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External validation of the Manchester Acute Coronary Syndromes ECG risk model within a pre-hospital setting

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ABSTRACT

Objectives The Manchester Acute Coronary Syndromes ECG (MACS-ECG) prediction model calculates a score based on objective ECG measurements to give the probability of a non-ST elevation myocardial infarction (NSTEMI). The model showed good performance in the emergency department (ED), but its accuracy in the pre-hospital setting is unknown. We aimed to externally validate MACS-ECG in the pre-hospital environment.

Methods We undertook a secondary analysis from the Pre-hospital Evaluation of Sensitive Troponin (PRESTO) study, a multi-centre prospective study to validate decision aids in the pre-hospital setting (26 February 2019 to 23 March 2020). Patients with chest pain where the treating paramedic suspected acute coronary syndrome were included. Paramedics collected demographic and historical data and interpreted ECGs contemporaneously (as 'normal' or 'abnormal'). After completing recruitment, we analysed ECGs to calculate the MACS-ECG score, using both a pre-defined threshold and a novel threshold that optimises sensitivity to differentiate AMI from non-AMI. This was compared with subjective ECG interpretation by paramedics. The diagnosis of AMI was adjudicated by two investigators based on serial troponin testing in hospital.

Results Of 691 participants, 87 had type 1 AMI and 687 had complete data for paramedic ECG interpretation. The MACS-ECG model had a C-index of 0.68 (95% CI: 0.61 to 0.75). At the pre-determined cut-off, MACS-ECG had 2.3% (95% CI: 0.3% to 8.1%) sensitivity, 99.5% (95% CI: 98.6% to 99.9%) specificity, 40.0% (95% CI: 10.2% to 79.3%) positive predictive value (PPV) and 87.6% (87.3% to 88.0%) negative predictive value (NPV). At the optimal threshold for sensitivity, MACS-ECG had 50.6% sensitivity (39.6% to 61.5%), 83.1% specificity (79.9% to 86.0%), 30.1% PPV (24.7% to 36.2%) and 92.1% NPV (90.4% to 93.5%). In comparison, paramedics had a sensitivity of 71.3% (95% CI: 60.8% to 80.5%) with 53.8% (95% CI: 53.8% to 61.8%) specificity, 19.7% (17.2% to 22.45%) PPV and 93.3% (90.8% to 95.1%) NPV.

Conclusion Neither MACS-ECG nor paramedic ECG interpretation had a sufficiently high PPV or NPV to 'rule in' or 'rule out' NSTEMI alone.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The Manchester Acute Coronary Syndromes ECG (MACS-ECG) prediction model has been derived and validated to identify non-ST elevation myocardial infarction (NSTEMI) in patients with acute chest pain in the emergency department.
⇒ MACS-ECG has similar diagnostic accuracy to an emergency physician.
⇒ MACS-ECG uses objective parameters without requiring subjective ECG interpretation, which is an advantage for use in the prehospital environment.

WHAT THIS STUDY ADDS

⇒ In this secondary analysis of the PRESTO data, MACS-ECG had a relatively low c-index and showed very low sensitivity at both the pre-determined and optimum cut-off in the prehospital environment.
⇒ Paramedic ECG interpretation had superior sensitivity but lower specificity.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Future research should focus on using different methods to extract digital ECG data and derive prediction models that can detect NSTEMI, for example, by using deep learning with a large dataset. Focusing on paramedic training and other diagnostic information, such as point of care troponin testing, may have a greater yield.

BACKGROUND

Chest pain is one of the most common reasons for an emergency ambulance to be requested.[1 2] A diagnosis of acute myocardial infarction (AMI) is often suspected from the clinical history. In such cases, the ECG is the first-line investigation and should be recorded in the pre-hospital environment.[3] This will identify an ST elevation myocardial infarction (STEMI), which is indicative of acute coronary occlusion, in some patients. Patients with STEMI require immediate revascularisation and should be transported to a heart attack centre.

All other patients with suspected AMI (non-ST elevation AMI (NSTEMI)) will require transport to hospital for further diagnostic tests. However, only a minority of these patients have NSTEMI.[4] Most patients do not require inpatient treatment. There

is, therefore, great potential to reduce unnecessary transport to hospital by improving pre-hospital diagnostics for NSTEMI.

In hospital emergency departments (EDs), decision aids such as the HEART (History, ECG, Age, Risk factors, Troponin) score or Troponin-only Manchester Acute Coronary Syndromes (T-MACS) are widely used to rapidly identify patients in whom the diagnosis of NSTEMI can be safely 'ruled out'.[5 6] There has been growing interest in deploying such decision aids in the pre-hospital environment. One barrier to implementation is the requirement for paramedics to interpret ECGs for signs of acute ischaemia (other than STEMI). This is not currently a routine element of clinical practice for paramedics.

The Manchester Acute Coronary Syndromes ECG (MACS-ECG) prediction model was recently derived and externally validated within an in-hospital setting (table 1).[7] MACS-ECG uses objective ECG measurements to calculate a score, which can be used to determine the probability of NSTEMI. At a cut-off of 27.4% calculated probability, MACS-ECG had a specificity of 95.2% and a sensitivity of 23.5% for NSTEMI when externally validated.[7] This is similar to the accuracy obtained with subjective ECG interpretation by emergency physicians. For example, in a validation study of the HEART score, we calculated that the sensitivity of significant ST depression (as interpreted by the treating emergency physician) was 20.0% for acute coronary syndrome (ACS), whereas the specificity was 97.2%.[8] However, the predictive accuracy of this model within a pre-hospital setting is unknown.

MACS-ECG may have particular advantages in the pre-hospital setting. Paramedics are generally trained to recognise STEMI but are not routinely trained to detect ECG signs of NSTEMI. Avoiding the need for subjective interpretation could therefore facilitate pre-hospital diagnostics, for example, alongside point of care troponin testing or by identifying high-risk patients who may benefit from immediate transport to a heart attack centre, bypassing local hospitals. This would reduce the need for secondary ambulance transfer for patients requiring coronary intervention, an approach that has been shown to reduce time to angiography.[9 10] At present, calculating the output of the MACS-ECG model requires manual measurements (of T wave height and ST depression). However, if shown to be sufficiently accurate for clinical use, it could be incorporated in ECG software applications to produce automated interpretation for possible NSTEMI.

Therefore, we aimed to evaluate the diagnostic accuracy of the MACS-ECG prediction model in the pre-hospital environment. Next, we aimed to compare the accuracy of the MACS-ECG prediction model to that of paramedic ECG interpretation.

METHODS

Study design and setting

This is a secondary analysis of the Pre-hospital Evaluation of Sensitive Troponin (PRESTO) study data.[11] The PRESTO study was a multi-centre prospective diagnostic test accuracy study taking place at 12 hospitals and 4 NHS ambulance trusts in the UK (listed in the online supplemental appendix 1) and funded by the National Institute for Health and Care Research for Patient Benefit scheme. Its primary objective was to evaluate the diagnostic accuracy of decision aids (T-MACS and the HEART score) used with point of care cardiac troponin assays for identifying AMI in the pre-hospital setting. Data were collected between 26 February 2019 and 23 March 2020. The study received ethical approval from the East of Scotland Research Ethics Service (reference 18/ES/0101) and was prospectively registered at clinicaltrials.gov (reference NCT03561051).

Table 1 Variables included in the MACS-ECG model

Variables	Coefficient
T wave height in V1 if above 0.2 mV	0.001200244
Wellens type A	1.28139031
Mean ST depression in leads 2 and 3	0.026625591
Mean ST depression in leads V2 and V3	0.007130889
Mean ST depression in leads V5 and V6	0.01802942
Constant	−2.248037534

Participants

We included adult patients aged >18 years who received an emergency ambulance response for a primary complaint of chest pain in whom participating paramedics suspected the diagnosis of an ACS. We excluded participants who had STEMI on the pre-hospital ECG, those who had no pre-hospital ECG available for analysis and participants who had an uninterpretable ECG. All participants provided initial verbal consent in the pre-hospital environment. Full written informed consent was then sought in hospital or once the patient had been discharged home. We excluded participants who declined to provide written informed consent and those who could not be contacted to obtain written consent.

Paramedics who participated in screening and data collection during the PRESTO study were provided with bespoke training. This included training in the fundamentals of Good Clinical Practice, study protocol training and training in the interpretation of ECGs for signs of acute ischaemia. Training was made available in both face-to-face and online formats.

Data collection

Paramedics recorded ECGs as part of the routine clinical care they provided for patients with suspected ACS, prior to transporting patients to hospital. The ECGs were then uploaded to the electronic case report form environment (Castor EDC). Paramedics interpreted the ECGs during the pre-hospital phase of patient care. They were asked to interpret each ECG as 'normal' or 'abnormal' and to specifically note the presence or absence of left bundle branch block (LBBB), abnormal T wave inversion and ST depression. At the time of interpretation, paramedics were blinded to all biomarker results (all troponin testing, including point of care troponin testing, was undertaken in the hospital) and, because of the timing of interpretation, to patient outcome.

ECG data for calculation of the output of the MACS-ECG model were extracted using a bespoke digital calliper.[12] EP Calipers is a computer programme designed to measure electronic ECG for heart rate, voltage and ECG changes in millimetres.[12] The software is not automated. Researchers must select two points on the ECG (a reference point and the point of interest) and the software will measure the distance between those. First, measurements were calibrated against the original ECG calibration waveform. Second, measurements were taken to the nearest 0.5 mm using digital callipers. The primary researcher extracted ECG data. A sample of approximately 15% of all ECGs, including all ECGs with imperfect resolution, were also checked by a second investigator. Any discrepancies were resolved by discussion. All participants with ECGs that had insufficient quality to allow clear measurement of the required parameters were excluded from this analysis.

Researchers measured all ECG parameters required for calculation of the MACS-ECG prediction model output including the height of the T wave in V1, the presence or absence of Wellen's syndrome type A, the mean ST depression in leads II and III, the mean ST depression in leads V2 and V3 and the mean ST depression in leads V5 and V6. In accordance with the original study, ST depression was measured 80 ms after the J point.

Using a bespoke case report form, participating paramedics also collected data on patient demographics, the time and date of the ambulance response, past medical history and physical observations.

Outcomes

The primary outcome (or target condition) was a diagnosis of type 1 AMI. The diagnosis of AMI was adjudicated by two investigators acting independently (EC and JC). AMI was adjudicated in accordance with the fourth universal definition of myocardial infarction, which requires a rise and/or fall of cardiac troponin with at least one concentration above the 99th percentile upper reference limit, combined with at least one of the following: symptoms of myocardial ischaemia, new ischaemic echocardiogram changes, pathological Q wave or ECG changes.[13] All patients were transported to hospital and underwent laboratory troponin testing in accordance with contemporary national and/or international guidance, which formed the reference standard investigations for AMI.

Secondary outcomes included major adverse cardiac events (MACEs). MACE was defined as the occurrence of death (all cause), coronary revascularisation or incident AMI within 30 days.

Sample size

The sample size for the PRESTO study was calculated assuming that the prevalence of the primary outcome would be approximately 10%, assuming that the index test evaluated had a specificity of approximately 45% and assuming that the index test would achieve 100% sensitivity. We also accounted for 5%–10% of patients having missing data. This would require a total sample size of 700 participants. This sample size calculation applied to the primary analyses for the PRESTO study. As this is a secondary analysis of data from PRESTO, no formal sample size calculation was performed for this work.

Statistical methods

Continuous data were summarised using mean and SD, while categorical variables were summarised using frequencies and percentages. We summarised the data both as a whole cohort and across subgroups of those who did and did not have the primary outcome.

Predictive performance of the model was quantified using calibration (agreement between the observed and expected event proportions) and discrimination (ability of the model to differentiate those who had the event from those who did not). For calibration, we produced calibration plots. For discrimination, we constructed a receiver operating characteristic (ROC) curve, with this summarised using the C-index was calculated with 95% CIs (where a C-index of 0.5 indicates discrimination no better than change, and values closer to 1 being better discrimination). Additionally, we calculated test characteristics (sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)) with respective 95% CIs using the cut-off defined in the original derivation study for MACS-ECG (27.44% probability). In an exploratory analysis, we also proceeded to calculate test characteristics at the cut-off with maximum sensitivity for AMI. Finally, we calculated the sensitivity, specificity, PPV and NPV of paramedic ECG interpretation (normal vs abnormal ECG) for type 1 AMI.

Statistical analyses were undertaken using SPSS, V.27.0 (SPSS) except for calculation of sensitivity, and specificity, for which we used MedCalc software online.[14]

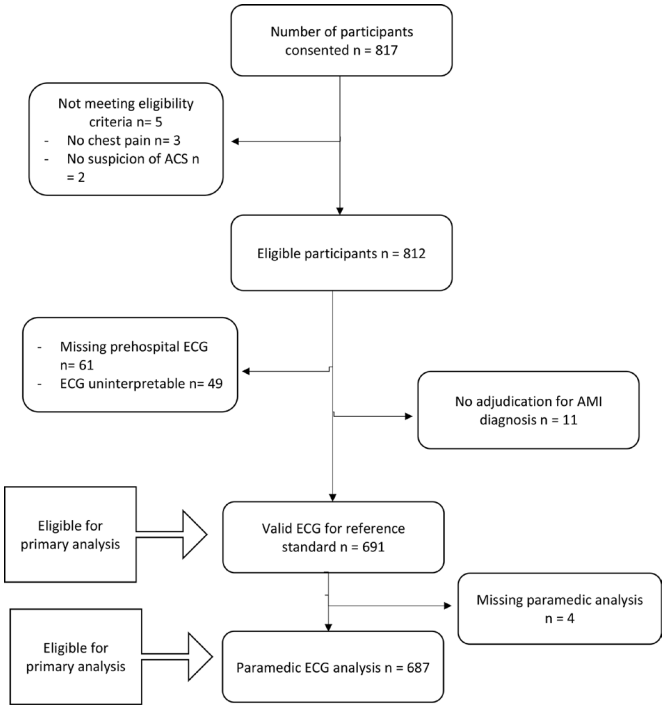

Figure 1 Flow diagram of patient's inclusion. ACS, acute coronary syndrome; AMI, acute myocardial infarction.

RESULTS

A total of 817 patients were included in the original PRESTO study, of which 691 were eligible for inclusion in the primary analysis of validating MACS-ECG for type 1 AMI prediction and 687 were eligible in the analysis of paramedic's ECG analysis accuracy for type 1 AMI prediction (figure 1). Baseline characteristics of the included participants are reported in table 2. Among the 691 participants, 87 (12.6%) patients had an adjudicated diagnosis of type 1 AMI.

Using the originally derived cut-off (27.4% calculated probability of NSTEMI), MACS-ECG had a C-index of 0.68 (95% CI: 0.61 to 0.75). The diagnostic performance for prevalent AMI is summarised in tables 3 and 4. The model had low sensitivity of 2.3% (95% CI: 0.3% to 8.1%) and high specificity 99.5% (95% CI: 98.6% to 99.9%). In an exploratory analysis, we identified that the ROC-optimised cut-off to maximise the sensitivity of MACS-ECG was at a probability of 9.56% for NSTSEMI. The test characteristics at that optimised cut-off are shown in table 4. The optimised model showed a sensitivity of 50.6% (95% CI: 39.6% to 61.5%) and specificity of 83.1% (95% CI: 79.9% to 86.0%).

By categorising pre-hospital ECGs as 'normal' or 'abnormal', paramedic ECG interpretation had a sensitivity of 71.3% (95% CI: 60.7% to 80.5%) and specificity of 53.8% (95% CI: 53.8% to 61.8%). The diagnostic performance of paramedic ECG analysis is summarised in tables 5 and 6.

Table 2 Summary of baseline characteristics

	All n (%) 691	Had AMI n (%) 87 (12.6)	Did not have AMI n (%) 604 (87.4)	Missing n (%)
Age, mean (SD)	63.68 (15.3)	68.11 (13.8)	63.04 (15.4)	0
Male sex, n (%)	398 (57.6)	59 (67.8)	339 (56.1)	0
Female sex, n (%)	293 (42.4)	28 (32.3)	265 (43.9)	0
Hypertension, n (%)	360 (52.2)	56 (64.4)	304 (50.4)	1 (.1)
Hyperlipidaemia, n (%)	162 (23.5)	22 (25.3)	140 (23.2)	1 (.1)
Diabetes, n (%)	141 (20.4)	25 (28.7)	116 (19.2)	1 (.1)
Previous CVA or TIA, n (%)	64 (9.3)	13 (14.9)	51 (8.5)	2 (.3)
Peripheral vascular disease, n (%)	28 (4.1)	7 (8.0)	21 (3.5)	2 (.3)
Prior PCI or CABG, n (%)	163 (23.6)	34 (39.1)	129 (21.4)	1 (.1)
Previous AMI, n (%)	194 (28.1)	40 (46.0)	154 (25.5)	0 (.0)
Heart failure, n (%)	47 (6.8)	7 (8.0)	40 (6.7)	3(.4)
Pre-hospital ECG normal, n (%)*	372 (54.1)	25 (28.7)	347 (57.8)	4 (.6)
Pre-hospital ECG shows LBBB, n (%)*	23 (3.4)	5 (5.7)	18 (3.0)	10 (1.4)
Pre-hospital ECG shows ST depression, n (%)*	87 (12.8)	29 (33.3)	58 (9.8)	10 (1.4)
Pre-hospital ECG shows abnormal T inversion, n (%)*	102 (15)	24 (27.6)	78 (13.1)	10 (1.4)

*ECG interpretation by the treating paramedic.
AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CVA, cerebral vascular accident; LBBB, left bundle branch block; PCI, Percutaneous coronary intervention; TIA, transient ischaemic attack.

We further evaluated the accuracy of paramedic interpretation of specific ECG parameters (including ST elevation, ST depression, T wave inversion and LBBB). Those findings are reported in online supplemental appendix 2. In general, paramedics achieved high specificity when interpreting these parameters, with sensitivity varying between 10.3% (for ST elevation), 5.7% (for LBBB), 33.3% (for ST depression) and 40% (for T wave inversion).

A calibration plot for the MACS-ECG model is shown in online supplemental appendix 3. This demonstrates systematic underprediction of risk with a gradient of 0.0628 (whereas a perfectly calibrated model will have a gradient of 1) with an intercept of 0.0852. Only six probability deciles could be created for the calibration plot because over 80% of participants had no abnormalities on ECG and thus had the same expected probability of AMI.

DISCUSSION

In this paper, we have evaluated the validity of the MACS-ECG model for pre-hospital detection of NSTEMI in chest pain patients with suspected ACS. The MACS-ECG model showed very low sensitivity and had a relatively low C-index. Even identifying the cut-off for predicted probability (calculated by MACS-ECG) that had maximum sensitivity would not yield a satisfactory balance between sensitivity and specificity to inform clinical decision making. However, paramedic ECG interpretation had superior sensitivity in this study. Specificity was lower, though this may reflect the nature of the question ('normal' vs 'abnormal' ECG). Of the two approaches, it appears that paramedic interpretation of an ECG as 'abnormal' is more likely to add clinical value given the extremely low sensitivity of the MACS-ECG model.

The MACS-ECG model showed higher sensitivity during the initial derivation study than in this external validation study, reflecting that this study focused on the performance within a pre-hospital setting. In the derivation, the model had a sensitivity of 25.6% and specificity of 96.3%.[7] It is unclear why there was such a discrepancy in sensitivity between studies, though there are many differences between hospital and pre-hospital environments. Pre-hospital ECGs may, for example, have been more subject to movement artefact or the precision of the ECG machines could be different.

The optimal sensitivity, specificity, PPV and NPV for an ECG prediction model are hard to specify and will depend on how the ECG interpretation is to be used. It is unlikely that the ECG alone could ever be used to rule out AMI and accounting for other information, such as cardiac troponin concentrations, is likely to be important. In this study, we hoped to show that MACS-ECG would be at least no worse than paramedic ECG interpretation. Had that been proven, it may have been possible to replace the need for subjective interpretation (and with it the ongoing training requirements) with an automated calculation. However, our findings clearly suggest that paramedic ECG

Table 3 Proportion of patients with AMI in validation of the MACS-ECG

Total : 691	AMI	No AMI
Prediction model positive	2	3
Prediction model negative	85	601

AMI, acute myocardial infraction; MACS-ECG, Manchester Acute Coronary Syndromes ECG.

Table 4 Diagnostic performance of MACS-ECG

Original cut-off	Original cut-off	Optimised cut-off
Sensitivity (95% CI)	2.3% (0.28% to 8.06%)	50.57% (39.6% to 61.5%)
Specificity (95% CI)	99.5% (98.6% to 99.9%)	83.11% (79.9% to 86.0%)
NPV (95% CI)	87.6% (87.3% to 88.0%)	92.1% (90.4% to 93.5%)
PPV (95% CI)	40.0% (10.2% to 79.7%)	30.1% (24.7% to 36.2%)

Original cut-off: predicted probability for NSTEMI of 27.4%.
Optimised cut-off: predicted probability for NSTEMI of 9.56% AMI.
AMI, acute myocardial infraction; MACS-ECG, Manchester Acute Coronary Syndromes ECG; NPV, negative predictive value; NSTEMI, non-ST elevation myocardial infarction; PPV, positive predictive value.

Table 5 2×2 table for the diagnostic accuracy of paramedic ECG interpretation ('normal' vs 'abnormal') for NSTEMI

Total : 687	AMI	No AMI
Abnormal ECG	62	253
Normal ECG	25	347

AMI, acute myocardial infraction; NSTEMI, non-ST elevation myocardial infarction.

interpretation is superior to use of the MACS-ECG model in the pre-hospital environment.

Focusing future efforts on enhancing paramedic training may add greater value than continued attempts to implement automated systems for interpretation. A Canadian study investigated the sensitivity of paramedics detecting STEMI in pre-hospital environment before and after taking an ECG interpretation course.[15] Prior to the additional training, paramedics had a sensitivity of 78%. This increased to 99% with a specificity of 68% after 21 hours of training.[15] Another study investigated the feasibility of improving NSTEMI identification in the pre-hospital environment by sending electronic copies of ECGs from paramedics to cardiologists; this demonstrated a 32% (95% CI: 14% to 55%) sensitivity for the NSTEMI cases that were identified by the cardiologist and patients were transferred directly to PCI.[16] Taken in conjunction with our findings, these data suggest that pre-hospital ECG diagnosis of NSTEMI is likely to be challenged by low sensitivity, regardless of how the ECG is interpreted.

Strengths and limitations

We collected data prospectively and included a comparison with paramedic interpretation. In this study, patients were subjected to robust reference standard testing for AMI in hospital. Our study does have some limitations; for example, this is a substudy nested within PRESTO, meaning that our sample size was calculated for the primary objective of the main study and not specifically for this analysis. It is also possible that paramedics who recruited to the study were more confident in ECG interpretation than paramedics who did not enrol patients. Finally, because of the challenges of working in the pre-hospital environment with unstable patients, clinical urgency and variable environmental conditions, 49 ECGs were excluded from our analysis due to poor recording quality or unsatisfactory resolution. This may reflect differences in the hardware available for recording ECGs, movement artefact or artefact introduced when uploading ECGs to the electronic case report form. Unfortunately, it is an unavoidable limitation of research in this environment and therefore our study likely represents the best possible evaluation of the MACS-ECG prediction model in real-world pre-hospital practice.

Table 6 Test characteristics showing the diagnostic accuracy of paramedic ECG interpretation ('normal' vs 'abnormal') for NSTEMI

	AMI
Sensitivity (95% CI)	71.3% (60.6% to 80.5%)
Specificity (95% CI)	57.8% (53.8% to 61.8%)
NPV (95% CI)	93.3% (90.8% to 95.1%)
PPV (95% CI)	19.7% (17.2% to 22.4%)

AMI, acute myocardial infraction; NPV, negative predictive value; NSTEMI, non-ST elevation myocardial infarction; PPV, positive predictive value.

Future research

If we had demonstrated that MACS-ECG had similar or better diagnostic accuracy to subjective interpretation by paramedics, then we could have incorporated it within decision aids (eg, T-MACS or the HEART score) to provide an objective method to extract diagnostic information from the ECG. Evaluating the accuracy of T-MACS and the HEART score incorporating the output of MACS-ECG in the place of subjective ECG interpretation may be a valuable goal for future work. However, with such low sensitivity it seems unlikely that MACS-ECG could be used in that manner.

It may therefore be wise for future research to focus on refining the MACS-ECG model or using different methods to derive prediction models that can detect NSTEMI, for example, by using more granular digital data extracted from ECG images and applying techniques such as deep learning with large datasets. Also, previous research has shown that paramedics are able to improve their identification of STEMI after several hours of additional training[15]; therefore, future work should evaluate if the same is true for identification of NSTEMI.

CONCLUSION

We found that the MACS-ECG prediction model has very low sensitivity and high specificity for identifying NSTEMI in the pre-hospital environment. Subjective ECG interpretation by paramedics had higher sensitivity but lower specificity. Neither approach had a sufficiently high PPV or NPV to 'rule in' or 'rule out' NSTEMI alone. Future work should evaluate their value alongside other information, for example, as part of a validated decision aid.

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Contributors AAlotaibi collected and analysed the data and wrote the study protocol and manuscript. RB contributed to study protocol planning, monitoring data and revising manuscript. GPM designed the study protocol, reviewed the study protocol and the manuscript. AAlghamdi, ECarlton, JGC, ECook, ANS, JP, AT, SB, KLK, AR and EP part of PRESTO team which helped in collecting primary data and reviewing the manuscript. AA is the gurnatour.The study team approved the final version of the manuscript.

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PRe-hospital Evaluation of Sensitive TrOponin (PRESTO) Study: multicentre prospective diagnostic accuracy study protocol

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ABSTRACT

Introduction Within the UK, chest pain is one of the most common reasons for emergency (999) ambulance calls and the most common reason for emergency hospital admission. Diagnosing acute coronary syndromes (ACS) in a patient with chest pain in the prehospital setting by a paramedic is challenging. The Troponin-only Manchester Acute Coronary Syndromes (T-MACS) decision rule is a validated tool used in the emergency department (ED) to stratify patients with suspected ACS following a single blood test.

We are seeking to evaluate the diagnostic accuracy of the T-MACS decision aid algorithm to 'rule out' ACS when used in the prehospital environment with point-of-care troponin assays. If successful, this could allow paramedics to immediately rule out ACS for patients in the 'very low risk' group and avoid the need for transport to the ED, while also risk stratifying other patients using a single blood sample taken in the prehospital setting.

Methods and analysis We will recruit patients who call emergency (999) ambulance services where the responding paramedic suspects cardiac chest pain. The data required to apply T-MACS will be prospectively recorded by paramedics who are responding to each patient. Paramedics will be required to draw a venous blood sample at the time of arrival to the patient. Blood samples will later be tested in batches for cardiac troponin, using commercially available troponin assays. The primary outcome will be a diagnosis of acute myocardial infarction, established at the time of initial hospital admission. The secondary outcomes will include any major adverse cardiac events within 30 days of enrolment.

Ethics and dissemination The study obtained approval from the National Research Ethics Service (reference: 18/ES/0101) and the Health Research Authority. We will publish our findings in a high impact general medical journal.

Trial registration number Registration number: ClinicalTrials.gov, study ID: NCT03561051

Strengths and limitations of this study

- Prehospital Evaluation of Sensitive Troponin is a multicentre prospective observational diagnostic accuracy study recruiting patients from four ambulance services in the UK, so we anticipate that our result truly reflects UK practice.
- The future clinical use of Troponin-only Manchester Acute Coronary Syndromes in the prehospital setting will be limited due to the observational study design pending a definitive randomised controlled trial.
- The study captures a large amount of data which allow the study team to evaluate different emergency department strategies used to risk stratify patients with chest pain in the prehospital setting.
- The study evaluates three different point-of-care troponin assays in conjunction with multiple validated decision aids.

INTRODUCTION

Chest pain is one of the most common reason for emergency hospital admission. Clinicians will suspect a diagnosis of acute coronary syndromes (ACS) in approximately half of the patients presenting to emergency departments (EDs) with chest pain, accounting for the majority of these admissions. However, less than 20% of those admitted to hospital on the suspicion of ACS actually have that diagnosis. Most of these admissions could be avoided with improved diagnostic technology.[1–3]

In recent years, there has been much work performed in the ED setting with the aim of rapidly risk-stratifying patients with cardiac chest pain with a view to early discharge of those who are at low risk. The Troponin-only Manchester Acute Coronary Syndromes (T-MACS) is a scientifically derived mathematical model that combines clinical and historical features with ECG and cardiac biomarker results to determine the probability of ACS and assign patients to one of four risk groups: very low risk (<2% probability), low risk

(2%–5% probability), moderate risk (5%–95% probability) and high risk (probability ≥95%).

T-MACS has been shown to effectively reduce unnecessary hospital admissions when used in the ED.[4] It identifies 45% of patients as eligible for safe, immediate discharge following a single blood test.[4 5] This is demonstrably superior to other early rule-out strategies, including that recommended by National Institute for Health and Care Excellence (NICE) prior to publication of our findings. In addition to 'ruling out' a diagnosis of ACS and reducing the need for unnecessary investigations and hospital admission, T-MACS can also 'rule in' the diagnosis in approximately 5% of patients with 95% positive predictive value, facilitating early specialist treatment.[4–7]

The original T-MACS model relies on laboratory-based troponin testing. In the multicentre Bedside Evaluation of Sensitive Troponin (BEST) study, we have evaluated the accuracy of T-MACS with point-of-care (POC) troponin assays that use portable/handheld analysers, which could be used in ambulances. Results from the BEST study demonstrate that, with a contemporary POC test, T-MACS 'ruled out' ACS in 42.7% of patients with 95.5% sensitivity and 98.7% negative predictive value.[5]

Using portable POC tests, T-MACS could remove the requirement for many patients with suspected ACS to be assessed in the hospital, enabling even earlier reassurance for patients and cost savings for the National Health Service (NHS). Given the high prevalence of chest pain, avoiding ED attendances will reduce crowding, which leads to more patient safety incidents and higher mortality. Similarly, avoiding unnecessary transfer to hospital will free up ambulances to answer other emergency calls. However, as blood tests will be taken sooner after symptom onset, it is not safe to assume that T-MACS will be accurate in the prehospital environment. We must formally evaluate its accuracy in that setting.

Aims and objectives

The primary objective of Pre-hospital Evaluation of Sensitive Troponin is to evaluate whether paramedics can use troponin testing by a handheld device with a computerised algorithm at the time of arrival to patients with symptoms that cause the treating paramedic to suspect the diagnosis of ACS. This would avoid unnecessary transfer and enable accurate identification of: (1) patients who do not have acute myocardial infarction (AMI) and therefore do not need to be taken to hospital; and (2) patients who do have AMI and therefore need to be given early treatment in the prehospital environment for their condition. Secondary objectives include validating the T-MACS decision aid that could be used to enhance the early diagnosis of AMI.

METHODS AND ANALYSIS

Design and setting

We will undertake a multicentre, prospective diagnostic accuracy study involving ambulance services and EDs in the UK. We started participants recruitment on February 2019 and we will complete recruitment within 12 months.

Within each ambulance service, research activity will be focused at ambulance stations or hubs with (1) a track record for successful delivery of similar research; and (2) which feed into hospitals with (a) adequate central laboratory support for sample processing and storage, and (b) clinical protocols that adhere to national and international standards for the investigation of patients with suspected ACS.

Data collection

Prehospital environment

Paramedics will record basic clinical data using a brief case report form at the time of inclusion. The data collected will be sufficient to enable calculation of the T-MACS decision aid outcome, including the treating paramedic's interpretation of the patient's 12-lead ECG. However, in this observational study, the T-MACS rule outcome will not be known to paramedics.

Paramedics will receive bespoke study training before signing the signature log. After participating paramedics have provided any necessary urgent treatment and obtained verbal consent, they will undertake venepuncture prior to transferring the patient. If paramedics are inserting an intravenous cannula, blood will be drawn at the same time. Less than 5 mL venous blood will be drawn and stored in a lithium heparin bottle labelled with a unique study identifier. The date and time of venepuncture will be logged on the case report form and on the blood bottle. All patients will then be transferred to hospital in accordance with routine care.

Hospital environment

On arrival at the hospital, all patients will undergo reference standard troponin testing in accordance with contemporary national and international guidance. Acceptable protocols for reference standard troponin testing include:

- If a contemporary (not high sensitivity) troponin assay is used: laboratory-based troponin testing on arrival and either 6 hours after arrival, or 10–12 hours after the onset of peak symptoms.
- If a high sensitivity troponin assay is used: laboratory-based troponin testing on arrival and either 3 hours after arrival, or 6 hours after the onset of peak symptoms, unless the patient has undergone investigation according to a validated rule-out protocol as advocated in national international guidelines.

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

When the patient arrives at the ED, the local study team will be informed. A member of the study team will either send the lithium heparin sample drawn in the prehospital environment up to the central laboratory for processing and storage, or the sample will be processed and stored

by a member of the study team who has had appropriate training. Once the patient has received all initial treatment in accordance with routine care, a member of the local research team will then approach them to answer any questions they may have about the study and obtain written informed consent.

If the research team cannot obtain written informed consent at the time of participant admission to the ED, the research paramedic will follow this up and obtain written informed consent via post, electronically or over the phone. The research paramedic will have 4 weeks to obtain written informed consent before the participant is withdrawn from the study and their samples destroyed. The participant will be made aware of this deadline in the information that is sent to them before they are approached for consent. If the participant is followed up via postal consent, a 1-week grace period will be given to allow for delays in the postal service. After this, the participant will be withdrawn from the study and their study data and samples will be destroyed.

One hour (±30 min) after the prehospital blood has been taken; a member of the research team will draw another sample of venous blood (<5 mL) into the provided lithium heparin bottle labelled with the participant's unique study identifier. The date and time the blood was drawn will be logged on the case report form and on the blood bottle. This venous blood sample will be sent up to the central labs for processing and storage or will be processed and stored by the local research team.

Follow-up

Patients will be followed up by reviewing clinical records relating to their inpatient course, including data from serial troponin testing; other laboratory analyses; length of stay; all imaging investigations and procedures and details of any haemorrhagic complications. We will also contact the participant's primary care practitioner after 60 days to obtain information about any additional relevant events occurring within 30 days of the initial ambulance call. In the small percentage of cases where participants do not have a primary care practitioner, we will contact participants directly after 30 days. If this is not possible and the participant is lost to follow up, then this will be recorded on the electronic case report form.

Resource use

We will collect comprehensive data about secondary healthcare resource use at baseline and 30 days, which may be used to subsequently develop a cost-effectiveness model. Total direct healthcare costs will be identified and quantified according to the UK NHS perspective relevant to decision-makers within the NHS.[8] At baseline, data will be collected with regards to the initial ambulance call, such as the date and time of the call, the time of ambulance dispatch to the patient, the time of arrival to the patient and whether a rapid response unit was dispatched. Resource-use data collected at 30 days will include: time (hours) and length (days) of hospital stay (total; on coronary care, high dependence and intensive care units); laboratory, radiological and cardiological investigations during the initial hospital stay; nature and duration of any procedures or cardiac surgery; management of haemorrhagic complications; details of admissions and further ED attendances. Data on resource use will be collected using structured data collection forms from patient medical records and supplemented by information obtained from the patient's primary care practitioner at follow-up.

Sample processing

On arrival at the destination hospital, the labelled whole blood sample that was drawn in the prehospital environment for research will either be sent to the hospital laboratory for processing and storage along with study-specific instructions, or this will be carried out by members of the local research team. The local laboratory personnel/research team members will test the whole blood for POC troponin using the Roche cobas h 232 TnT and the leftover will be centrifuged to separate out the plasma. The plasma will then be stored in separate aliquots and transferred to the freezer within 8 hours of collection, pending subsequent analysis in batches. The relevant manufacturers of commercially available assays have verified sample stability under these conditions.

The laboratory/research team will process a second lithium heparin sample, drawn by the research nurse, 1 hour (±30 min) after the initial prehospital blood draw. For this sample, the local laboratory personnel/research team will centrifuge the blood sample and the plasma will then be divided into separate aliquots. This will then be stored in the freezer within 8 hours of collection. As above, samples will be stored pending subsequent analysis in batches.

Plasma will later be analysed for POC troponin assays, as follows: Abbott i-Stat troponin I and LumiraDx troponin I by the central study team. Leftover plasma will continue to be stored at the central study site to permit evaluation of additional, new POC troponin assays when developed.

Participant selection

We will prospectively approach patients who have called for an emergency (999) ambulance with symptoms that the attending paramedic suspects may have been caused by an ACS.

Inclusion criteria

- Adult patients (>18 years).
- Called 999 for an emergency ambulance because they have experienced pain, discomfort or pressure in the:
  - Chest.
  - Epigastrium.
  - Neck.
  - Jaw.
  - Upper limb without an apparent non-cardiac source (compatible with the American Heart Association case definitions).[9]

- Attending paramedic suspects these symptoms may be caused by ACS.

Exclusion criteria

- Patients with unequivocal evidence of ST-elevation myocardial infarction who are being immediately transferred for primary percutaneous coronary intervention.
- Patients in whom an alternative diagnosis (other than ACS) is suspected, which would necessitate transfer to hospital.
- Patients who have not experienced symptoms in the previous 24 hours.

Patients who are unable to provide written informed consent, either because they lack the mental capacity to provide written informed consent or because effective communication is not possible (eg, non-English speakers in the absence of adequate translation services).

Sample size

The specificity of T-MACS is approximately 45%[10] and the prevalence of the primary outcome in this cohort will be approximately 10%. Assuming that we identify an algorithm with 100% sensitivity and negative predictive value, 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 (~5%–10% based on experience in previous similar studies), we plan to include a total of 700 participants.

Participant withdrawal

If the participant gives verbal consent for the paramedic to proceed with the blood sample, but loses capacity before the blood is drawn, the participant will be withdrawn from the study. All data and samples collected up to this point will be destroyed as we will be unable to obtain written informed consent. In the event that written informed consent cannot be obtained from the participant for any other reason, the participant will be withdrawn from the study. As above, all data and samples collected up to this point will be destroyed.

In the event that a patient who has given written informed consent loses capacity before the 30-day follow-up, the participant will be withdrawn from the study. Any identifiable data or tissue collected up to this point would be retained and used in the study as written consent had been given. The participant would not be followed up at 30 days.

If at any time, the study team believes that remaining on the study is not in the participant's best interest, they will approach the participant directly to discuss withdrawal from the study. However, if their withdrawal is recommended from their primary caregiver or a relative due to psychological distress or a similar reason, the study team will not seek to contact the participant any further and they will be withdrawn from the study. Any identifiable data or tissue collected up to this point would be retained and used in the study as consent had been given.

Outcomes

The primary outcome will be a diagnosis of AMI, established at the time of initial hospital admission. To diagnose AMI according to internationally accepted standards requires serial troponin sampling. This will help to ensure adequate reference standards for the diagnosis of AMI. Outcomes will be adjudicated by two independent investigators with reference to relevant clinical information but blinded to the results of research investigations. Discrepancies will be resolved by a third independent investigator. AMI will be defined according to the Fourth Universal Definition.[11] By virtue of the inclusion criteria, all patients will have symptoms and signs consistent with myocardial ischaemia. Briefly, therefore, patients will be deemed to have met this outcome if they develop a rise and/or fall of troponin to above the 99th percentile.

The secondary outcomes will include any major adverse cardiac events, which include cardiovascular death, coronary revascularisation and incident AMI within 30 days. All causes of death occurring within 30 days and the final diagnoses of all patients will also be recorded.

Statistical analysis

Primary analysis

We will determine the output of the T-MACS decision aid using the original, predetermined algorithm. This algorithm computes the probability that each patient has a diagnosis of ACS and stratifies patients into four groups on the basis of that probability, as follows: very low risk (<2% probability)—ACS can be considered ruled out. We hope our findings will justify avoiding transport to hospital in this group; low risk (2%–5% probability): this group requires serial troponin sampling, which could be taken in an ambulatory care setting; moderate risk (5%–95% probability): this group requires serial troponin sampling but may also require additional imaging and therefore requires transfer to hospital; high risk (≥95% probability): ACS is 'ruled in' for this group, which could facilitate direct transfer to a specialist centre, facilitating early coronary intervention.

We will calculate the diagnostic accuracy of T-MACS as a 'rule-out' tool by dichotomising the probability at a threshold of 2%. We will then calculate sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios and their respective 95% CIs. We will also report the number and percentage of patients with ACS stratified by T-MACS risk group. The proportion of transfers to the ED that could have been avoided will be calculated.

Secondary analyses

We are planning to conduct several secondary analyses. First, we will evaluate the diagnostic accuracy of T-MACS as a 'rule-in' tool, which would facilitate direct transfer to tertiary care heart attack centres and may enable patients to benefit from earlier specialist treatment such as

percutaneous coronary intervention in future. To do this, we will dichotomise T-MACS at the probability threshold of 95% (ie, analysing classification as 'high risk' vs all other risk groups). We will again calculate sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios and their respective 95% CIs. Finally, we will calculate the proportion of patients with and without ACS who would have been transported to tertiary care facilities if T-MACS had been used in practice, and we will compare those findings to the observed practice in routine care. As some patients may have final diagnoses other than ACS, we will also retrieve the final coded diagnosis for all patients and present a descriptive analysis stratified by T-MACS risk group.

Second, we will evaluate the diagnostic accuracy of other hospital-based strategies used to rule-out, rule-in or 'risk-stratify' patients with AMI or ACS such as the HEART (History, ECG, Age, Risk factors, Troponin) score, History and ECG only Manchester Acute Coronary Syndromes (HE-MACS) decision aid, limit of detection strategy and selected cut-offs (eg, the 99th percentile of a reference population).

Economic analyses

Total direct healthcare costs (resource use × unit costs data) will be calculated using a microcosting study run by our team (ISRCTN 86818215) and will compare the novel diagnostic pathway versus estimates for current care.[12] Where appropriate, we will proceed to formal cost-effectiveness analysis using a de novo decision-analytic model populated with data collected during this study and other externally published data. The model would extrapolate the effects of implementing the novel diagnostic pathway derived in this work on healthcare resource use and health status (quality adjusted life years as informed by the EQ-5D) versus current diagnostic and treatment pathways. Economic analyses will be led by AT.

Patient and public involvement

To maximise the potential for clinical impact, this study has been designed in collaboration/consultation with a rounded group of stakeholders including patient and public representatives (eg, the Withington Heart Help Group and the Ticker Club) and industry (we have consulted with numerous manufacturers to confirm that work in this area is currently a high priority). Manchester University NHS Foundation Trust sponsors the study. Our consent procedure has been informed by prior experience within our national network of ambulance services, initial feedback from patient and public representatives (who have agreed with concern that judgement may be clouded in this acute situation) and the experience of AS in the Wellcome-funded 'Network Exploring Ethics in Ambulance Trials (NEAT)' project.[13]

DISSEMINATION

Following completion of our analysis, we will discuss the significance of our findings and the key messages to be communicated at meetings of the Trial Steering Committee, Trial Management Group and Patient Advisory Group. Following this, we will finalise our dissemination strategy. We will aim to publish our findings (positive or negative) in a high impact general medical journal with a relevant target audience (eg, British Medical Journal; The Lancet). In addition, we aim to present our findings to relevant target audiences at national and international conferences (eg, Royal College of Emergency Medicine Annual Scientific Conference; European Society of Cardiology Annual Conference).

If our findings are positive, we will also develop an implementation strategy. This will involve working with commissioning groups (including NHS England and the Greater Manchester Joint Commissioning Board), NICE and Ambulance NHS Trusts to make the case for the clinical and cost effectiveness of our technology. Template clinical guidelines and training guides will be disseminated to ambulance services, and we anticipate proceeding to support pilot evaluations with a view to larger scale clinical implementation within 2 years.

Finally, we will work with stakeholder organisations including the National Ambulance Research Steering Group (NARSG; AS is a member) and the International Federation of Clinical Chemistry Committee for Cardiac Biomarkers (RB is a member) to enhance communication of our findings within the field.

DISCUSSION

Based on our experience with previous studies, if our findings are positive we will aim to achieve clinical implementation within 2 years. Clearly, this will involve additional work to demonstrate the feasibility and acceptability of 'live application' of T-MACS in the ambulance; to develop new clinical guidelines and training regimes and to robustly communicate the clinical and cost effectiveness of the strategy.

The recent update to NICE Guideline CG95 incorporated a novel diagnostic strategy (originally developed by our group) for in-hospital use based on data from observational studies with a similar design. Given that precedent, we anticipate that our findings will generate the evidence required by NICE to issue a recommendation for the clinical use of T-MACS with a POC troponin assay in the prehospital environment.

We also implemented T-MACS in the hospital environment primarily based on observational data. The algorithm has been applied in 8000 patients and has led to 2/3 patients being safely treated in an ambulatory care environment without requiring hospital admission. Health Innovation Manchester, with access to a Joint Commissioning Board, has adopted T-MACS as an exemplar project for rapid implementation across Greater Manchester. We will conduct a 'phase 4 evaluation' of that regional implementation, aiming to achieve more widespread clinical implementation within 24 months of completion. If the findings of the proposed study are

positive, we will use a similar methodology to achieve rapid implementation in the prehospital environment.

If successfully implemented in practice, we anticipate that our findings will avoid the need for unnecessary ambulance transfers and hospital admission in approximately 40% of patients. As chest pain is the second most common reason for emergency ambulance calls and most common reason for emergency hospital admission, this is likely to have a substantial economic impact while reducing hospital overcrowding and its associated complications.

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Table 1: proportion of patients with AMI in paramedic ECG analysis for ST-Elevation

Total : 681	AMI	No AMI
ST-elevation	9	38
No ST-elevation	78	556
AMI: Acute Myocardial Infraction, ECG: Electrocardiogram		

Table 2: Diagnostic performance of paramedics ECG analysis for ST-elevation:

	AMI
Sensitivity (95% CI)	10.3% (4.8-18.7)
Specificity (95% CI)	93.6% (91.3-95.4)
NPV (95% CI)	87.7% (86.9-88.5)
PPV (95% CI)	19.1% (10.6-32.1)
AMI: Acute Myocardial Infraction, NPV: Negative Predictive Value, PPV: Positive Predictive Value.	

Table 3: proportion of patients with AMI in paramedic ECG analysis for Left Bundle Branch Block (LBBB)

Total : 681	AMI	No AMI
LBBB	5	18
No LBBB	82	576
AMI: Acute Myocardial Infraction, ECG: Electrocardiogram LBBB: Left Bundle Branch Block.		

Table 4: Diagnostic performance of paramedics ECG analysis for LBBB:

	AMI
Sensitivity (95% CI)	5.7% (1.9-12.9)
Specificity (95% CI)	97.0% (95.2-98.2)
NPV (95% CI)	87.5% (86.9-88.1)
PPV (95% CI)	21.7% (9.6-42.2)
AMI: Acute Myocardial Infraction, NPV: Negative Predictive Value, PPV: Positive Predictive Value.	

Table 5: proportion of patients with AMI in paramedic ECG analysis ST-depression

Total : 681	AMI	No AMI
ST-depression	29	58
No ST-depression	58	536
AMI: Acute Myocardial Infraction, ECG: Electrocardiogram		

Table 6: Diagnostic performance of paramedics ECG analysis for ST-depression:

	AMI
Sensitivity (95% CI)	33.3% (23.6-44.2)
Specificity (95% CI)	90.2% (87.6-92.5)
NPV (95% CI)	90.2% (88.8-91.5)
PPV (95% CI)	33.3% (25.4-42.3)
AMI: Acute Myocardial Infraction, NPV: Negative Predictive Value, PPV: Positive Predictive Value.	

Table 7: proportion of patients with AMI in paramedic ECG analysis for T wave inversion:

Total : 681	AMI	No AMI
T-wave inverted	42	78
No T-wave inversion	63	516
AMI: Acute Myocardial Infraction, ECG: Electrocardiogram		

Table 8: Diagnostic performance of paramedics ECG analysis for T-wave inversion:

	AMI
Sensitivity (95% CI)	40.0% (30.6-50)
Specificity (95% CI)	86.9% (83.9-89.5)
NPV (95% CI)	89.1% (87.5-90.6)
PPV (95% CI)	35.0% (28.3-42.4)
AMI: Acute Myocardial Infraction, NPV: Negative Predictive Value, PPV: Positive Predictive Value.	

Table 9: proportion of patients with AMI in paramedic ECG analysis for other abnormalities:

Total : 687	AMI	No AMI
Other abnormalities ECG	7	94
No other abnormalities	80	506
AMI: Acute Myocardial Infraction, ECG: Electrocardiogram		

Table 10: Diagnostic performance of paramedics ECG analysis for other abnormalities:

	AMI

Sensitivity (95% CI)	8.05% (3.3-15.9)
Specificity (95% CI)	84.3% (81.2-87.1)
NPV (95% CI)	86.3% (85.5-87.2)
PPV (95% CI)	6.9% (3.4-13.4)
AMI: Acute Myocardial Infraction, NPV: Negative Predictive Value, PPV: Positive Predictive Value.	

Calibration plot of MACS ECG validation