The RATPAC Trial

(Randomised Assessment of Treatment using Panel Assay of Cardiac markers)

A randomised controlled trial of point-of-care cardiac markers in the emergency department

1. Summary of the project

Design: Pragmatic randomised controlled trial and economic evaluation

Setting: Six emergency departments in the United Kingdom.

Target population: People presenting to the emergency department with chest pain due to suspected AMI in whom a negative point-of-care marker test could potentially rule out AMI and allow discharge home. We will exclude those with: a) Diagnostic ECG changes for AMI or acute coronary syndrome (>1mm ST deviation or >3mm inverted T waves), b) Known coronary heart disease presenting with prolonged (>1 hour) or recurrent episodes of typical cardiac-type pain, c) Proven or suspected serious non-coronary pathology (e.g. pulmonary embolus), d) An obvious non-cardiac cause (e.g. pneumothorax or muscular pain), and e) Co-morbidity or social problems that require hospital admission.

Health technologies being assessed: We will evaluate the effectiveness of a point-of-care cardiac marker panel, comprising of CK-MB, myoglobin and troponin I. We will randomly allocate patients to receive either: a) Diagnostic assessment using the point-of-care biochemical marker panel, or b) Conventional diagnostic assessment without the panel. The use of all other tests and treatments, and decision-making in the emergency department will be at the discretion of the attending clinician. The only difference between the two arms of the trial will be that patients in the intervention arm will receive testing with the point-of-care panel. We will also store blood samples to test new and alternative markers to explore whether these might be more effective or cost-effective than the CK-MB, myoglobin, troponin I panel.

Measurement of costs and outcomes: Cost and outcome data will be collected using routine data sources and self-complete questionnaires mailed to participants at one and three months. The primary outcome will be the proportion of patients successfully discharged home after emergency department assessment, defined as discharge with no adverse event (as defined below) during the following three months. Secondary outcomes will include: 1) Health-related quality of life measured at one and three months after attendance*; 2*) Satisfaction with care; 3) The proportion of patients managed on the coronary care unit and receiving cardiac treatments, such as heparin, clopidogrel or glycoprotein inhibitors; 4) Re-attendance at and/or re-admission to hospital over the following three months; 5) Adverse events (death, non-fatal AMI, emergency revascularisation or hospitalisation for myocardial ischaemia).

Health service costs will be measured for three months from initial attendance, including diagnostic tests, emergency department attendances and hospital admissions, outpatient reviews, and cardiac procedures. Cost analysis will compare bootstrap estimates of the mean cost per patient of the two groups. Cost-effectiveness analysis will estimate the incremental cost per quality-adjusted life year of using point-of-care cardiac marker testing compared to management without point-of-care testing. We will also model the potential cost-effectiveness of alternative marker strategies and explore the generalisability of findings to hospitals with different baseline admission rates.

Sample size: We will recruit 3000 patients to provide 80% power to detect a 5% absolute increase in the proportion of patients successfully discharged after emergency department assessment, from 50% to 55%, whilst also having 80% power to detect a doubling in the major adverse cardiac event rate from 2% to 4% (alpha=0.05). It will also provide sufficient power to allow us to explore potential heterogeneity between participating hospitals.

Project timetable: Months 1-6: Staff recruitment, local ethics and research governance. Months 7-18: Patient recruitment. Months 19-24: completion of follow-up, data analysis, writing-up and dissemination. Based on previous studies by members of our research team we estimate that we will require six hospitals to recruit for 12 months each to achieve the sample size of 3000,

assuming that we recruit 70% of those eligible (Goodacre). We have undertaken a number of studies of this patient group and have shown that recruitment of 500 suitable patients per year is easily attainable at a typical hospital.

Expertise in team: The trial will be co-ordinated by a Trial Manager in the Sheffield Clinical Trials Support Unit, working with full statistical, clinical trials and health economic support. The applicants are a multi-disciplinary team with expertise in health service research, emergency medicine, cardiology, chemical pathology, epidemiology, health economics and statistics. The researchers are leading experts in the management of acute chest pain and have undertaken previous landmark investigations in this field, including the ESCAPE trial of chest pain units (SG, SC, SD), randomised evaluation of point-of-care cardiac markers in coronary care (PC), and evaluation of ischaemia modified albumin in emergency care (JB, PC, SG). A CHD user group, led by Enid Hirst, a health service user representative, is providing patient involvement in the development of the proposal.

Reference for power calculation: Goodacre S, Nicholl J, Dixon S et al. Randomised controlled trial and economic evaluation of a chest pain observation unit compared with routine care. *BMJ* 2004;328:254-7.

2. Importance of the health problem to the NHS

Acute chest pain is responsible for around 700,000 patient presentations per year to emergency departments in England and Wales, with an estimated cost to the NHS of around £0.5 billion for emergency and inpatient care (1). Many of these patients are admitted to hospital unnecessarily because acute myocardial infarction (AMI) is suspected and cannot be reliably excluded in the emergency department. The Secretary of State for Health has recently highlighted the need to reduce unnecessary emergency admissions, which could save the NHS over £400 million per year, and has identified suspected angina as one of the biggest contributors to unnecessary admissions (2).

Patients are unnecessarily admitted with chest pain because the tests currently available to the emergency department are inadequate. Clinical assessment for AMI is known to be unreliable, the electrocardiograph (ECG) is specific but has insufficient sensitivity to rule out AMI, while the sensitivity of biochemical cardiac markers is dependent upon the time delay between symptom onset and blood sampling. Traditionally a delay of 12 hours has been considered necessary to allow the development of sensitivity that is sufficient to rule out AMI, yet patients typically present to the emergency department 2-3 hours after their symptoms. Hence admission is usually required until an appropriate time has elapsed.

A rapid, reliable diagnostic test to rule out AMI shortly after presentation to the emergency department could substantially reduce unnecessary admissions with chest pain and save the NHS millions of pounds per year. It could also help to reduce the estimated 6% of patients who are inappropriately discharged home with AMI (3). However, because chest pain is so common, an ineffective diagnostic test that did not alter patient management could cost the NHS millions of pounds per year. We therefore need randomised controlled trial evidence that any new test is effective (i.e. reduces unnecessary admissions) and is cost-effective before widespread implementation can be recommended.

1. Goodacre S, Cross E, Arnold J, Angelini K, Capewell S, and Nicholl J. The health care burden of acute chest pain. *Heart* 2005; 91:229-230.
2. Department of Health, Press Release 2006/0104. Improve healthcare by reducing unnecessary emergency admissions - Hewitt. Department of Health, London, 20th March 2006.
3. Collinson PO, Premachandram S, Hashemi K. Prospective audit of incidence of prognostically important myocardial damage in patients discharged from the emergency department. BMJ 2000;320:1702-5.

3. A description of the technology and its possible effectiveness range

Recent studies have suggested that newer biochemical markers might be used to rule-out AMI within 90 minutes of presentation to the emergency department. This approach involves combining multiple markers in a "panel" and measuring the change in marker levels over a short time period. These marker panels have been developed as "point of care" tests that can be used by the emergency department staff attending the patient, thus reducing turnaround times for test results and ensuring 24 hour availability of tests, even when laboratory access is limited.

The point-of-care cardiac marker panel will comprise CK-MB(mass), myoglobin and troponin I, measured at presentation and 90 minutes later, using the Stratus-CS point-of-care analyser. This combination has been widely evaluated in practice (1-5). Of the systems currently available or soon to be available the latest version of the Dade Behring Stratus CS has the most data as an instrument suitable both for the emergency laboratory and for use as a POCT instrument (6).

Many new biochemical cardiac markers are currently being developed, but none have yet been demonstrated to have superior diagnostic performance to the CK-MB, myoglobin, troponin combination. To maximise the benefit gained from this study and ensure that the findings are not rendered redundant by new technology, we will collect blood samples for storage and testing to evaluate the role of new biochemical markers.

4. Summary of the current evidence base

Meta-analyses have estimated the diagnostic accuracy of individual cardiac markers, but there have been no systematic reviews specifically of point-of-care cardiac panels. We have reviewed the literature and identified several studies that evaluate the diagnostic accuracy of the marker combination of CK-MB(mass), myoglobin and troponin I. These show that it has high sensitivity and can accurately rule out AMI by 90 minutes after presentation (1-5). This results in earlier identification of AMI than laboratory testing (3). The study by Caragher et al (4) also showed that point-of-care testing expedited decision-making by reducing turnaround times by 55%, while Ng et al (5) compared patient management with the panel to previous practice to conclude that use of the panel reduced coronary care unit admissions.

These studies show that the point-of-care cardiac marker panel has appropriate diagnostic accuracy, but they do not reliably tell us whether the panel will alter patient care, improve outcomes or reduce health service costs. Early diagnostic accuracy and reduced turnaround times will only lead to changes in practice if clinicians act upon the additional diagnostic information. The before and after study by Ng (5) may be confounded by changes in coronary care referrals over time and, originating from the United States where coronary care usage is much higher than the United Kingdom, may not be applicable to the NHS. Audit data from the United Kingdom suggest that point-of-care cardiac testing can reduce hospital admissions, but this finding is based on before and after audit that has yet to be published in a peer reviewed journal (7).

Randomised trials of point-of-care testing are few in number and report conflicting results. The only randomised trial specifically of cardiac tests, by Collinson et al (8), showed that point-of-care measurement of troponin T in patients admitted to a coronary care unit reduced overall length of hospital stay. However, Kendall et al (9) showed that use of a variety of point-of-care tests for a heterogeneous group of patients in the emergency department produced shorter decision times, but did not reduce overall length of stay in the department.

1. McCord J, Nowak RM, McCullough PA et al. Ninety-minute exclusion of acute myocardial infarction by use of quantitative point-of-care testing of myoglobin and troponin I. Circulation 2001;104:1483-8.
http://circ.ahajournals.org/cgi/content/full/104/13/1483
2. Apple FS, Christensen RH, Valdes R et al. Simultaneous rapid measurement of whole blood myoglobin, creatinine kinase MB and cardiac troponin I by the Triage cardiac panel for detection of myocardial infarction. Clin Chem 1999;45:199-205.
http://www.clinchem.org/cgi/reprint/45/2/199

3. Newby LK, Storrow AB, Gibler WB et al. Bedside multimarker testing for risk stratification in chest pain units: The CHECKMATE Study. Circulation 2001;103:1832-7.
http://circ.ahajournals.org/cgi/reprint/103/14/1832
4. Caragher TE, Fernandez BB, Jacobs FL & Barr LA. Evaluation of quantitative cardiac biomarker point of care testing in the emergency department. J Emerg Med 2002;22:1-7.
doi:10.1016/S0736-4679(01)00429-2
5. Ng SM, Krishnaswamy P, Morissey R et al. Ninety-minute accelerated critical pathway for chest pain evaluation. Am J Cardiol 2001;88:611-7.
doi:10.1016/S0002-9149(01)01801-X
6. Panteghini M, Pagani F, Yeo KT, Apple FS, Christenson RH, Dati F et al. Evaluation of imprecision for cardiac troponin assays at low-range concentrations. Clin Chem 2004;50:327-32.
http://www.clinchem.org/cgi/reprint/50/2/327
7. Rocke LGR et al. Chest pain observation units - are they really necessary?
http://www.bmj.com/cgi/eletters/328/7434/254
8. Collinson PO, John C, Lynch S et al. A prospective randomised controlled trial of point-of-care testing on the coronary care unit. Ann Clin Biochem 2004;41:397-404.
http://acb.rsmjournals.com/cgi/reprint/41/5/397
9. Kendall J, Reeves B & Clancy M. Point of care testing: randomised controlled trial of clinical outcomes. BMJ 1998;316:1052-7.
http://www.bmj.com/cgi/reprint/316/7137/1052

5. What outcomes will be measured?

The primary outcome will be the proportion of patients successfully discharged home after emergency department assessment. Successful discharge home is defined as discharge home without a subsequent major adverse event (death, non-fatal AMI, emergency revascularisation or hospitalisation for myocardial ischaemia) during the following three months. Avoidance of unnecessary hospital admission is important to patients and a key objective of recent NHS initiatives. We will also measure health service costs, quality of life and survival to allow estimation of the cost-effectiveness of point-of-care cardiac marker testing, along with use of coronary care and cardiac treatments, hospital re-attendance and re-admission, major adverse events, and patient satisfaction with care.

Objectives

We plan to evaluate the clinical effectiveness and cost-effectiveness of the most promising point-of-care cardiac marker panel currently used in the emergency department.

We will measure, in patients presenting to the emergency department with suspected AMI, the effect of using a point-of-care cardiac marker panel upon:

1. The proportion of patients successfully discharged home after emergency department assessment
2. Health-related quality of life and satisfaction with care
3. The use of coronary care beds and cardiac treatments.
4. Subsequent re-attendance at and/or re-admission to hospital
5. Major adverse events (death, non-fatal AMI, emergency revascularisation or hospitalisation for myocardial ischaemia)
6. Health service costs

We also plan to use trial data and blood samples to:

1. Evaluate clinical prediction rules, such as the TIMI and GRACE scores
2. Evaluate potential new or alternative markers, such as ischaemia modified albumin, brain-type natriuretic peptide, myeloperoxidase and fatty acid binding protein.