) for detection of AMI and superior to the CK-MB mass assay as a marker for major cardiac events early in the hospital course among those who were ruled out for an AMI. Further study is required to determine how this assay can be used to provide more appropriate, cost-effective care.

Peacock WI, Emerman CL, McErlean ES, et al. Prediction of short- and long-term outcomes by troponin T levels in low-risk patients evaluated for acute coronary syndromes. *Annals of Emergency Medicine* 2000;**35**(3):213-20.

STUDY OBJECTIVE: Recent reports suggest a short series of cardiac troponin (cTnT) testing effectively identifies patients at risk for cardiac events. However, there are few studies validating this strategy. The purpose of this study was to determine the ability of cTnT levels to predict short- and long-term outcomes in low-risk patients with suspected acute coronary syndromes. **METHODS:** This prospective longitudinal study was conducted in a 20-bed emergency department observation unit. Patients at low risk for acute coronary ischemia, with a normal creatine kinase-isoenzyme subunit MB (CKMB) index, were admitted to an observation unit for chest pain evaluation. Serum cTnT levels were measured at baseline and at 4, 8, and 16 hours after admission. The main outcome measures were adverse cardiac events (death, acute myocardial infarction, unstable angina, revascularization) during the index visit and within 6 months after discharge. Using manufacturer's recommendations, the cTnT level was considered abnormal if it exceeded 0.2 microg/L. **RESULTS:** Two hundred sixty-six patients were evaluated. Twenty-one (7.9%) had an adverse event during their index hospitalization. Troponin testing identified only 2 (9.5%) of these patients. Twenty (7.5%) had a cardiac event within 6 months; none were identified by cTnT testing. The sensitivity and specificity were 9.5% and 99.2%, respectively, at the index visit, and 0% and 98.4% at 6 months. The positive and negative predictive values were 50% and 93%, respectively, at the index visit; and 0% and 92% at 6 months. **CONCLUSION:** Determination of troponin T levels has a low sensitivity and high specificity for predicting outcomes in low-risk patients evaluated for suspected acute coronary syndromes. This study does not support a strategy of relying solely on troponin testing for disposition decisions.

Van Lente F, McErlean ES, DeLuca SA, Peacock WF, Rao JS, Nissen SE. Ability of troponins to predict adverse outcomes in patients with renal insufficiency and suspected acute coronary syndromes: a case-matched study. *Journal of the American College of Cardiology* 1999;**33**(2):471-8.

OBJECTIVES: The purpose of this study was to investigate the utility of cardiac troponin T and troponin I for predicting outcomes in patients presenting with suspected acute coronary syndromes and renal insufficiency relative to that observed in similar patients without renal disease. **BACKGROUND:** Cardiac troponin T and troponin I have shown promise as tools for risk stratification of patients with acute coronary syndromes. However, there is uncertainty regarding their cardiac specificity and utility in patients with renal disease. **METHODS:** We measured troponin T, troponin I and creatine kinase MB in 51 patients presenting with suspected acute coronary syndromes and renal insufficiency and in 102 patients without evidence of renal disease matched for the same peak troponin T or I value, selected from a larger patient cohort. Blood samples were obtained at presentation to an emergency room 4 hours, 8 hours and 16 hours later. The ability of biochemical markers to predict adverse outcomes in both groups including infarction, recurrent ischemia, bypass surgery, heart failure, stroke, death or positive angiography/angioplasty during hospitalization and at six months was assessed by receiver-operator curve analysis. The performance of both troponins was compared between groups. **RESULTS:** Thirty-five percent of patients in the renal group and 45% of patients in the nonrenal group experienced an adverse initial outcome; over 50% of patients in all groups had experienced an adverse outcome by 6 months, but these differences were not significant. The area under the curve (AUC) for the ROC curve for troponin T as predictor of initial outcomes was significantly lower in the renal group than in the nonrenal group: 0.56+/-0.07 and 0.75+/-0.07, respectively. The area under the curve was also significantly lower in the renal group compared with the nonrenal group for troponin T as predictor of six month outcomes: 0.59+/-0.07 and 0.74+/-0.07, respectively. The area under the curve was also significantly lower in the renal group compared to the nonrenal group for troponin I as predictor of both initial and six month outcomes: 0.54+/-0.06 vs. 0.71+/-0.07 and 0.53+/-0.06 vs. 0.65+/-0.07, respectively. The sensitivity of troponin T for both initial and six month adverse outcomes was significantly lower in the renal group than in the nonrenal group at a similar level of specificity (0.87): 0.29 vs. 0.60 and 0.45 vs. 0.56, respectively. Troponin I also exhibited similar differences in sensitivity in the renal group (0.29 vs. 0.50 and 0.33 vs. 0.40, respectively). **CONCLUSIONS:** The ability of cardiac troponin T and troponin I to predict risk for subsequent adverse outcomes in patients presenting with suspected acute coronary syndromes is reduced in the presence of renal insufficiency.

Wilcox G, Archer PD, Bailey M, Dziukas L, Lim CF, Schneider HG. Measurement of cardiac troponin I levels in the emergency department: predictive value for cardiac and all-cause mortality. *Medical Journal of Australia* 2001;**174**(4):170-3.

OBJECTIVE: To assess the predictive value of cardiac troponin I levels in cardiac and all-cause mortality in patients presenting to an emergency department. **DESIGN:** A prospective cohort study. **SETTING:** The emergency department of a major tertiary teaching hospital in metropolitan Melbourne over a six-week period in 1998. **PATIENTS:** All patients with requests for cardiac enzyme level measurement. **MAIN OUTCOME MEASURES:** Cardiac and all-cause mortality within 30 days of presentation. **RESULTS:** 424 patients (232 men, 192 women; age range, 16-93 years) were reviewed. The 30-day mortality rate was 7.3% (31/424); in patients with raised levels of both creatine kinase (CK)-MB isoenzyme and troponin I this rate was 27% (7/26; 95% CI, 13%-44%); and in those with troponin I levels above 2 microg/L, but normal CK-MB values, it was 24% (5/21; 95% CI, 5%-43%). The mortality rate in the group with normal results of cardiac markers was 4.3% (14/328; 95% CI, 2.1%-6.5%). Patients with minor increases in troponin I levels (minimal myocardial damage) showed an intermediate 30-day mortality rate (13%, 5/39; 95% CI, 2%-24%). Other predictors of 30-day mortality included age, presentation with shortness of breath, and electrocardiography (ECG) changes diagnostic of acute myocardial infarction or consistent with ischaemia. Cardiovascular causes were responsible for most of the deaths in patients with raised troponin I levels. Multivariate logistic regression analysis showed that raised levels of troponin (> 2.0 microg/L), but not of CK-MB, predict 30-day mortality rate. **CONCLUSIONS:** Compared with CK-MB, cardiac troponin I more accurately predicts 30-day mortality rates in patients presenting to the emergency department. Moreover, troponin I levels identify additional groups of patients at increased risk of death not so identified by measuring CK-MB values.

Myoglobin

Green GB, Skarbek-Borowski GW, Chan DW, Kelen GD. Myoglobin for early risk stratification of emergency department patients with possible myocardial ischemia. *Academic Emergency Medicine* 2000;**7**(6):625-36.

OBJECTIVES: To determine and compare the prognostic abilities of early, single-sample myoglobin measurement with that of creatine kinase-MB (CK-MB), with cardiac troponin T (cTnT), and with physician judgment in the absence of marker results among emergency department (ED) patients with possible myocardial ischemia. **METHODS:** Prospective collection of clinical and serologic data using an identity-unlinked technique from patients with possible myocardial ischemia at two urban EDs. Outcome data concerning the occurrence of adverse events (AEs) during the 14 days after enrollment were used to calculate and compare the relative risks (RRs) and predictive values (with 95% confidence intervals) of the various markers for predicting AEs. **RESULTS:** Among 396 analyzed patients, 65 (16.4%) accrued 104 AEs, including 13 deaths (3.3%) and 31 (7.8%) myocardial infarctions. Myoglobin predicted AEs (RR = 3.36 [95% CI = 2.19 to 5.15]) with significantly higher sensitivity (50.8% [95% CI = 38.6 to 62.9]) than either CK-MB (15.4% [95% CI = 6.6 to 24.2]) or cTnT (24.6% [95% CI = 14.1 to 35.1]), but with lower specificity (81.9% [95% CI = 77.7 to 86.0]; CK-MB = 99.7% [95% CI = 99.1 to 100]; cTnT = 93.1% [95% CI = 90.3 to 95.8]). Myoglobin had prognostic ability among patients with chest pain (3.86 [95% CI = 2.39 to 6.22]) and atypical (non-chest pain) presentations (2.71 [95% CI = 1.09 to 6.71]), including those with a nondiagnostic electrocardiogram (3.11 [95% CI = 1.44 to 6.69]). The combination of myoglobin and physician decision making identified 63 of the 65 patients (96.9% [95% CI = 92.7 to 100]) with subsequent AEs. **CONCLUSIONS:** The early prognostic sensitivity of myoglobin may allow identification of some high-risk patients missed by physician judgment, CK-MB, and cTnT. Myoglobin should be considered for use in the ED based on both its diagnostic and prognostic abilities.

Other Biomarkers

Bayes-Genis A, Mateo J, Santalo M, et al. D-Dimer is an early diagnostic marker of coronary ischemia in patients with chest pain. *American Heart Journal* 2000;**140**(3):379-84.

BACKGROUND: Chest pain is a frequent symptom in the emergency department and often presents a diagnostic challenge. Because coronary thrombosis is a hallmark of acute ischemic syndromes, the substrates of the coagulation and fibrinolysis cascades may be markers of coronary ischemia. The objective of this study was to determine the diagnostic value of several hemostatic markers in patients presenting to the emergency department (ED) with chest pain syndromes. **METHODS:** Two hundred fifty-seven consecutive patients with acute chest pain were studied in this prospective study conducted in an urban ED. D-Dimer levels were measured at admission to the ED in all patients. We also measured thrombin-antithrombin complexes, prothrombin fragment 1+2, activated factor VII, and fibrinogen. We used regression analysis to estimate the likelihood of myocardial infarction and the diagnostic value of D-dimer. **RESULTS:** D-Dimer and fibrinogen levels were significantly higher in patients with acute ischemic events (myocardial infarction and unstable angina) than in nonischemic patients ($P < .01$ and $P = .02$, respectively). The other hemostatic markers were not significantly elevated in patients with ischemic events. D-Dimer level >500 microg/L had an independent diagnostic value for myocardial infarction and increased the diagnostic sensitivity of the electrocardiogram and history from 73% to 92%. **CONCLUSION:** D-Dimer, an expression of ongoing thrombus formation and lysis, is a marker of substantial incremental value for the early diagnosis of acute coronary syndromes presenting with chest pain. It adds independent information to the traditional assessment for myocardial infarction. D-Dimer can be incorporated into clinical decision models in the ED.

Combination of biomarkers

Huggon AM, Chambers J, Nayeem N, Tutt P, Crook M, Swaminathan S. Biochemical markers in the management of suspected acute myocardial infarction in the emergency department. *Emerg Med J* 2001;**18**(1):15-9.

OBJECTIVES: To compare cardiac troponin T, myoglobin, CK, CKMB activity, CKMB mass and the initial electrocardiogram in the early diagnosis of myocardial infarction in the emergency department. **Methods-** Biochemical markers were measured at presentation in patients with a possible diagnosis of acute myocardial infarction. Based on the clinical notes, patients were grouped as "definite myocardial infarction" ($n = 50$), "definite no myocardial infarction" ($n = 81$) and "uncertain" ($n = 96$). Sensitivity and specificity and positive and negative predictive values were calculated using the 131 patients with definitely present or absent

myocardial infarction. RESULTS: The initial electrocardiogram was more sensitive than any of the markers in the first six hours from symptom onset-sensitivity 74% (95%CI 61% to 88%). The positive predictive value of the initial electrocardiogram was 97% in the first six hours; the markers ranged from 47% to 67%. The negative predictive value of the initial electrocardiogram was 85% in the first six hours; the markers ranged from 61% to 70%. Four patients with non-diagnostic electrocardiograms presenting beyond six hours after pain onset had a myocardial infarct detected by at least three of the biochemical markers in each case. CONCLUSIONS: The electrocardiogram is of more diagnostic use than biochemical markers in the first six hours after the onset of pain, but biochemical markers give additional positive diagnostic information in patients presenting later than this. The negative predictive accuracy of biochemical markers is too low for a single sample to be useful for excluding myocardial infarction in the first six hours after onset of symptoms.

Jurlander B, Clemmensen P, Wagner GS, Grande P. Very early diagnosis and risk stratification of patients admitted with suspected acute myocardial infarction by the combined evaluation of a single serum value of cardiac troponin-T, myoglobin, and creatine kinase MB(mass). *European Heart Journal* 2000;**21**(5):382-9.

AIMS: The diagnostic and prognostic capacity of biochemical markers of acute myocardial infarction in the emergency department were evaluated in consecutive patients (n=155) with suspected acute myocardial infarction. METHODS AND RESULTS: Serum myoglobin ≥ 110 microg. l(-1) and creatine kinase MB(mass) ≥ 5 microg. l(-1) had a high accuracy (0.77-0.85) (ns) for acute myocardial infarction diagnosis in patients presenting >2 h after symptom onset. Troponin-T (≥ 0.10 microg. l(-1)) had a lower accuracy (0.53-0.70) for acute myocardial infarction diagnosis, but was the most important 1-year prognostic marker (cardiac death or non-fatal acute myocardial infarction). In patients without ST elevation, combined analysis of two biochemical tests would accurately identify an additional 20% of acute myocardial infarction patients (predictive value of a positive test=0.82) and also identify those without acute myocardial infarction (predictive value of a negative test=0.80). One-year event-free survival was excellent (96%) for patients with two negative biochemical tests, intermediate (74%) for those with discordant tests, and only 53% for patients with two positive biochemical tests. CONCLUSIONS: Analysis of biochemical tests in the emergency department prior to hospital admission could accurately identify approximately 20% additional acute myocardial infarction patients. The prognosis of these patients is poor, and they may be a target for primary PTCA or new early initiated aggressive medical therapies. Copyright 2000 The European Society of Cardiology.

Ooi SB, Lim YT, Lau TC, Chia BL, Pillai S, Liu T. Value of troponin-T rapid assay, cardiac enzymes, electrocardiogram and history of chest pain in the initial diagnosis of myocardial infarction in the emergency department. *European Journal of Emergency Medicine* 2000;**7**(2):91-8.

We conducted a prospective study of 152 adult patients presenting to an emergency department with chest pain or symptoms suggestive of acute myocardial infarction (AMI) to evaluate the first electrocardiogram (ECG), creatine kinase (CK)-MB and Troponin-T Rapid Assay (TnT) alone or in combination with chest pain in the initial diagnosis of AMI. A provisional diagnosis was made after the history, physical examination and the first ECG reading. Blood specimens were taken for TnT, CK and CK-MB mass. A final discharge diagnosis of AMI was made according to World Health Organization criteria. Seventy-six (50%) of patients had a final diagnosis of AMI. The sensitivities of the first ECG, first CK-MB mass and first TnT were 76.3% (95% confidence interval (CI), 66.8-85.9), 38.2% (95% CI, 27.2-49.1) and 31.6% (95% CI, 21.2-42.0) respectively. The area under the curve for a combination of ECG, CK-MB mass, TnT and chest pain was the highest at 0.937 when compared with chest pain with varying combinations of tests. A combination of the first ECG, CK-MB mass and TnT had a negative predictive value (NPV) of 87.9% (95% CI, 80.0-95.8). The first ECG was the most sensitive test while the combination of chest pain, ECG, cardiac enzymes and TnT gave the best results in the initial diagnosis of AMI. If the first ECG, CK-MB mass and TnT are all negative, the probability of having an AMI is 12%.

Polaczyk CA, Kuntz KM, Sacks DB, Johnson PA, Lee TH. Emergency department triage strategies for acute chest pain using creatine kinase-MB and troponin I assays: a cost-effectiveness analysis. *Annals of Internal Medicine* 1999;**131**(12):909-18.

BACKGROUND: Evaluation of acute chest pain is highly variable. OBJECTIVE: To evaluate the cost-effectiveness of strategies using cardiac markers and noninvasive tests for myocardial ischemia. DESIGN: Cost-effectiveness analysis. DATA SOURCES: Prospective data from 1066 patients with chest pain and from the published literature. TARGET POPULATION: Patients admitted with acute chest pain. TIME HORIZON:

Lifetime. PERSPECTIVE: Societal. INTERVENTIONS: Creatine kinase (CK)-MB mass assay alone; CK-MB mass assay followed by cardiac troponin I assay if the CK-MB value is normal; CK-MB mass assay followed by troponin I assay if the CK-MB value is normal and electrocardiography shows ischemic changes; both CK-MB mass and troponin I assays; and troponin I assay alone. These strategies were evaluated alone or in combination with early exercise testing. OUTCOME MEASURES: Lifetime cost, life expectancy (in years), and incremental cost-effectiveness. RESULTS OF BASE-CASE ANALYSIS: For patients 55 to 64 years of age, measurement of CK-MB mass followed by exercise testing in appropriate patients was the most competitive strategy (\$43000 per year of life saved). Measurement of CK-MB mass followed by troponin I measurement had an incremental cost-effectiveness ratio of \$47400 per year of life saved for patients 65 to 74 years of age; it was also the most cost-effective strategy when early exercise testing could not be performed, CK-MB values were normal, and ischemic changes were seen on electrocardiography. RESULTS OF SENSITIVITY ANALYSIS: Results were influenced by age, probability of myocardial infarction, and medical costs. CONCLUSIONS: Measurement of CK-MB mass plus early exercise testing is a cost-effective initial strategy for younger patients and those with a low to moderate probability of myocardial infarction. Troponin I measurement can be a cost-effective second test in higher-risk subsets of patients if the CK-MB level is normal and early exercise testing is not an option.

Porela P, Pulkki K, Helenius H, et al. Prediction of short-term outcome in patients with suspected myocardial infarction. *Annals of Emergency Medicine* 2000;**35**(5):413-20

STUDY OBJECTIVE: Although specific cardiac injury markers have enhanced early patient classification, the ECG remains a necessary investigation in the acute phase of chest pain. Combined use of both tests could further improve the diagnostic and prognostic accuracy. METHODS: We studied 311 consecutive patients who came to the emergency department of a regional referral hospital for the differential diagnosis of acute chest discomfort. The admission ECG was classified using an automated interpretation program and tested together with elevated admission creatine kinase isoform MB (CK-MB) and cardiac troponin I (TnI) concentration for prediction of final myocardial injury (44%) and in-hospital mortality (14%). RESULTS: Combining the information from the admission ECG and cardiac markers, the sensitivity for becoming final myocardial injury (maximal CK-MB ≥ 11 microg/L) was 90% and specificity 61%. The proportion of false-negative results (10%) was independent of symptom duration. Age, positive ECG findings, and increased admission TnI levels were predictive for in-hospital mortality. CONCLUSION: The commonly available biochemical and ECG criteria allow risk stratification of patients with a suspected acute ischemic event. The data analysis can easily be automated and is independent of patient delay.

Wu AH, Ghani F, Prigent F, Petry C, Armstrong G, Graff L. Reflex testing II: evaluation of an algorithm for use of cardiac markers in the assessment of emergency department patients with chest pain. *Clinica Chimica Acta* 1999;**288**(1-2):97-109.

A reflex algorithm was developed and evaluated for the use of serum cardiac markers for the diagnosis and rule out of acute myocardial infarction (AMI), and risk stratification of unstable angina patients for those who present to emergency departments (ED) with chest pain. The process begins with testing of total CK and myoglobin at admission. Based on these results, the algorithm determines the need for subsequent testing for the CK-MB isoenzyme and cardiac troponin I (cTnI). The algorithm also directs the need for further blood collection and cardiac marker testing at 4, 8, and 12 h after presentation. A total of eleven stopping points were identified. For some of these stopping points, the algorithm concluded that further blood collections and testing was unnecessary and redundant. The algorithm was retrospectively evaluated on 101 non-consecutive chest pain patients who presented to the EDs at three hospitals. For the AMI group (n=34), six of nine possible different stopping points were reached: 64.7% of cases were diagnosed with the first sample at admission, an additional 32.3% after 4 h, and 2.9% at 8 h. The 12-h sample was not necessary for any of the AMI patients. For the non-AMI group (n=67), most reached the stopping point of no cardiac injury or risk. There were five unstable angina patients who had minor myocardial damage on the basis of a marginally increased cTnI. Of these, one patient subsequently suffered AMI, and three others required angioplasty or bypass surgery. Compared to performing four tests on all patient samples, the reflex algorithm would have reduced the number of necessary tests from 442 to 130 (71% reduction) for AMI patients, and 871 to 469 (46% reduction) for non-AMI patients, if prospectively implemented.

Zimmerman J, Fromm R, Meyer D, et al. Diagnostic marker cooperative study for the diagnosis of myocardial infarction. *Circulation* 1999;**99**(13):1671-7.

BACKGROUND: Millions of patients present annually with chest pain, but only 10% to 15% have myocardial infarction. Lack of diagnostic sensitivity and specificity of clinical and conventional markers prevents or delays treatment and leads to unnecessary costly admissions. Comparative data are lacking on the new markers, yet

using all of them is inappropriate and expensive. METHODS AND RESULTS: The Diagnostic Marker Cooperative Study was a prospective, multicenter, double-blind study with consecutive enrollment of patients with chest pain presenting to the emergency department. Diagnostic sensitivity and specificity and frequency of increase in patients with unstable angina were determined for creatine kinase-MB (CK-MB) subforms, myoglobin, total CK-MB (activity and mass), and troponin T and I on the basis of frequent serial sampling for ≤ 24 hours. Of 955 patients with chest pain, 119 (12.5%) had infarction identified by use of CK-MB mass, and 203 (21%) had unstable angina. CK-MB subforms were most sensitive and specific (91% and 89%) within 6 hours of onset, followed by myoglobin (78% and 89%). For late diagnosis, total CK-MB activity (derived from subforms) was the most sensitive and specific (96% and 98%) at 10 hours from onset, followed by troponin I (96% and 93%), but not until 18 hours, and troponin T (87% and 93% at 10 hours). In unstable angina, CK-MB subforms were increased in 29.5%, myoglobin in 23.7%, troponin I in 19.7%, and troponin T in 14.8%. All markers were increased in 99 patients. With each marker as the diagnostic standard, CK-MB subforms and myoglobin remained the most sensitive for early diagnosis. CONCLUSIONS: The CK-MB subform assay alone or in combination with a troponin reliably triages patients with chest pain and should lead to improved therapy and reduced cost

Grzybowski M, Zalenski RJ, Ross MA, Bock B. A prediction model for prehospital triage of patients with suspected cardiac ischemia. *Journal of Electrocardiology* 2000;**33**(Suppl):253-8.

The American College of Cardiology recommends that patients with high risk acute myocardial infarction (AMI) be triaged to hospitals with percutaneous transluminal coronary angioplasty capability. However, there are no prehospital triage criteria to select candidates for bypassing community hospitals and being taken directly to "cardiac centers." This article assesses which independent variables predict death within 7 days in patients with suspected AMI transported by EMS. This is a retrospective study of 291 AMI patients transported by ambulance to 3 hospitals during 1996-1997. Included were patients who were ($n = 244$) $> \text{ or } = 18$ years of age, had a ED chief complaint of chest pain or dyspnea for whom we had mortality data. Mortality at 7 days, our primary outcome measure, was obtained by using a metropolitan Detroit tricounty death index records. Differences between the survivors and nonsurvivors were assessed using the Student's t-test and chi-square tests. Multiple triage criteria were assessed for optimal identification of high risk patients by constructing a logistic multivariate model. Among the study population, 15% died within 7 days (95% confidence interval (CI) 10.3-19.2), and this group represented 63.2% of all deaths over a 2 year surveillance period. Survivors, compared to nonsurvivors, were 14.1 years younger ($P < \text{ or } = .001$) and more often men ($P < \text{ or } = 0.001$). The dispatch time to ED arrival was less among survivors than nonsurvivors (42.8 vs. 50.6 min, $P < \text{ or } = .01$). EMS vital signs differed by survivor status. Among survivors, HR was lower (-11.9 bpm; $P < \text{ or } = 0.01$), RR was lower (-6.7 rpm; $P < \text{ or } = .001$), SBP was higher (+14.5 mmHg; $P < \text{ or } = 0.05$) and DBP was higher (+13.2 mm Hg; $P < \text{ or } = .01$). A multivariate model identified the following as independent predictors of early mortality: female gender (OR = 2.3; $P < \text{ or } = .05$), age $> \text{ or } = 65$ (OR = 5.9; $P < \text{ or } = .01$), RR $> \text{ or } = 20$ (OR = 4.6; $P < \text{ or } = .001$), SBP < 120 (OR = 2.4; $P < \text{ or } = .05$). The overall model was 86% sensitive and 53% specific with an area under the receiving operating characteristic curve of 0.8 ($P < \text{ or } = .001$). A triage rule based on a multivariate model can identify the group at high risk of early cardiac death. This decision rule needs to be prospectively validated.

Echocardiography

No new data

Technetium-99m Sestamibi Myocardial Perfusion Imaging

Kontos MC, Jesse RL, Anderson FP, Schmidt KL, Ornato JP, Tatum JL. Comparison of myocardial perfusion imaging and cardiac troponin I in patients admitted to the emergency department with chest pain. *Circulation* 1999;**99**(16):2073-8.

BACKGROUND: Identification of patients with acute coronary syndromes (ACS) among those who present to emergency departments with possible myocardial ischemia is difficult. Myocardial perfusion imaging with ^{99m}Tc sestamibi and measurement of serum cardiac troponin I (cTnI) both can identify patients with ACS. METHODS AND RESULTS: Patients considered at low to moderate risk for ACS underwent gated single-photon emission CT sestamibi imaging and serial myocardial marker measurements of creatine kinase-MB, total creatine kinase activity, and cTnI over 8 hours. Positive perfusion imaging was defined as a perfusion defect

with associated abnormalities in wall motion or thickening. cTnI ≥ 2.0 ng/mL was considered abnormal. Among the 620 patients studied, 59 (9%) had myocardial infarction and 81 (13%) had significant coronary disease; of these patients, 58 underwent revascularization. Perfusion imaging was positive in 241 patients (39%), initial cTnI was positive in 37 (6%), and cTnI was ≥ 2.0 ng/mL in 74 (12%). Sensitivity for detecting myocardial infarction was not significantly different between perfusion imaging (92%) and cTnI (90%), and both were significantly higher than the initial cTnI (39%). Sensitivity for predicting revascularization or significant coronary disease was significantly higher for perfusion imaging than for serial cTnI, although specificity for all end points was significantly lower. Lowering the cutoff value of cTnI to 1.0 ng/mL did not significantly change the results. CONCLUSIONS: Early perfusion imaging and serial cTnI have comparable sensitivities for identifying myocardial infarction. Perfusion imaging identified more patients who underwent revascularization or who had significant coronary disease, but it had lower specificity. The 2 tests can provide complementary information for identifying patients at risk for ACS.

Kosnik JW, Zalenski RJ, Grzybowski M, Huang R, Sweeny PJ, Welch RD. Impact of technetium-99m sestamibi imaging on the emergency department management and costs in the evaluation of low-risk chest pain. *Academic Emergency Medicine* 2001;**8**(4):315-23.

OBJECTIVES: To assess the impact of rest sestamibi scanning on emergency physicians' (EPs') diagnostic certainty and decision making (as assessed by the hypothetical disposition of patients) for 69 consenting stable patients with suspected acute cardiac ischemia and nondiagnostic electrocardiograms. The resultant impact on costs was examined as a secondary outcome. METHODS: Patients with suspected acute cardiac ischemia were injected with 25 mCi of sestamibi within two hours of active pain in one of three emergency department study sites. The probability of acute myocardial infarction (AMI) and unstable angina (UA), and hypothetical disposition decisions were recorded immediately before and after physicians were notified of scan results. Changes in disposition were classified as optimal or suboptimal. For the cost determinations, a cost-based decision support program was used. RESULTS: For the subgroup found to be free of acute cardiac events (ACEs) (n = 62), the EPs' post-sestamibi scan probabilities for AMI decreased by 11% and UA by 18% (p < 0.001 for both conditions). In seven patients with ACEs, the post-scan probabilities of AMI and UA increased, but neither was statistically significant. Scan results led to hypothetical disposition changes in 29 patients (42%), of which 27 (93%) were optimal (nine patients were reassigned to a lower level of care, two to a higher level, and 16 additional patients to "discharge-home" status). The strategy of scanning all patients who were low to moderate risk for acute cardiac ischemia would result in an increase of direct costs of care of \$222 per patient evaluated, due to added cost of sestamibi scanning. CONCLUSIONS: Sestamibi scanning results appropriately affected the EPs' estimates of the probability of AMI and UA and improved disposition decisions. Scanning all low-risk patients would likely be associated with increased costs at this medical center.

Mariani G, Villa G, Rossettin PF, et al. Detection of acute myocardial infarction by 99mTc-labeled D-glucuronic acid imaging in patients with acute chest pain. *Journal of Nuclear Medicine* 1999;**40**(11):1832-9.

Definitive diagnosis of acute myocardial infarction early in the process is often difficult. An imaging agent that localized quickly and specifically in areas of acute necrosis could provide this critical diagnostic information. To determine whether imaging with 99mTc-labeled D-glucuronic acid (GLA) could provide this information, we imaged a group of patients presenting with symptoms suggestive of acute infarction. METHODS: Twenty-eight patients presenting to the emergency department with symptoms highly suggestive of acute infarction were injected with 99mTc-GLA and imaged about 3 h later. RESULTS: The sensitivity of lesion detection was remarkably time dependent. Fourteen patients with acute infarction injected within 9 h of onset of chest pain had positive scans, even in the presence of persistent occlusion. The remaining 14 patients had negative scans. Nine patients with negative scans had acute infarction but were injected more than 9 h after onset of chest pain. The final diagnosis in the remaining 5 patients was unstable angina (3 injected <9 h and 2 injected >9 h after onset of chest pain). Six patients were reinjected with 99mTc-GLA 4-6 wk after their initial study to determine whether persistent positive scans occurred with this agent. All 6 had negative scans. CONCLUSION: This study suggests that 99mTc-GLA localizes in zones of acute myocardial necrosis when injected within 9 h of onset of infarction.

Paventi S, Parafati MA, Di Luzio E, Pellegrino CA. Safety and feasibility of two-dimensional echocardiography and myocardial perfusion imaging in patients with chest pain. *Angiology* 2001;**52**(5):305-9.

The accurate identification of patients at high risk for acute coronary syndromes among those seen in the emergency department with possible myocardial ischemia and nonischemic electrocardiograms is a problem. Two-dimensional echocardiography and myocardial perfusion imaging with 99m-technetium sestamibi can identify patients at low and high risk; however, comparative studies are lacking. The authors studied 555 patients considered at low or moderate risk for myocardial ischemia in our emergency department on the basis of the presenting history, and results of physical examination and electrocardiography. These patients underwent echocardiography and myocardial perfusion imaging within 4 hours of presentation. Endpoints included myocardial infarction, percutaneous transluminal coronary angioplasty, and positive results on stress perfusion imaging. Both imaging procedures were performed in the emergency department on 370 patients. Overall agreement between the two techniques was high (concordance, 89%) in the patients who had myocardial infarction or underwent coronary angiography. Agreement between the two techniques is high when used in patients with possible myocardial ischemia. Both techniques helped identify patients at high risk who required admission and those who could be safely discharged.

Electron beam computed tomography

Laudon DA, Vukov LF, Breen JF, Rumberger JA, Wollan PC, Sheedy PF, 2nd. Use of electron-beam computed tomography in the evaluation of chest pain patients in the emergency department. *Annals of Emergency Medicine* 1999;**33**(1):15-21.

Study objective: We sought to determine whether electron-beam computed tomography (EBCT) could be used as a triage tool in the emergency department for patients with angina-like chest pain, no known history of coronary disease, normal or indeterminate ECG findings, and normal initial cardiac enzyme concentrations. METHODS: We conducted a prospective observational study of 105 patients admitted between December 1995 and October 1997 to the ED of a large tertiary care hospital with 70,000 annual ED visits. The study group was comprised of women aged 40 to 65 years and men aged 30 to 55 years who presented with angina-like chest pain requiring admission to the hospital or chest pain observation unit. All patients underwent EBCT of the coronary arteries, along with other cardiac testing as deemed necessary by staff physicians. RESULTS: Of the 105 patients, 100 underwent other cardiac testing during hospitalization. Evaluation included treadmill exercise testing in 58, coronary angiography in 25, radionuclide stress testing in 19, and echocardiography in 11. Results of EBCT and cardiac testing were negative for both in 53 patients (53%), positive for both in 14 (14%), positive for tomography and negative for cardiac testing in 32 (32%), and negative for tomography and positive for cardiac testing in only 1 patient. This positive test result, on a treadmill exercise test, was ruled a false positive by an independent staff cardiologist. Two other female patients with normal exercise sestamibi or coronary angiography and EBCT findings also had false-positive treadmill exercise results. The sensitivity of EBCT was 100% (95% confidence interval, 77% to 100%), with a negative predictive value of 100% (95% confidence interval, 94% to 100%). Specificity was 63% (95% confidence interval, 54% to 75%). CONCLUSION: EBCT is a rapid and efficient screening tool for patients admitted to the ED with angina-like chest pain, normal cardiac enzyme concentrations, indeterminate ECG findings, and no history of coronary artery disease. Our study suggests that patients with normal initial cardiac enzyme concentrations, normal or indeterminate ECG findings, and negative results on EBCT may be safely discharged from the ED without further testing or observation. Larger studies are required to confirm this conclusion.

Acute Cardiac Ischemia Time-Insensitive Predictive Instrument (ACI-TIPI)

No new data.

Goldman Chest Pain Protocol

Durairaj L, Reilly B, Das K, et al. Emergency department admissions to inpatient cardiac telemetry beds: a prospective cohort study of risk stratification and outcomes.

American Journal of Medicine 2001;**110**(1):7-11.

PURPOSE: Little is known about physicians' use of inpatient cardiac telemetry units among emergency department patients at risk for cardiac complications. We therefore studied the outcomes of patients admitted to inpatient telemetry beds to identify a subset of patients from whom cardiac monitoring could be withheld safely. **SUBJECTS AND METHODS:** We conducted a prospective cohort study of 1,033 consecutive adult patients admitted to an inpatient telemetry unit from the emergency department of a 700-bed urban public teaching hospital. Subjects with or without chest pain were risk-stratified using a prediction rule and observed for in-hospital cardiac complications, acute myocardial infarction, and transfer to an intensive care unit (ICU). **RESULTS:** There were no significant differences between patients with (n = 677) or patients without chest pain (n = 356) in the rates of major cardiac complications, myocardial infarctions, or transfers to an ICU. Among 318 patients with chest pain who were classified as being very low risk, none suffered major complications (negative predictive value 100%; 95% confidence interval [CI]: 98.8% to 100%). Among 214 very low risk patients without chest pain, 1 (0.5%) had a major complication (negative predictive value 99.5%; 95% CI: 97.4% to 99.9%). **CONCLUSIONS:** The prediction rule accurately identified patients with or without chest pain who were at very low risk of major complications, identifying a subset from whom cardiac monitoring could be withheld safely.

Reilly B, Durairaj L, Husain S, et al. Performance and potential impact of a chest pain prediction rule in a large public hospital. *American Journal of Medicine* 1999;**106**(3):285-91.

PURPOSE: To evaluate the performance of a previously validated prediction rule for patients presenting to the emergency department with chest pain and the potential impact of the rule on triage decisions. **SUBJECTS AND METHODS:** In a prospective cohort study, physician investigators interviewed consecutive patients admitted for suspected acute ischemic heart disease (n = 207) by emergency department attending physicians who had not used the prediction rule. We measured the accuracy of the rule in predicting cardiac complications in these patients, and compared actual triage decisions with those that might have been recommended by use of the prediction rule. We also measured comorbid illnesses among patients stratified as very low risk by the prediction rule, as well as the effect of standardizing the definition of unstable angina and interpretation of electrocardiograms (ECG) on the rule's sensitivity and specificity. **RESULTS:** Overall, the rate of major cardiac complications (4.3%) was similar to that reported in the original study (3.6%). The prediction rule performed well in predicting these complications in our patients (area under receiver operating characteristic curve 0.84 versus 0.80 in the original study; difference 0.04, 95% confidence interval [CI] -0.07, 0.14). Standardized definitions of unstable angina and interpretation of ECGs improved the specificity of the prediction rule in predicting complications (55% versus 47%; difference 8%, 95% CI 1.5%, 13.7%). The prediction rule recommended admission to telemetry units in 65 fewer patients than actually occurred (31% of the entire cohort). None of these patients had major complications. A substantial minority of "very low risk" patients (27%) had comorbid illnesses requiring inpatient treatment. **CONCLUSIONS:** This independent validation of the prediction rule suggests that it can improve triage decisions for patients admitted with suspected acute ischemic heart disease. Additional studies are needed to test prospectively the performance of the prediction rule in actual decision making, its acceptance by clinicians, and its cost effectiveness.

Other Computer-Based Decision Aids

Aase O. Clinical experience with a decision support computer program using Bayes' theorem to diagnose chest pain patients. *Cardiology* 1999;**92**(2):128-34.

A decision support computer program (DSP) was used by the emergency room physician as a diagnostic tool on patients admitted with acute chest pain to guide the referral of these patients either to the Coronary Care Unit (CCU) or general ward. The DSP used Bayes' theorem on 38 anamnestic and clinical variables to classify patients into one of nine diagnoses. During a six months trial period 32 physicians used the DSP to diagnose 493 patients admitted with acute chest pain. The physicians referred the patients to CCU or general ward based on their clinical judgements, the ECG findings and the diagnostic estimates given by the DSP. The program correctly diagnosed 150 (84%) of 178 patients with acute myocardial infarction and 63 of 112 patients with unstable angina. However, acute ischemic heart disease (acute myocardial infarction or unstable angina) was

correctly classified by the DSP for 259 (89%) of 290 patients. By using the DSP, the number of patients unnecessarily referred to CCU was reduced from 35% to 19% and the number of patients in need of CCU observation misallocated to general ward was reduced from 13% to 10%. Thus, use of the DSP in the emergency room on easily available anamnestic and clinical variables may improve referrals to the CCU, optimize therapy and resource use. Copyright 2000 S. Karger AG, Basel

Left bundle-branch block subpopulation specific studies

Kontos MC, McQueen RH, Jesse RL, Tatum JL, Ornato JP. Can myocardial infarction be rapidly identified in emergency department patients who have left bundle-branch block? [see comments]. *Annals of Emergency Medicine* 2001;**37**(5):431-8.

STUDY OBJECTIVES: Fibrinolytic therapy is recommended for patients who have chest pain and left bundle-branch block (LBBB). However, the presence of baseline ECG abnormalities makes early accurate identification of acute myocardial infarction (AMI) difficult. The predictive ability of clinical and ECG variables for identifying patients with LBBB and AMI has not been well studied. We sought to determine the prevalence and predictors of myocardial infarction among patients presenting to the emergency department with LBBB on the initial ECG who were evaluated for myocardial infarction. **METHODS:** All patients presenting to the ED were prospectively risk stratified on the basis of clinical and historical variables. ECGs from patients with LBBB were compared retrospectively with previously published criteria for identification of AMI. The ability of a new LBBB to predict AMI was also determined. **RESULTS:** Twenty-four (13%) of the 182 patients with LBBB had AMI. Clinical and historical variables were similar in patients with and without AMI. A new LBBB had a sensitivity of 42% and a specificity of 65%. The presence of concordant ST-segment elevation or depression had specificities and positive predictive values of 100%; however, sensitivities were only 8% and 17%, respectively. The best diagnostic criterion was the presence of concordant ST-segment elevation or depression on the ECG or an initially elevated creatine kinase MB (sensitivity, 63%; specificity, 99%). **CONCLUSION:** ECG criteria for identifying patients with AMI and LBBB identify only a small minority of patients with AMI. Treating all patients with LBBB and chest pain with fibrinolytics would result in treatment of a significant number of patients without AMI.

Shlipak MG, Lyons WL, Go AS, Chou TM, Evans GT, Browner WS. Should the electrocardiogram be used to guide therapy for patients with left bundle-branch block and suspected myocardial infarction? [see comments]. *JAMA* 1999;**281**(8):714-9.

CONTEXT: Recently, an algorithm based on the electrocardiogram (ECG) was reported to predict myocardial infarction (MI) in patients with left bundle-branch block (LBBB), but the clinical impact of this testing strategy is unknown. **OBJECTIVE:** To determine the diagnostic test characteristics and clinical utility of this ECG algorithm for patients with suspected MI. **DESIGN:** Retrospective cohort study to which an algorithm was applied, followed by decision analysis regarding thrombolysis made with or without the algorithm. **SETTING:** University emergency department, 1994 through 1997. **PATIENTS:** Eighty-three patients with LBBB who presented 103 times with symptoms suggestive of MI. **MAIN OUTCOME MEASURES:** Myocardial infarction determined by serial cardiac enzyme analyses and stroke-free survival. **RESULTS:** Of 9 ECG findings assessed, none effectively distinguished the 30% of patients with MI from those with other diagnoses. The ECG algorithm indicated positive findings in only 3% of presentations and had a sensitivity of 10% (95% confidence interval, 2%-26%). The decision analysis showed that among 1000 patients with LBBB and chest pain, 929 would survive without major stroke if all received thrombolysis compared with 918 if the ECG algorithm was used as a screening test. **CONCLUSIONS:** The ECG is a poor predictor of MI in a community-based cohort of patients with LBBB and acute cardiopulmonary symptoms. Acute thrombolytic therapy should be considered for all patients with LBBB who have symptoms consistent with MI.

Appendix 4 Disclaimer and NHMRC Levels of Evidence

Disclaimer

The information in this report is a summary of the available evidence in excluding acute cardiac ischaemic events in patients presenting to emergency departments with chest pain. The report is designed to give the reader a starting point for considering the research evidence and for continuing to search out further evidence. Whilst great care has been taken in the preparation of the materials included in this publication, the authors and Melbourne Health do not warrant the accuracy of this document, any representation, implied or expressed, concerning the efficacy, appropriateness or suitability of any treatment or product. In view of the possibility of human error or further advances in medical knowledge the authors and Melbourne Health cannot and do not warrant that the information contained in these pages is in every aspect accurate and complete. Accordingly, they are not and will not be held responsible or liable for any errors of omissions that may be found in this report. You are therefore encouraged to consult other sources in order to confirm the information contained in this report and, in the event that medical treatment is required, to take professional expert advice from a legally qualified and appropriately experienced medical practitioner.

Levels of evidence used in searching for research material by the Clinical Epidemiology and Health Service Evaluation Unit

As defined by “How to use the evidence: assessment and application of scientific evidence” from the National Health and Medical Research Council, Canberra 2000.

Level	Type of Evidence
I	Evidence obtained from a systematic review (or meta-analysis) of all relevant randomised controlled trials.
II	Evidence obtained from at least one randomised controlled trial.
III - 1	Evidence obtained from pseudorandomised controlled trials (alternate allocation or some other method).
III - 2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomized, cohort or case-control studies or interrupted time series with a control group.
III - 3	Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pretest/post test.