Performance of a prehospital HEART score in patients with possible myocardial infarction: a prospective evaluation

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Handling editor Edward Carlton

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/emermed-2022-213003).

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The preliminary results of the ACCESS study were presented at the Royal College of Emergency Medicine Annual Scientific Conference on 1–3 October 2019 in Gateshead, UK, and further results were presented virtually to the European Congress on Emergency Medicine on 19–22 September 2020.

Received 25 November 2022
Accepted 14 May 2023

To cite: Cooper JG, Ferguson J, Donaldson LA, *et al*. *Emerg Med J* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/emermed-2022-213003

ABSTRACT

Introduction The History, Electrocardiogram (ECG), Age, Risk Factors and Troponin (HEART) score is commonly used to risk stratify patients with possible myocardial infarction as low risk or high risk in the Emergency Department (ED). Whether the HEART score can be used by paramedics to guide care were high-sensitivity cardiac troponin testing available in a prehospital setting is uncertain.

Methods In a prespecified secondary analysis of a prospective cohort study where paramedics enrolled patients with suspected myocardial infarction, a paramedic Heart, ECG, Age, Risk Factors (HEAR) score was recorded contemporaneously, and a prehospital blood sample was obtained for subsequent cardiac troponin testing. HEART and modified HEART scores were derived using laboratory contemporary and high-sensitivity cardiac troponin I assays. HEART and modified HEART scores of ≤3 and ≥7 were applied to define low-risk and high-risk patients, and performance was evaluated for an outcome of major adverse cardiac events (MACEs) at 30 days.

Results Between November 2014 and April 2018, 1054 patients were recruited, of whom 960 (mean 64 (SD 15) years, 42% women) were eligible for analysis and 255 (26%) experienced a MACE at 30 days. A HEART score of ≤3 identified 279 (29%) as low risk with a negative predictive value of 93.5% (95% CI 90.0% to 95.9%) for the contemporary assay and 91.4% (95% CI 87.5% to 94.2%) for the high-sensitivity assay. A modified HEART score of ≤3 using the limit of detection of the high-sensitivity assay identified 194 (20%) patients as low risk with a negative predictive value of 95.9% (95% CI 92.1% to 97.9%). A HEART score of ≥7 using either assay gave a lower positive predictive value than using the upper reference limit of either cardiac troponin assay alone.

Conclusions A HEART score derived by paramedics in the prehospital setting, even when modified to harness the precision of a high-sensitivity assay, does not allow safe rule-out of myocardial infarction or enhanced rule-in compared with cardiac troponin testing alone.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The History, ECG, Age, Risk Factors and Troponin (HEART) score is in widespread usage in EDs to discriminate risk in patients with chest pain suspicious for a myocardial infarction and particularly to identify a population at low risk who are suitable for early discharge.

⇒ Studies evaluating the low-risk HEART score in the prehospital setting using a contemporary point of care troponin assay have failed to demonstrate the sensitivity and negative predictive value to safely identify patients who could be managed without hospital transfer.

⇒ Laboratory troponin tests, especially those with high sensitivity, have much improved analytical performance compared to those in current use at the point of care.

WHAT THIS STUDY ADDS

⇒ We found that paramedic-derived prehospital HEART scores of ≤3 incorporating both laboratory contemporary and high-sensitivity cardiac troponin assays did not reach sufficient sensitivity and negative predictive value to safely rule out myocardial infarction.

⇒ Performance for rule-out was improved when modifying the HEART score to accommodate measurement below the limit of detection for the high-sensitivity cardiac troponin assay, but still did not reach recognised safety thresholds accepted for rule-out in ED populations.

⇒ A HEART score of ≥7 with either assay is not superior to a finding of cardiac troponin above the 99th percentile upper reference limit alone.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study will inform how newer point-of-care cardiac troponin assays with enhanced diagnostic capabilities should be evaluated in the prehospital setting and lead researchers to explore further strategies in this clinical sphere.

INTRODUCTION

The identification of patients with ST-segment elevation on an electrocardiogram (ECG) by paramedics and direct transfer to cardiac centres is now established in many countries. However, most patients do not have diagnostic electrocardiographic changes,[1] and ambulance transfer to the nearest receiving hospital for further investigation is the standard of care, where less than one in five patients will be diagnosed with a myocardial

infarction.[2 3] In the prehospital setting, the rule-in of patients with myocardial infarction using cardiac troponin testing at the point of care has been comprehensively evaluated.[4–6] However, the major benefit of enhanced prehospital assessment for patients, ambulance services and hospitals would be a strategy that permitted the rule-out of myocardial infarction and identification of low-risk individuals eligible for management without ambulance conveyance to hospital.

In the Emergency Department (ED), the use of risk scores and rapid diagnostic pathways to identify low-risk patients suitable for discharge within a few hours of presentation are well established.[3 7–9] The History, ECG, Age, Risk Factors and Troponin (HEART) score attributes a score of 0, 1 or 2 to each of its component parts to give a total score between 0 and 10, classifying patients as low (0–3), intermediate (4-6)or high (7-10) risk.[10] Data required for completion of the Heart, ECG, Age, Risk Factors (HEAR) components are routinely collected by paramedics,[11] and the score is simple to calculate. Recent work investigating a paramedic-derived prehospital HEART score demonstrated that the addition of a point-of-care cardiac troponin test conferred improved discrimination over the HEAR components alone, but a score of ≤3 was unable to safely rule out myocardial infarction.[12 13]

However, the cardiac troponin assays available at the point of care that have been evaluated to date have inferior analytical performance to assays on central laboratory platforms.[1 14] High-sensitivity cardiac troponin assays permit the quantification of troponin within the normal reference range and, at the assay limit of detection (LoD)[15] or optimised thresholds,[3] permit the safe rule-out of myocardial infarction at presentation in the ED. Secondary analysis of a large prehospital cohort highlighted the potential for high-sensitivity troponin to improve risk stratification in this environment,[16] and modification of the HEART score using lower cardiac troponin thresholds may improve rule-out performance.[9] Whether this approach could be applied in the prehospital setting remains uncertain.

Our aim was to determine the accuracy of a prehospital HEART score performed by paramedics to rule-in and rule-out major adverse cardiac events (MACEs) in patients with possible acute myocardial infarction using a high-sensitivity cardiac troponin assay.

METHODS

Study design and setting

This prespecified analysis was undertaken as part of the Ambulance Cardiac Chest Pain Evaluation in Scotland Study (ACCESS),[12] a prospective cohort study performed in the north-east of Scotland, UK. Eleven ambulance stations cover a population of 600 000 across a large geographical area. Paramedic training covering good clinical practice, venesection from a cannula, ECG interpretation and HEAR score completion was described previously.[12]

Study participants and recruitment

Patients ≥16 years old with chest pain in whom a study trained paramedic suspected a diagnosis of myocardial infarction were eligible. Exclusion criteria included persistent ST-segment elevation on the prehospital ECG, inability to give verbal consent, pregnancy, refusal to go to hospital, being in custody or previous enrolment in the study within 30 days. Consenting patients had a HEAR score recorded in the ambulance on a structured form by the attending paramedic and a blood sample was drawn. HEAR scores were not used to guide clinical care.

Sample handling and cardiac troponin testing

On arrival to the hospital, the prehospital sample was tested using the Siemens ADVIA Centaur Ultra contemporary cardiac troponin I assay (Siemens, Munich, Germany). This assay has a LoD of 6 ng/L and an interassay coefficient of variation (CV) of 8.8% at 40 ng/L; the manufacturers recommended 99th centile upper reference limit (URL).[17] Samples that did not reach the laboratory within 4 hours of venesection were not processed due to risk of degradation. Surplus material was stored at −80°C and subsequently tested with the Abbott ARCHITECT$_{STAT}$ high-sensitivity troponin I assay (Abbott Laboratories, Illinois, USA). This assay has a LoD of 2 ng/L, an interassay CV of <10% at 4.7 ng/L[18] and a sex-specific 99th centile of 16 ng/L in women and 34 ng/L in men.[19]

HEART score

The prehospital HEART score was calculated separately for both the contemporary and high-sensitivity cardiac troponin assays as originally described: troponin concentrations ≤URL = 0 points, 1–3 x URL=1 point and ≥3 x URL=2 points, (online supplemental table S1) with HEART≤3 and ≥7 representing low- and high-risk respectively.[10] A HEAR score of ≤3 and ≥7 was also derived to enable comparison with previous work.[12 13] In addition, a modified HEART score[20] was calculated using the high-sensitivity assay in which the cardiac troponin component was allocated 0 point if concentration was below the LoD, 1 point if concentration was between the LoD and the URL, and 2 points if concentration was above the URL.

Primary and secondary outcome measures

The primary outcome measure was MACE at 30 days, a which included all myocardial infarction, all coronary revascularisation procedures, all-cause death, cardiac arrest, cardiogenic shock or life-threatening cardiac arrhythmias. The secondary outcome was a composite of type I, type IVb (in-stent thrombosis) or type IVc (in-stent restenosis) myocardial infarction[21] or cardiac death at 30 days The diagnosis of myocardial infarction and cause of death was adjudicated by two cardiologists (KKL and AA) independently with access to the contemporary assay results, all clinical information, investigation results and clinical outcomes up to 30 days. The adjudicators were not aware of the HEART score, or high-sensitivity cardiac troponin results on the pre-hospital samples and any disagreements were resolved with a third cardiologist adjudicator (NLM). All patients with a standard of care cardiac troponin I concentration above the URL were adjudicated according to the Fourth Universal Definition of Myocardial Infarction,[21] as previously described.[22] Those patients who were alive and not in hospital at 30 days were contacted in order of preference by patient telephone call, patient's general practitioner or through scrutiny of the electronic medical record. A full description of the primary and secondary outcomes, along with other adjudicated patient characteristics are reported in the online supplemental material. Non-adjudicated index hospital discharge diagnoses were also recorded using the electronic patient record.

Sample size calculation and statistical analysis

A sample size calculation for the ACCESS study[12] estimated that 1000 patients were required (online supplemental material). Data were expressed as frequencies and percentages or as mean and SD or median with an IQR, depending on normality of distribution. Discrimination of the HEART score for the primary and secondary outcomes was determined by the area

under the receiver operator curve (AUROC) with 95% confidence intervals (CI). Performance of the HEART scores to identify low- and high-risk patients was evaluated by calculating the sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and likelihood ratios for positive (LR+) and negative (LR-) results at these thresholds. A subgroup analysis in those with a time from symptom onset to testing less than or equal to 3 hours or greater than 3 hours was performed based on European Society of Cardiology guideline recommendations that patients presenting within 3 hours should undergo serial cardiac troponin measurement.[1] Statistical analysis was performed using IBM SPSS version 27.0 (IBM Corp., Armonk, NY, United States).

There was no direct patient or public involvement in this study.

RESULTS

Between November 2014 and April 2018, 1275 patients with possible myocardial infarction gave verbal consent to 85 paramedics. Written consent was later not obtained in 219 patients and 2 patients withdrew. Of the 1054 patients providing written consent, 960 had samples that enabled testing with both the contemporary and high-sensitivity assays (online supplemental figure S1). These constitute the study population of which 42% (401/960) were women and the average age was 64 (SD 15) years (table 1 and online supplemental table S2). The distribution of the HEART score for both assays, and the modified HEART score was determined in those with and without a primary outcome event and follow-up at 30 days was complete in all 960 participants (figure 1).

Primary and secondary outcome events

In 960 patients at 30 days, 255 (26%) had a primary outcome event; 233 (24%) had any myocardial infarction; and 18 (2%) died from any cause (table 2). Most events occurred during the index presentation (95%, 241/255). At 30 days, 19% (181/960) of patients had a secondary outcome of type I, type IVb or type IVc myocardial infarction or cardiac death.

Other index admission clinical outcome events

The index hospital diagnoses in all 960 patients whether or not they were found to have myocardial injury and underwent adjudication are reported in online supplemental table S3, including 9 patients diagnosed with a pulmonary embolism and 4 with a pneumothorax, along with 6 patients who died from non-cardiac causes during the index presentation.

Performance of HEART score with and without prehospital cardiac troponin testing

In 960 patients, the AUROC for the primary outcome was 0.70 (95% CI 0.66 to 0.74) for the HEAR score and 0.79 (95% CI 0.76 to 0.82) and 0.78 (95% CI 0.75 to 0.81) for the HEART score using contemporary and high-sensitivity assays, respectively. When the modified HEART score was calculated with the high-sensitivity assay, discrimination was unchanged at 0.78 (95% CI 0.75 to 0.81) (figure 2). Results were not significantly different for the secondary outcome (online supplemental figure S2).

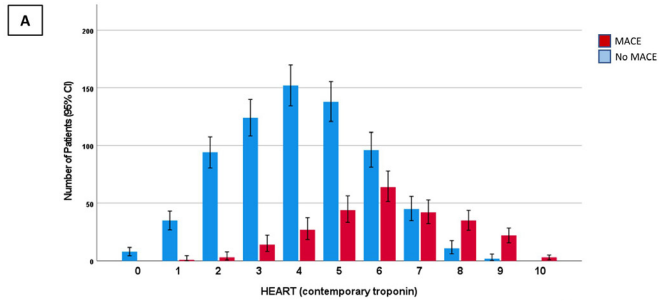
Rule-out

With respect to the primary outcome, a HEAR score of ≤3 identified 301 (31%) patients as low-risk with a sensitivity of 84.7% (95% CI 79.8% to 88.6%) and NPV of 87.0% (95% CI 82.8% to 90.4%) (table 3). A HEART score of ≤3 using the contemporary assay identified 279 (29%) patients as low-risk with a sensitivity of 92.9% (95% CI 89.1% to 95.5%) and an NPV of 93.5% (95% CI 90.0% to 95.9%), where as a HEART score of ≤3 using the high-sensitivity assay identified 279 (29%) patients as low-risk with a sensitivity of 90.6% (95% CI 86.4% to 93.6%) and an NPV of 91.4% (95% CI 87.5% to 94.2%). A modified HEART score of ≤3 using the high-sensitivity assay categorised 194 (20%) patients as low-risk with a sensitivity of 96.9% (95% CI 93.9% to 98.4%) and an NPV of 95.9% (95% CI 92.1% to 97.9%). Results were similar for the secondary outcome (table 4).

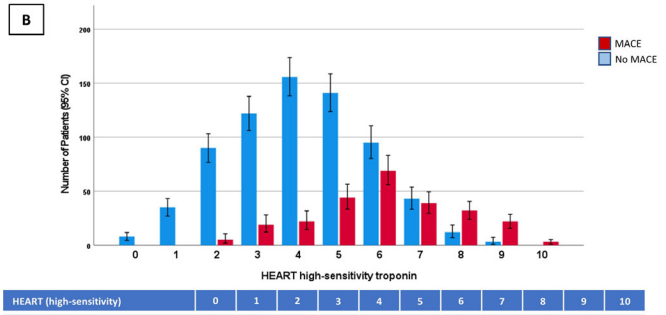
Table 1 Baseline characteristics of the study population with and without a MACE at 30 days

	Study population	MACE at 30 days	No MACE at 30 days
Number	960	255	705
Age (years) (SD)	64 (15)	70 (14)	62 (15)
Women	401 (42)	86 (34)	315 (45)
Medical history			
Diabetes mellitus	188 (20)	71 (28)	117 (17)
Hypertension	632 (66)	198 (78)	434 (62)
Hypercholesterolaemia	545 (57)	174 (68)	371 (53)
Cerebrovascular disease	104 (11)	37 (15)	67 (10)
Myocardial infarction	267 (28)	87 (34)	180 (26)
Ischaemic heart disease	419 (44)	135 (53)	284 (40)
Smoker	177 (18)	53 (21)	124 (18)
Previous revascularisation			
PCI	183 (19)	59 (23)	124 (18)
CABG	64 (7)	27 (11)	37 (5)
Medication at presentation			
Aspirin	350 (37)	106 (42)	244 (35)
Clopidogrel	118 (12)	41 (16)	77 (11)
Other P2Y12 inhibitor	43 (4)	12 (5)	31 (4)
Statin	501 (52)	159 (62)	342 (49)
ACE inhibitor or ARB	339 (35)	104 (41)	235 (33)
Beta blocker	325 (34)	107 (42)	218 (31)
Oral anticoagulant	104 (11)	38 (15)	66 (9)
ECG*			
ST-segment elevation†	11 (1)	9[4]	2 (0)
ST-segment depression	144 (15)	84 (33)	60 (9)
T-wave inversion	119 (12)	59 (23)	60 (9)
Left bundle branch block	95 (10)	40 (16)	55 (8)
Right bundle branch block	93 (10)	25 (10)	68 (10)
Acute ischaemia	107 (11)	73 (29)	34 (5)
Clinical features			
Heart rate (beats/min) (SD)	83 (21)	86 (25)	83 (20)
Systolic blood pressure (mm Hg) (SD)	144 (29)	144 (32)	144 (28)
Chest pain to troponin ≤3 hours	490 (51)	132 (52)	358 (51)
HEAR score (SD)	4.4 (1.7)	5.3 (1.5)	4.1 (1.7)
High-sensitivity cardiac troponin I (ng/L) (IQR)	4.0 (1.7–13.0)	25.2 (9.3–93.3)	2.7 (1.4–5.9)

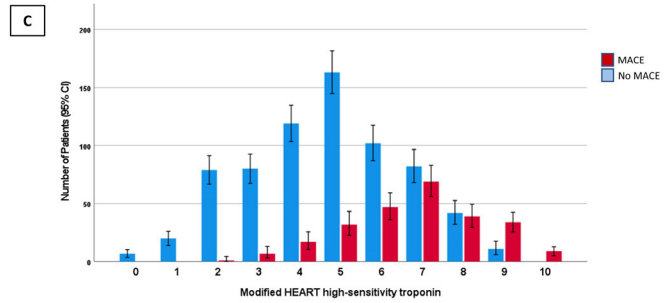
Data presented as number of patients (%), mean and SD, or median and IQR.
*Three patients had missing prehospital ECGs for formal interpretation.
†Eleven patients had ST-segment elevation that was not persistent or diagnostic for ST-elevation myocardial infarction.
ACE, Angiotensin Converting Enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; HEAR, Heart, ECG, Age, Risk Factors Score; MACE, major adverse cardiac event; PCI, percutaneous coronary intervention.



HEART (contemporary troponin)	0	1	2	3	4	5	6	7	8	9	10
Number (total 960)	8	36	97	138	179	182	160	87	46	24	3
Number with 30 day MACE (255)	0	1	3	14	27	44	64	42	35	22	3
% MACE	0	3	3	6	13	24	40	48	76	92	100



HEART (high-sensitivity)	0	1	2	3	4	5	6	7	8	9	10
Number (total 960)	8	35	95	141	178	185	164	82	44	25	3
Number with 30 day MACE (255)	0	0	5	19	22	44	69	39	32	22	3
% MACE	0	0	5	14	12	24	42	48	79	88	100



Modified HEART (high-sensitivity)	0	1	2	3	4	5	6	7	8	9	10
Number (total 960)	7	20	80	87	136	195	149	151	81	45	9
Number with 30 day MACE (255)	0	0	1	7	17	32	47	69	39	34	9
% MACE	0	0	1	8	13	16	32	46	48	76	100

Figure 1 Clustered bar charts and tables showing frequencies (with 95% CIs) and proportions of HEART scores with and without MACEs at 30 days. (A) HEART with a contemporary cardiac troponin I assay, (B) HEART with a high-sensitivity troponin I assay and (C) modified HEART score with high-sensitivity troponin I assay. MACE, major adverse cardiac event; HEART, History, ECG, Age, Risk Factors and Troponin score.

Table 2 Primary and secondary endpoints during the index presentation and at 30 days in the total study population (n=960)

	Index presentation	At 30 days
Adjudicated death		
All death	10 (1)	18 (2)
Cardiac death	4 (0)	8 (1)
Adjudicated diagnoses		
Myocardial infarction	227 (24)	233 (24)
Type I	168 (18)	172 (18)
Type IVb	0 (0)	2 (0)
Type IVc	5 (1)	5 (1)
Type II	54 (6)	56 (6)
Acute myocardial injury	15 (2)	22 (2)
Chronic myocardial injury	6 (1)	6 (1)
Other MACE		
PCI	81 (8)	87* (9)
CABG	21 (2)	22 (2)
Thrombolysis	1 (0)	1 (0)
Cardiac arrest	8 (1)	10 (1)
Ventricular arrhythmia	6 (1)	7 (1)
AV block	3 (0)	3 (0)
Cardiogenic shock	5 (1)	5 (1)
All MACE†	241 (25)	255 (26)
Type I or IVb or IVc myocardial infarction or cardiac death	175 (18)	181 (19)

Data presented as number of patients (%).
*Three patients underwent elective PCI; all other revascularisation procedures were urgent or emergency.
†MACE encompasses: death (all cause), myocardial infarction (all types), revascularisation (PCI, CABG or thrombolysis), cardiac arrest, ventricular arrhythmia (requiring electrical cardioversion), AV block (requiring electrical pacing) and cardiogenic shock (a hypoperfusion state with evidence of ventricular failure in which the circulation required sustained mechanical or inotropic support).
AV, atrioventricular block; CABG, coronary artery bypass grafting; MACE, major adverse cardiac event; PCI, percutaneous coronary intervention.

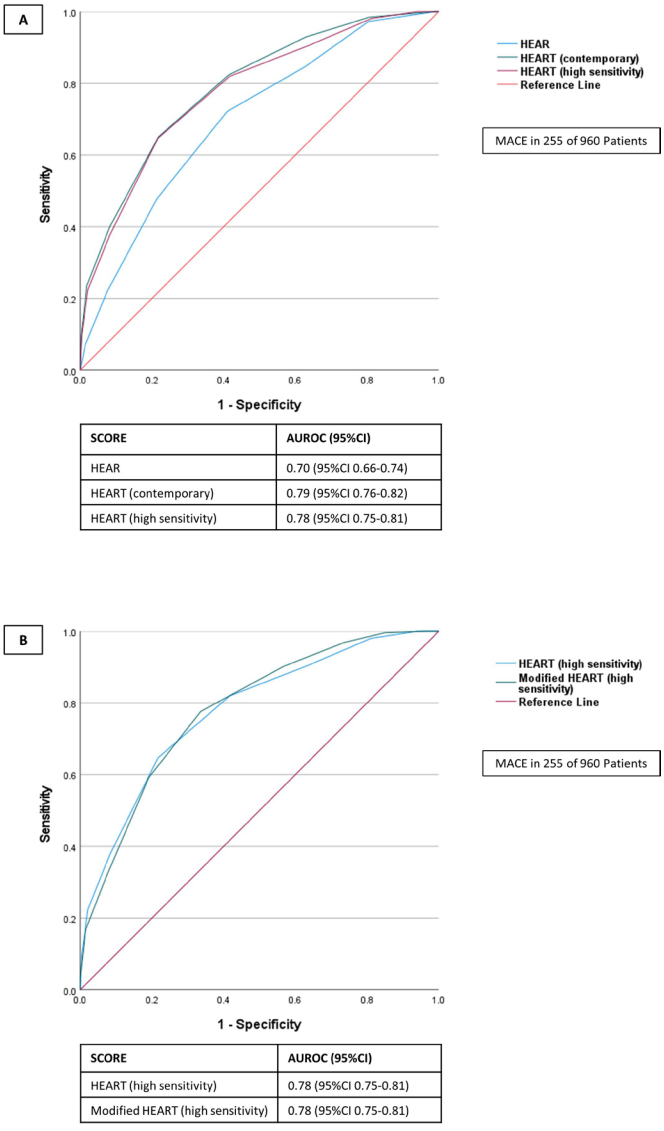
Rule-in

With respect to the primary outcome, a HEAR score≥7 identified 109 (11%) patients as high-risk with a specificity of 92.5% (95% CI 90.3 to 94.2%) and PPV 51.4% (95% CI 42.1 to 60.6%) (table 3). A HEART score≥7 using the contemporary assay identified 160 (17%) patients as high-risk with a specificity of 91.8% (95% CI 89.5 to 93.6%) and PPV of 63.8% (95% CI 56.1 to 70.8%), where as a HEART score≥7 using the high-sensitivity assay identified 154 (16%) patients as high-risk with a specificity of 91.8% (95% CI 89.5 to 93.6%) and a PPV of 62.3% (95% CI 54.5 to 69.6%). A modified HEART score≥7 with the high-sensitivity assay identified more patients as high-risk (30%, 286/960) but with a reduced specificity of 80.9% (95% CI 77.8 to 83.6%) and PPV of 53.1% (95% CI 47.0 to 58.5%). For comparison, a cardiac troponin concentration above the URL alone for either assay identified 150 (16%) patients as high-risk with a specificity of 98.2% (95% CI 96.9 to 98.9%) and PPV of 91.3% (95% CI 85.7 to 94.9) using the contemporary assay, and a specificity of 96.6% (95% CI 95.0% to 97.7%) and PPV of 84.0% (95% CI 77.3% to 89.0%) using the high-sensitivity assay. Results were similar for the secondary outcome (online supplemental table S4).

Subgroup analyses

In the 490 (51%) patients presenting early (≤3 hours from symptom onset), a HEART score of ≤3 using the contemporary assay identified 138 (28%) as low risk with a sensitivity of 91.7% (95% CI 85.7% to 95.3%) and an NPV of 92.0% (95% CI 86.3% to 95.5%), where as a HEART score of ≤3 using the high-sensitivity assay identified 142 (29%) patients as low risk with a sensitivity of 87.1% (95% CI 80.3% to 91.8%) and an NPV of 88.0% (95% CI 81.7% to 92.4%). Likewise, a modified HEART score of ≤3 identified 98 (20%) as low risk with a sensitivity of 97.0% (95% CI 92.5% to 98.8%) and an NPV of 95.9% (95% CI 90.0% to 98.4%) (table 4).

In the 470 patients presenting later, a HEART score of ≤3 with either assay had slightly improved sensitivity and NPV



SCORE	AUROC (95%CI)
HEAR	0.70 (95%CI 0.66-0.74)
HEART (contemporary)	0.79 (95%CI 0.76-0.82)
HEART (high sensitivity)	0.78 (95%CI 0.75-0.81)

SCORE	AUROC (95%CI)
HEART (high sensitivity)	0.78 (95%CI 0.75-0.81)
Modified HEART (high sensitivity)	0.78 (95%CI 0.75-0.81)

Figure 2 Receiver operating curves of (A) HEAR, contemporary HEART and high-sensitivity HEART and (B) high-sensitivity HEART and modified high-sensitivity HEART in prediction of MACEs at 30-days. AUROC, Area Under the Receiver Operator Curve; HEAR, Heart, ECG, Age, Risk Factors score; HEART, History, ECG, Age, Risk Factors and Troponin score; MACE, major adverse cardiac event.

compared with early presenters, but the sensitivity and NPV were 95% or lower for both. The modified HEART score of ≤3 performed similarly in both early and late presenters (table 4).

Results were similar for the secondary outcome (online supplemental table S5).

DISCUSSION

We prospectively evaluated whether applying a laboratory contemporary or high-sensitivity measured cardiac troponin concentration to a paramedic-derived HEAR score improved performance to rule-out or rule-in myocardial infarction in the prehospital setting. A HEART score of ≤3 with either assay identified one in three patients as low-risk, but the sensitivity and NPV to rule out MACE, or a composite outcome of myocardial infarction or cardiac death, at 30 days was too low to be safely used in practice. Incorporation of the LoD of the high-sensitivity assay into a modified HEART score of ≤3

Table 3 Performance of HEAR score, HEART score using a contemporary and high-sensitivity assay and a modified HEART score for MACEs at 30 days

		MACE at 30 days		No MACE at 30 days						
Rule-out*	Proportion of low risk	Not low risk	Low risk	Not low risk	Low risk	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
HEAR score ≤3	301 (31%)	216	39	443	262	84.7 (79.8 to 88.6)	37.2 (33.7 to 40.8)	32.8 (29.3 to 36.5)	87.0 (82.8 to 90.4)	1.35 (1.25 to 1.46)	0.41 (0.30 to 0.56)
HEART (cTnI) score ≤3	279 (29%)	237	18	444	261	92.9 (89.1 to 95.5)	37.0 (33.5 to 40.6)	34.8 (31.3 to 38.5)	93.5 (90.0 to 95.9)	1.48 (1.38 to 1.58)	0.19 (0.12 to 0.30)
HEART (hs-cTnI) score ≤3	279 (29%)	231	24	450	255	90.6 (86.4 to 93.6)	36.2 (32.7 to 39.8)	33.9 (30.5 to 37.6)	91.4 (87.5 to 94.2)	1.42 (1.33 to 1.52)	0.26 (0.18 to 0.39)
Modified HEART score ≤3	194 (20%)	247	8	519	186	96.9 (93.9 to 98.4)	26.4 (23.3 to 29.8)	32.2 (29.0 to 35.6)	95.9 (92.1 to 97.9)	1.32 (1.25 to 1.38)	0.12 (0.06 to 0.24)
Rule-in	**Proportion of high risk**	**MACE at 30 days**		**No MACE at 30 days**		**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**	**Positive LR (95% CI)**	**Negative LR (95% CI)**
		High risk	**Not high risk**	**High risk**	**Not high risk**						
HEAR score ≥7	109 (11%)	56	199	53	652	22.0 (17.3 to 27.4)	92.5 (90.3 to 94.2)	51.4 (42.1 to 60.6)	76.6 (73.7 to 79.3)	2.92 (2.06 to 4.13)	0.84 (0.79 to 0.90)
HEART (cTnI) score ≥7	160 (17%)	102	153	58	647	40.0 (34.2 to 46.1)	91.8 (89.5 to 93.6)	63.8 (56.1 to 70.8)	80.9 (78.0 to 83.5)	4.86 (3.64 to 6.49)	0.65 (0.59 to 0.72)
HEART (hs-cTnI) score ≥7	154 (16%)	96	159	58	647	37.6 (31.9 to 43.7)	91.8 (89.5 to 93.6)	62.3 (54.5 to 69.6)	80.3 (77.4 to 82.9)	4.58 (3.41 to 6.13)	0.68 (0.62 to 0.75)
Modified HEART score ≥7	286 (30%)	151	104	135	570	59.2 (53.1 to 65.1)	80.9 (77.8 to 83.6)	53.1 (47.0 to 58.5)	84.6 (81.6 to 87.1)	3.09 (2.58 to 3.71)	0.50 (0.43 to 0.59)
cTnI >URL alone	150 (16%)	137	118	13	692	53.7 (47.6 to 59.7)	98.2 (96.9 to 98.9)	91.3 (85.7 to 94.9)	85.4 (82.8 to 87.7)	29 (17 to 51)	0.47 (0.41 to 0.54)
hs-cTnI >URL alone	150 (16%)	126	129	24	681	49.4 (43.3 to 55.5)	96.6 (95.0 to 97.7)	84.0 (77.3 to 89.0)	84.1 (81.4 to 86.4)	15 (9.61 to 22.0)	0.52 (0.46 to 0.59)

*Statistics reported for HEAR and HEART scores of ≤3 refer to a positive test result being HEART score of >3.
cTnI, contemporary cardiac troponin I; HEAR, Heart, ECG, Age, Risk Factors score; HEART, History, ECG, Age, Risk Factors and Troponin score; hs-cTnI, high-sensitivity cardiac troponin I; LR, likelihood ratio; MACE, major adverse cardiac event; NPV, negative predictive value; PPV, positive predictive value; URL, upper reference limit.

Table 4 Performance of HEART score using a contemporary and high-sensitivity assay, and a modified HEART score for MACEs at 30 days in early (≤3 hours) and late (>3 hours) presenters

Rule-out*	Proportion of low risk	MACE		No MACE		Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
		Not low risk	Low risk	Not low risk	Low risk						
Early presenters (≤3 hours), n=490											
HEART (cTnI) score ≤3	138 (28%)	121	11	231	127	91.7 (85.7 to 95.3)	35.5 (30.7 to 40.6)	34.4 (29.6 to 39.5)	92.0 (86.3 to 95.5)	1.42 (1.30 to 1.56)	0.23 (0.13 to 0.42)
HEART (hs-cTnI) score ≤3	142 (29%)	115	17	233	125	87.1 (80.3 to 91.8)	34.9 (30.2 to 40.0)	33.0 (28.3 to 38.1)	88.0 (81.7 to 92.4)	1.34 (1.21 to 1.48)	0.37 (0.23 to 0.59)
Modified HEART score ≤3	98 (20%)	128	4	264	94	97.0 (92.5 to 98.8)	26.3 (22.0 to 31.1)	32.7 (28.2 to 37.4)	95.9 (90.0 to 98.4)	1.31 (1.23 to 1.41)	0.12 (0.04 to 0.31)
Late presenters (>3 hours), n=470											
HEART (cTnI) score ≤3	141 (30%)	116	7	213	134	94.3 (88.7 to 97.2)	38.6 (33.6 to 43.8)	35.3 (30.3 to 40.6)	95.0 (90.1 to 97.6)	1.54 (1.40 to 1.69)	0.15 (0.07 to 0.31)
HEART (hs-cTnI) score ≤3	137 (29%)	116	7	217	130	94.3 (88.7 to 97.2)	37.5 (32.5 to 42.7)	34.8 (29.9 to 40.1)	94.9 (89.8 to 97.5)	1.51 (1.38 to 1.65)	0.15 (0.07 to 0.32)
Modified HEART score ≤3	96 (20%)	119	4	255	92	96.7 (91.9 to 98.7)	26.5 (22.1 to 31.4)	31.8 (27.3 to 36.7)	95.8 (89.8 to 98.4)	1.32 (1.23 to 1.41)	0.12 (0.05 to 0.33)

*Statistics reported for HEART score of ≤3 refer to a positive test result being HEART score of >3.
cTnI, contemporary cardiac troponin I; HEART, History, ECG, Age, Risk Factors and Troponin score; hs-cTnI, high-sensitivity cardiac troponin I; LR, likelihood ratio; MACE, major adverse cardiac event; NPV, negative predictive value; PPV, positive predictive value; URL, upper reference limit.

classified one in five patients as low-risk with improved diagnostic performance but did not reach the required NPV of 99.5%[18] for safe rule-out, even in those presenting later than 3 hours from symptom onset. A prehospital HEART score of ≥7 derived with either assay had reasonable specificity and PPV, but was inferior to use of the 99th centile URL of cardiac troponin alone to rule-in myocardial infarction. Our findings suggest that alternative approaches to risk stratify patients are needed when high-sensitivity cardiac troponin testing becomes available in the prehospital setting.

Our findings add to two previous studies that demonstrated paramedics can perform the HEART score in the prehospital setting and that a contemporary point of care cardiac troponin test improves discrimination over the HEAR components alone.[12 13] Incorporation of high-sensitivity cardiac troponin further improved overall discrimination, though no gain in performance was seen over a contemporary laboratory assay. In comparison to a Dutch study in which patients with possible myocardial infarction were evaluated with a prehospital HEART score incorporating a high-sensitivity cardiac troponin test,[23] we found similar overall discrimination for the primary outcome but less than that observed in ED cohorts.[24] In order to harness the analytical superiority of the high-sensitivity test, we also evaluated a modified HEART score using the LoD of the high-sensitivity assay to define low-risk,[20] but discrimination for both primary and secondary outcomes was unchanged. These findings need to be validated using a high-sensitivity assay measured at the point of care.

In our study, a HEART score of ≤3 using either assay identified one in three patients as low-risk, comparable to in-hospital studies of the HEART score[24] and higher than that demonstrated in a prehospital Dutch cohort, where a HEART score of ≤3 recognised fewer patients (24%), but with greater sensitivity (95.7%) and NPV (97.3%) than demonstrated in our study.[23] The sensitivity and NPV for MACE were improved compared with the HEAR score alone, but even when using a modified HEART score of ≤3, the central estimate and the upper bounds of the 95% CI of the sensitivity and NPV did not meet previously recognised performance thresholds of 99%%[25] and 99.5%,[18] respectively, to enable the safe rule-out of myocardial infarction. It is plausible that our findings reflect the high proportion of patients enrolled within 3 hours of symptom onset when it is more challenging to rule out myocardial infarction.[1] However, performance of a HEART score of ≤3 was only marginally better in patients presenting with more than 3 hours of symptoms, and a modified HEART score of ≤3 performed similarly in both early and later presenters.

Despite this performance, use of the HEART score in early rule-out pathways is widespread, and evidence of effectiveness[26] and safety[27] exists from randomised trials. A clear understanding of the limitations of any risk stratification method and the importance of clinical acumen in the application of these approaches in the prehospital setting are paramount. Our study demonstrates that other serious conditions may present with chest pain and that identification of a patient as low-risk may not obviate the need for paramedics to conveyance to the hospital. Interestingly, a recent evaluation of the feasibility of using the HEART score to help identify those low-risk patients who can be managed without hospital transfer[28] demonstrated that one in four patients with a HEART score of ≤3 were subsequently still transferred to the hospital. Such a pathway needs evaluation in randomised trials, of which one has recently completed recruitment in the Netherlands,[29] to demonstrate safety and cost–benefit within different healthcare systems before widespread implementation.

Safety in the prehospital setting, where access to diagnostics and medical records is limited, is paramount, and our findings do not support the use of the HEART score in the ambulance to rule out myocardial infarction even if high-sensitivity cardiac troponin were to be available.

We observed that a HEART score of ≥7, using either a contemporary or high-sensitivity assay, identified one in eight patients as high-risk with good specificity and PPV for myocardial infarction or a broader outcome of MACE. However, use of a cardiac troponin concentration above the 99th centile URL alone with either assay identified a similar proportion of patients as high-risk with greater specificity and PPV. This is consistent with previous prehospital studies demonstrating that an elevated cardiac troponin using a point of care device has good specificity for acute myocardial infarction.[4–6] While the direct transfer of patients to a cardiac centre in whom the diagnosis of myocardial infarction without ST-segment elevation on the ECG made in the ambulance could enable earlier revascularisation and reduce healthcare resources, the clinical benefits of this approach have yet to be demonstrated in practice.[30]

Our study had a number of strengths and limitations. First, this was a large prospective study designed to evaluate the original and a modified HEART score using the LoD of a high-sensitivity cardiac troponin assay in the prehospital setting. Second, the components of the HEAR score were recorded contemporaneously by paramedics and not derived retrospectively by researchers, an important consideration when applying our findings in practice. Third, we evaluated both a contemporary sensitive and high-sensitivity cardiac troponin assay to provide insight into the potential impact of new point of care assays with enhanced analytical performance.[31] Finally, follow-up was complete in all study participants, and we did not rely on routinely collected data but adjudicated all study outcomes.

The major limitation of our study was that cardiac troponin testing was performed on a central laboratory platform rather than at the point of care. However, if the performance of the HEART score is insufficient for use in clinical practice using a gold-standard laboratory assay, then it is unlikely that use of any point of care device would improve performance. Second, the proportion of patients with a myocardial infarction was high at 19% and may reflect some selection bias by paramedics, but is not markedly different from other large European cohorts.[2 3] Third, though we used a primary outcome of MACE as a surrogate measure of safety, our study does not directly address the safety of using the HEART score to make clinical decisions regarding conveyance to the hospital. Finally, we have only evaluated the performance of the HEART score using two specific cardiac troponin I assays, and further validation using other assays including those measuring cardiac troponin T is necessary.

CONCLUSIONS

A HEART score derived by paramedics in the prehospital setting, even when modified to facilitate using a high-sensitivity assay, does not allow safe rule-out of myocardial infarction or enhanced rule-in compared with cardiac troponin testing alone.

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Acknowledgements We acknowledge the invaluable contribution of all the participating SAS paramedics and technicians as well as the support of the regional and national SAS managerial structures. We are also thankful for the involvement of numerous medical, nursing, reception and portering staff within the ED of Aberdeen Royal Infirmary and the assistance of Gary Robinson, Chaloner Chute and Susan Scotland from the DHI.

Contributors JGC, JF, KJL and EMD conceived the study and its design. JGC, JF, LAD, KMMB, KJL and JLH developed and delivered the paramedic training. JGC, LAD, KMMB, JLH, EMD, TF, KL, AA and ASVS acquired the data. JGC, NWS and AJL performed the analysis. JGC, JF, NWS, AJL and NLM interpreted the data. JGC and NLM drafted the manuscript. All authors reviewed the manuscript critically for intellectually important content, provided their final approval of the version to be submitted and were accountable for the work. JGC is the guarantor of the study.

Funding The study was supported financially by the Digital Health & Care Institute (DHI) (reference DHI/MCADAM), Scotland, and by the NHS Grampian Endowment Fund (grant number N0042903). Samsung provided the POC devices and test discs, and the University of Aberdeen contributed to the design and administration of the study. The funders had no role in the study design, data collection, interpretation or writing of the report. JGC was supported by a National Research Scotland Clinical Research Fellowship. KL and NLM are supported by the British Heart Foundation through a Clinical Research Training Fellowship (FS/18/25/33454) and a Chair Award, Programme Grant, and Research Excellence Award (CH/F/21/90010, RG/20/10/34966 and RE/18/5/34216), respectively.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by the National Ethics Committee (REC 14/NS/1037), registered in the Research Registry (UIN 2671) and conducted in accordance with the Declaration of Helsinki. A brief study information sheet was provided and verbal consent to particpate was given in the ambulance, with formal written consent obtained on arrival to the hospital.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information. All relevant study data is included within the article and the online supplemental material.

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REFERENCES

1 Collet J-P, Thiele H, Barbato E, *et al*. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021;42:1289–367.
2 Reichlin T, Hochholzer W, Bassetti S, *et al*. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med* 2009;361:858–67.
3 Shah ASV, Anand A, Strachan FE, *et al*. High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial. *Lancet* 2018;392:919–28.
4 Stengaard C, Sørensen JT, Rasmussen MB, *et al*. Prehospital diagnosis of patients with acute myocardial infarction. *Diagnosis (Berl)* 2016;3:155–66.
5 Rasmussen MB, Stengaard C, Sørensen JT, *et al*. Predictive value of routine point-of-care cardiac troponin T measurement for prehospital diagnosis and risk-stratification in patients with suspected acute myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2019;8:299–308.

6 Stopyra JP, Snavely AC, Scheidler JF, *et al*. Point-of-care troponin testing during ambulance transport to detect acute myocardial infarction. *Prehosp Emerg Care* 2020;24:751–9.
7 Body R, Morris N, Reynard C, *et al*. Comparison of four decision AIDS for the early diagnosis of acute coronary syndromes in the emergency Department. *Emerg Med J* 2020;37:8–13.
8 Greenslade JH, Carlton EW, Van Hise C, *et al*. Diagnostic accuracy of a new high-sensitivity troponin I assay and five accelerated diagnostic pathways for ruling out acute myocardial infarction and acute coronary syndrome. *Ann Emerg Med* 2018;71:439–51.
9 Chapman AR, Hesse K, Andrews J, *et al*. High-sensitivity cardiac troponin I and clinical risk scores in patients with suspected acute coronary syndrome. *Circulation* 2018;138:1654–65.
10 Six AJ, Backus BE, Kelder JC. Chest pain in the emergency room: value of the HEART score. *Neth Heart J* 2008;16:191–6.
11 Stopyra JP, Harper WS, Higgins TJ, *et al*. Prehospital modified HEART score predictive of 30-day adverse cardiac events. *Prehosp Disaster Med* 2018;33:58–62.
12 Cooper JG, Ferguson J, Donaldson LA, *et al*. The ambulance cardiac chest pain evaluation in Scotland study (ACCESS): a prospective cohort study. *Ann Emerg Med* 2021;77:575–88.
13 van Dongen DN, Fokkert MJ, Tolsma RT, *et al*. Value of prehospital troponin assessment in suspected non-ST-elevation acute coronary syndrome. *Am J Cardiol* 2018;122:1610–6.
14 Collinson PO, Saenger AK, Apple FS, *et al*. High sensitivity, contemporary and point-of-care cardiac troponin assays: educational aids developed by the IFCC Committee on Clinical Application of Cardiac Bio-Markers. *Clin Chem Lab Med* 2019;57:623–32.
15 Body R, Carley S, McDowell G, *et al*. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. *J Am Coll Cardiol* 2011;58:1332–9.
16 Cooper JG, Ferguson J, Donaldson LA, *et al*. Could high-sensitivity cardiac troponin testing rule out acute myocardial infarction in the prehospital setting? *J Am Coll Cardiol* 2021;78:2392–4.
17 Collinson PO, Clifford-Mobley O, Gaze D, *et al*. Assay imprecision and 99th-percentile reference value of a high-sensitivity cardiac troponin I assay. *Clin Chem* 2009;55:1433–4.
18 Shah ASV, Anand A, Sandoval Y, *et al*. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. *Lancet* 2015;386:2481–8.
19 Shah ASV, Griffiths M, Lee KK, *et al*. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. *BMJ* 2015:g7873.
20 Khand A, Frost F, Chew P, *et al*. Modified HEART score improves early safe discharge for suspected acute coronary syndromes: a prospective cohort study with recalibration of risk scores to undetectable high sensitivity troponin T limits. *Journal of the American College of Cardiology* 2017;69:238.
21 Thygesen K, Jaffe AS. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2019;40:237–69.
22 Chapman AR, Adamson PD, Shah ASV, *et al*. High-sensitivity cardiac troponin and the universal definition of myocardial infarction. *Circulation* 2020;141:161–71.
23 van Dongen DN, Fokkert MJ, Tolsma RT, *et al*. Accuracy of pre-hospital HEART score risk classification using point of care versus high sensitive troponin in suspected NSTE-ACS. *Am J Emerg Med* 2020;38:1616–20.
24 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.
25 Than M, Herbert M, Flaws D, *et al*. What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the emergency department?: a clinical survey. *Int J Cardiol* 2013;166:752–4.
26 Poldervaart JM, Reitsma JB, Backus BE, *et al*. Effect of using the HEART score in patients with chest pain in the emergency department: a stepped-wedge, cluster randomized trial. *Ann Intern Med* 2017;166:689–97.
27 Frisoli TM, Nowak R, Evans KL, *et al*. Henry Ford HEART score randomized trial: rapid discharge of patients evaluated for possible myocardial infarction. *Circ Cardiovasc Qual Outcomes* 2017;10:e003617.
28 Tolsma RT, Fokkert MJ, van Dongen DN, *et al*. Referral decisions based on a pre-hospital HEART score in suspected non-ST-elevation acute coronary syndrome: final results of the famous triage study. *Eur Heart J Acute Cardiovasc Care* 2022;11:160–9.
29 Aarts GWA, Camaro C, van Geuns R-J, *et al*. Acute rule-out of non–ST-segment elevation acute coronary syndrome in the (Pre)hospital setting by HEART score assessment and a single point-of-care troponin: rationale and design of the ARTICA randomised trial. *BMJ Open* 2020;10:e034403.
30 Rasmussen MB, Stengaard C, Sørensen JT, *et al*. Comparison of acute versus subacute coronary angiography in patients with NON-ST-elevation myocardial infarction (from the NONSTEMI trial). *Am J Cardiol* 2019;124:825–32.
31 Gunsolus IL, Schulz K, Sandoval Y, *et al*. Diagnostic performance of a rapid, novel, whole blood, point of care high-sensitivity cardiac troponin I assay for myocardial infarction. *Clin Biochem* 2022;105–106:70–4.

SUPPLEMENTARY MATERIAL

Performance of a prehospital HEART score in patients with possible myocardial infarction: a prospective evaluation

SAMPLE SIZE CALCULATION

Using pooled data from four previous (1-4) it was expected that 69% of patients would have a HEART score >3 of which 22.3% would have a MACE within 30 days compared with a 1.6% risk of 30-day MACE with a HEART score of 0-3. Based on these figures, a study of 1,000 patients would be able to estimate the sensitivity and specificity of a HEART score >3 to predict a MACE to the following levels of accuracy: sensitivity: 96.9% (95% CI 94.2%-99.6%) and specificity: 36.3% (95% CI: 33.1%-39.5%).

DEFINITION OF PRIMARY OUTCOME

A Major Adverse Cardiac Event (MACE) was a composite outcome that included any patient meeting any of the following criteria.

1. Any myocardial infarction, independently adjudicated according to the 4th Universal Definition of Myocardial Infarction. (5)
2. Any coronary revascularisation
    a. Thrombolysis
    b. Percutaneous coronary intervention (including elective).
    c. Coronary artery by-pass graft surgery (including elective).
3. Death – all causes.
4. Cardiogenic shock – defined as a hypoperfusion state with evidence of ventricular failure in which the circulation required sustained mechanical or inotropic support

5. Life-threatening arrhythmias – defined as any ventricular arrhythmia that required emergency cardioversion or any atrio-ventricular block that required an isoprenaline infusion or urgent pacing.
6. Cardiac arrest – defined as sudden cessation of cardiac output requiring initiation of cardiac chest compressions and or immediate unsynchronised DC cardioversion.

DEFINITION OF SECONDARY OUTCOME

The secondary outcome was a composite of cardiac death or a type 1, 4b or 4c myocardial infarction at 30 days (5). Cardiac death was defined as death resulting from myocardial infarction, sudden cardiac death, or death due to heart failure and was independently adjudicated. Type 4b myocardial infarction, due to stent thrombosis, and type 4c myocardial infarction, due to in-stent re-stenosis were included with type 1 myocardial infarction, caused by atherogenic plaque rupture and thrombosis, since these patients present similarly and are diagnosed and treated in a similar manner.

DEFINITION OF OTHER PATIENT POPULATION CHARACTERISTICS

Adjudicated patient population characteristics pertaining to prior medical history, previous revascularisation, medication at presentation and initial electrocardiogram were described in line with previous guidance (6), except for cigarette smoking, which was defined as current or ceased <90 days (2).

REFERENCES

(1) Six AJ, Backus BE, Kelder JC. Chest pain in the emergency room: value of the HEART score. *Neth Heart J* 2008;16(6):191-196.

(2) Backus BE, Six AJ, Kelder JC, et al. Chest pain in the emergency room: a multicenter validation of the HEART Score. *Crit Path Cardiol* 2010;9(3):164-169.

(3) Backus BE, Six AJ, Kelder JC, Bosschaert MAR, et al. A prospective validation of the HEART score for chest pain patients at the emergency department. *Int J Cardiol* 2013;168(3):2153-2158.

(4) Six AJ, Cullen L, Backus BE, et al. The HEART score for the assessment of patients with chest pain in the emergency department: a multinational validation study. *Crit Path Cardiol* 2013;12(3):121-126.

(5) Thygesen K, Alpert JS, Jaffe AS, et al. Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2019;40:237-269.

(6) Cullen L, Than M, Brown AFT, et al. Comprehensive standardized data definitions for acute coronary syndrome research in emergency departments in Australasia. *Emerg Med Australas* 2010;22(1):35-55.

SUPPLEMENTARY TABLES

Table S1. The HEART score.

			Points
1.	History	Highly suspicious for acute coronary syndrome	2
		Moderately suspicious for acute coronary syndrome	1
		Slightly or non-suspicious for acute coronary syndrome	0
2.	Electrocardiogram	Significant ST-segment depression	2
		Non-specific repolarisation disturbance	1
		Normal	0
3.	Age	≥65 years	2
		45–64 years	1
		<45 years	0
4.	Risk factors	≥3 risk factors, **or** a history of atherosclerotic disease*	2
		1 or 2 risk factors	1
		No known risk factors	0
5.	Troponin†	≥ 3 x upper reference limit	2
		>1 to <3 x upper reference limit	1
		Within the reference range	0

* Risk factors: Family history of ischaemic heart disease, hypertension (>140/90 mmHg or on treatment), diabetes mellitus, hypercholesterolaemia (or on treatment), cigarette smoker (<90 days), or obesity (body mass index >30). Atherosclerotic disease = history of transient ischemic attack /stroke, peripheral vascular disease or myocardial infarction/ischemic heart disease.

† For the modified HEART score with a high-sensitivity troponin assay, the troponin component scores 0 points if below the limit of detection (LoD), 1 point if between the LOD and the 99th upper reference limit (URL) and 2 points if above the URL.

Table S2. Baseline characteristics of the study population with and without secondary outcome of Type 1 or 4 myocardial infarction or cardiac death at 30 days

	Study population	**Myocardial Infarction or Cardiac Death at 30 days**	**No Myocardial Infarction or Cardiac Death at 30 days**
Number	960	181	779
Age, years (SD)	64 (15)	69 (14)	63 (15)
Women	401 (42)	50 (28)	351 (45)
Prior medical history			
Diabetes mellitus	188 (20)	52 (29)	136 (17)
Hypertension	632 (66)	138 (76)	494 (63)
Hypercholesterolaemia	545 (57)	120 (66)	425 (55)
Cerebrovascular disease	104 (11)	22 (12)	82 (11)
Myocardial infarction	267 (28)	63 (35)	204 (26)
Ischaemic heart disease	419 (44)	89 (49)	330 (42)
Smoker	177 (18)	42 (23)	135 (17)
Previous revascularisation			
PCI	183 (19)	44 (24)	139 (18)
CABG	64 (7)	21 (12)	43 (6)
Medication at presentation			
Aspirin	350 (37)	79 (44)	271 (35)
Clopidogrel	118 (12)	23 (13)	95 (12)
Other P2Y12 Inhibitor	43 (4)	10 (6)	33 (4)
Statin	501 (52)	107 (59)	394 (51)
ACE inhibitor or ARB	339 (35)	72 (40)	267 (34)
Beta-blocker	325 (34)	71 (39)	254 (33)
Oral anticoagulant	104 (11)	16 (9)	88 (11)
Electrocardiogram*			
ST-segment elevation†	11 (1)	8 (4)	3 (0)
ST-segment depression	144 (15)	56 (31)	88 (11)
T-wave inversion	119 (12)	43 (24)	76 (10)
Left bundle branch block	95 (10)	28 (16)	67 (9)
Right bundle branch block	93 (10)	19 (11)	74 (10)
Acute ischaemia	107 (11)	52 (29)	55 (7)

Clinical features			
Heart rate, beats per minute (SD)	83 (21)	79 (18]	84 (22)
Systolic blood pressure, mmHg (SD)	144 (29)	150 (31)	143 (28)
Chest pain to troponin ≤3 hrs	490 (51)	96 (53)	394 (51)
HEAR (SD)	4.4 (1.7)	5.2 (1.5)	4.2 (1.7)
High-sensitivity cardiac troponin I (ng/L) [IQR]	4.0 [1.7-13.0]	29.8 [12.1-119.5]	2.9 [1.5-7.0]

Data presented as number of patients (%), mean and standard deviation (SD) or median and interquartile range [IQR]

*3 patients had missing pre-hospital ECGs for formal interpretation

†11 patients had ST-segment elevation that was not persistent or diagnostic for STEMI

Abbreviations: ACE = Angiotensin Converting Enzyme; ARB = Angiotensin Receptor Blocker; CABG = Coronary Artery Bypass Grafting; HEAR = Heart, Electrocardiogram, Age, Risk Factors Score; PCI = Percutaneous Coronary Intervention

Figure S1. Patient Flow Diagram

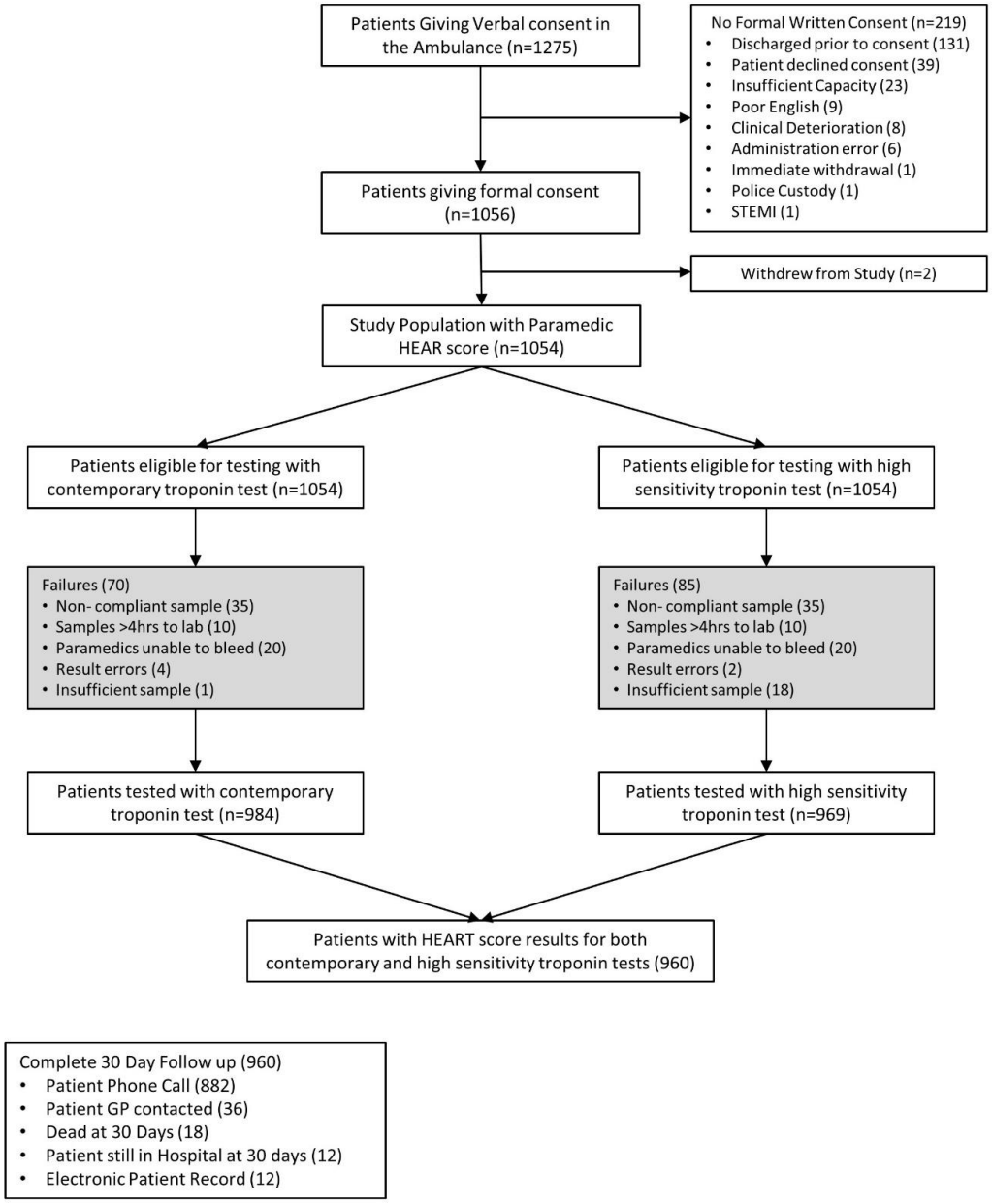
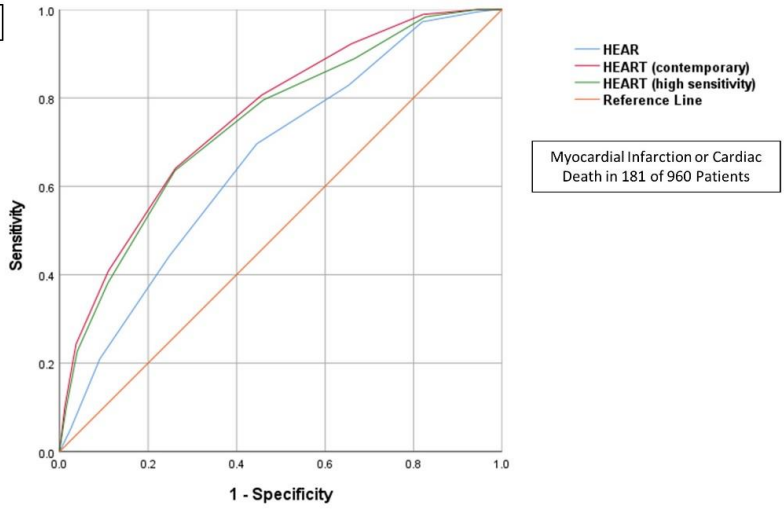


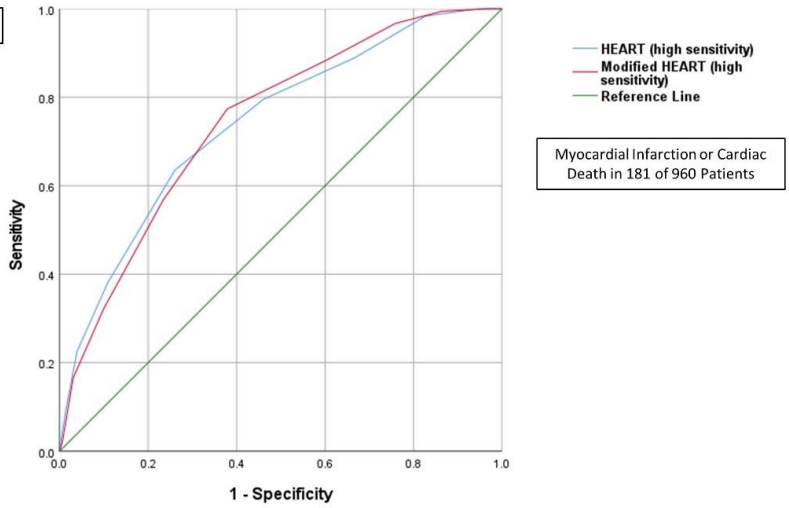
Figure S2. Receiver operating curves of A) HEAR, contemporary HEART and high sensitivity HEART and B) High sensitivity HEART and modified high sensitivity HEART for the prediction of type 1 or 4b or 4c myocardial infarction or cardiac death at 30-days.

A



SCORE	AUROC (95%CI)
HEAR	0.66 (95%CI 0.62-0.70)
HEART (contemporary)	0.76 (95%CI 0.72-0.80)
HEART (high sensitivity)	0.74 (95%CI 0.70-0.78)

B



SCORE	AUROC (95%CI)
HEART (high sensitivity)	0.74 (95%CI 0.70-0.78)
Modified HEART (high sensitivity)	0.75 (95%CI 0.71-0.78)

Table S3. Index episode hospital discharge diagnoses.

Diagnosis	**Number (%)**	**Pulmonary Embolism**	**Index Cardiac Death**	**Index Non-cardiac Death**
Myocardial infarction*	227 (24)	2†	3	2††
Acute myocardial injury*	15 (2)	0	0	1¶
Chronic myocardial injury*	6 (1)	1†	1	0
Chest Pain – 'non-cardiac' or 'non-specific'	237 (25)	0	0	0
Chest Pain – 'cardiac' or 'angina'	172 (18)	0	0	0
Chest Pain – 'oesophageal' or 'gastric'	102 (11)	0	0	0
Chest Pain – 'musculoskeletal'	98 (10)	0	0	0
Respiratory – 'infection' or 'pneumonia'	32 (3)	0	0	1
Acute Abdominal Pain – various pathologies	31(3)	0	0	2
Respiratory – exacerbation of chronic respiratory condition	15 (2)	0	0	0
Pericarditis	10 (1)	0	0	0
Pulmonary Embolism	6 (1)	6	0	0
Other	5 (1)	0	0	0
Pneumothorax	4 (0)	0	0	0
Total	**960**	**9**	**4**	**6**

*All patients with elevated cardiac troponin concentrations had the index diagnosis adjudicated according to the Fourth Universal Definition of Myocardial Infarction. The index diagnosis for the remainder was determined from the medical records. Cardiac death was also adjudicated.

†Two patients adjudicated to have a Type 2 myocardial infarction and one patient adjudicated to have a chronic myocardial injury were also noted to have developed a pulmonary embolism**.**

Six patients were adjudicated to have died during the index admission due to non-cardiac reasons.
Three patients died from respiratory illness, including two†† with adjudicated Type 2 myocardial infarction and three patients, one¶ with adjudicated acute myocardial injury, died due to complications from bowel obstruction.

Table S4. Performance of HEAR score, HEART score using a contemporary and high-sensitivity assay, and a modified HEART score for myocardial infarction or cardiac death at 30 days.

Rule-out*		Myocardial Infarction or Cardiac Death at 30 days		No Myocardial Infarction or Cardiac Death at 30 days						
	Proportion low-risk	Not low-risk	Low-risk	Not low-risk	Low-risk	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	Positive LR (95%CI)	Negative LR (95%CI)
HEAR ≤3	301 (31%)	150	31	509	270	82.9% (76.7-87.7)	34.7% (31.4-38.1)	22.8% (19.7-26.1)	89.7% (85.8-92.6)	1.27 (1.17-1.38)	0.49 (0.35-0.69)
HEART (cTnI) ≤3	279 (29%)	167	14	514	265	92.3% (87.4-95.3)	34.0% (30.8-37.4)	24.5% (21.4-27.9)	95.0% (91.8-97.0)	1.40 (1.31-1.49)	0.23 (0.14-0.38)
HEART (hs-cTnI) ≤3	279 (29%)	161	20	520	259	89.0% (83.5-92.7)	33.2% (30.0-36.6)	23.6% (20.6-27.0)	92.8% (89.2-95.3)	1.33 (1.24-1.43)	0.33 (0.22-0.51)
Modified HEART ≤3	194 (20%)	175	6	591	188	96.7% (93.0-98.5)	24.1% (21.3-27.3)	22.8% (20.0-26.0)	96.9% (93.4-98.6)	1.27 (1.21-1.34)	0.14 (0.06-0.30)
Rule-in		Myocardial Infarction or Cardiac Death at 30 days		No Myocardial Infarction or Cardiac Death at 30 days						
	Proportion high-risk	High-risk	Not high-risk	High-risk	Not high-risk	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	Positive LR (95%CI)	Negative LR (95%CI)
HEAR ≥7	109 (11%)	38	143	71	708	21.0% (15.7-27.5)	90.9% (88.7-92.7)	34.9% (26.6-44.2)	83.2% (80.5-85.6)	2.30 (1.61-3.30)	0.87 (0.80-0.94)
HEART (cTnI) ≥7	160 (17%)	74	107	86	693	40.9% (34.0-48.2)	89.0% (86.6-91.0)	46.3% (38.7-54.0)	86.6% (84.1-88.8)	3.70 (2.84-4.83)	0.66 (0.59-0.75)
HEART (hs-cTnI) ≥7	154 (16%)	69	112	85	694	38.1% (31.4-45.4)	89.1% (86.7-91.1)	44.8% (37.2-52.7)	86.1% (83.5-88.3)	3.49 (2.66-4.59)	0.69 (0.62-0.78)
Modified HEART ≥7	286 (30%)	103	78	183	596	56.9% (49.6-63.9)	76.5% (73.4-79.4)	36.0% (30.7-41.7)	88.4% (85.8-90.6)	2.42 (2.02-2.90)	0.56 (0.47-0.67)
cTnI >URL alone	150 (16%)	109	72	41	738	60.2% (52.9-67.1)	94.7% (92.9-96.1)	72.7% (65.0-79.2)	91.1% (89.0-92.9)	11 (8.3-16)	0.42 (0.35-0.50)
hs-cTnI >URL alone	150 (16%)	96	85	54	725	53.0% (45.8-60.2)	93.1% (91.1-94.6)	64.0% (56.1-71.2)	89.5% (87.2-91.4)	7.65 (5.72-10)	0.50 (0.43-0.59)

*Statistics reported for HEART ≤3 refer to a positive test result being HEART >3.

Abbreviations: cTnI = contemporary cardiac troponin I; hs-cTnI = high sensitivity cardiac troponin I; CI = confidence interval; LOD = limit of detection; NPV = negative predictive value; PPV = positive predictive value; LR = likelihood ratio; URL = upper reference limit.

Table S5. Performance of HEART score using a contemporary and high-sensitivity assay, and a modified HEART score for myocardial infarction or cardiac death at 30 days for myocardial infarction or cardiac death at 30 days in early (≤3 hours) and late (>3 hours) presenters.

Rule-out*		Myocardial Infarction or Cardiac Death		NO Myocardial Infarction or Cardiac Death							
Early presenters (≤3 hours), n=490	Proportion low-risk	Not low-risk	Low-risk	Not low-risk	Low-risk	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	Positive LR (95%CI)	Negative LR (95%CI)
HEART (cTnI) ≤3	138 (28%)	87	9	265	129	90.6% (83.1-95.0)	32.7% (28.3-37.5)	24.7% (20.5-29.5)	93.5% (88.1-96.5)	1.35 (1.23-1.48)	0.29 (0.15-0.54)
HEART (hs-cTnI) ≤3	142 (29%)	81	15	267	127	84.4% (75.8-90.3)	32.2% (27.8-37.0)	23.3% (19.1-28.0)	89.4% (83.3-93.5)	1.25 (1.12-1.39)	0.48 (0.30-0.79)
Modified HEART ≤3	98 (20%)	92	4	300	94	95.8% (90.0-98.4)	23.9% (19.9-28.3)	23.5% (19.5-27.9)	95.9% (90.0-98.4)	1.26 (1.17-1.35)	0.17 (0.07-0.46)
Late presenters (>3 hours), n=470	Proportion low-risk	Not low-risk	Low-risk	Not low-risk	Low-risk	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	Positive LR (95%CI)	Negative LR (95%CI)
HEART (cTnI) ≤3	141 (30%)	80	5	249	136	94.1% (87.0-97.5)	35.3% (30.7-40.2)	24.3% (20.0-29.2)	96.5% (92.0-98.5)	1.46 (1.33-1.59)	0.17 (0.07-0.39)
HEART (hs-cTnI) ≤3	137 (29%)	80	5	253	132	94.1% (87.0-97.5)	34.3% (29.7-39.2)	24.0% (19.7-28.9)	96.4% (91.7-98.4)	1.43 (1.31-1.57)	0.17 (0.07-0.41)
Modified HEART ≤3	96 (20%)	83	2	291	94	97.6% (91.8-99.4)	24.4% (20.4-28.9)	22.2% (18.3-26.7)	97.9% (92.7-99.4)	1.29 (1.21-1.38)	0.10 (0.02-0.38)

*Statistics reported for HEART ≤3 refer to a positive test result being HEART >3.

Abbreviations: cTnI = contemporary cardiac troponin I; hs-cTnI = high sensitivity cardiac troponin I; CI = confidence interval; LOD = limit of detection; NPV = negative predictive value; PPV = positive predictive value; LR = likelihood ratio; URL = upper reference limit.