Evaluation of the European Society of Cardiology recommended rapid diagnostic algorithms in a challenging low risk cohort.

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ABSTRACT

AbsObjectives: To examine diagnostic efficiency of the proposed European Society of Cardiology rapid diagnostic algorithms in a challenging low risk cohort.
Methods: Samples analysed were from the point of care arm of the RATPAC trial (Randomised Assessment of Treatment using Panel Assay of Cardiac markers), set in the emergency departments of six hospitals. Prospective admissions with chest pain and a non-diagnostic electrocardiogram were randomised to point of care assessment or conventional management. Blood samples were taken on admission and 90 minutes from admission. Patients were admitted if the initial of 90 minute sample exceeded the 99th percentile for cardiac troponin I (cTnI) analysed using the Stratus CS (CS) (Siemens Healthcare Diagnostics), range 30-50,000 ng/L 10% CV 60ng/L 99th percentile 70 ng/L. An additional blood sample was taken at admission and 90 minutes from admission, separated and the serum stored frozen until subsequent analysis for cTnI by using the Architect hs cTnI (Abbott Diagnostics), range 1.1-50,000 ng/L 10% CV 4.7ng/L and high sensitivity cardiac troponin T (hs cTnT) by the Roche high sensitivity cardiac troponin T assay hs-cTnT (Elecsys 2010, Roche diagnostics), range 3 - 10,000ng/L, 10% CV 13ng/L, 99th percentile 14 ng/L.
The universal definition of myocardial infarction (MI) utilising laboratory measurements of cardiac troponin performed at the participating sites together with measurements performed in a core laboratory was used for diagnosis. Myocardial infarction was diagnosed by the combination of a delta troponin plus a value exceeding the 99th percentile. The two proposed algorithms for ruling out and ruling in MI were then applied to the admission and serial samples to directly compare diagnostic efficiency of the two analytes.
Results: 276 patient samples were available (169 male, median age 54.5 years, range 23.7-90.6) with 165 serial samples. The incidence of MI was 276 (9.4%). A single measurement on admission excluded MI in 174/276 (63%) for hs cTnI with no missed cases, negative predictive value (NPV) 100% and in 219/276 (79.3%) for hs cTnT with 2 missed cases, NPV 99.1%. Serial sampling excluded 128/165 (77.6%) for hs cTnT with no missed cases, NPV 100% and 149/165 (90.3%) for hs cTnT with 1 missed case, NPV 99.3%. 27/165 (16.4%) were classed as indeterminate for hs cTnI and 8/165 (4.8%) for hs cTnT. Rule in sensitivity for hs cTnI was 100% (5/5) at 96.9% specificity with no indeterminate cases. For hs cTnT rule in sensitivity was 40% (2/5) at 96.3% specificity with 2 intermediate cases.
Conclusion: Both single measurement and serial measurement algorithms proved excellent rule out tools but the rule in algorithm was less reliable in this patient group. This probably reflects the difficulty of diagnoses in low risk patients with relatively small troponin changes.
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METHODS

Full details of the RATPAC trial had been published[1,2]. The trial (ISRCTN37823923) randomized low risk patients presenting with chest pain to either diagnostic assessment by a cardiac panel measured by POCT or to diagnosis when biomarker measurement was based on central laboratory testing (CLT). Patients 18 years or older presenting with acute chest pain to the emergency department (ED) of 6 participating hospitals were screened for eligibility. Exclusion criteria for enrolment were; ECG changes for myocardial infarction or high-risk acute coronary syndrome (>1mm ST deviation or >3mm inverted T waves), known coronary heart disease presenting with prolonged (>1 hour) or recurrent episodes of cardiac-type pain, proven or suspected serious non-coronary pathology (e.g. pulmonary embolus), co-morbidity or social problems that require hospital admission, an obvious non-cardiac cause (e.g. pneumothorax or muscular pain), more than 12 hours since their most significant episode of pain, previous participants, those unable to understand the trial information and those unwilling to consent.

All those eligible for enrolment were then randomized to either the POCT or CLT arm. Patients randomized to POCT were scheduled to have a blood sample drawn on admission and at 90 minutes from admission for POCT measurement. An additional sample for subsequent biomarker measurement was drawn at the same time as the POCT sample and the serum separated and frozen prior to -20° C prior to transfer to long-term storage at -70° C in the central laboratory. The admission and 90 minute samples were subsequently analyzed for cTnI (two high sensitivity methods) and cTnT (high sensitivity).

Final diagnostic classification was performed by two independent clinicians with access to all the relevant information, utilizing the 99th percentile value for the cardiac troponin value from POCT measurement, from the local laboratory and from troponin measurements performed in the central laboratory. All patients had POCT measurement with a cTnI method which meets current analytical goals. Four of the local laboratories used a troponin method which meets the current analytical goals for the 99th percentile, one used a cTnI method which just fails to reach these goals and one used the current generation cTnT method. Central laboratory measurements were performed using a cTnI method that meets current analytical goals.

Patients with a troponin rise and a final diagnosis other than ACS or AMI were reviewed to decide whether AMI was the most likely diagnosis. Disagreements were resolved by discussion and patients classified as having AMI or no AMI. Patients were categorized as AMI (type 1 AMI, primary ischaemic cardiac injury), patients with troponin elevation not due to AMI but with a probable background of underlying coronary atheroma (type 2 MI, secondary ischaemic cardiac injury) and those with no myocardial injury.

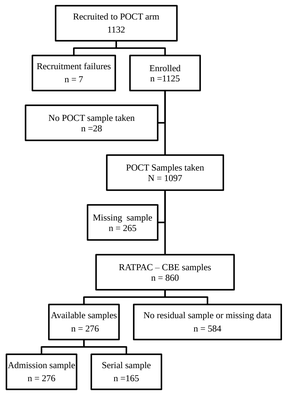
Residual samples from the biomarker evaluation (RATPAC-CBE)[3] were thawed and analyzed for cardiac troponin I (Abbott hs cTnI) and cardiac troponin T (Roche hs cTnT). All patients were followed up to 30 days for major adverse cardiac events (MACE) including death, readmission with myocardial infarction or acute coronary syndrome and presentation with life threatening dysrhythmia. Patients were classified according to the recent recommendations for admission and delta troponin using recent European Society of Cardiology (ESC) guidfelines. The groups were then dichotomised according to final diagnosis into those with or without AMI. All statistical analyses were performed using Analyse-it for Microsoft Excel (version 2.30, www.analyse-it.com).

POCT measurements were performed using the Stratus CS (Siemens Healthcare Diagnostics). The analytical characteristics of the assays were as follows: cTnI detection limit 30 ng/L, analytical range 30 to 50000 µg/L, inter assay CV 4.0-8.2% (67 to 344 ng/L). The 99th centile of the assay is 70 ng/L. At the individual sites cardiac troponin was measured as follows; Siemens cTnI ultra (3 sites) 99th percentile limit 40 ng/L, Abbott cTnI (1 site) 99th percentile limit 50 ng/L, Beckman AccuTnI (1 site) 99th percentile limit 60 ng/L and Roche cTnT (1 site) 99th percentile limit 10 ng/L.

Central laboratory assays were as follows. For cTnI, Siemens cTnI Ultra (ADVIA Centaur, Siemens Healthcare Diagnostics), range 20-50,000 ng/L. 10% CV is 30 ng/L with a 99th centile of 40 ng/L, Abbott Architect hsTnI (Abbott Diagnostics), range 1.1-50,000 ng/L 10% CV 4.7ng/L and cardiac troponin T (cTnT) by the Roche high sensitivity cardiac troponin T assay hs-cTnT (Elecsys 2010, Roche diagnostics), range 3 - 10,000ng/L, 10% CV 13ng/L, 99th percentile 14 ng/L.

RESULTS

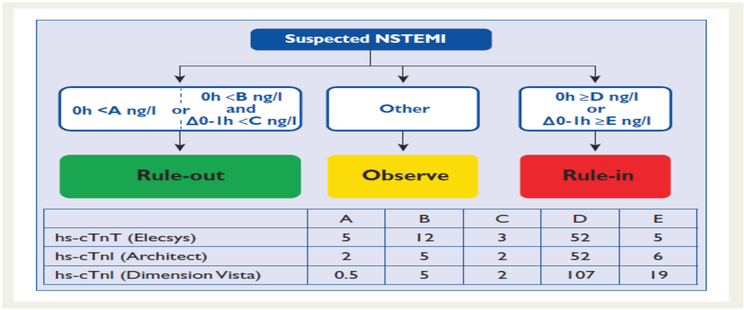
Enrollment



Demographics

Risk factors	RATPAC	ESC
	n (%)	n (%)
Previous MI	60 (5.3)	15 (5.4)
Previous angina	46 (4.1)	12 (4.3)
Previous CABG	12 (1.1)	4 (1.4)
Previous PCI	37 (3.3)	10 (3.6)
Previous angio with CHD	14 (1.2)	1 (0.4)
Previous CHD	36 (3.2)	6 (2.2)
DM	86 (7.6)	27 (9.8)
Hypertension	376 (33.4)	97 (35.1)
Hyperlipidaemia	271 (24.1)	63 (22.8)
Smoker	310 (27.6)	82 (29.7)
Ex smoker	144 (12.8)	40 (14.5)
Cocaine	6 (0.5)	2 (0.7)
FH IHD	344 (30.6)	100 (36.2)
Aspirin	207 (18.4)	56 (20.3)
Angina	75 (6.7)	15 (5.4)
Distribution of risk factors was not significantly different between the two groups (Chi^2)		

Diagnosis	RATPAC	ESC	
	n (%)	n (%)	p
Acute Myocardial Infarction	93 (8.3)	26 (9.4)	ns
Angina	126 (11.2)	35 (12.7)	ns
Anxiety	36 (3.2)	13 (4.7)	ns
Gastro-oesophageal	124 (11.0)	40 (14.5)	ns
Musculoskeletal	143 (12.7)	46 (16.7)	ns
Non-specific	359 (31.9)	79 (28.6)	0.05
Other	184 (16.4)	29 (10.5)	0.02
Unknown	60 (5.3)	8 (2.9)	0.05
	1125	276	



	A	B	C	D	E
hs-cTnT (Elecsys)	5	12	3	52	5
hs-cTnI (Architect)	2	5	2	52	6
hs-cTnI (Dimension Vista)	0.5	5	2	107	19

Admission diagnosis				
cTnI	Rule out	Intermediate	Rule in	
MI	0	14	12	26
No MI	174	75	1	250
	174	89	13	276
% Total cases	63.0	32.2	4.7	100.0
Sensitivity for rule out	100			
cTnT	Rule out	Intermediate	Rule in	
MI	2	7	17	26
No MI	217	31	2	250
	219	38	19	276
% Total cases	79.3	13.8	6.9	100.0
Sensitivity for rule out	99.1			

Serial diagnosis										
Admission sample (Discriminants for rule in and rule out)						**Second sample (Discriminants plus delta)**				
cTnI	Rule out	Indeterminate	Rule in			cTnI	Rule out	Indeterminate	Rule in	
MI	0	5	0	5		MI	0	0	5	5
No MI	111	49	0	160		No MI	28	18	3	49
	111	54	0	165			28	18	8	54
% Total cases	67.3	32.7	0.0	100			17.0	33.3	14.8	100
Sensitivity for rule out	100						25.2	36		
cTnT	Rule out	Indeterminate	Rule in			cTnT	Rule out	Indeterminate	Rule in	
MI	1	4	0	5		MI	0	3	2	5
No MI	137	23	0	160		No MI	10	6	6	22
	138	27	0	165			10	9	8	27
% Total cases	83.6	16.4	0.0	100			6.1	33.3	29.6	100
Sensitivity for rule out	99.3						7.2	18		

CONCLUSION

The ESC algorithm allows for efficient rule out. Both single measurement and serial measurement algorithms proved excellent rule out tools but the rule in algorithm was less reliable in this patient group. This probably reflects the difficulty of diagnoses in low risk patients with relatively small troponin changes.

References

1. Goodacre SW, Bradburn M, Cross E, Collinson P, Gray A, Hall AS. The Randomised Assessment of Treatment using Panel Assay of Cardiac Markers (RATPAC) trial: a randomised controlled trial of point-of-care cardiac markers in the emergency department. *Heart* 2011;**97**:190-6.
2. Goodacre S, Bradburn M, Fitzgerald P, Cross E, Collinson P, Gray A *et al*. The RATPAC (Randomised Assessment of Treatment using Panel Assay of Cardiac markers) trial: a randomised controlled trial of point-of-care cardiac markers in the emergency department. *Health Technol.Assess.* 2011;**15**:1-108.
3. Collinson P, Gaze D, Thokala P, Goodacre S. Randomised Assessment of Treatment using Panel Assay of Cardiac markers - Contemporary Biomarker Evaluation (RATPAC CBE). Health Technol Assess 2013;17:1-122.