

Risk stratifying chest pain patients in the emergency department using HEART, GRACE and TIMI scores, with a single contemporary troponin result, to predict major adverse cardiac events

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ABSTRACT

Background The majority of patients presenting to the ED with cardiac sounding chest pain have a non-diagnostic ECG and the problem of differentiating those suffering an acute coronary syndrome from those without is familiar to all ED clinical staff. To stratify risk in these patients, specific scores have been developed. Recent work has focused on incorporating newer high-sensitivity cardiac troponin (hs-cTn) assays; however, issues regarding performance and availability of these assays remain.

Aim Prospectively compare HEART, Global Registry of Acute Coronary Events (GRACE) and Thrombolysis in Myocardial Infarction (TIMI) scores, using a single contemporary cTn at admission, to predict a major adverse cardiac event (MACE) at 30 days.

Method Prospective observational cohort study performed in a UK tertiary hospital in patients with suspected cardiac chest pain and no significant ST elevation on initial ECG. Data collection took place 2 December 2014 to 8 February 2016. The treating clinician recorded risk score data real time and a single contemporary cTn taken at presentation was used in score calculation. The primary endpoint was 30-day MACE. C-statistic was determined for each score and diagnostic characteristics of high-risk and low-risk cut-offs were calculated.

Results 189/1000 patients in the study developed a 30-day MACE. The c-statistic of HEART for 30-day MACE (0.87 (95% CI 0.84 to 0.90)) was higher than TIMI (0.78 (95% CI 0.74 to 0.81)) and GRACE (0.74 (95% CI 0.70 to 0.78)). HEART score ≤ 3 identified low-risk patients with sensitivity 99.5% (95% CI 97.1% to 99.9%) and negative predictive value (NPV) 99.6% (95% CI 97.3% to 99.9%) exceeding TIMI 0 (sensitivity 97.4% (95% CI 93.9% to 99.1%) and NPV 97.8% (95% CI 94.8% to 99.1%)) and GRACE score 0–55 (sensitivity 95.2% (95% CI 91.1% to 97.8%) and NPV 95.8% (95% CI 92.2% to 97.7%)).

Conclusion HEART outperformed both TIMI and GRACE in overall discriminative capacity for 30-day MACE. Using a single contemporary cTn at presentation, a HEART score of ≤ 3 demonstrated sensitivity and NPV of $\geq 99.5\%$ for 30-day MACE. These results reach the threshold for a safe discharge strategy but should be interpreted thoughtfully in light of other work.

INTRODUCTION

Chest pain is a concerning symptom to both patients and physicians and represents one of the most common reasons for ED attendance.¹ The potential causes are numerous and vary from benign to

Key messages

What is already known on this subject

► Different strategies exist to risk stratify patients who present to the ED with cardiac sounding chest pain with particular emphasis on the identification of a low-risk population who would be suitable for early discharge, avoiding hospital admission. Recent guidance highlights the clinical use of 1-hour and 3-hour rule-out strategies using high-sensitivity cardiac troponin (hs-cTn) assays. However, numerous centres in the UK, and many more worldwide, continue to operate without access to hs-cTn and some large organisations do not yet advocate their use. Objective risk scoring in these patients is often recommended and History, ECG, Age, Risk Factors and Troponin (HEART), Thrombolysis in Myocardial Infarction (TIMI) and Global Registry of Acute Coronary Events (GRACE) are three tools used for such purposes though these have not yet been prospectively compared in a UK population using a contemporary cTn assay.

What this study adds

► In this prospective observational UK cohort of 1000 ED patients with suspected cardiac chest pain, the HEART score outperformed TIMI and GRACE in its ability to predict 30-day major adverse cardiac event (MACE) when incorporating a single contemporary cTn taken at presentation. Further, a HEART score ≤ 3 identified 25% of patients as low risk with a sensitivity of 99.5% (95% CI 97.1 to 99.9) and negative predictive value of 99.6% (97.3–99.9) for the development of MACE at 30 days.

life threatening, but often the main issue is to identify whether the patient is suffering from an acute coronary syndrome (ACS) or not. Patients with ST elevation on ECG usually provide little diagnostic difficulty, but of those with suspected cardiac chest pain and a non-diagnostic ECG, about 20% are suffering from an ACS.² The difficulty in promptly and reliably identifying patients with an ACS from those with non-cardiac chest pain is familiar to anyone working in the ED and, in most centres,



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hospital admission and serial cardiac biomarker measurement has been the rule.

Strategies to safely identify low-risk patients in this population who may be suitable for early discharge from the ED with resultant benefits for the patient and the hospital continue to develop. Much recent work has focused on the use of highly sensitive cardiac troponin (hs-cTn) assays to rule out acute myocardial infarction (AMI) early in the patient journey, and these have been incorporated into 1-hour and 3-hour AMI rule-out strategies recommended by the European Society of Cardiology.³ Further, single very low levels of hs-cTn may be sufficient to rule out AMI in patients considered low risk,^{4–7} an approach that appears in the most recent National Institute for Health and Care Excellence (NICE) guidance.⁸

Elevated cardiac biomarkers need to be interpreted in the clinical context. Even with excellent tests, accurate clinical assessment of risk is important. Gestalt may be effective,⁹ but objective risk scores incorporating clinical and historical features with ECG findings and cardiac biomarker results have been adopted in many centres. Both the widely adopted Global Registry of Acute Coronary Events (GRACE) score¹⁰ and the Thrombolysis in Myocardial Infarction (TIMI) score¹¹ were developed from large numbers of patients with a proven ACS and have subsequently been recommended for use in populations with suspected ACS presenting to the ED. TIMI has been successfully evaluated as part of an accelerated diagnostic protocol (ADP) in this clinical setting^{12–14} and is still recommended in the latest NICE guidance.⁸

The HEART score, developed in the Netherlands specifically for use in an ED population with cardiac sounding chest pain, is an acronym of its five components: History, ECG, Age, Risk Factors and Troponin¹⁵ with each element scored 0, 1 or 2 to give a total out of 10. HEART is simple to apply and initial evaluation showed HEART outperformed both GRACE and TIMI in its identification of ED patients at low risk of ACS,¹⁵ results that were later confirmed in other cohorts.^{16–18}

Akin to guidance on the use of D-dimer in association with a risk score for the rule-out of venous thromboembolic disease,¹⁹ the future of rapid rule-out AMI strategies may be a combination of a risk score and a single admission draw of hs-cTn,²⁰ but questions still remain regarding the clinical use of such an approach,²¹ particularly the performance of hs-cTn assays early after symptom onset.⁵ Such caveats have resulted in national guidance in some westernised nations, including the USA, that continue to recommend risk stratification using a contemporary (not high-sensitivity) cTn assay.²² Further, hs-cTn testing is not yet ubiquitous in the UK and remains largely unavailable out with Europe where the use of contemporary cTn assays is the rule.

Aims

The primary aim of this study was to determine the accuracy of TIMI, GRACE and HEART scores in combination with a single contemporary cardiac troponin result at presentation to predict a major adverse cardiac event (MACE) within 30 days in adult patients presenting to the ED of a UK hospital with suspected cardiac chest pain. Secondary outcomes included the ability of the scores to determine AMI and to assess the potential clinical implications of prespecified low-risk and high-risk cut-offs.

METHODS

Design and setting

This was a prospective observational study performed in the ED of Aberdeen Royal Infirmary, a large teaching hospital in

the Northeast of Scotland serving a population of approximately 500 000 people.

Participants

Adult patients (≥ 18 years) presenting with chest pain suspicious of ACS without ST elevation on ECG were eligible for the study. Among these patients, those who had real-time completion of the Chest Pain Evaluation Form, with data required for calculation of HEART, TIMI and GRACE scores, were included.

Patients were excluded if any of the following existed: a clear non-cardiac cause of chest pain, cTn drawn solely as part of risk stratification for pulmonary embolism; patients proceeding directly for revascularisation before cTn results are available; or prior study inclusion within the previous 30 days.

Data acquisition and management

The Chest Pain Evaluation Form was completed in two stages; data gained from the patient history, examination and interpretation of the initial ECG were entered by the attending doctor. The first admission cTn and creatinine results were then recorded, allowing calculation of HEART, TIMI and GRACE scores. Variables for each score are displayed in [table 1](#). GRACE score calculation was made using an online calculator (<https://www.mdcalc.com/grace-acs-risk-mortality-calculator>).

The standard of care for clinical decision-making was a contemporary troponin assay (Siemens Troponin I ADVIA Centaur Ultra). For a cTn assay to be characterised as high sensitivity, it has to meet two base criteria.²³ First, the coefficient of variance (CV) at the 99th percentile value of the reference health population should be $\leq 10\%$; and second, the assay should detect cTn above the limit of detection in at least 50% of the reference population. The Siemens assay has a CV of 8.8% at the 99th centile (40 ng/L) and so meets the first criterion, but cTn could only be detected in 47% of the reference population above the limit of detection of 6 ng/L.²⁴ A single value of cTnI >40 ng/L was considered a measure of 'elevated cardiac biomarker' for the purposes of the TIMI and GRACE scores. For the HEART score, values >40 ng/L to ≤ 120 ng/L and >120 ng/L resulted in 1 and 2 points, respectively.

Information from the Chest Pain Evaluation Form was transferred on to a Case Report Form (CRF) and entered on to a securely held Microsoft Excel database.

Data collection

Initially, patients were recruited continuously over 5-day periods in 9 weeks between 2 December 2014 and 16 February 2015 (45 days in total). Due to researcher availability, recruitment continued non-continuously thereafter until 8 February 2016, dependent on the attending clinician completing the appropriate paperwork. The two samples were compared and assessed for any significant differences to ensure the study sample was representative.

Outcomes and definitions

The primary outcome was the development of MACE at 30 days (including the date of presentation). MACE is a composite endpoint that includes AMI, revascularisation procedures (percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG)), cardiac death, cardiogenic shock and life-threatening arrhythmias (VT, VF, complete heart block) requiring emergency intervention. The secondary outcome evaluated was the presence of AMI in the same time frame.

Table 1 Risk score elements and score value

HEART	GRACE	TIMI
History (0–2) Typical features only (2) Typical and atypical features (1) Atypical features only (0)	Age (0–100) Heart rate (0–46)	Age ≥ 65 (1) Regular aspirin usage (1) —
ECG (0–2) >0.5 mm ST depression, new LBBB (2) Repolarisation changes, old ischaemic changes (1) No ischaemic changes (0)	Systolic blood pressure (0–58)	Severe angina (1) ≥ 2 episodes in 24 hours
Age (0–2) ≥ 65 years (2) 45–64 years (2) <45 years (0)	Creatinine (1–28)	Significant ST deviation (1) ST deviation >0.5 mm
Risk factors (0–2) Three risk factors or atherosclerotic disease (2) 1–2 Risk factors (1) No risk factors (0) Risk factors: HTN, HC, DM, BMI>30, smoker, FH CAD Atherosclerotic disease: previous AMI, PCI, CABG, CVA, PVD	Killip score (0–59) Killip class I, II, III, IV	Elevated cardiac enzyme (1) Troponin >40 ng/L
Troponin (0–2) >120 ng/L (2) >40 and ≤ 120 ng/L (1) ≤ 40 ng/L (0)	Cardiac arrest at admission (39)	Known coronary artery disease (1) Previous AMI, >50% stenosis on angiography
	Significant ST deviation (28) ST deviation >0.5 mm	3 Known risk factors (1) HTN, HC, smoker, DM, FH CAD
	Elevated cardiac enzymes (24) Troponin >40 ng/L	

AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass graft; CVA, cerebrovascular accident; DM, diabetes; FH CAD, family history of coronary artery disease; GRACE, Global Registry of Acute Coronary Events; HC, hypercholesterolaemia; HEART, History, ECG, Age, Risk Factors and Troponin; HTN, hypertension; LBBB, left bundle branch block; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; TIMI, Thrombolysis in Myocardial Infarction.

Acute myocardial infarction was defined according to the Third Universal Definition of Myocardial Infarction.²⁵ At the time of data collection, local policy indicated that patients admitted with suspected cardiac chest pain had a second troponin sample taken at 12 hours following presentation. All potential endpoints were reviewed by one author (JGC) independent of the risk scores. Patients with all of a clearly demarcated acute rise and/or fall of cTnI above the 99th percentile, an attending specialist opinion of AMI, and angiographic or other imaging evidence of culprit coronary artery disease were considered to have a diagnosis of AMI. All other potential AMI endpoints were adjudicated by a cardiologist (AN) who was blinded to the risk scores. Any discrepancies between the adjudication of AN, JGC and the attending specialist opinion were resolved by consensus.

PCI included both emergency and elective procedures and was defined as any therapeutic catheter intervention in the coronary arteries. CABG was defined as any cardiac surgery in which coronary arteries were operated on. Cardiogenic shock was defined as a hypoperfusion state with evidence of primary ventricular failure, requiring mechanical or inotropic support, and deaths were considered cardiac unless there was clear documentary evidence to the contrary.

Follow-up

Data regarding the patient's hospital admission and any re-admission to the only regional secondary care facility, within 30 days, were retrieved and transcribed on to the CRF from paper and digital case notes, discharge letters, investigation results, cardiac procedures and other relevant documentation.

NHS Grampian holds an electronic patient record that is linked with primary care facilities in the region. Patients who were registered with a general practitioner in the area had these

scrutinised for evidence of the development of an endpoint at 30 days. These records were interrogated again at a period of 1 year from the index episode to establish there had not been a 30-day MACE that was missed. Patients not registered with a general practice in the region or in whom the presence of an endpoint at 30 days could not be established were considered not to have sufficient data to generate an endpoint.

Sample size calculation

Using pooled data from four previous studies,^{15–17,26} it is expected that 69% of patients would have a HEART score of ≥ 4 (with 22.3% progressing to a 30-day MACE) and 31% would have a HEART score ≤ 3 (with 1.6% progressing to a MACE). Based on these figures, 1000 patients would be able to estimate the sensitivity and specificity of a HEART score ≥ 4 to predict 30-day MACE with sensitivity of 96.9% (95% CI 94.2% to 99.6%) and specificity of 36.3% (95% CI 33.1% to 39.5%).

Statistical analysis

Statistical analysis was carried out using SPSS V.24. Categorical data are presented using frequencies and percentages and continuous data using mean and SD. Differences between groups were assessed with the Student t-test for continuous variables and the χ^2 test for dichotomous variables.

Receiver operator characteristic (ROC) curves were plotted for each of the risk scores. The area under the ROC curve (c-statistic) is an overall summary measure of the diagnostic performance of each of the risk scores.

Sensitivities and specificities (with 95% CI) are calculated for low-risk and high-risk score cut-offs. Low-risk cut-off was defined as a score with sensitivity $\geq 95\%$ and high-risk cut-off

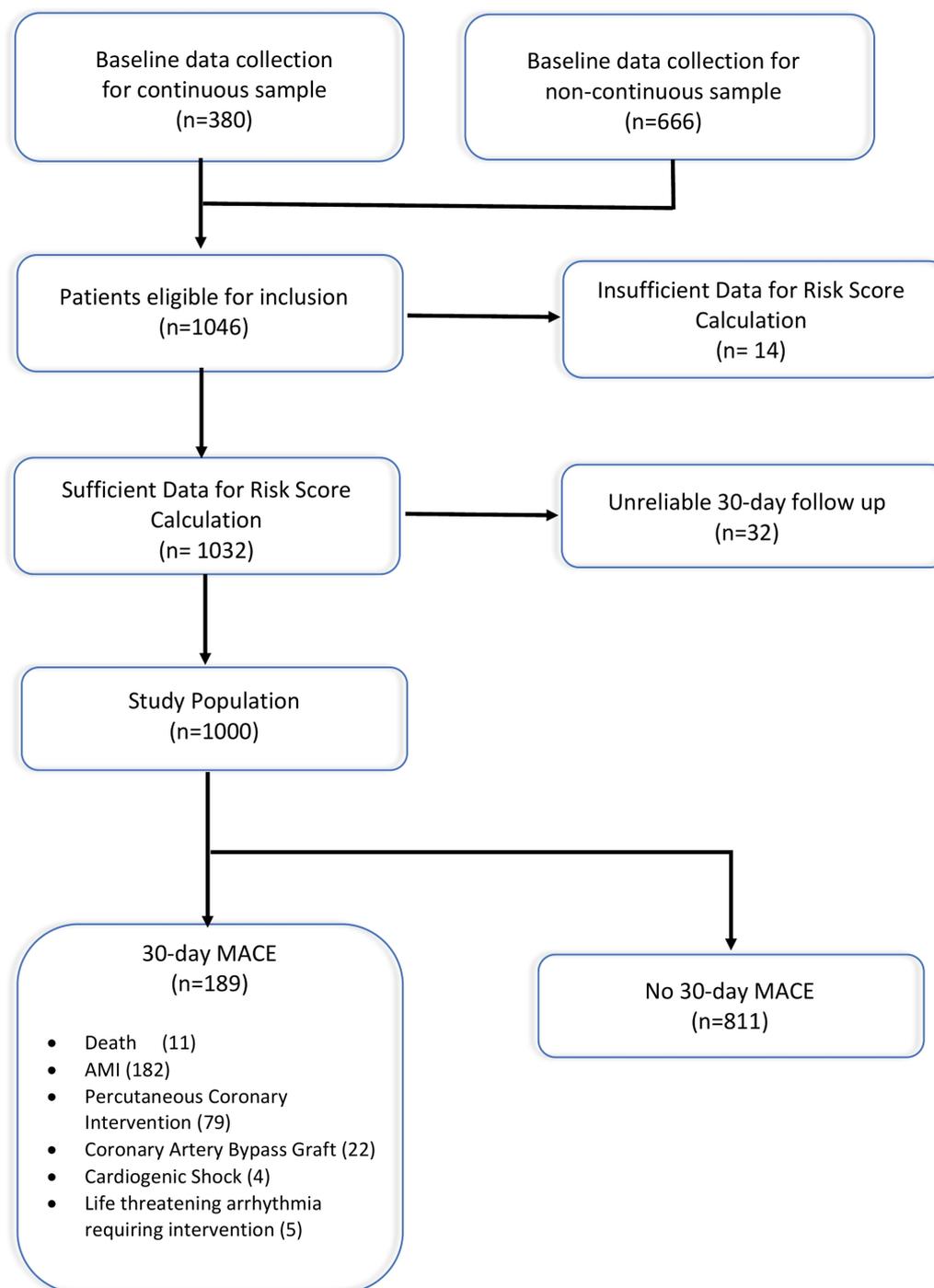


Figure 1 Flow chart of study population. AMI, acute myocardial infarction; MACE, major adverse cardiac event.

was set at a specificity of $\geq 90\%$ (TIMI (low 0; high 5–7), GRACE (low 0–55; high ≥ 119), HEART (low 0–3; high 7–10)). Statistical significance was defined as $P < 0.05$.

RESULTS

Study population

A total of 1046 patients met the study inclusion criteria, and 46 were later excluded, 14 due to absence of data required to calculate risk scores and 32 because of unreliable 30-day follow-up (figure 1). Comparison of baseline data showed that patients included in the study during continuous and non-continuous sampling were similar, with 10 of 13 variables sampled showing no significant difference between the two groups (table 2). Using

the continuous sample as a standard, we estimate during the total study period 28.1% (1046/3724) of eligible patients had Chest Pain Evaluation Forms completed and were considered for study inclusion. The final study population, of 1000 patients, was predominantly men (57.4%) with a mean age of 62.4 years (SD 15.6) and is described in table 3.

Primary endpoint

Of 1000 patients included, 189 (18.9%) developed a 30-day MACE and 182 (18.2%) suffered 30-day AMI. Revascularisation procedures were performed in 101 (10.1%) patients (79 PCI and 22 CABG). Five patients had a life-threatening arrhythmia requiring emergency intervention, four patients developed

Table 2 Comparison of baseline characteristics in continuous and non-continuous samples

	Continuous sample (%)	Non-continuous sample (%)	P values (χ^2 or t-test)	Study population (%)
Total	378	622		1000
Age	62.2 (SD 15.2)	62.6 (SD 15.8)	0.69	62.5 (SD 15.6)
Male gender	221 (58.5)	355 (56.9)	0.62	576 (57.6)
AMI	92 (24.3)	163 (26.1)	0.53	255 (25.5)
PCI	55 (14.6)	95 (15.2)	0.80	150 (15)
CABG	33 (8.7)	43 (6.9)	0.30	76 (7.6)
CVA	31 (8.2)	52 (8.3)	0.96	83 (8.3)
PVD	8 (2.1)	45 (7.2)	<0.001	53 (5.3)
Hypertension	226 (59.8)	357 (57.2)	0.42	583 (58.3)
Hypercholesterolaemia	190 (50.3)	339 (54.3)	0.22	529 (52.9)
Smoker	84 (22.2)	176 (28.2)	0.036	260 (26.0)
Obesity (BMI>30)	88 (23.3)	187 (30.0)	0.021	275 (27.5)
Diabetes	77 (20.4)	124 (19.9)	0.85	201 (20.1)
Family history of CAD	66 (17.5)	94 (15.1)	0.32	160 (16)

AMI, acute myocardial infarction; CAD, coronary artery disease; BMI, body mass index; CABG, coronary artery bypass graft; CVA, cerebrovascular accident; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

cardiogenic shock and 11 patients were classified as cardiac deaths (figure 1).

Patients developing a 30-day MACE were significantly likely to be older, male, hypertensive, hypercholesterolaemic, diabetic and have a history of AMI, PCI, CABG and PVD (table 3).

Risk score distribution and discriminative capacity

All three risk scores displayed significantly higher mean values in patients reaching a 30-day MACE compared with MACE-free patients (table 4). Figure 2 displays, using ROC curves, that the overall discriminatory capacity of the HEART score to predict

Table 3 Study population characteristics in MACE and no MACE patients

	Study population (%)	No 30-day MACE (%)	30-day MACE (%)	P value
Total	1000	811 (81.1)	189 (18.9)	
Age (mean, SD)	62.4 (15.6)	60.8 (SD 15.3)	69.2 (SD 13.9)	<0.001
Gender (male)	574 (57.4)	448 (55.2)	126 (66.7)	0.006
History of AMI	253 (25.3)	189 (23.3)	64 (33.7)	0.003
History of PCI	150 (15.0)	111 (13.7)	39 (20.6)	0.016
History of CABG	76 (7.6)	50 (6.2)	26 (13.8)	<0.001
History of CVA	83 (8.3)	62 (7.6)	21 (11.1)	0.12
History of PVD	53 (5.3)	34 (4.2)	19 (10.1)	0.001
Hypertensive	583 (58.3)	442 (54.5)	141 (74.6)	<0.001
Hypercholesterolaemia	527 (52.7)	402 (49.6)	125 (66.1)	<0.001
Smoker (current/recent <90 days)	260 (26.0)	210 (25.9)	50 (26.5)	0.874
Obese (BMI>30)	275 (27.5)	224 (27.6)	51 (27.0)	0.860
Diabetes	201 (20.1)	144 (17.8)	57 (30.2)	<0.001
Family history of CAD	160 (16.0)	138 (17.0)	22 (11.6)	0.069

AMI, acute myocardial infarction; CAD, coronary artery disease; BMI, body mass index; CABG, coronary artery bypass graft; CVA, cerebrovascular accident; MACE, major adverse cardiac event; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

30-day MACE (0.87 (95% CI 0.84 to 0.9)) was significantly higher than TIMI (0.78 (95% CI 0.74 to 0.81)) and GRACE (0.74 (95% CI 0.7 to 0.78)).

Low risk

A HEART score of ≤ 3 defined 251 patients as low risk, of whom one (0.4%) developed 30-day MACE. GRACE 0–55 and TIMI 0 incorrectly classified 9/212 (4.2%) and 5/224 (2.2%) as low risk, respectively (table 5). Table 6 shows characteristics of patients classified as low risk who developed a MACE.

Further, a HEART score ≤ 3 identified 25.1% of patients as low risk of MACE with a sensitivity of 99.5% (95% CI 97.1% to 99.9%) and negative predictive value (NPV) of 99.6% (95% CI 97.3% to 99.9%) exceeding TIMI 0 and GRACE 0–55 (table 5). HEART score ≤ 3 'ruled out' AMI with a sensitivity of 99.4% (95% CI 96.9% to 99.9%) and NPV of 99.6% (95% CI 97.3% to 99.9%) exceeding TIMI 0 (sensitivity 97.2% (95% CI 93.5% to 99.1%) and NPV 97.8% (95% CI 94.8% to 99.1%)) or GRACE 0–55 (sensitivity 94.9% (95% CI 90.6% to 97.7%) and NPV 95.8% (95% CI 92.2% to 97.7%)).

High risk

The HEART score cut-off of 7–10 identified 195 patients as high risk with a specificity of 90.9% for 30-day MACE compared with GRACE ≥ 119 (160 patients; specificity 89.8%) and TIMI 5–7 (70 patients; specificity 96.8%) (table 5).

With respect to 30-day AMI, a TIMI score of 5–7 had greater specificity (96.7% (95% CI 95.3 to 97.8)) and positive predictive value (PPV) (61.4% (95% CI 50.3 to 71.5)) than HEART 7–10 (specificity 90.6% (95% CI 88.5% to 92.6%); PPV 60.5% (95% CI 54.7% to 66.0%)) and GRACE ≥ 119 (specificity 89.7% (95% CI 87.4% to 91.7%); PPV 46.9% (95% CI 40.4% to 53.5%)), but TIMI 5–7 only recognised 7% patients as high risk compared with the 20% delineated by HEART 7–10.

Troponin alone

Thirty-five patients with an initial cTn ≤ 40 ng/L (99th percentile) developed a 30-day MACE (sensitivity 81.5% (95% CI 75.2% to 86.8%) and NPV 95.6% (95% CI 94.2% to 96.7%)), 22 of whom suffered AMI, and 49 patients with an initial cTn >40 ng/L did not have 30-day MACE (specificity 94.0% (95% CI 92.1% to 95.5%) and PPV 75.9% (95% CI 70.4% to 80.6%)).

Secondary endpoint

Thirty-day AMI was reached in 182 (18.2%) patients and the c-statistic for HEART, GRACE and TIMI were 0.88 (95% CI 0.85 to 0.90), 0.74 (95% CI 0.70 to 0.79) and 0.77 (95% CI 0.73 to 0.81), respectively.

Index admission endpoints

A MACE developed in 185 (18.5%) patients during the index hospital visit. Twelve patients developed MACE after discharge and four of these had been discharged without a MACE. Of these four patients, three developed AMI requiring revascularisation and one underwent PCI without AMI.

DISCUSSION

In 1000 patients presenting to a UK teaching hospital with suspected ACS and no significant ST elevation on initial ECG, 189 (18.9%) proceeded to a MACE at 30 days. The overall discriminatory capacity of HEART exceeds TIMI and GRACE to

Table 4 Mean risk score values and c-statistics of three risk scores

Risk score	Mean (SD)	Mean score with MACE (SD)		P values		C-statistic (95% CI)
		Mean score with MACE (SD)	Mean score no MACE (SD)	MACE vs no MACE	MACE vs no MACE	
HEART	4.9 (2.0)	7.0 (1.6)	4.4 (1.8)	<0.001	<0.001	0.87 (0.84 to 0.9)
GRACE	84.9 (33.2)	107.7 (34.3)	80.2 (31.0)	<0.001	<0.001	0.74 (0.70 to 0.78)
TIMI	2.00 (1.6)	1.7 (1.5)	3.3 (1.5)	<0.001	<0.001	0.78 (0.74 to 0.81)

GRACE, Global Registry of Acute Coronary Events; HEART, History, ECG, Age, Risk Factors and Troponin; TIMI, Thrombolysis in Myocardial Infarction.

predict 30-day MACE (table 4 and figure 2) and is comparable with previous prospective work.^{16–18}

This study demonstrates that, using a single draw contemporary cTn at presentation, a HEART score ≤ 3 identified 25% of patients as low risk for 30-day MACE with excellent sensitivity (99.5% (95% CI 97.1% to 99.9%)) and NPV (99.6% (95% CI 97.3% to 99.9%)) and demonstrated similar performance for 30-day AMI (sensitivity 99.4% (95% CI 96.9% to 99.9%) and NPV 99.6% (95% CI 97.3% to 99.9%)). In both instances, the point estimates meet the criteria for a diagnostic rule-out test in this clinical setting.²⁷

We used the primary outcome of 30-day MACE, a composite endpoint that collects important outcomes additional to AMI. It is recognised that revascularisation and death are likely influenced by other aspects of the healthcare system, so evidence in this cohort that a HEART score ≤ 3 performed with comparable sensitivity and NPV in detecting 30-day AMI was reassuring.

Only one patient was ascribed a low-risk HEART score and subsequently developed a MACE. He was a 63-year-old man with no known cardiovascular risk factors. He was diagnosed with a non-ST-elevated myocardial infarction and received PCI. He was also classified as low risk by the TIMI score (table 6).

These results are inconsistent with a recently published meta-analysis of the HEART score²⁸ in which the authors state a lower pooled sensitivity for HEART score ≤ 3 to predict MACE (96.7% (95% CI 94.0% to 98.2%)). Though they acknowledge the flaws in their analysis, the authors recommend caution when using HEART score ≤ 3 . Previously, lowering the cut-off

to HEART ≤ 2 has been suggested,¹⁷ but while increasing sensitivity, this may dramatically reduce the clinical use. Others have adopted repeat cTn sampling at 2–3 hours in an ADP. This is not ideal for prompt ‘rule out’ but does appear to heighten diagnostic performance both for TIMI^{12,13} and HEART.²⁹

It is not clear why our study should demonstrate better results regarding the ‘rule out’ potential of HEART ≤ 3 than previous work. Aberdeen Royal Infirmary serves a large geographic area and transit times to hospital are often prolonged. The Siemens assay is well established and, though not high, sensitivity is close to it.²⁴ However, when analysed in isolation, an admission cTn <99th centile demonstrated sensitivity of only 81.5% (95% CI 75.2% to 86.8%) and NPV 95.6% (95% CI 94.2% to 96.7%). We did not record time from pain to cTn draw, but this would have been useful.

Newer bespoke tools have been developed for assessing risk in ED populations such as the Manchester Acute Coronary Syndromes rule,³⁰ the Christchurch Emergency Department Acute Coronary Syndrome ADP³¹ and the Triage rule-out using hs-cTnI ADP,³² and future prospective comparison of these scores with HEART will prove important.

The HEART score has been prospectively evaluated using hs-cTn^{20,33} but with varying performance. Since the Troponin aspect of the HEART score is expressed as multiples of the 99th percentile (to allow use with different assays), how this translates into its use with hs-cTn below the limit of detection (LoD), in line with recent NICE guidance,⁸ is also a matter for further work.

The initial evaluation of the NICE single-draw strategy²¹ identified that a hs-cTnT <5 ng/L (LoD) in conjunction with a normal ECG and TIMI 0 had a sensitivity of 99.5% (95% CI 98.1% to 99.9%) and NPV 99.6% (95% CI 98.7% to 100%) for 30-day MACE and using a hs-cTnI <2 ng/L (LoD) sensitivity 98.9% (95% CI 97.4% to 99.6%) and NPV 99.5% (95% CI 98.8% to 99.8%) identifying 17.9% and 21.0% as low risk, respectively, though it may be that higher thresholds of each assay could be employed to identify more patients without compromising sensitivity and NPV.

One might contend that there is no need for structured clinical risk scoring at all and that a normal ECG and very low level of cTn at presentation⁴ and a clinical impression of low risk⁹ is sufficient to adequately identify this population. However, risk scores allow an objective, if perhaps perceived, level of safety in ensuring that all important aspects of risk stratification are considered regardless of the level of experience of the attending doctor. The HEART score is simple to calculate at the bedside and its elements (History, ECG, Age, Risk Factors and Troponin) are intuitive. Chest pain typicality is often not discriminatory³⁴ but other aspects of the history may be important³⁰ and ECG interpretation can vary with experience, but these subjective elements are balanced by objective recording of age, risk factors and cTn level.

With regard to rule-in of 30-day MACE and AMI, TIMI 5–7 allocated 70 patients to the high-risk group with specificity

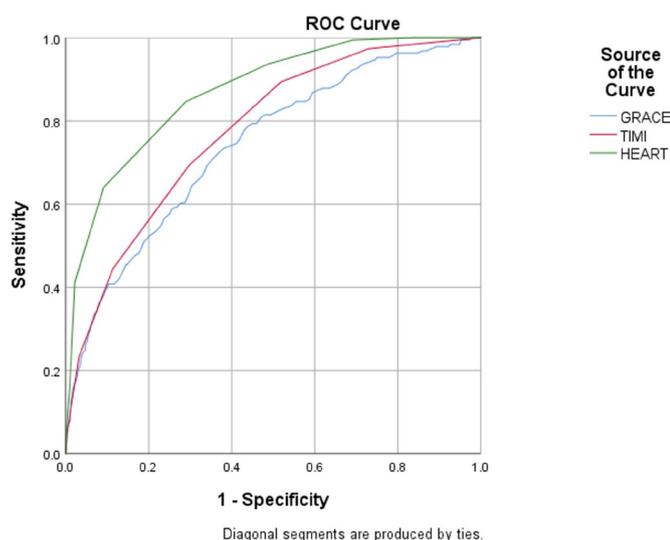


Figure 2 Receiver operating characteristic (ROC) curve for HEART (History, ECG, Age, Risk Factors and Troponin), TIMI (Thrombolysis in Myocardial Infarction) and GRACE (Global Registry of Acute Coronary Events)—30-day major adverse cardiac event. C-statistic: HEART (0.87 95% CI 0.84 to 0.90), TIMI (0.78 95% CI 0.74 to 0.81), GRACE (0.74 95% CI 0.70 to 0.78).

Table 5 Risk stratification (high and low risk) of three risk scores

	GRACE	TIMI	HEART
Low risk score sensitivity $\geq 95\%$	0–55	0	0–3
No of low-risk patients (% total (95% CI))	212 (21.2 (18.8 to 23.8))	224 (22.4 (19.9 to 25.1))	251 (25.1 (22.5 to 27.9))
Low risk developing MACE/total low risk (% (95% CI))	9/212 (4.2 (2.3 to 7.9))	5/224 (2.2 (0.1 to 5.1))	1/251 (0.4 (0.07 to 2.2))
Sensitivity (95% CI)	95.2 (91.1 to 97.8)	97.4 (93.9 to 99.1)	99.5 (97.1 to 99.9)
NPV (95% CI)	95.8 (92.2 to 97.7)	97.8 (94.8 to 99.1)	99.6 (97.3 to 99.9)
Specificity (95% CI)	25.0 (22.1 to 28.2)	27.0 (24.0 to 30.2)	30.8 (27.7 to 34.1)
PPV (95% CI)	22.8 (22.0 to 23.8)	23.7 (22.9 to 24.6)	25.1 (24.2 to 26.0)
High risk score specificity $\geq 90\%$	≥ 119	5–7	7–10
No of high-risk patients (% total (95% CI))	160 (16.0 (13.9 to 18.4))	70 (7.0 (5.6 to 8.8))	195 (19.5 (17.1 to 22.1))
High-risk patients developing MACE/total high risk (% (95% CI))	69/160 (43.1 (35.7 to 50.9))	44/70 (62.9 (51.2 to 73.2))	121/195 (62.1 (55.1 to 68.6))
Sensitivity (95% CI)	40.7 (33.7 to 48.1)	23.3 (17.5 to 30.0)	64.0 (56.7 to 70.9)
NPV (95% CI)	86.7 (85.2 to 88.0)	84.4 (83.3 to 85.4)	91.6 (90.0 to 92.9)
Specificity (95% CI)	89.8 (87.5 to 91.8)	96.8 (95.3 to 97.0)	90.9 (88.7 to 92.8)
PPV (95% CI)	48.1 (41.5 to 54.8)	62.9 (51.7 to 72.8)	62.1 (56.2 to 67.6)

GRACE, Global Registry of Acute Coronary Events; HEART, History, ECG, Age, Risk Factors and Troponin; MACE, major adverse cardiac event; NPV, negative predictive value; PPV, positive predictive value; TIMI, Thrombolysis in Myocardial Infarction.

(96.8% (95% CI 95.3 to 97.0) greater than HEART 7–10 (90.9 (95% CI 88.7 to 92.8)), but 195 people were identified as high risk using the HEART cut-off and PPVs were comparable. These

results may help streamline regional processes and access to invasive management strategies in the future.

Table 6 Characteristics of patients classified as low risk with missed MACE

Age, gender risk score	Risk factors	Endpoint	HEART	GRACE	TIMI
HEART					
63, Male*	Nil	NSTEMI and PCI	3	57	0
GRACE					
40, Male	HTN, smoker	NSTEMI and PCI	4	35	1
33, Female	HC, smoker	NSTEMI	5	42	1
40, Male	HTN, HC, smoker, DM	NSTEMI and PCI	4	35	2
39, Male	HTN, HC, smoker, FH CAD	NSTEMI and PCI	7	45	3
41, Male	HTN, smoker, FH CAD	NSTEMI	6	53	4
43, Male	HTN, smoker, FH CAD	NSTEMI and PCI	7	47	2
38, Male	AMI, PCI, HC, smoker, FH CAD	NSTEMI	4	28	3
42, Male	FH CAD	NSTEMI and PCI	4	38	1
41, Female	FH CAD	NSTEMI	5	52	1
TIMI					
63, Male*	Nil	NSTEMI and PCI	3	57	0
73, Male	Nil	NSTEMI	5	133	0
60, Female	HTN	NSTEMI	4	79	0
60, Male	Smoker	NSTEMI	4	87	0
64, Female	Nil	NSTEMI	6	85	0

*Indicates patient appears both in HEART and TIMI low-risk group. DM, diabetes mellitus; FH CAD, family history of coronary artery disease; GRACE, Global Registry of Acute Coronary Events; HC, hypercholesterolaemia; HEART, History, ECG, Age, Risk Factors and Troponin; HTN, hypertension; NSTEMI, non-ST-elevated myocardial infarction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

Limitations

This is only a single-centre study, and though a sample size calculation was performed a priori and the results strongly recommend the use of the HEART score in our population to identify patients at low risk, we note that the lower 95% CI for sensitivity is 97.1% and NPV 97.3%. We would therefore recommend that these results are thoughtfully interpreted. The prospective design and collection of real-time data was a strength of the study, but practicalities restricted the duration over which a continuous sample could be taken. During the study period, only 1046 of 3724 (28.1%) potentially eligible patients were included on account of the fact that completion of the documentation to calculate the scores was reliant on the attending physician. While non-continuous recruitment to the study may have resulted in a potential source of selection bias, we attempted to address this by comparing the non-continuous sample with the more comprehensive continuous sample. Table 2 shows that both these groups are largely similar with no statistically significant difference evident in 10 of the 13 variables sampled.

The AMI adjudication procedure is outlined in the methods. Though we believe the adjudication process to be robust, it is recognised that it would have been ideal to have all potential endpoints verified independently by two independent cardiologists.

The 30-day follow-up via the methods described is very effective in the region. We excluded anyone in whom we could not find reliable medical information on beyond 30 days from the study population but understand that the gold standard would have been to make direct patient contact at 30 days.

CONCLUSIONS

In a prospective UK cohort of patients presenting to the ED with cardiac sounding chest pain and a non-diagnostic ECG, the HEART score is superior to both TIMI and GRACE in ability to determine 30-day MACE and AMI. Also, using a single draw contemporary cTn as biomarker, a HEART score ≤ 3 demonstrated high sensitivity and NPV, which may allow this cut-off to be incorporated into an early discharge strategy. However,

the NPV is higher than that reported in previously published work and therefore should be interpreted thoughtfully and with caution.

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Contributors PDWR: planning, data collection, data recording, statistical analysis, writing and review. JGC: planning, data collection, data recording, endpoint review, statistical analysis, document writing and review. HIE: data collection, data recording, statistical analysis, document review. AN: endpoint review, document review.

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