ORIGINAL RESEARCH ARTICLE

Diagnostic accuracy of the T-MACS decision aid with a contemporary point-of-care troponin assay

Richard Body,[1,2,3] Malak Almashali,[3] Niall Morris,[1,2] Phil Moss,[4] Heather Jarman,[4] Andrew Appelboam,[5] Richard Parris,[6] Louisa Chan,[7] Alison Walker,[8] Mark Harrison,[9] Andrea Wootten,[10] Garry McDowell[3]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2018-313825).

For numbered affiliations see end of article.

Correspondence to
Prof Richard Body, Emergency Department, Manchester Royal Infirmary, Manchester M13 9WL, UK; richard.body@manchester.ac.uk

Received 4 July 2018
Revised 10 October 2018
Accepted 17 October 2018

To cite: Body R, Almashali M, Morris N, *et al*. *Heart* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/heartjnl-2018-313825

ABSTRACT

Objectives The rapid turnaround time of point-of-care (POC) cardiac troponin (cTn) assays is highly attractive for crowded emergency departments (EDs). We evaluated the diagnostic accuracy of the Troponin-only Manchester Acute Coronary Syndromes (T-MACS) decision aid with a POC cTn assay.

Methods In a prospective diagnostic accuracy study at eight EDs, we included patients with suspected acute coronary syndromes (ACS). Blood drawn on arrival and 3 hours later was analysed for POC cTnI (i-Stat, Abbott Point of Care). The primary outcome was a diagnosis of ACS, which included both an adjudicated diagnosis of acute myocardial infarction (AMI) based on serial laboratory cTn testing and major adverse cardiac events (death, AMI or coronary revascularisation) within 30 days.

Results Of 716 patients included, 105 (14.7%) had ACS. Using serial POC cTnI concentrations over 3 hours could have 'ruled out' ACS in 198 (31.2%) patients with a sensitivity of 99.0% (95% CI 94.4% to 100.0%) and negative predictive value 99.5% (95% CI 96.5% to 99.9%). No AMIs were missed. T-MACS 'ruled in' ACS for 65 (10.4%) patients with a positive predictive value of 91.2% (95% CI 82.1% to 95.9%) and specificity 98.9% (97.6% to 99.6%).

Conclusion With a POC cTnI assay, T-MACS could 'rule out' ACS for approximately one-third of patients within 3 hours while 'ruling in' ACS for another 10%. The rapid turnaround time and portability of the POC assay make this an attractive pathway for use in crowded EDs or urgent care centres. Future work should also evaluate use in the prehospital environment.

BACKGROUND

Chest pain is the second most common reason for emergency hospital admission.[1] However, as the prevalence of acute coronary syndromes (ACS) in those who are admitted on suspicion of that diagnosis is <20%,[2 3] many hospital admissions could be avoided with improved diagnostic technology. It may now be possible to 'rule out' ACS following a single blood test in the emergency department (ED) for some patients. This can be achieved, for example, by using the limit of detection (LoD) of a high-sensitivity cardiac troponin (hs-cTn) assay as a 'rule out' threshold,[4 5] the History, electrocardiogram, Age, Risk factors and Troponin (HEART) score[6] or the Troponin-only Manchester Acute Coronary Syndromes (T-MACS) decision aid.[2 7]

These algorithms, however, currently rely on the use of central laboratory troponin assays, which have a relatively long turnaround time (TAT). The target TAT is 60 min from receipt of the sample in the laboratory[8] but this does not account for preanalytical (including time to collect and transport samples) and postanalytical factors. The use of near-patient cTn testing could help to reduce overall TAT. Because contemporary point-of-care (POC) cTn assays do not have the same sensitivity and precision as laboratory assays, diagnostic algorithms must be specifically validated with these assays before clinical use.

The T-MACS decision aid could be used to both 'rule in' and 'rule out' ACS by using an algorithm (derived by logistic regression) to calculate the probability of ACS using basic data about a patient's symptoms, signs, ECG and cTn concentrations. To date, T-MACS has only been validated using high-sensitivity[7] and contemporary[9] central laboratory-based cTn assays. However, successful validation with a POC cTn assay would reduce turnaround time, helping to unburden crowded EDs. Because contemporary POC cTn assays generally have inferior sensitivity and precision to central laboratory assays, we recognised that serial sampling may be required in order to achieve adequate diagnostic accuracy. However, given that the TAT of POC cTn assays is as little as 10–15 min, serial sampling over 3 hours could still facilitate rapid decision making. Importantly, this would enable rapid diagnosis even in situations where central laboratory cTn assays are not immediately available. We therefore aimed to prospectively validate T-MACS generated with a contemporary POC cTn assay, using (1) a single admission blood sample and (2) two samples drawn 3 hours apart.

METHODS

Design and setting

We undertook a multicentre, prospective diagnostic test accuracy study at eight EDs in England (see online supplementary appendix for details of each site). The study was prospectively registered on the National Institute for Health Research (NIHR) portfolio (reference UK CRN 18000).

Study participants

We included adults (aged >18 years) who presented to the ED with pain, discomfort or pressure in the chest, epigastrium, neck, jaw or upper limb without

an apparent non-cardiac source,[10] which the treating physician believed warranted investigation for possible ACS. We excluded patients whose peak symptoms had occurred >12 hours prior to presentation at the ED, patients with unequivocal evidence of ST elevation myocardial infarction requiring referral for immediate revascularisation, patients with another medical condition requiring hospital admission and patients who lacked the mental capacity to provide written informed consent. To expedite recruitment and avoid delays to blood sampling and clinical care, the initial blood samples for this study could be drawn at the time of arrival in the ED and at the same time as routine clinical samples without delay, with written consent obtained thereafter. In the event that written consent could not be obtained, samples were discarded and patients were not included in the study. Because of logistical, training and governance requirements, we included a convenience sample dictated by the availability of research nurses or study investigators. Sites were opened in phases with the first site commencing recruitment on 9 February 2015 and the final site completing recruitment on 25 October 2016.

Data collection

The treating clinician and study nurse recorded comprehensive clinical data at the time of inclusion using a bespoke case report form, in accordance with contemporary international standards. These data included details of the presenting complaint; medical history; medication history; social history (including alcohol intake and tobacco use); family history of ischaemic heart disease; findings on physical examination; 12-lead ECG findings (including the presence or absence of dynamic ECG changes such as T wave inversion or ST segment depression); medications received during the active study phase; disposition; findings of relevant laboratory tests and medical imaging. The variables required for calculation of T-MACS were recorded by the treating clinician. 'Worsening angina' was determined to be present or absent at the discretion of the clinician, but included patients with known angina or those with symptoms suspicious for new angina who had symptoms with increasing frequency, intensity or duration, or with less provocation (eg, exertion) than usual. The interobserver reliability of all constituent variables in T-MACS has previously been established, and all variables had a kappa score >0.6.[2] Interobserver reliability was not re-evaluated in this study.

In this observational study, patients were treated according to local guidelines, but in order to be selected for the study all sites were required to confirm that local practices were consistent with the guidance issued by the National Institute for Health and Care Excellence[11] and the European Society of Cardiology.[12]

Laboratory analyses

Patients underwent venepuncture at the time of arrival in the ED and 3 hours (±30 min) later. Whole blood (collected in lithium heparin vials) was analysed for cTn using the i-Stat assay (Abbott Point of Care, New Jersey, 99th percentile 80 ng/L, LoD 20 ng/L, coefficient of variation 16.5% at the 99th percentile), in accordance with the manuacturer's instructions. All staff responsible for undertaking these analyses received bespoke training to run the i-Stat assays.

In addition, patients also underwent central laboratory cTn testing, which formed part of the reference standard for the diagnosis of AMI. In order to ensure that participants underwent adequate reference standard investigations for AMI, sites were asked to confirm that their local practice was consistent with current national and international guidance. Specifically, sites were required to confirm that patients would undergo the following cTn testing:

- *If a contemporary (not high sensitivity) troponin assay was used:* Laboratory-based troponin testing on arrival and either 6 hours after arrival or 10–12 hours after the onset of peak symptoms.[11 12]
- *If a high-sensitivity troponin assay was used:* Laboratory-based troponin testing on arrival and either 3 hours after arrival or 10–12 hours after the onset of peak symptoms.[11 12]

A high-sensitivity troponin assay was defined as an assay that can detect troponin concentrations in at least 50% of apparently healthy individuals with a coefficient of variation of <10% at the 99th percentile cut-off.[13]

Outcomes

The primary outcome was the diagnosis of ACS. ACS was defined as either acute myocardial infarction (AMI), occurring during the initial hospital admission (prevalent AMI), or incident major adverse cardiac events (MACE) occurring within 30 days. MACE included death (all cause), incident AMI and coronary revascularisation. All coronary revascularisation procedures were considered to be relevant if they occurred within 30 days of the initial ED attendance. The diagnosis of AMI was allocated by two independent investigators, blinded to T-MACS and i-Stat cTnI concentrations. AMI was defined in accordance with the third universal definition of AMI[14] based on a rise and/or fall of cTn with at least one troponin concentration above the 99th percentile of the assay, in conjunction with at least one of symptoms of myocardial ischaemia, ECG changes or imaging evidence of new loss of viable myocardium. All relevant clinical notes and imaging reports were available for review by the adjudicators.

Follow-up

Patients were 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 were collected. If it was not possible to contact participants directly after repeated attempts, we obtained follow-up information from patients' primary care practitioners where possible.

Statistical analysis

For the primary analyses, we evaluated the diagnostic accuracy of T-MACS used with POC cTnI testing (i-Stat) at presentation and at 3 hours. For comparison, we also determined the diagnostic accuracy of the i-Stat cTnI assay when used alone (at presentation and after 3 hours) and in combination with ECG findings (as interpreted by the treating clinician), and we evaluated the diagnostic accuracy of T-MACS using the POC cTnI assay to the diagnostic accuracy when the central laboratory assay was used. For the latter evaluation, we used the cTn assay used in clinical practice. Four sites (Bolton, Harrogate, Northumbria and Basingstoke) were excluded from this analysis because the laboratory did not release cTn results at low concentrations, precluding calculation of T-MACS (which relies on the use of low cTn concentrations to identify 'very low risk' patients). Each of the remaining sites used the hs-cTnT assay (Roche Diagnostics Elecsys).

To evaluate diagnostic accuracy, we calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), positive and negative likelihood ratios. We summarised the overall diagnostic accuracy of T-MACS and

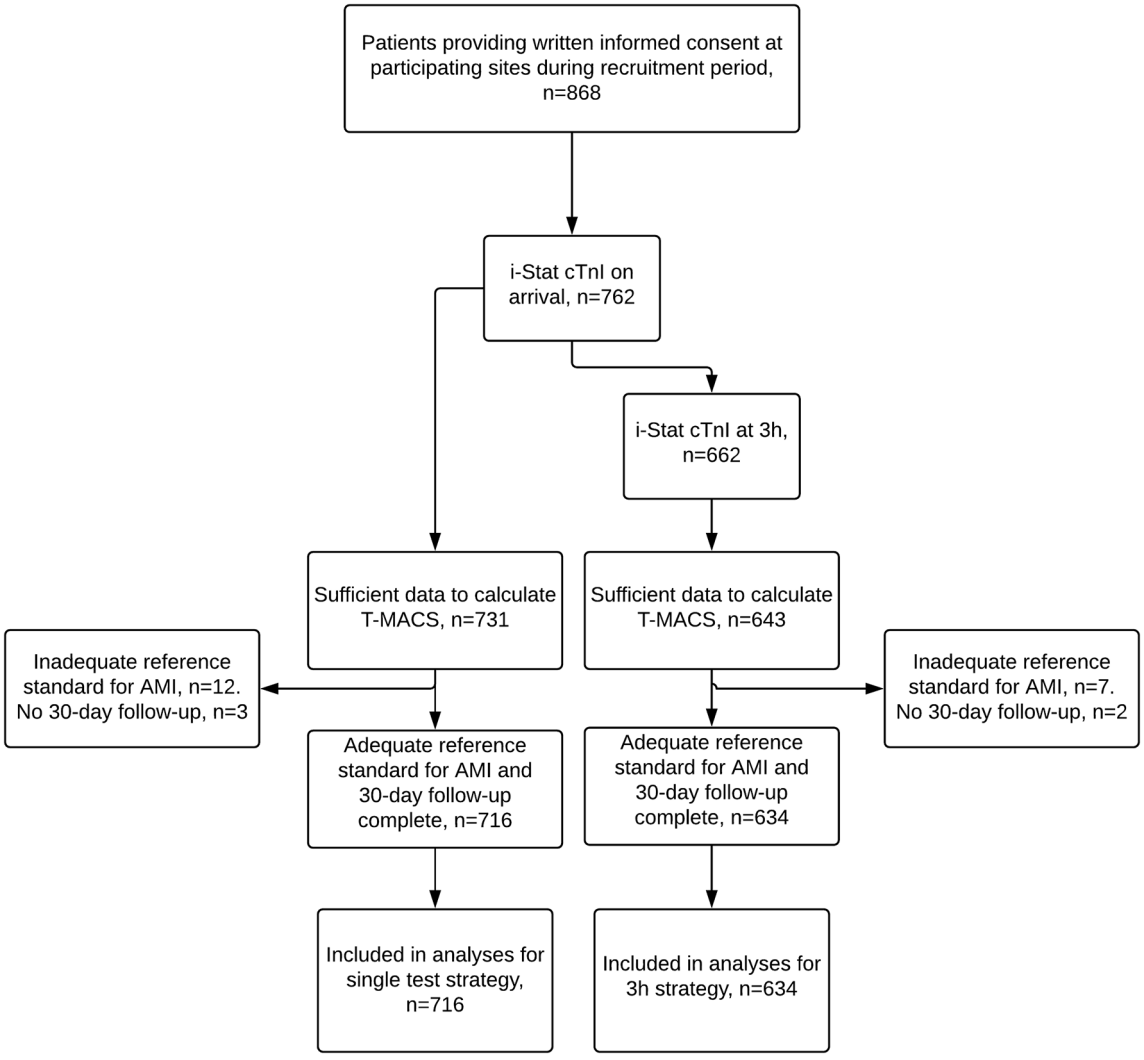

Figure 1 Flow chart of study participants. AMI, acute myocardial infarction; cTn, cardiac troponin; T-MACS, Troponin-only Manchester Acute Coronary Syndromes.

cTnI (i-Stat) by calculating the area under the receiver operating characteristic (ROC) curve. For these analyses, we excluded patients who did not have adequate reference standard investigations for AMI, those who were lost to follow-up at 30 days and those who had missing data for T-MACS. Statistical analyses were completed in SPSS V.23.0 and/or MedCalc V.13.1.2.0 (Mariakerke, Belgium).

To evaluate T-MACS, we applied the previously derived formula to estimate the probability of ACS, entering cTnI concentrations in ng/L.[7] Consistent with our approach in the original model derivation, patients with cTnI concentrations below the LoD of the assay (10 ng/L) were considered to have concentrations of 9 ng/L. For this evaluation, we used a minor modification to the original formula based on feedback from clinicians after implementation of the T-MACS algorithm. Clinicians had noted that patients with 'worsening (crescendo) angina' could be classified as 'low risk' (suitable for further evaluation in a low-dependency inpatient environment) in the absence of other risk factors. However, they felt that such patients should be classified as 'moderate risk'. The coefficient for this variable was therefore manually recalibrated to the minimum required to achieve this. Thus, the probability (p) of ACS was calculated as follows:

$$p = 1/\left(1 + e^{-(-4.65+1.828a+1.54b+0.849c+1.783d+1.878e+1.412f+0.08g)}\right)$$

where a denotes acute ECG ischaemia; b denotes a pattern of worsening (or crescendo) angina; c is pain radiation to the right arm or right shoulder; d is pain associated with vomiting; e is visible diaphoresis in the ED; f is hypotension (defined as systolic blood pressure <100 mm Hg); and g is cTn concentration. For all variables except g, a value of '1' is entered if the feature is present and a value of '0' is entered if it is absent.

The T-MACS model classifies patients into four distinct risk groups based on their calculated risk probability according to the cut-offs applied in the derivation of the original MACS rule. The four risk groups with associated suggestion for patient disposition include (1) very low risk ($p<0.02$; patients eligible for immediate discharge); (2) low risk ($0.02 \leq p<0.05$; suitable for serial cTn sampling in an ED observation ward or comparable alternative); (3) moderate risk ($0.05 \leq p<0.95$; serial cTn sampling required in general ward such as an Acute Medical Ward); and (4) high risk ($p \geq 0.95$; ACS considered ruled in, best managed in a high-dependency unit or specialist ward).

Sample size

Assuming that the prevalence of the primary outcome was approximately 10%,and that the algorithm would achieve 100% sensitivity, the lower bound of the 95% CI would be >90% for

Table 1 Baseline characteristics of included patients

	Total (n=716)	ACS present (n=105)	ACS absent (n=611)
Age in years, mean (SD)	57.6 (15.6)	66.1 (14.6)	56.2 (15.3)
Men (%)	445 (62.2)	78 (74.3)	367 (60.1)
Previous myocardial infarction (%)	169 (23.6)	35 (33.3)	134 (21.9)
Previous percutaneous coronary intervention (%)	138 (19.3)	25 (23.8)	113 (18.5)
Previous coronary artery bypass graft (%)	51 (7.1)	12 (11.4)	39 (6.4)
Hypertension (%)	332 (46.4)	59 (56.2)	273 (44.7)
Hyperlipidaemia (%)	256 (35.8)	48 (45.7)	208 (34.0)
Type 1 diabetes mellitus (%)	14 (2.0)	4 (3.8)	10 (1.6)
Type 2 diabetes mellitus (%)	123 (17.2)	31 (29.5)	92 (15.1)
Current smoking (%)	139 (19.4)	28 (26.7)	111 (18.2)
Time from symptom onset to arrival in the ED (hours)			
0–3	354 (49.4)	54 (51.4)	300 (49.1)
3–6	153 (21.4)	25 (23.8)	128 (20.9)
6–9	88 (12.3)	14 (13.3)	74 (12.1)
>9	73 (10.2)	9 (8.6)	64 (10.5)
Components of the (T-)MACS rule			
Acute ECG ischaemia (%)	64 (8.9)	29 (27.6)	35 (5.7)
Worsening angina (%)	124 (17.3)	33 (31.4)	91 (14.9)
Pain associated with vomiting (%)	38 (5.3)	6 (5.7)	32 (5.2)
Sweating observed (%)	39 (5.4)	7 (6.7)	32 (5.2)
Systolic blood Pressure<100 mm Hg (%)	23 (3.2)	3 (2.9)	20 (3.3)
Pain radiating to right arm or shoulder (%)	63 (8.8)	15 (14.3)	48 (7.9)
POC cTnI (i-Stat)≥10 ng/L (%)	263 (36.7)	90 (85.7)	173 (28.3)

ACS, acute coronary syndrome; cTn, cardiac troponin; ED, emergency department; POC, point of care; T-MACS, Troponin-only Manchester Acute Coronary Syndromes.

sensitivity and >99% for NPV with a sample size of 605 participants. Accounting for potential loss to follow-up and missing data (estimated to be approximately 5%), we planned to include a total of approximately 650 participants. Recruitment was continued until we had verified data collection from all sites to ensure that this minimum sample size had been exceeded.

RESULTS

We included a total of 716 patients at eight centres, of which 105 (14.7%) had ACS, including 89 (12.4%) with prevalent AMI. During the recruitment period at participating centres, a total of 868 patients were recruited, although it was not possible to undertake the POC cTnI test for 126 patients because the analyser or cartridges were unavailable. This left 762 patients eligible for the analysis, of which 716 had full data and were included in the analysis of diagnostic accuracy (figure 1). The baseline characteristics of participants are summarised in table 1. A total of 634 patients underwent POC i-Stat testing at 3 hours, of which 97 (15.3%) had ACS including 82 (12.9%) with AMI. Based on a single i-Stat POC cTnI measurement at the time of arrival in the ED, the area under the ROC curve (AUC) for T-MACS was 0.86 (95% CI 0.82 to 0.90). Accounting for the 3-hour POC cTnI concentration increased the AUC to 0.92 (95% CI 0.89 to 0.95).

The proportions of patients with ACS and AMI in each T-MACS risk group (based on i-Stat POC cTnI concentrations) are shown in tables 2 and 3. Table 2 shows the proportions in each risk group based on a single POC cTnI test taken at the time of arrival in the ED. Table 3 shows the proportions based on two POC cTnI tests taken 3 hours apart. For the latter analysis, the maximum cTnI concentration detected was used.

Table 2 Proportion of patients with acute coronary syndrome (ACS) and acute myocardial infarction (AMI) in the four risk groups for the Troponin-only Manchester Acute Coronary Syndromes model (test on arrival only)

	Very low risk	Low risk	Moderate risk	High risk
Total number of patients (%)	306 (42.7)	134 (18.7)	227 (31.7)	49 (6.8)
Number (%) with ACS	6 (2.0)	16 (11.9)	39 (17.2)	44 (89.8)
Number (%) with AMI	4 (1.3)	16 (12.3)	26 (11.6)	43 (87.8)

Table 3 Proportion of patients with acute coronary syndrome (ACS) and acute myocardial infarction (AMI) in the four risk groups for the Troponin-only Manchester Acute Coronary Syndromes (T-MACS) model (test on arrival and at 3 hours)

	Very low risk	Low risk	Moderate risk	High risk
Total number of patients (%)	198 (31.2)	159 (25.1)	209 (33.0)	68 (10.7)
Number (%) with ACS	1 (0.5)	7 (4.4)	27 (12.9)	62 (91.2)
Number (%) with AMI	0 (0.0)	6 (3.8)	15 (7.2)	61 (89.7)

T-MACS as a 'rule out' test ('very low risk' vs all other risk groups)

T-MACS could have been used to 'rule out' 306 (42.7%) patients based on a single test at the time of arrival, or 196 (31.4%) patients following a repeat cTnI test at 3 hours. Based on the initial POC cTnI concentration, there were six false negative results with T-MACS, including four patients with prevalent AMI and two patients who developed MACE within 30 days (both MACEs were percutaneous coronary intervention (PCI)).

Of those patients, only one remained 'false negative' once the second POC cTnI concentration measured at 3 hours had been taken into account. That patient did not have prevalent AMI (high sensitivity cTnT concentrations 4 and 5 ng/L, respectively) but underwent invasive coronary angiography and PCI as an outpatient following discharge from hospital. The test characteristics of T-MACS using POC cTnI on arrival and at 3 hours are shown in table 4.

For comparison, if patients were 'ruled out' based on a single POC cTnI concentration <10 ng/L on arrival and the absence of acute ECG ischaemia without accounting for T-MACS, a sensitivity of 87.4% (95% CI 79.4% to 93.1%) and NPV of 97.0% (95% CI 95.0% to 98.2%) could have been achieved, and ACS would have been immediately 'ruled out' in 426 (60.4%) patients. Similarly, accounting for the 3-hour cTnI concentration with this strategy would have achieved a sensitivity of 93.7% (95% CI 86.8% to 97.7%) and an NPV of 98.3% (95% CI 96.3% to 99.2%), 'ruling out' 348 (55.8%) patients.

T-MACS as a 'rule in' test ('high risk' vs all other risk groups)

T-MACS could have 'ruled in' ACS in 49 (6.8%) patients using the initial cTnI concentration with a PPV of 89.8% (95% CI 78.1% to 95.6%) and specificity 99.2% (95% CI 98.1% to 99.7%). In comparison, measuring POC cTnI concentration on arrival alone, with the 99th percentile cut-off (80 ng/L), could have 'ruled in' ACS for 42 (6.0%) patients. This would have

Table 4 Diagnostic performance of the Manchester Acute Coronary Syndromes (MACS) and Troponin-only Manchester Acute Coronary Syndromes (T-MACS) models as 'rule out' strategies (ie, 'very low risk' vs all other risk groups; 95% CI in parentheses)

	T-MACS, 0 hour only		T-MACS, 0 hour + 3 hours	
	For ACS	For AMI	For ACS	For AMI
Sensitivity	94.3 (88.0 to 97.9)	95.5 (88.9 to 98.8)	99.0 (94.4 to 100.0)	100.0 (95.6 to 100.0)
Specificity	49.1 (45.1 to 53.1)	48.2 (44.2 to 52.2)	36.7 (32.6 to 40.9)	35.9 (31.9 to 40.0)
PPV	24.2 (22.5 to 25.9)	20.7 (19.3 to 22.2)	22.0 (20.9 to 23.2)	18.8 (17.9 to 19.8)
NPV	98.0 (95.8 to 99.1)	98.7 (96.7 to 99.5)	99.5 (96.5 to 99.9)	100.0 (NA)
LR+	1.85 (1.69 to 2.03)	1.84 (1.69 to 2.01)	1.57 (1.46 to 1.68)	1.56 (1.47 to 1.66)
LR-	0.12 (0.05 to 0.25)	0.09 (0.04 to 0.24)	0.03 (0.00 to 0.20)	0.00 (NA)

ACS, acute coronary syndromes; AMI, acute myocardial infarction; LR+, positive likelihood ratio; LR-, negative likelihood ration; NA, not available; NPV, negative predictive value; PPV, positive predictive value.

achieved a PPV of 90.5% (95% CI 77.6% to 96.3%) with a specificity of 99.3% (95% CI 98.3% to 99.8%).

Also accounting for POC cTnI concentrations measured at 3 hours, T-MACS could have 'ruled in' ACS for 68 (10.7%) patients. This achieved a PPV of 91.2% (95% CI 82.1% to 95.9%) and a specificity of 98.9% (95% CI 97.6% to 99.6%). Using POC cTnI concentrations alone with the 99th percentile cut-off (80 ng/L, considering the maximum concentration measured at presentation and 3 hours and without T-MACS) would have 'ruled in' ACS for a similar proportion of patients (10.4%) with similar test characteristics (PPV 92.3% and specificity 99.1%).

Diagnostic accuracy of T-MACS with a central laboratory assay

A total of 565 patients were included in this analysis, of which 65 (11.5%) had AMI and 78 (13.8%) had ACS. T-MACS identified 267 (47.2%) patients as 'very low risk' with the central laboratory (hs-cTnT) assay. Of those, two patients with AMI were wrongly identified as being 'very low risk' using the central laboratory assay and three had ACS. This gave a sensitivity of 98.9% (95% CI 96.8% to 99.8%) and an NPV of 98.6% (95% CI 95.6% to 99.6%) for ACS. For 'ruling in' ACS by identifying 30 (5.3%) patients as 'high risk', T-MACS had a specificity of 99.4% (95% CI 98.2% to 99.9%) and PPV 90.0% (95% CI 73.7% to 96.7%).

Diagnostic accuracy of the POC cTn assay alone

Without T-MACS, the POC cTn assay alone (tested at 0 and 3 hours using the 99th percentile cut-off) had a sensitivity of 63.9% (95% CI 53.5% to 73.4%), specificity 99.2% (95% CI 98.2% to 99.8%), PPV 92.5% (83.6% to 96.8%) and NPV 94.8% (93.3% to 95.9%). If only patients with no ECG ischaemia were 'ruled out', test characteristics were as follows: sensitivity 73.2% (95% CI 63.2% to 81.7%), specificity 93.1% (90.6% to 95.1%), PPV 65.7% (57.9% to 72.8%) and NPV 95.1% (93.3% to 96.4%).

DISCUSSION

In this work we have achieved two important goals with significant implications for practice. Our findings have identified wider clinical applications for (1) the POC cTnI i-Stat assay and (2) the T-MACS decision aid. By using the i-Stat cTnI assay alongside T-MACS, ACS could be 'ruled out' with serial sampling over 3 hours. Until now, guidelines have stated that the 3-hour rule out pathway should be reserved for use with high-sensitivity cTn assays.[11 12 15] Our work suggests that the same can be achieved with a contemporary, POC assay, when used alongside the T-MACS decision aid.

In addition to 'ruling out' ACS, the algorithm could also enable the diagnosis to be 'ruled in' with >90% PPV, thus facilitating early access to specialist care for patients who will benefit the most. This compares very favourably to existing rapid 'rule in' algorithms. For example, using troponin criteria alone the PPV of a single test has been reported to be <90%, even at very high cut-offs.[16] Even with serial sampling over 1 hour, the 1-hour rule-in and rule-out algorithm achieves a PPV of <80%.[17] These are not direct comparisons, and our work therefore does not suggest that the T-MACS is superior to these alternatives. However this other work does emphasise the value of achieving a PPV >90%, as reported here.

Until now, the T-MACS decision aid had only been validated for use with hs-cTn T (Roche)[7 18] and contemporary (cardiac troponin I, Siemens cTnI-Ultra)[9] laboratory-based assays. Validation of the model with a POC cTnI assay enhances the possibilities for future clinical application. These possibilities include (1) expedited diagnostic evaluation in the ED, helping to reduce crowding; (2) enabling the use of biomarker testing in ambulatory care environments without a central laboratory on-site (eg, urgent care centres); and (3) diagnostic evaluation in the prehospital environment, including in the ambulance. The latter will require another prospective clinical study to establish the feasibility of using POC cTnI assays alongside the T-MACS decision aid in the prehospital environment. Because the algorithm is likely to be used sooner after symptom onset, it will also be important to verify its diagnostic accuracy in that environment. The Pre-hospital Evaluation of Sensitive Troponin study, led by members of our group, will shortly address that objective.

Importantly, to obtain the benefits offered by POC testing, use of the accompanying T-MACS algorithm (which takes account of additional clinical information) is required to achieve sufficient diagnostic accuracy. Using POC cTnI concentrations alone, even with an unconventional 'rule out' cut-off at the extreme of the reportable range of the assay, could not 'rule out' ACS. These findings are entirely consistent with previous work which has shown that POC cTn assays used alone have suboptimal sensitivity.[19 20]

Our findings are also consistent with previous research evaluating other rapid rule out strategies using POC biomarker assays in the ED. In the Randomised Assessment of Treatment using Panel Assay of Cardiac markers study, who were randomised to receive POC biomarker (cTn, myoglobin and creatine kinase MB (CK-MB) fraction) testing over 90 min were more likely to be successfully discharged from the ED within 4 hours of arrival than patients who received central laboratory testing.[21] However,

the strategy was not found to be cost-effective (possibly caused by over-triage relating to the use of non-specific biomarkers)[22] and the diagnostic accuracy of the POC biomarkers (including cTn measured using the Siemens Stratus CS assay) was found to be inferior to central laboratory assays when used alone.[23] In Australasia, serial testing for cTn, myoglobin and CK-MB over 2 hours was found to rule out ACS with high sensitivity when used alongside the Thrombolysis in Myocardial Infarction risk score.[24] However, the strategy only identified 9.8% patients as eligible for early discharge, whereas using a central laboratory cTn assay maintained sensitivity while identifying 20% of patients as eligible for early discharge.[3] This current work adds to the literature by identifying that POC cTn testing used alongside the T-MACS decision aid could identify >30% patients as eligible for early discharge, while also 'ruling in' the diagnosis in other patients with high specificity.

Limitations

Although this is a multicentre study at eight EDs and our total sample size of 716 patients exceeded the calculated requirement, our 95% CIs were sufficiently wide to incorporate values that, if true, are unlikely to be clinically acceptable. Therefore, further prospective confirmation of our findings is desirable. We should also note that 126 patients did not undergo POC cTnI testing during the study period due to a lack of available analysers or cTnI cartridges. A smaller number of patients had insufficient data recorded to calculate T-MACS or to verify the final diagnosis. It seems unlikely that this would substantially affect the results of our study as there is no suggestion that the missing data would introduce a systematic source of bias. Finally, we should acknowledge that while sites were encouraged to recruit a consecutive sample of patients, recruitment was ultimately dictated by researcher (predominantly research nurse) availability, meaning that this is ultimately a convenience sample.

One key advantage of POC cTn assays is that the turnaround time is faster than central laboratory assays. In this work, it was not possible to quantify the time saving as our objective was to evaluate diagnostic accuracy. Thus, the POC tests were predominantly undertaken by research nurses who also had other non-clinical tasks to complete (such as seeking consent). Future work evaluating the implementation of POC cTn tests in practice should therefore seek to quantify the potential time saving when POC cTn assays are used.

The POC troponin assays were also run by clinical research nurses and clinicians who had received all appropriate study training and had been delegated responsibility to undertake the assays by the local principal investigator at each site. While this was required for governance reasons, and while the staff running the analyses have a similar background to all other clinical staff working in the ED, it will be important for future research to evaluate the assay when used as part of routine clinical practice.

Key messages

What is already known about this subject?

- The Troponin-only Manchester Acute Coronary Syndromes (T-MACS) decision aid has previously been shown to be an accurate tool to enable acute coronary syndromes to be ruled in and ruled out following a single blood test in the Emergency Department. However, T-MACS has to date only been validated with central laboratory cardiac troponin assays.

What does this study add?

- In this work we validated T-MACS using a contemporary point of care cardiac troponin assay. While the assay was insufficiently sensitive when used alone, it had comparable accuracy to central laboratory assays when used to inform the T-MACS decision aid.

How might this impact on clinical practice?

- Our work shows that acute coronary syndromes could be ruled in or ruled out by using T-MACS and two point of care troponin tests taken 3 hours apart. This could expedite the patient journey in the Emergency Department and may enable future care to delivered in ambulatory or community-based settings.

CONCLUSION

The T-MACS decision aid could be used to 'rule in' and 'rule out' ACS with the POC cTnI i-Stat assay with serial samples drawn 3 hours apart. This would enable expedited diagnostic evaluation in EDs and may facilitate future use of both T-MACS and POC cTnI testing in ambulatory care and prehospital environments.

Author affiliations
[1]Emergency Department, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK
[2]Cardiovascular Sciences Research Group, Manchester Academic Health Science Centre, The University of Manchester, Manchester, UK
[3]School of Healthcare Science, Manchester Metropolitan University, Manchester, UK
[4]Emergency Department, St. George's NHS Foundation Trust, Manchester, UK
[5]Emergency Department, Royal Devon & Exeter Hospital NHS Foundation Trust, Exeter, UK
[6]Emergency Department, Bolton NHS Foundation Trust, Bolton, UK
[7]Emergency Department, Hampshire Hospitals NHS Foundation Trust, Hampshire, UK
[8]Emergency Department, Harrogate and District NHS Foundation Trust, Harrogate, UK
[9]Emergency Department, Northumbria Healthcare NHS Foundation Trust, Northumbria, UK
[10]Emergency Department, Arrowe Park Hospital, Wirral University Teaching Hospital NHS Foundation Trust, Wirral, UK

Contributors All authors contributed substantially to this work, the revision and final approval of the manuscript, and meet the ICMJE criteria for authorship.

Funding This study was funded by a research grant from Abbott Point of Care. The study was sponsored by Manchester University NHS Foundation Trust.

Competing interests RB Speaker fees from Singulex; Roche (consultancy, research grant); Abbott Point of Care (speaker fee, research grant); FABPulous BV (consultancy); Alere (donation of reagents for research).

Patient consent Obtained.

Ethics approval The study was approved by the National Research Ethics Service (reference 14/NW/1344), was sponsored by Manchester University NHS Foundation Trust and was undertaken in full compliance with the Declaration of Helsinki and according to the principles of Good Clinical Practice.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement For queries about unpublished data, please contact Professor Richard Body at richard.body@manchester.ac.uk.

REFERENCES

1 Hospital Episode Statistics. Hospital admitted patient care activity, 2016-17: diagnosis. 2017 https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2016-17 (accessed 19 Jun 2018).
2 Body R, Carley S, McDowell 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 Than M, Cullen L, Aldous S, *et al*. 2-Hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: the ADAPT trial. *J Am Coll Cardiol* 2012;59:2091–8.

4 Pickering JW, Than MP, Cullen L, *et al*. Rapid rule-out of acute myocardial infarction with a single high-sensitivity cardiac troponin T measurement below the limit of detection: a collaborative meta-analysis. *Ann Intern Med* 2017;166:715–24.
5 Carlton E, Greenslade J, Cullen L, *et al*. Evaluation of high-sensitivity cardiac troponin I levels in patients with suspected acute coronary syndrome. *JAMA Cardiol* 2016;1:405.
6 Van Den Berg P, Body R. The HEART score for early rule out of acute coronary syndromes in the emergency department: a systematic review and meta-analysis. *Eur Heart J Acute Cardiovasc Care* 2018;7:111–9.
7 Body R, Carlton E, Sperrin M, *et al*. Troponin-only Manchester Acute Coronary Syndromes (T-MACS) decision aid: single biomarker re-derivation and external validation in three cohorts. *Emerg Med J* 2017;34:349–56.
8 Wu AHB, Christenson RH, Greene DN, *et al*. Clinical laboratory practice recommendations for the use of cardiac troponin in acute coronary syndrome: expert opinion from the academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine. *Clin Chem* 2018;64:645–55.
9 Va Den Berg P, Burrows G, Lewis P, *et al*. Validation of the (Troponin-only) Manchester ACS decision aid with a contemporary cardiac troponin I assay. *Am J Emerg Med* 2018;36:602–7.
10 Amsterdam EA, Wenger NK, Brindis RG, *et al*. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;130:2354–94.
11 National Clinical Guideline Centre for Acute and Chronic Conditions. Chest pain of recent onset: NICE Clinical Guideline CG95. 2010 https://www.nice.org.uk/guidance/cg95 (accessed 20 Jun 2018).
12 Roffi M, Patrono C, Collet J-P, *et al*. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2016;37:267–315.
13 Apple FS, Collinson PO. IFCC Task Force on Clinical Applications of Cardiac Biomarkers. Analytical characteristics of high-sensitivity cardiac troponin assays. *Clin Chem* 2012;58:54–61.
14 Thygesen K, Alpert JS, Jaffe AS, *et al*. Third universal definition of myocardial infarction. *Eur Heart J* 2012;33:2551–67.
15 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). 2014 https://www.nice.org.uk/guidance/dg15 (accessed 13 Feb 2015).
16 Mueller-Hennessen M, Mueller C, Giannitsis E, *et al*. Serial sampling of high-sensitivity cardiac troponin T may not be required for prediction of acute myocardial infarction diagnosis in chest pain patients with highly abnormal concentrations at presentation. *Clin Chem* 2017;63:542–51.
17 Mueller C, Giannitsis E, Christ M, *et al*. Multicenter evaluation of a 0-hour/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac troponin T. *Ann Emerg Med* 2016;68:76–87.
18 Greenslade JH, Nayer R, Parsonage W, *et al*. Validating the Manchester Acute Coronary Syndromes (MACS) and Troponin-only Manchester Acute Coronary Syndromes (T-MACS) rules for the prediction of acute myocardial infarction in patients presenting to the emergency department with chest pain. *Emerg Med J* 2017;34:517–23.
19 Palamalai V, Murakami MM, Apple FS. Diagnostic performance of four point of care cardiac troponin I assays to rule in and rule out acute myocardial infarction. *Clin Biochem* 2013;46:1631–5.
20 Bruins Slot MH, van der Heijden GJ, Stelpstra SD, *et al*. Point-of-care tests in suspected acute myocardial infarction: a systematic review. *Int J Cardiol* 2013;168:5355–62.
21 Goodacre SW, Bradburn M, Cross E, *et al*. 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.
22 Fitzgerald P, Goodacre SW, Cross E, *et al*. Cost-effectiveness of point-of-care biomarker assessment for suspected myocardial infarction: the randomized assessment of treatment using panel Assay of cardiac markers (RATPAC) trial. *Acad Emerg Med* 2011;18:488–95.
23 Collinson P, Gaze D, Goodacre S. Comparison of contemporary troponin assays with the novel biomarkers, heart fatty acid binding protein and copeptin, for the early confirmation or exclusion of myocardial infarction in patients presenting to the emergency department with chest pain. *Heart* 2014;100:140–5.
24 Than M, Cullen L, Reid CM, *et al*. A 2-h diagnostic protocol to assess patients with chest pain symptoms in the Asia-Pacific region (ASPECT): a prospective observational validation study. *Lancet* 2011;377:1077–84.