The RAPIDEX (Rapid Exclusion) study

Prospective diagnostic cohort study

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Summary and key objectives

Approximately 3% of patients who attend an Emergency Department have chest pain that the clinician who treats them initially suspects may have been caused by an acute coronary syndrome. The majority of these patients are admitted to hospital meaning that chest pain is the most common reason for emergency hospital admission. However, tests will later identify that only a minority of those patients actually have an acute coronary syndrome. If better investigations had been available at the time of arrival in the Emergency Department, many of these hospital admissions could have been avoided, which would lead to earlier reassurance for patients and more efficient use of health In this study we aim to determine whether a novel point of care device for heart-type fatty acid binding protein (H-FABP) can be used to accurately rule out AMI when used alongside other clinical information including the Manchester Acute Coronary Syndromes (MACS) decision rule within 3 hours of arrival in the ED.

Synopsis of the methodology

Plan of investigation:

We will conduct a prospective diagnostic cohort study in the EDs at eligible sites. Patients who present to the ED with possible acute coronary syndromes warranting hospital admission for further investigation will be invited to participate. Patients with unequivocal evidence of ST elevation myocardial infarction who are being transferred for immediate primary percutaneous coronary intervention (PCI) will be excluded.

Comprehensive clinical, electrocardiographic and biochemical data will be collected at the time of presentation using a custom-designed case report form. Patients will undergo blood tests at the time of presentation and after 3 hours. As part of their routine clinical care, all patients will also be subjected to reference standard laboratory-based troponin testing in accordance with the latest national and international guidance.

Patients will be followed up throughout their inpatient course and after 30 days. Data regarding length of stay; cardiac investigations and procedures; details of any haemorrhagic complications; healthcare resource use and health status (EQ-5D) will be collected.

Primary outcome: A composite of acute myocardial infarction (AMI), defined according to the Third Universal Definition of Acute Myocardial Infarction, and major adverse cardiac events (death, incident AMI or urgent coronary revascularisation) within 30 days.

Impact: This study will inform clinicians about the value of several promising diagnostic strategies for 'ruling out' and 'ruling in' AMI within 3 hours of a patient arriving in the ED, thus potentially facilitating (a) a reduction in unnecessary hospital admissions; and (b) triage to an appropriate level of care within the hospital. If successful, such a strategy would be expected to substantially reduce healthcare costs, reduce ED overcrowding and enable targeting of early treatment to those patients

who stand to benefit while reducing inconvenience and enabling earlier reassurance for patients who do not have acute coronary syndromes.

Background

Heart-type fatty acid-binding protein (H-FABP) is a cytosolic protein that is abundantly expressed in human myocardial cells, where it facilitates intracellular fatty acid transport within cardiac myocytes. While levels of cardiac troponin may take several hours to rise after the onset of AMI, because of the lower molecular weight of H-FABP its plasma levels rise early after onset. Previous research has suggested that H-FABP has superior sensitivity to contemporary cardiac troponin assays when measured at presentation in early presenters (<4h from symptom onset) (1). A meta-analysis of 16 studies including 3,709 patients with suspected AMI demonstrated that H-FABP alone had a pooled sensitivity of 84% (95% confidence intervals 76 – 90%) and a pooled specificity of 84% (95% CI 76 – 89%), although there was significant heterogeneity between studies (13).

From the existing evidence it is clear that measurement of H-FABP alone cannot enable safe 'rule out' of AMI. However, there is evidence that, when combined with other clinical information, H-FABP can be used to help 'rule in' and 'rule out' acute coronary syndromes at the time of presentation to the ED. The Manchester Acute Coronary Syndromes (MACS) decision rule was derived by multivariate analysis to identify patients with acute coronary syndromes in the ED. The decision rule takes account of eight variables, each of which is recorded or measured at the time of arrival in the ED: high sensitivity cardiac troponin T concentration; H-FABP concentration; the presence or absence of ECG ischaemia; hypotension (systolic blood pressure <100mmHg on arrival); vomiting in association with the patient's chest pain; pain radiating to the right arm or shoulder; worsening (or crescendo) angina; and visible sweating on arrival in the ED. Using a computer model, the MACS rule calculates the probability that the patient will experience a major adverse cardiac event (MACE) within the next 30 days. Based on that estimated probability, the rule assigns patients to one of four risk groups: very low risk (acute coronary syndrome 'ruled out'; suitable for immediate discharge); low risk (suitable for serial troponin testing in a low dependency environment such as an ED observation unit); moderate risk (requires admission to an Acute Medical Unit); and high risk ('ruled in' and therefore requires admission to a cardiologist).

In the derivation and external validation studies the MACS rule was shown to have 100% sensitivity for AMI with a very low (1.2%, n=2) incidence of MACE, both of which were isolated coronary stenoses identified at outpatient coronary angiography (2,3). Ultimately use of the MACS rule could avoid unnecessary hospital admission for over one quarter of patients based on the results of a single blood test, while also immediately identifying 10% of patients as being at high risk (with over 95% positive predictive value).

The MACS rule utilises a laboratory-based H-FABP assay, which can be run with commercially available analysers in hospital laboratories. However, this requires a new assay to be set up and run by laboratory staff, which is a barrier to clinical implementation. A novel point of care H-FABP test is now available (FABP-ulous, Netherlands), which provides dichotomous (positive/negative) results within 5 minutes and can be used at the bedside.

Objectives

We aim to evaluate the use of this assay as follows:

(a) We aim to determine the diagnostic accuracy of the MACS rule incorporating the novel point of care H-FABP assay, both:
    i. When H-FABP is measured at the time of arrival in the ED; and
    ii. When H-FABP is measured 3 hours after arrival in the ED

(b) We aim to determine the interobserver reliability of the H-FABP assay

(c) We aim to compare the projected effects of implementing serial point of care troponin testing over 3 hours with current practice on hospital admission rates and resource utilisation

Detailed plan of investigation

Design and Setting

We will undertake a prospective diagnostic cohort study. The work will take place at Manchester Royal Infirmary, which has an Adult Emergency Department (ED) with an annual census of approximately 110,000 patients, and at other sites across the United Kingdom subject to feasibility evaluations.

Governance and ethics

We have obtained approval from the National Research Ethics Service (reference 14/NW/1344). Central Manchester University Hospitals NHS Foundation Trust will sponsor the study, which will be undertaken in compliance with the Declaration of Helsinki and local governance requirements. As this study will be undertaken in the NIHR-funded time of the Chief Investigator and NIHR Portfolio adoption has been obtained (reference UK CRN 18000).

Sampling Strategy

Recruitment commenced in February 2015. Experience from previous studies suggests that it will be possible to recruit approximately 2 participants per day. Recruitment is expected to continue for approximately 12 to 18 months.

Inclusion criteria: Adults patients (>18 years) who present to the ED with pain, discomfort or pressure in the chest, epigastrium, neck, jaw, or upper limb without an apparent non-cardiac source (compatible with the American Heart Association case definitions (4)), which the treating physician believes warrants investigation for possible ACS; peak symptoms occurred <12 hours prior to presentation at the ED.

Exclusion criteria: Patients with unequivocal evidence of ST elevation myocardial infarction who are being immediately transferred for primary percutaneous coronary intervention; Patients with

another medical condition that would necessitate hospital admission; Patients who lack the capacity to provide written informed consent.

Data collection and processing

Comprehensive clinical data will be recorded in the case report form at the time of inclusion by the treating physician and study nurse, in accordance with contemporary international standards. These data will include details of: the presenting complaint; previous medical history; medication history; social history (including alcohol intake and tobacco use); family history of ischaemic heart disease; findings on physical examination; clinician's impression (including the clinician's judgement about whether or not AMI is present); 12-lead ECG findings (including the presence or absence of dynamic ECG changes such as T wave inversion or ST segment depression); medications received pre-hospital and during the active study phase; disposition; findings of relevant laboratory tests and medical imaging. In this observational study, patients will be treated according to current departmental guidance for the management of cardiac chest pain, which is consistent with the guidance issued by the National Institute of Health and Care Excellence (5) and the European Society of Cardiology (6,7).

Laboratory analyses

The times of each blood draw and result will be recorded in the case report form. Point of care testing will be undertaken immediately following venepuncture by a Clinical Research Nurse or investigator with similar training to clinical personnel working in the ED. Point of care tests will be undertaken in accordance with the manufacturer's instructions. Following analysis the time and result will be recorded in the participant's case report form.

The overall schedule for blood sampling during this study is outlined in Table 1. Additional samples will be stored in SST II Advance, lithium heparin and EDTA vials and labelled with a unique study number. After processing relevant point of care testing, the additional samples will be centrifuged within 30 minutes of venepuncture at 2,500G for 10 minutes. Plasma and serum will be separated and aliquots of 500 to 2,000µL will be stored in vials labelled with the patient's unique study

number. Sample characteristics (haemolysis, lipaemia, icterus) will be recorded in the case report form. The serum and plasma will be frozen at or -20^{o}C or below within 4 hours of collection. Within 28 days, all samples will be stored at -70^{o}C or below pending later analysis. Samples will remain frozen and stored with a view to future testing for promising biomarkers that may become of interest. Storage of frozen samples will obviate the need for recruitment of an entirely new cohort of patients when new biomarkers are discovered or new generations of existing biomarker assays are developed.

Central cardiac troponin testing

We will analyse stored serum and/or plasma samples for cardiac troponin concentrations using contemporary and high sensitivity cardiac troponin assays to determine the diagnostic accuracy of each of these strategies. Analyses will take place at St. George's NHS Trust, Central Manchester University Hospitals NHS Foundation Trust or a similarly equipped clinical biochemistry laboratory subject to appropriate agreements.

Screening and consent

Patients will be identified at the time of arrival by clinical staff and Clinical Research Nurses. Eligible participants will be approached by investigators and given verbal and written information about the study. All patients undergo routine venepuncture for clinical purposes at the time of presentation to the ED. In order that clinical procedures including intravenous cannulation and routine blood tests are not delayed and because it is not feasible to obtained informed consent within minutes of arrival in the ED, we will draw initial blood samples prior to obtaining written informed consent. This will allow potential participants more time before providing full written informed consent. The small volume of blood drawn (approximately 12.5ml for research purposes or two and a half teaspoons) will not cause any harm to participants, who are already undergoing a blood test, and this will be discarded in the event that participants decide not to participate in the study. Our previous work demonstrates that approximately 97% of patients do agree to participate in a study of this design. Initially, we sought to obtain verbal consent prior to obtaining the initial blood sample. However,

obtaining verbal consent is a research procedure and should be undertaken by a staff member who has undertaken appropriate Good Clinical Practice and study protocol training. This process risks either (a) delaying clinical care at a potentially critical time, or (b) missing eligible participants, which reduces the scientific integrity of this study. The approach described has been taken in another study run within our group with a similar rationale.

Full written consent will subsequently be sought following venepuncture. All participants will have the right to withdraw from the study at any time, without causing any disadvantage. In the event of withdrawal of consent for storage, all remaining samples will be discarded.

Follow up

All patients will undergo reference standard troponin testing in accordance with contemporary national and international guidance. Acceptable protocols for reference standard troponin testing include:

- *If a contemporary (not high sensitivity) troponin assay is used:* Laboratory-based troponin testing on arrival and either 6 hours after **arrival** or 10 to 12 hours after **the onset of peak symptoms** (5,7,8)

- *If a high sensitivity troponin assay is used:* Laboratory-based troponin testing on arrival and either 3 hours after **arrival** or 10 to 12 hours after **the onset of peak symptoms** (9,10)

A high sensitivity troponin assay is defined as an assay that can detect troponin concentrations in at least 50% of apparently healthy individuals with a co-efficient of variation of <10% at the 99th percentile cut-off (11). At the time of writing this protocol, this includes two commercially available troponin assays: the Roche troponin T high sensitivity assay; and the Abbott ARCHITECT high sensitivity troponin I assay.

Patients will be followed up throughout their inpatient course and by telephone, email, letter or in person after 30 days. Data on length of stay; cardiac investigations and procedures; and details of

any haemorrhagic complications will be collected. If it is not possible to contact participants directly after 30 days, we will obtain follow up information from their primary care practitioner where possible.

Economic evaluation

We will collect comprehensive data about healthcare resource use and health status (EQ-5D) at baseline and 30 days, which may be used to subsequently develop a cost-effectiveness model. Total direct healthcare costs will be identified and quantified according to the UK National Health Service perspective using methods advocated in the NICE Methods Guide for Technology Appraisal (12). Resource use data collected will include: time (hours) and length (days) of stay (total; on coronary care, high dependency and intensive care units); laboratory, radiological and cardiological investigations during the initial hospital stay; nature and duration of any procedures or cardiac surgery; management of haemorrhagic complications; details of admissions and further ED attendances; outpatient visits; visits to and home visits from the general practitioner; nurse and social worker visits. Data on resource use will be collected using structured data collection forms from patient medical records and supplemented by telephone interviews with patients after discharge at 30 days.

Outcomes

The primary outcome will be a composite of prevalent AMI or incident MACE (all cause death, coronary revascularisation or incident AMI) within 30 days.

Secondary outcomes will include:

- Prevalent AMI (analysed as a single outcome)
- Projected hospital admission rate
- Healthcare resource use

- Health state (EQ-5D at baseline and 30 days)

- Time from arrival in the ED to blood results and time from venepuncture to blood results

Measuring and defining outcomes

Outcomes will be adjudicated by two independent investigators with reference to relevant clinical information but blinded to the results of research investigations. Discrepancies will be resolved by consultation with a third independent investigator. AMI will be defined according to the Third Universal Definition of AMI (8). By virtue of the inclusion criteria, all patients will already have symptoms and signs consistent with myocardial ischaemia. Briefly, therefore, patients will be deemed to have met this outcome if they develop a rise and/or fall of troponin to above the 99th percentile. At the time of writing and pending further evidence and international guidance, a significant rise and/or fall of troponin will be considered to be >9.2ng/L for high sensitivity troponin T (13) and at least 20% for all other assays.

Disposition (the patient's destination) after leaving the ED will be determined by review of hospital records. Time from arrival at the ED to troponin results will be determined from hospital records (including the upload time for troponin results from the central laboratory) and from calibrated point of care devices. The time of venepuncture will be directly recorded in the case report form by a Clinical Research Nurse.

Analysis

To determine diagnostic accuracy, we will first calibrate the co-efficients of the MACS rule to incorporate the novel point of care H-FABP assay, which is qualitative in nature and provides dichotomous results with a cut-off set at 4ng/ml. This will be undertaken in a separate cohort of 140 patients included in a randomised controlled trial comparing the use of the MACS clinical decision rule to standard care.

Having calibrated the MACS rule appropriately, we will validate the performance of the MACS rule in this cohort with the novel point of care assay by calculating sensitivity, specificity, positive and negative predictive value with their respective 95% confidence intervals. The proportion of admissions that could have been avoided will be calculated.

Evaluation of interobserver reliability

To evaluate interobserver reliability we will ask two independent investigators to interpret the H-FABP result, blinded to each other's interpretation, in a subgroup of approximately 40 patients. We will then report a kappa score. This sample size was calculated by consulting guidelines regarding sample size for reliability studies (14). To demonstrate a κ of 0.8 with the minimal acceptable κ set at 0.6 and, setting the alpha at 0.05 and beta at 0.2, we would require 39 patients to be assessed by two independent observers.

Economic analyses:

Total direct healthcare costs (resource use *x* unit costs data) will be calculated using published unit cost sources supplemented by hospital specific costs where necessary (15). Given the observational nature of this study, we will create a model using data collected during this study, data that will be collected during a micro-costing study run by our team (ISRCTN 86818215) and other externally published data. We will then extrapolate the effects of implementing the novel diagnostic pathway derived in this work on healthcare resource use and health status (quality adjusted life years as informed by the EQ-5D). Where appropriate, we will proceed to formal cost-effectiveness analysis in collaboration with a designated health economist.

Sample size

Sample size for this study is determined based on the required precision of the estimates for sensitivity and negative predictive value. The specificity of a troponin-based algorithm would be expected to be approximately 90% (16). The primary driver of sample size in a study of this nature is

the number of patients with the primary outcome, which makes a conservative estimate of its prevalence desirable. Based on subtle differences in the inclusion criteria compared to similar studies run by our group, we anticipate that the prevalence of the primary outcome could be as low as 10% in this cohort (16–18). Assuming that we identify an algorithm with 100% sensitivity and negative predictive value, the lower bound of the 95% confidence interval would be >95% for sensitivity and >99% for negative predictive value with a sample size of 1,500 participants. Accounting for potential loss to follow up and missing data (approximately 5%), we plan to include a total of approximately 1,575 participants. At a recruitment rate of 1-3 participants per day, we anticipate that recruitment will be complete within approximately 18 months. Our team has an excellent track record of delivering similar studies ahead of time and target.

Impact

We will disseminate the findings by: (a) publication in peer reviewed academic journals, aiming for journals with high impact and a relevant target audience (e.g. Journal of the American College of Cardiology); (b) presentation at national and international scientific conferences (aiming specifically for the European Society of Cardiology and American Heart Association annual conferences); (c) publication on the trial and research group websites; (d) dissemination via press releases (including by Central Manchester University Hospitals NHS Foundation Trust; The University of Manchester; the NIHR Clinical Research Network) and, to promote public engagement, social media.

Timescale

We anticipate that recruitment will continue for approximately 12-18 months. Following completion of recruitment and 30-day follow up the primary analysis is expected to be complete within 3 months.

Intellectual property

The project is not expected to generate novel intellectual property that is potentially patentable.

References

1. McCann CJ, Glover BM, Menown IBA, Moore MJ, McEneny J, Owens CG, et al. Novel biomarkers in early diagnosis of acute myocardial infarction compared with cardiac troponin T. European Heart Journal. 2008 Oct 30;29(23):2843–50.

2. Body R, Carley S, McDowell G, Pemberton P, Burrows G, Cook G, et al. The Manchester Acute Coronary Syndromes (MACS) decision rule for suspected cardiac chest pain: derivation and external validation. Heart. 2014;100:1462–8.

3. Body R, Burrows G, Carley S, Lewis PS, Jarvis J. The Manchester Acute Coronary Syndromes (MACS) decision rule: validation with a new automated assay for heart-type fatty acid binding protein. Emergency Medicine Journal [Internet]. 2014 Dec 24 [cited 2015 Feb 27]; Available from: http://emj.bmj.com/cgi/doi/10.1136/emermed-2014-204235

4. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, et al. ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction) Developed in Collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. Journal of the American College of Cardiology. 2007;50(7):e1–157.

5. National Clinical Guideline Centre for Acute and Chronic Conditions. Chest pain of recent onset: NICE Guideline. 2010.

6. Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012 Oct;33(20):2569–619.

7. Authors/Task Force Members, Hamm CW, Bassand J-P, Agewall S, Bax J, Boersma E, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal. 2011 Aug 26;32(23):2999–3054.

8. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third Universal Definition of Myocardial Infarction. Journal of the American College of Cardiology. 2012 Oct;60(16):1581–98.

9. NICE Diagnostics Guidance DG15. Myocardial infarction (acute): Early rule out using high-sensitivity troponin tests (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 assays) [Internet]. National Institute for Health and Care Excellence; 2014 [cited 2015 Feb 13]. Available from: https://www.nice.org.uk/guidance/dg15

10. Apple FS, Wu AHB, Jaffe AS. European Society of Cardiology and American College of Cardiology guidelines for redefinition of myocardial infarction: How to use existing assays clinically and for clinical trials. American Heart Journal. 2002;144:981–6.

11. Apple FS, Collinson PO, for the IFCC Task Force on Clinical Applications of Cardiac Biomarkers. Analytical Characteristics of High-Sensitivity Cardiac Troponin Assays. Clinical Chemistry. 2011 Sep 30;58(1):54–61.

12. National Institute of Clinical Excellence. Guide to the methods of Technology Appraisal. National Institute of Clinical Excellence; 2004.

13. Mueller M, Biener M, Vafaie M, Doerr S, Keller T, Blankenberg S, et al. Absolute and Relative Kinetic Changes of High-Sensitivity Cardiac Troponin T in Acute Coronary Syndrome and in Patients with Increased Troponin in the Absence of Acute Coronary Syndrome. Clinical Chemistry. 2011 Dec 1;58(1):209–18.

14. Walter SD, Eliasziw M, Donner A. Sample size and optimal designs for reliability studies. 1998.

15. Curtis L. Unit costs of health and social care. Personal Social Services Research Unit, Kent, United Kingdom; 2010.

16. Body R, Carley S, McDowell G, Jaffe AS, France M, Cruickshank K, et al. Rapid Exclusion of Acute Myocardial Infarction in Patients With Undetectable Troponin Using a High-Sensitivity Assay. Journal of the American College of Cardiology. 2011 Sep;58(13):1332–9.

17. Body R, McDowell G, Carley S, Mackway-Jones K. Do risk factors for chronic coronary heart disease help diagnose acute myocardial infarction in the Emergency Department? Resuscitation. 2008;79:41–5.

18. Body R, Carley S, Wibberley C, McDowell G, Ferguson J, Mackway-Jones K. The value of symptoms and signs in the emergent diagnosis of acute coronary syndromes. Resuscitation. 2010;81(2):281–6.