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

SHORT TITLE:

T-MACS with point of care troponin

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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 8 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 – 100.0%) and negative predictive value 99.5% (95% CI 96.5 – 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 – 95.9%) and specificity 98.9% (97.6 – 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 pre-hospital 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 less than 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 (ECG), 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 minutes from receipt of the sample in the laboratory [8] but this does not account for pre-analytical (including time to collect and transport samples) and post-analytical factors. The use of near-patient cardiac troponin testing could help to reduce overall TAT. Because contemporary point of care (POC) cardiac troponin 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, electrocardiogram and cardiac troponin (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 point of care (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 minutes, 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 (a) a single admission blood sample; and (b) two samples drawn 3 hours apart.

Methods

Design and setting

We undertook a multi-centre, prospective diagnostic test accuracy study at eight EDs in England (see Supplementary Appendix for details of each site). 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. The study was prospectively registered on the National Institute for Health Research (NIHR) portfolio (reference UK CRN 18000). All participants provided written informed consent.

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 9th February 2015 and the final site completing recruitment on 25th 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; previous 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 (e.g. 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 of 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 minutes) later. Whole blood (collected in lithium heparin vials) was analysed for cardiac troponin using the i-Stat assay (Abbott Point of Care, New Jersey, 99th percentile 80ng/L, LoD 20ng/L, co-efficient 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 to 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 to 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 co-efficient 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 revascularization 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 cardiac troponin 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 point of care 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 cardiac troponin 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 and negative predictive values (PPV and NPV), positive and negative likelihood ratios. We summarised the overall diagnostic accuracy of T-MACS and 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 version 23.0 (SPSS Inc, Chicago, Illinois) and/or MedCalc version 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 limit of detection of the assay (10ng/L) were considered to have concentrations of 9ng/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 co-efficient for this variable was therefore manually re-calibrated to the minimum required to achieve this. Thus, the probability (*p*) of ACS was calculated as follows:

$$p = 1 / (1 + e^{-(-4.65 + 1.828a + 1.54b + 0.849c + 1.783d + 1.878e + 1.412f + 0.084g)})$$

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 <100mmHg); 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≤p<0.05; suitable for serial cardiac troponin sampling in an ED observation ward or comparable alternative); (3) moderate risk (0.05≤p<0.95; serial cardiac troponin sampling required in general ward such as an Acute Medical Ward); and (4) high risk (p≥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 sensitivity and >99% for negative predictive value 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 8 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 reciever operating characteristic (ROC) curve (AUC) for T-MACS was 0.86 (95% CI 0.82 – 0.90). Accounting for the 3h POC cTnI concentration increased the AUC to 0.92 (95% CI 0.89 – 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 utilised.

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 3h. Based on the initial POC cTnI concentration, there were six false negative results with T-MACS, including 4 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 4ng/L and 5ng/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 <10ng/L on arrival and the absence of acute ECG ischaemia without accounting for T-MACS, a sensitivity of 87.4% (95% CI 79.4 – 93.1%) and NPV of 97.0% (95% CI 95.0 – 98.2%) could have been achieved, and ACS would have been immediately 'ruled out' in 426 (60.4%) patients. Similarly, accounting for the 3h cTnI concentration with this strategy would have achieved a sensitivity of 93.7% (95% CI 86.8% - 97.7%) and an NPV of 98.3% (95% CI 96.3– 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 – 95.6%) and specificity 99.2% (95% CI 98.1 – 99.7%). In comparison, measuring POC cTnI concentration on arrival alone, with the 99th percentile cut-off (80ng/L), could have 'ruled in' ACS for 42 (6.0%) patients. This would have achieved a PPV of 90.5% (95% 77.6 – 96.3%) with a specificity of 99.3% (95% CI 98.3 – 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 – 95.9%) and a specificity of 98.9% (95% CI 97.6 – 99.6%). Using POC cTnI concentrations alone with the 99th percentile cut-off (80ng/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 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 – 99.8%) and an NPV of 98.6% (95% CI 95.6 – 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% - 99.9%) and PPV 90.0% (95% CI 73.7 – 96.7%).

Diagnostic accuracy of the POC cTn assay alone

Without T-MACS, the POC cTn assay alone (tested at 0 & 3h using the 99th percentile cut-off) had a sensitivity of 63.9% (95% CI 53.5 – 73.4%), specificity 99.2% (95% CI 98.2 – 99.8%), PPV 92.5% (83.6– 96.8%) and NPV 94.8% (93.3 – 95.9%). If only patients with no ECG ischaemia were 'ruled out', test characteristics were as follows: sensitivity 73.2% (95% CI 63.2 – 81.7%), specificity 93.1% (90.6 – 95.1%), PPV 65.7% (57.9 – 72.8%) and NPV 95.1% (93.3 – 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 (a) the POC cTnI i-Stat assay; and (b) 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 over 90% positive predictive value, 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 less than 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 less than 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 high sensitivity cardiac troponin 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 (a) expedited diagnostic evaluation in the ED, helping to reduce crowding; (b) enabling the use of biomarker testing in ambulatory care environments without a central laboratory on-site (for example, urgent care centres); and (c) diagnostic evaluation in the pre-hospital 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 pre-hospital 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 (PRESTO) 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 point of care biomarker assays in the Emergency Department. In the Randomised Assessment of Treatment using Panel Assay of Cardiac markers (RATPAC) study, who were randomised to receive point of care biomarker (cTn, myoglobin and creatine kinase MB [CK-MB] fraction) testing over 90

minutes 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 point of care 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 (TIMI) 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 point of care cTn

testing used alongside the T-MACS decision aid could identify over 30% patients as eligible for early

discharge, while also 'ruling in' the diagnosis in other patients with high specificity.

Limitations

Although this is a multi-centre 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 point of care troponin assays were also run by clinical research nurses and clinicians who had been 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.

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 pre-hospital environments.

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Legends to figures

Figure 1: Flow chart of study participants

Tables

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:			
0 – 3h	354 (49.4)	54 (51.4)	300 (49.1)
3 – 6h	153 (21.4)	25 (23.8)	128 (20.9)
6 – 9h	88 (12.3)	14 (13.3)	74 (12.1)
>9h	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 <100mmHg (%)	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)

Table 2: Proportion of patients with ACS and AMI in the four risk groups for the T-MACS 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 ACS and AMI in the four risk groups for the 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)

Table 4: Diagnostic performance of the MACS and T-MACS models as 'rule out' strategies (i.e. 'very low risk' versus all other risk groups; 95% confidence intervals in parentheses)

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

PPV= positive predictive value, NPV= negative predictive value, LR+= positive likelihood ratio, LR-= negative likelihood ration, ACS= acute coronary syndromes, AMI= acute myocardial infarction