Randomised Assessment of Treatment using Panel Assay of Cardiac markers – Contemporary Biomarker Evaluation (RATPAC CBE)

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Executive summary

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Executive summary

Background

Patients admitted with chest pain and a suspected diagnosis of acute coronary syndrome (heart attack or unstable angina, usually referred to as ACS) constitute the largest single group of individuals attending a hospital emergency department. The majority of such individuals do not have a final diagnosis of coronary artery disease and are retained in hospital unnecessarily. Conversely, a proportion of patients attending with chest pain have had a heart attack (acute myocardial infarction, AMI) and are inappropriately sent home. For the clinician the challenge is to identify those patients at the highest risk of having had an AMI for further investigation and to discharge home those at low risk.

The diagnosis of an AMI is based on three factors: the history and clinical features of the patient, the findings on performing an electrocardiogram (ECG) and the results of laboratory investigations (measurement of cardiac biomarkers). History and clinical features can be incorporated into formal risk-scoring methods. Risk-scoring systems have limited diagnostic efficiency in patients attending the emergency department with chest pain. In the majority of patients, the ECG may be entirely normal or ECG changes are non-specific. The ECG is useful only if there are typical features that support the diagnosis of an AMI, such as ST-segment elevation or changes suggestive of ACS. These patients constitute a high-risk group and require admission and further investigation. In the majority of patients the ECG does not show a high-risk pattern and laboratory investigation is required to determine whether or not an AMI has occurred. The key test for diagnosis of an AMI is the measurement of one of the cardiac structural proteins of the heart, cardiac troponin. There are two cardiac troponins, cardiac troponin T (cTnT) and cardiac troponin I (cTnI). Elevation of cTnT or cTnI is absolutely specific for myocardial injury and is included as the gold standard biochemical test in the universal definition of myocardial infarction. Current guidelines recommend keeping patients in hospital for up to 12 hours for repeat measurement of cTnT or cTnI to confirm or exclude the diagnosis of an AMI.

To speed up diagnosis it has been suggested that other biomarkers, said to be more sensitive in the early phases of an AMI, might be combined with cTnT or cTnI measurement. Other proteins present within the myocardial cell cytoplasm – cytoplasmic markers – may be released into the circulation earlier than troponin following myocardial injury. An alternative strategy would be to measure hormones affected by myocardial injury (neurohormones). Neurohormones are produced either directly by the heart [B-type natriuretic peptide (BNP)] or in response to circulatory stress (copeptin). Finally, it has been suggested that, as the formation of an atheromatous plaque is the underlying cause of an AMI, novel markers which indicate that an individual is at high risk for rupture of an atheromatous plaque might also be useful. The strategy that has been proposed is the combined measurement of existing or new markers on admission to hospital. The hypothesis is that, if neither troponin nor one of the novel markers is elevated, the patient could be immediately discharged from hospital safely.

The concept of measurement of a number of different biomarkers, in addition to troponin, is based on the apparent inability to detect troponin elevation soon after myocardial infarction has occurred. Failure to detect early troponin rise was due to the relative insensitivity of the methods for troponin measurement in use. This is no longer the case. There has been progressive improvement in the laboratory methodology for cTnT and cTnI measurement and methods are now highly sensitive. The role of such sensitive troponin measurement methods is in the process of being evaluated with a view to their widespread introduction into clinical practice. Preliminary evidence suggests that these new sensitive methods will detect troponin elevation very early after an AMI has occurred, possibly at the time of hospital admission.

The progressive improvement in the sensitivity of troponin measurement methods has been accompanied by an increase in the number of clinical conditions, apart from an AMI, in which measurable troponin elevation occurs. This varies from more obvious clinical conditions, such as direct myocardial injury from trauma caused by road traffic accidents or stabbing, to more subtle injury, such as ingesting cocaine or pulmonary embolus. Concerns have, therefore, been expressed that the widespread use of sensitive troponin assays will result in an increase in the number of patients inappropriately retained in hospital for investigation for suspected cardiac disease.

The role of additional markers of myocardial injury and sensitive troponin measurements for the differential diagnosis of the patient presenting with chest pain remains an area of ongoing study. The challenge is to reduce the time within which a definitive diagnosis can be obtained, which will ensure prompt discharge from hospital of patients without an AMI while retaining only those patients at high risk of cardiac disease for further investigation and treatment. However, measurement of additional biomarkers in addition to troponin measurement alone has an increased cost and so would have to be cost-effective.

Objectives

The objective of the study was to examine the role of combinations of existing laboratory tests for the diagnosis of an AMI together with a range of new tests that have been proposed for this role. In addition, the role of the newer, sensitive troponin assays compared with more conventional but less sensitive assays would be studied.

The particular questions to be answered were:

1. Should troponin measurement be combined with measurement of two well-established cytoplasmic markers of myocardial injury, myoglobin and the MB isoenzyme of creatine kinase (CK-MB), to achieve an earlier diagnosis than that recommended in current guidelines?
2. Should troponin measurement be combined with measurement of new markers said to be very sensitive for myocardial infarction and an already existing marker, N-terminal pro-B-type natriuretic peptide (NTproBNP), to achieve an earlier diagnosis than that recommended in current guidelines?
3. Is there any diagnostic advantage to using the newer, more sensitive methods for troponin measurement rather than the already well-established troponin measurement methods?
4. How good were both the established and new cytoplasmic markers and the newer troponin measurement methods at predicting risk of a major adverse cardiac event (MACE) over the follow-up period to allow early, safe discharge of patients admitted with chest pain but considered not to have had an AMI?
5. What would be the cost-effectiveness of measuring a combination of biomarkers compared with measurement of cardiac troponin alone?

Methods

The population studied was recruited as part of a multicentre trial comparing point-of-care testing with conventional hospital management of patients with chest pain. This clinical trial, the Randomised Assessment of Treatment using Panel Assay of Cardiac markers (RATPAC), has been reported in full and was performed at six emergency departments in hospitals throughout the UK. Patients were recruited to the trial if they had chest pain but no clinical or ECG evidence of an AMI and would be admitted for exclusion of an AMI by the measurement of cTnT or cTnI according to current guidelines. All patients who consented and did not meet trial exclusion criteria were randomised to measurement of a panel of cardiac biomarkers by point-of-care testing on admission and 90 minutes from admission or the conventional pathway in the participating hospital for management of chest pain. Patients randomised to point-of-care testing

had additional blood samples taken on admission and 90 minutes from admission that were separated and frozen for subsequent analysis. A protocol was used to interpret the point-of-care testing results for cTnI, myoglobin and CK-MB. Patients showing an elevation of any of these markers consistent with AMI were admitted to hospital. Failure of the markers to rise by 90 minutes from admission was considered to exclude an AMI. The subsequent decision by the attending physician to admit or discharge the patient was on the basis of the results of point-of-care testing plus clinical features. RATPAC was a pragmatic clinical trial with the objective of comparing the management of patients for whom test results were available by point-of-care testing on admission and at 90 minutes from admission with the management of those managed conventionally. The RATPAC study found that patients randomised to point-of-care testing were discharged earlier than those managed conventionally, with an equivalent rate of MACE during the follow-up period. Blood samples from patients randomised to the point-of-care testing arm of the trial were available for further study. Patient recruitment was prospective, but subsequent biomarker analysis was retrospective. The patients had been fully characterised and followed up so provided an ideal cohort for assessment of the role of existing and novel cytoplasmic markers of myocardial injury, the role of sensitive troponin measurement methods and the role of neurohormones for the diagnosis and prognostic risk assessment of patients admitted with chest pain.

The population was representative of the patients seen in routine clinical practice. The population studied did not include patients at high risk as determined by ECG changes characteristic of an AMI. Biochemical laboratory tests are not required for this group as they have a presumptive diagnosis of an AMI (ST-segment elevation myocardial infarction, STEMI) that requires immediate hospital admission. Patients with STEMI are often inappropriately included in diagnostic studies of laboratory testing. In addition, the study excluded patients with ECG changes that would automatically suggest that myocardial injury was a high probability, patients with a very high risk of ACS who would also be admitted to hospital.

An extensive and detailed literature review was performed of the existing evidence for both current and novel biomarkers for the detection of myocardial injury. In choosing the tests to be evaluated it was important that the existing sample was appropriate for the analysis to be performed. The method selected also needed to have the potential for automation and introduction into routine clinical practice. Ideally, an automated method would already be available. Finally, the review of the literature needed to show that there was consistent evidence that the biomarker might be useful in routine clinical practice. The final choice of biomarkers for measurement was as follows. Two existing cytoplasmic biomarkers were selected as a reference standard. These were CK-MB by mass measurement, as these data were already available from the RATPAC study, and myoglobin, both from the original RATPAC study data and using a different method. Myoglobin is considered the prototype for a rapid release cytoplasmic marker and could be measured by a multiplex technique without further sample loss. As a novel cytoplasmic biomarker, heart-type fatty acid-binding protein (H-FABP) was measured simultaneously with myoglobin (Randox laboratories, Crumlin, Co Antrim, UK) using the same sample. Data from one conventional troponin assay used in the original RATPAC study – cTnI measured on the Stratus® CS analyser (Siemens Healthcare Diagnostics, Camberley, Surrey, UK) – were available. Three contemporary sensitive troponin measurement methods were studied: measurement of cTnI using the Siemens Ultra assay (Siemens Healthcare Diagnostics, Camberley, Surrey, UK) and the Beckman AccuTnI™ enhanced assay (Beckman-Coulter, High Wycombe, Buckinghamshire, UK) and measurement of cTnT using a new high-sensitivity assay (Roche Diagnostics, Burgess Hill, West Sussex, UK). The novel marker copeptin (B·R·A·H·M·S ThermoFisher, Cambridge, UK) was measured together with NTpro-BNP (Roche Diagnostics, Burgess Hill, West Sussex, UK). The literature review suggested that there was insufficient evidence to support the measurement of potential markers of plaque destabilisation for use as a diagnostic test in patients with acute chest pain or that the sample collected would be suitable.

The final diagnosis on all patients studied was performed by two independent reviewers, who examined the original diagnosis from the RATPAC study, all of the available clinical information and the results of cardiac troponin measurement from the original trial sites and that performed in the core clinical laboratory. Diagnosis utilised the universal definition of myocardial infarction based on the 99th percentile

of the troponin method in use at the trial sites combined with troponin measurement on the study samples performed using the Siemens Ultra assay, as this is known to achieve the performance criteria recommended for sensitive troponin assay. Patients with a troponin rise and a final diagnosis other than ACS or an AMI were reviewed in detail and it was decided whether or not an AMI was the most likely diagnosis. Disagreements were resolved by discussion and patients were classified as having an AMI or not.

The diagnostic performance of the biomarkers was examined using two different techniques. Individual biomarkers were assessed by construction of receiver operating characteristic (ROC) curves, a continuous plot of sensitivity against specificity utilising the final diagnosis as the classifier. Statistical analysis was by comparison of the area under the curve (AUC). Individual biomarkers and the biomarker combinations were then examined using prespecified diagnostic thresholds to classify patients into those with or those without an AMI. Patients with one biomarker value exceeding the threshold were classified as an AMI. When a combination of biomarkers was used, any one biomarker value exceeding the threshold was considered to classify the patient as having had an AMI. Comparison between strategies was then performed by construction of 2×2 tables and comparison by Fisher's exact probability test. Statistical analysis was performed using a commercially available Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) add-in, Analyse-it (version 2.2.1; www.analyse-it.com).

A decision-analysis model developed for another project [HTA 09/22/21: Goodacre S, Thokala P, Carroll C, Stevens JW, Leaviss J, Al Khalaf M, *et al*. Systematic review, meta-analysis and economic modelling of diagnostic strategies for suspected acute coronary syndrome. *Health Technol Assess* 2013;**17**(1)] was used to evaluate the cost-effectiveness of a 10-hour troponin strategy and the most promising early biomarker strategies identified in this study. The model applied diagnostic strategies to a hypothetical cohort of patients with a suspected AMI to determine the costs and outcomes associated with each strategy. We tested the model in three different scenarios, depending on the availability of doctors to act on 10-hour troponin results. Cost and utility estimates were derived from previous studies and routine data sources. The economic model was developed using Simul8 software (Simul8 Corporation, Boston, MA, USA), taking a health service perspective and a lifetime horizon with mean life expectancy based on UK interim life tables. Deterministic and probabilistic analyses were undertaken.

Results

Samples were obtained from 850 out of 1132 patients enrolled in the RATPAC study. Measurement of the conventional cytoplasmic biomarkers myoglobin and CK-MB did not significantly improve diagnostic sensitivity compared with measurement of cTnT or cTnI by any of the methods examined. Measurement of cTnT and cTnI was a significantly better outcome predictor than measurement of the conventional cytoplasmic biomarkers. As there is no diagnostic efficiency gained from measurement of myoglobin and CK-MB in addition to troponin, simultaneous measurement of all three markers would not be a cost-effective strategy. Measurement of H-FABP and troponin using a high-sensitivity assay did improve diagnostic sensitivity compared with measurement of troponin alone using a high-sensitivity assay. However, this was equivalent to measurement of troponin on admission and at 90 minutes from admission. Combined measurement on admission of both H-FABP and troponin does not achieve 100% sensitivity for rule-out of an AMI on admission testing. Measurement of copeptin was not useful as a diagnostic or prognostic test, so by cost minimisation was not cost-efficient.

Cost-effectiveness analysis compared the following strategies: no testing, high-sensitivity cTnT testing at presentation, high-sensitivity cTnT testing at presentation and at 90 minutes from presentation, high-sensitivity cTnT and H-FABP testing at presentation, and 10-hour troponin testing. At the £20,000 per quality-adjusted life-year (QALY) threshold, 10-hour troponin testing was cost-effective (£12,090 per QALY) if the patient can be discharged as soon as a negative troponin result is available (doctor-on-demand scenario) but not in the other scenarios (once-daily ward round and twice-daily ward rounds), when high-sensitivity cTnT and H-FABP measurement at presentation was cost-effective. At the £30,000

per QALY threshold, 10-hour troponin testing was cost-effective in the doctor-on-demand scenario and twice-daily ward rounds scenario (£24,600 per QALY), whereas the troponin T and H-FABP measurement at presentation strategy was cost-effective (£14,806 per QALY) in the once-daily ward round scenario. Secondary analysis using cTnI (measured on the Stratus CS) instead of cTnT showed that cTnI testing at presentation and at 90 minutes was cost-effective in all three scenarios at the £20,000 per QALY threshold and in two of the scenarios at the £30,000 per QALY threshold, with 10-hour troponin being cost-effective only in the doctor-on-demand scenario at the £30,000 per QALY threshold (£24,327 per QALY).

Conclusions

Measurement of cardiac troponin using a sensitive method was the best test for the early diagnosis of an AMI. Although the study showed that diagnosis 90 minutes from admission was safe, 100% diagnostic sensitivity was not achieved at that time point and further studies are required to determine the optimal earliest time point when acceptable diagnostic sensitivity can be obtained. Measurement of myoglobin or CK-MB in addition to a sensitive troponin test is not recommended. H-FABP shows promise as an early marker and requires further study. Measurement of copeptin is not recommended as a routine test in patients presenting with acute chest pain. Ten-hour troponin testing is likely to be cost-effective compared with rapid rule-out strategies only if patients can be discharged as soon as a negative result is available and a £30,000 per QALY threshold is used.

Trial registration

This trial is registered as ISRCTN37823923.

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