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HEART-score can be simplified without loss of discriminatory power in patients with chest pain – Introducing the HET-score

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ABSTRACT

Background: The History, Electrocardiogram (ECG), Age, Risk factors and Troponin, (HEART) score is useful for early risk stratification in chest pain patients. The aim was to validate previous findings that a simplified score using history, ECG and troponin (HET-score) has similar ability to stratify risk.
Methods: Patients presenting with chest pain with duration of ≥10 min and an onset of last episode ≤12 h but without ST-segment elevation on ECG at 6 emergency departments were eligible for inclusion. The HEART-score and the simplified HET-score were calculated. The endpoint was a composite of myocardial infarction (MI) as index diagnosis, readmission due to new MI or death within 30 days.
Results: HEART-score identified 32% as low risk (0-2p), 47% as intermediate risk (3-5p), and 20% as high risk (6-10p) patients. The endpoint occurred in 0.5%, 7.3% and 35.7%, respectively. HET-score identified 39%, 42% and 19% as low- (0p), intermediate- (1-2p) and high-risk (3-6p) patients, with the endpoint occurring in 0.6%, 6.2% and 43.2%, respectively.
When all variables included in the HEART-score were included in a multivariable logistic regression analysis, only History (OR, CI [95%]): 2.97(2.16–4.09), ECG (1.61[1.14–2.28]) and troponin level (5.21[3.91–6.95]) were significantly associated with cardiovascular events. When HEART- and HET-score were compared in a ROC-analysis, HET-score had a significantly larger AUC (0.887 vs 0.853, $p < 0.001$).
Conclusions: Compared with HEART-score, HET-score is simpler and appears to have similar ability to discriminate between chest pain patients with and without cardiovascular event.

1. Introduction

Patients with chest pain account for a large number of visits to the Emergency Department (ED) and chest pain is the second most common complaint in the ED [1-3]. Patients present with a spectrum of signs and symptoms reflecting the many potential etiologies of chest pain. Diseases of the heart, aorta, lungs, esophagus, stomach, mediastinum, pleura, and abdominal viscera may all cause chest discomfort and make the assessment challenging. Among unselected patients with chest pain presenting to the ED, <10% are found to suffer from acute coronary syndrome (ACS) [4], whereas a small number of patients who indeed have ACS are mistakenly discharged from the ED [5].

To facilitate decision-making in the ED, a safe rule-in and rule-out algorithm of ACS is of great value. A number of recent studies have suggested that the combination of cardiac troponins and clinical data such as risk factors and electrocardiogram (ECG) are useful in terms of reducing admission rates, shorten hospital stays and lower healthcare costs without additional risks [6,7]. The HEART-score has been shown to be useful for early risk stratification in patients with suspected ACS [8,9]. The HEART-score involves five variables (History, ECG, Age, Risk factors,

Abbreviations: Emergency Departments, ED; acute coronary syndrome, ACS; electrocardiogram, ECG; left bundle branch block, LBBB; high-sensitive Troponin, hs-cTn; limit of detection, LoD; receiver operating curves, ROC; area under the curve, AUC; myocardial infarction, MI; odds ratio, OR; confidence interval, CI.

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Table 1
Baseline characteristics.

	All $n = 1181$	CV-event $n = 129$	No CV-event $n = 1052$	p
Demography				
Age (median) (IQR)	64 (53–73)	70 (61–77)	63 (53–72)	<0.001
Female	524 (44.4)	37 (28.7)	487 (46.4)	<0.001
Risk factors				
Family history CAD	392 (33.2)	38 (29.5)	354 (33.7)	0.336
Previuos or current smoking	597 (50.7)	73 (56.6)	524 (50.0)	0.155
Current smoker	140 (11.9)	18 (14.0)	122 (11.6)	0.442
BMI >30	222 (18.9)	20 (15.5)	202 (19.4)	0.291
Diabetes Mellitus	160 (13.6)	22 (17.1)	138 (13.1)	0.221
Treated hypertension	532 (45.1)	72 (55.8)	459 (43.8)	0.009
Chronic kidney disease	36 (3.1)	11 (8.5)	25 (2.4)	<0.001
Prev. cardiovacular disease				
Angina Pectoris	252 (21.4)	38 (29.5)	214 (20.4)	0.018
Previous PCI/CABG	248 (21.1)	23 (18.0)	225 (21.4)	0.362
Previous MI	248 (21.0)	28 (21.7)	220 (21.0)	0.943
Previous stroke	103 (8.7)	12 (9.3)	91 (8.7)	0.812
Known heart failure	55 (4.7)	4 (3.1)	51 (4.9)	0.375
Medication at presentation				
Aspirin/P2Y12-rec blockers	375 (31.8)	53 (41.4)	322 (30.7)	0.008
ACE-inhibitor	403 (34.2)	45 (35.2)	358 (34.1)	0.781
Betablocker	428 (36.3)	46 (35.9)	382 (36.4)	0.777
Lipid-lowering drugs	369 (31.3)	45 (35.2)	325 (30.9)	0.380
Presentation characteristics				
Heart rate (median) (IQR)	70 (61–82)	73 (61–88)	70 (61–81)	0.033
Pulmonary rales	49 (4.2)	10 (7.9)	39 (3.7)	0.028
Abnormal ECG	311 (26.3)	62 (48.1)	249 (23.7)	<0.001
Troponin elevation at arrival	266 (22.5)	101 (78.3)	165 (15.7)	<0.001

CV = Cardiovascular, IQR = Interquartile range, CAD = coronary artery disease, BMI= Body mass index, PCI=Percutaneous coronary intervention, CABG = Coronary artery by-pass grafting, MI = Myocardial infarction, ACE = Angiotensin converting enzyme, ECG = Electrocardiogram.

Troponin) and has been validated in previous studies [8-10]. Retrospective data have suggested a limited additional value of age and risk factors, and the simpler HET-score, involving only three variables (History, ECG and Troponin) to have similar discriminatory ability [11,12]. To the best of our knowledge, the HET-score has yet to be prospectively tested.

The objective of this study was to validate previous findings, suggesting that a simplified HET-score can replace the more complicated HEART-score, without compromising on diagnostic accuracy and risk stratification. We also wanted to compare these scores in patients with and without initial troponin values within the normal range.

2. Methods

The Fast ASsessment of Thoracic pain in the ED using high-Sensitive Troponins and a simple risk score (FASTEST) study was a prospective observational multicentre study conducted at six centers in two phases in Stockholm and Uppsala, Sweden. Patients presenting to the ED with symptoms suggestive of ACS were eligible for inclusion. Inclusion criteria were (1) age ≥ 18 years, (2) chest pain suggestive of ACS with duration of ≥10 min and an onset of last episode ≤12 h, (3) willingness to have blood samples drawn according to the study protocol and (4) a signed written informed consent. Exclusion criteria were (1) ST-segment elevation or new or presumed new left bundle branch block (LBBB) on ECG at presentation, (2) previous participation in the study or (3) presentation outside of office hours, defined as non-holiday weekdays from 8 am to 5 pm. The rationale for excluding new or presumed new LBBB was based on European guidelines available at the time the study was planned in 2013 [13]. We excluded patients presenting outside office hours because of the need of dedicated research nurses taking care of blood sampling and prospective entering of all data to a study database. FASTEST was conducted according to the principles of the Declaration of Helsinki and approved by the Regional Ethical Review Board in Stockholm, Sweden (approval number 2013/621–31/4).

The study evaluated two different diagnostic strategies for patients presenting to the ED with symptoms suggestive of ACS. Either according to guidelines or according to a new diagnostic strategy which applied a modified one-hour high-sensitive Troponin (hs-cTn) algorithm. The strategies were evaluated separately and thus the study was divided into two phases, before and after the implementation of a new diagnostic strategy. During phase 1 (June 4, 2013- September 2, 2014), patients were assessed according to local guidelines based on recommendations from the ESC and American College of Cardiology/American Heart Association [14,15]. This included clinical assessment, ECG recordings and measurement of troponin at presentation and after 3–6 h if ACS was still suspected. During this phase, the HEART-score was calculated retrospectively. Information on ECG, age, risk factors and troponin were prospectively collected whereas information on symptoms were obtained from medical records and scored 0–2 by a well-trained physician unaware about outcome. During phase 2 (January 27, 2015- May 20, 2016), patients were assessed prospectively by the attending physician, and the HEART-score was calculated at the time of presentation. In all patients with a baseline level of high-sensitivity cardiac troponin (hs-cTn) within the normal reference range, a one-hour hs-cTn sample was obtained and the delta value was calculated. In patients with a delta value <3 ng/L for hs-cTnT (Elecsys hs-cTnT assay, Roche Diagnostics, Basel, Switzerland) or < 6 ng/L for hs-cTnI (ARCHITECT STAT hs-cTnI assay, Abbott Laboratories, IL, USA) and a HEART-score ≤ 3, ACS was considered unlikely, and the patients could be discharged if no other serious condition was suspected. After discharge, patients were followed up by a telephone call 30 days from inclusion regarding procedures and clinical outcomes.

HEART score is an acronym consisting of the following variables: History, ECG, Age, Risk factors and Troponin. The tested HET-score includes only History, ECG and Troponin. History reflects the described chest pain, the character of the pain translates into a score according to the likelihood of pain to be due to ischemic myocardium, angina pectoris. Typical anginal features such as retrosternal central pressure, tightness and heaviness give the maximum of 2 points. Non-cardiac pain features such as pain reproduceable during motion or body positions, sharp or fleeting in character gives 0 point and a mixture of typical anginal and non-cardiac pain features 1 point. ECG indicative of ongoing ischemia with significant ST-deviation gives the maximum of 2 points, whereas non-specific disturbances result in 1 point and a normal ECG in no point. Age is as follows: 2 points if >65 years of age and 1 point if 46–65 years. Individuals 45 years or younger get 0 points. Risk factors such as family history, smoking, diabetes, and hypertension are counted and if 1 or 2 are noted it reflects 1 point whereas >2 risk factors or known atherosclerotic disease reflect 2 points and no known risk factors is 0 point. Troponin is included as the last variable and only the first analysed value is included in the score. The value corresponding to the 99th percentile was considered as the threshold for normal range and below this value is 0 points, between one to three times this threshold value received 1 point while more than three times the threshold value received 2 points. To create risk-groups of similar sizes, low-, intermediate and high-risk groups were retrospectively defined as score 0–2, 3–5 and 6–10 for HEART-score, and as score 0, 1–2 and 3–6 for HET-score.

The Elecsys hs-cTnT assay (Roche Diagnostics, Basel, Switzerland) was used during both phase 1 and 2 at five centers, whereas one centre used the ARCHITECT *STAT* hs-cTnI assay (Abbott Laboratories, IL, USA) or the Stratus CS instrument (Siemens Healthcare Diagnostics, Deerfield, IL) during phase 1 and only the hs-cTnI assay during phase 2. Hs-cTnT was analysed either with a Roche-Modular® E or a Roche-Cobas® 8000 e602. This assay has a limit of detection (LoD) of 5 ng/L, a 99th percentile of healthy controls of 14 ng/L and a coefficient of variation of <10% below the 99th percentile [16]. The ARCHITECT $i2000_{SR}$ assay has a LoD of 1.2 to 1.9 ng/L [17,18]. According to the manufacturer, the single and sex-specific (men/women) 99th percentiles of healthy controls are 26 ng/L and 34.2 /15.6 ng/L,

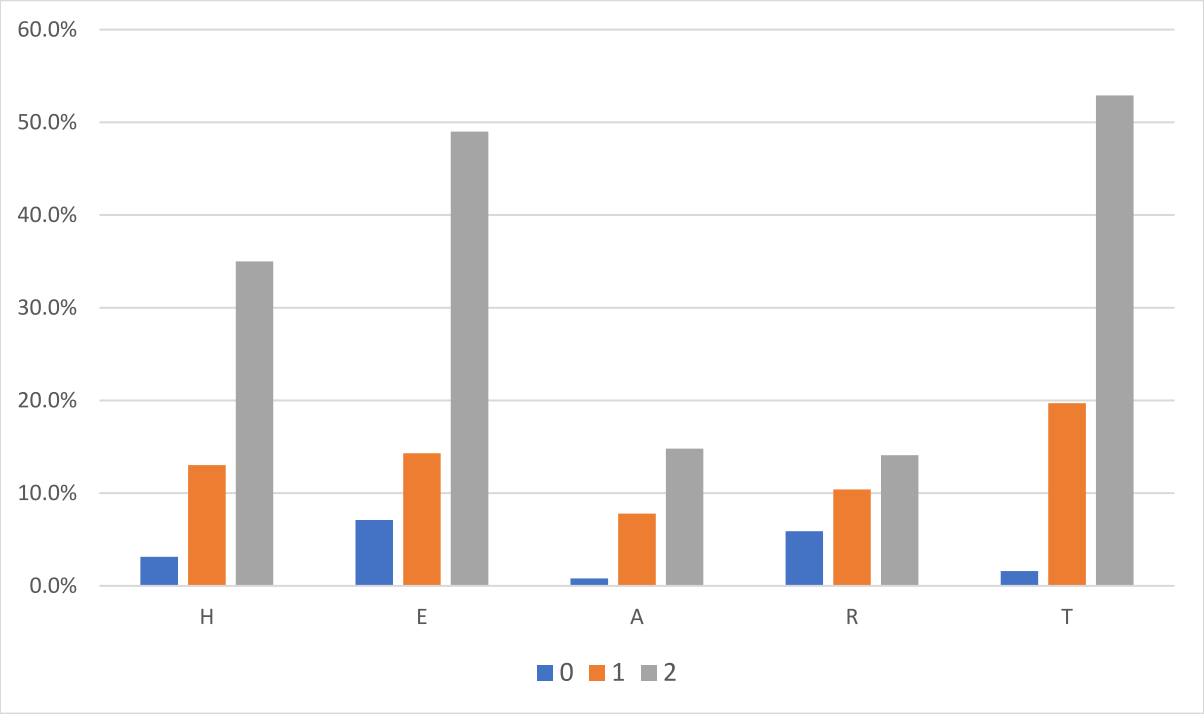

Fig. 1. Events in relation to score. Proportion of patients with cardiovascular events in relation to score given for History, ECG, Age, Risk factors and Troponin level.

respectively, and the assay has a coefficient of variation of <10% below the 99th percentile. The LoD of the Stratus CS assay is 0.03 μg/L, the 99th percentile of healthy controls is 0.07 μg/L, and the lowest concentration assuring a 10% coefficient of variation is 0.06 to 0.10 μg/L [19,20].

The endpoint was the composite of myocardial infarction (MI) as index diagnosis, readmission to the hospital due to a new MI or cardiovascular death within 30 days. All MI:s were centrally adjudicated by two independent cardiologists.

2.1. Statistical analyses

Categorical variables are presented as numbers and percentages and continuous data as medians with interquartile ranges [IQR]. The chi-square test or the Fisher's exact test were used to compare differences in proportions between the two groups. The Mann-Whitney *U* test was used to compare continuous variables.

Logistic regression analyses were performed as follows: Univariable analyses to examine the association between variables included in HEART-score and outcome. Multivariable analysis, in which all HEART-score variables were forced into the model, was performed on complete cases to compare the relative importance of each variable.

The HEART-score and the HET-score were compared by using receiver operating characteristic (ROC) curves and the area under the curve (AUC) presented. In addition to comparisons between HEART- and HET-score in all patients, we also compared these scores in those with and without normal levels of troponins at presentation. As sensitivity analyses multivariable analysis and estimation of AUC were also performed in patients included in phase 2 in which all HEART scoring was performed prospectively. All statistical analyses were performed using IBM SPSS Statistics version 28.

3. Results

During the two study periods, 1233 patients (612 in phase 1 and 621 in phase 2) with symptoms suggestive of ACS were included in the study cohort. Out of these, 52 patients had missing data for any variable included in the HEART-score, leaving 1181 patients in the present analyses. Baseline characteristics are detailed in Table 1. The median age was 64 [IQR 53–73] years and 524 (44%) were women. Overall, 532 (45%) had hypertension, 160 (14%) diabetes mellitus, 252 (21%) previously known angina pectoris. Previous revascularization (PCI/CABG) was observed in 248 (21%) and previous MI in 248 (21%).

A total of 129 (11%) patients were diagnosed with MI as index diagnosis ($n = 124$), were readmitted because of a new MI ($n = 6$) or

Table 2
Logistic regression analysis.

	Univariable analysis			Multivariable analysis All patients			Multivariable analysis Patients without troponin elevation			Multivariable analysis Patients with troponin elevation		
	OR	(95%CI)	p	OR	(95%CI)	p	OR	(95%CI)	p	OR	(95%CI)	p
History	3.95	(3.02–5.17)	<0.001	2.97	(2.16–4.09)	<0.001	2.93	(1.61–5.35)	<0.001	2.71	(1.86–3.95)	<0.001
ECG	2.95	(2.23–3.89)	<0.001	1.61	(1.14–2.28)	0.007	2.76	(1.49–5.13)	0.001	1.64	(1.12–2.42)	0.012
Age	2.33	(1.66–3.27)	<0.001	1.01	(0.66–1.56)	0.953	2.19	(0.99–4.82)	0.052	0.50	(0.29–0.86)	0.012
Risk Factors	1.54	(1.20–1.97)	0.001	0.72	(0.52–1.00)	0.051	1.09	(0.61–1.95)	0.764	0.64	(0.43–0.94)	0.022
Troponin	6.21	(4.83–7.99)	<0.001	5.21	(3.91–6.95)	<0.001	–	–	–	–	–	–

The multivariable analyses encompass adjustment for all listed variables. Endpoint is the composite of myocardial infarction (MI) as index diagnosis, readmission to the hospital due to a new MI or cardiovascular death within 30 days.

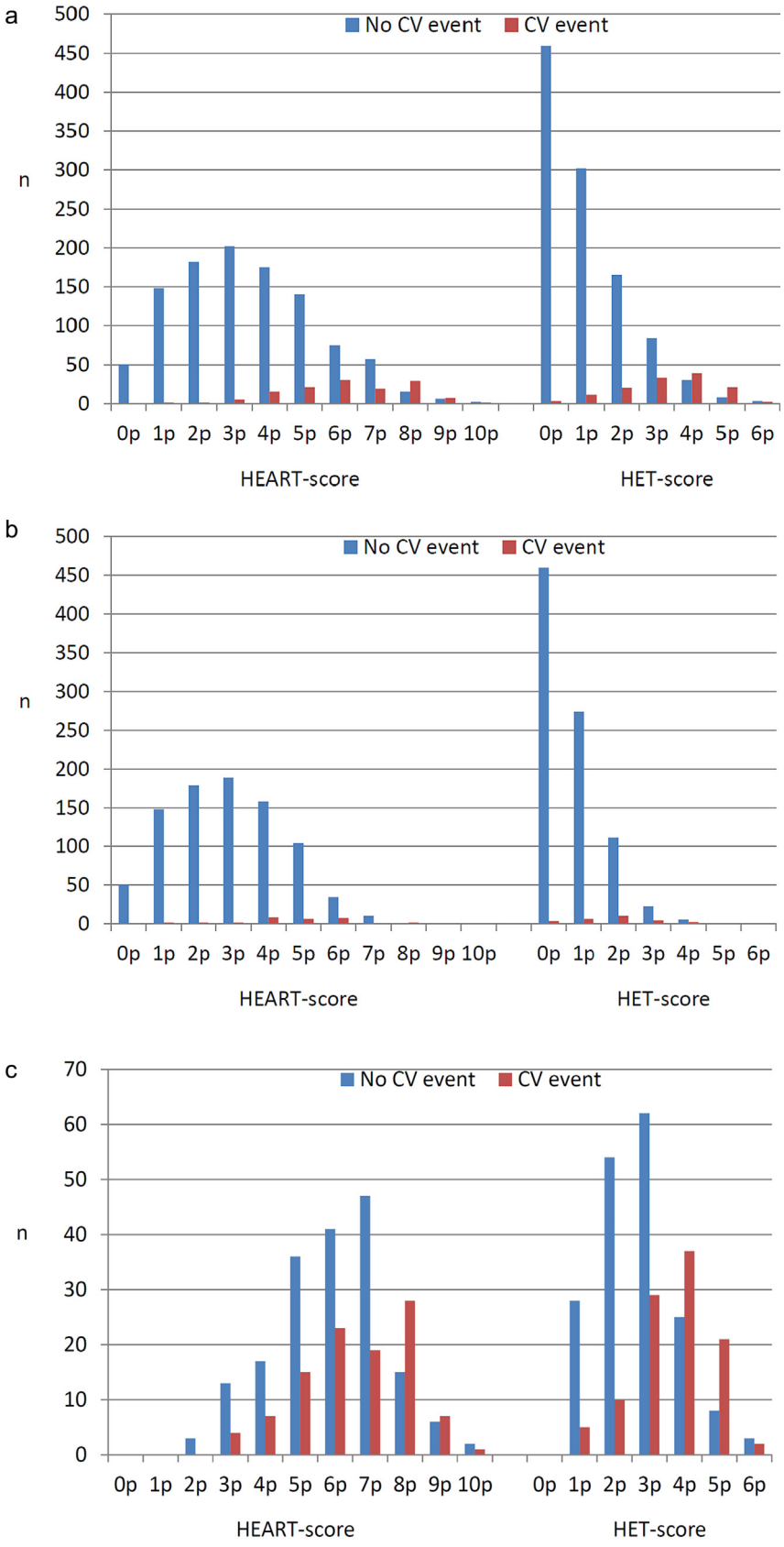

Fig. 2. Distribution of HEART- and HET-score in patients without and with a cardiovascular event: (a) all patients, (b) patients without and (c) with elevated troponin at presentation.

Table 3
Risk groups according to HEART- and HET-score.

a. All Patients			
HEART score			
Risk-group	score	n = 1181	Risk of CV-event
Low	0–2	382 (32.3%)	0.5%
Intermediate	3–5	558 (47.2%)	7.3%
High	6–10	241 (20.4%)	35.7%
HET score			
Risk-group	score	n = 1181	Risk of CV-event
Low	0	463 (39.2%)	0.6%
Intermediate	1–2	498 (42.2%)	6.2%
High	3–6	220 (18.6%)	43.2%
b. Patients without elevated troponin at presentation			
HEAR(T) score			
Risk-group	score	n = 897	Risk of CV-event
Low	0–4	735 (81.9%)	1.5%
Intermediate	5–8	162 (18.1%)	8.6%
HE(T) score			
Risk-group	score	n = 897	Risk of CV-event
Low	0–1	743 (82.8%)	1.2%
Intermediate	2–4	154 (17.2%)	10.4%
c. Patients with elevated troponin at presentation			
HEART score			
Risk-group	score	n = 284	Risk of CV-event
Low	0–4	44 (15.5%)	25.0%
Intermediate	5–8	240 (84.5%)	38.7%
HET score			
Risk-group	score	n = 284	Risk of CV-event
Low	0–1	33 (11.6%)	17.8%
Intermediate	2–4	251 (88.4%)	39.4%

died due to cardiovascular disease ($n = 2$) during the first 30 days from presentation and thus met the endpoint criteria. These were older, more often males, had more often a history of hypertension, chronic kidney disease and angina pectoris, and more often used antiplatelet therapy (Table 1). Patients with a cardiovascular event also presented with a higher heart rate and more often with pulmonary rales, abnormal ECG and an elevated troponin level.

All variables included in the HEART-score were associated with the risk of a cardiovascular event (Fig. 1 and S1). In univariable logistic regression analyses, the score-variable reflecting the troponin level had the strongest association with the risk of cardiovascular event (OR [95%CI]): 6.21 (4.83–7.99), followed by the score-variables based on history (3.95 [3.02–5.17]) and ECG (2.95 [2.23–3.89]) (Table 2).

The distributions of HEART- and HET-score in those with and without a cardiovascular event are shown in Fig. 2a. HEART-score identified 32% as low risk (0-2p), 47% as intermediate risk (3-5p), and 20% as high risk (6-10p) patients. The endpoint occurred in 0.5%, 7.3% and 35.7%, respectively (Table 3a). HET-score identified 39%, 42% and 19% as low risk (0p), intermediate risk (1-2p) and high-risk (3-6p) patients, with the endpoint occurring in 0.6%, 6.2% and 43.2%, respectively.

Also, when examining those without ($n = 897$) and with ($n = 284$) elevated troponin at presentation, HET-score had a similar ability to risk stratify individuals into low-, intermediate- and high risk (Fig. 2b-c, Table 3b-c). To reach a risk of CV-events <1% in those without elevated troponin at presentation, a cut-off <4 (566 [63%] with CV-risk of 0.5%) for HEART-score and < 1 (460 [51%] with CV-risk of 0.7%) for HET-score was needed.

When all variables included in HEART-score were included in a multivariable logistic regression analysis, only history (OR [95%CI]: 2.97 [2.16–4.09], ECG 1.61 [1.14–2.28] and troponin level 5.21 [3.91–6.95]) were significantly associated with cardiovascular events (Table 2). Age was not associated with an increased risk and for risk factors there was even a trend towards a lower risk (0.72 [0.52–1.00]) of a cardiovascular event. In patients without elevated troponin level, history and ECG were still significantly associated with cardiovascular events whereas age and risk factors were not. In patients with elevated troponin at presentation, history and ECG were significantly associated with higher risk of cardiovascular events whereas age and risk factors were significantly associated with a lower risk of events. When HEART- and HET-score were compared in a ROC-analysis, HET-score had a significantly larger AUC (0.887 vs 0.853, $p < 0.001$, Fig. 3a). Measures of diagnostic performance for different cut-off values are listed in table S1 (Supplemental material). When performing the same analysis in those without elevated troponin level on admission, the AUCs were similar (0.795 vs 0.802, $p = 0.828$, Fig. 3b), whereas in those with elevated troponin level, the HET-score had a significantly larger AUC (0.731 vs 0.619, $p < 0.001$) (Fig. 3c). As sensitivity analyses, the same multivariable logistic regressions analysis and ROC-analysis were performed in only patients included in phase 2 of the study, resulting in similar results (supplemental material, Table S2 and Fig. S2).

4. Discussion

The key finding of this study was that the simplified HET-score performed similar to the HEART-score when applied to patients presenting with chest discomfort at the ED. HET-score could identify almost 4 out 10 to be low-risk patients with a risk of cardiovascular event within 30 days of 0.6%. Another 4 out of 10 were identified as intermediate-

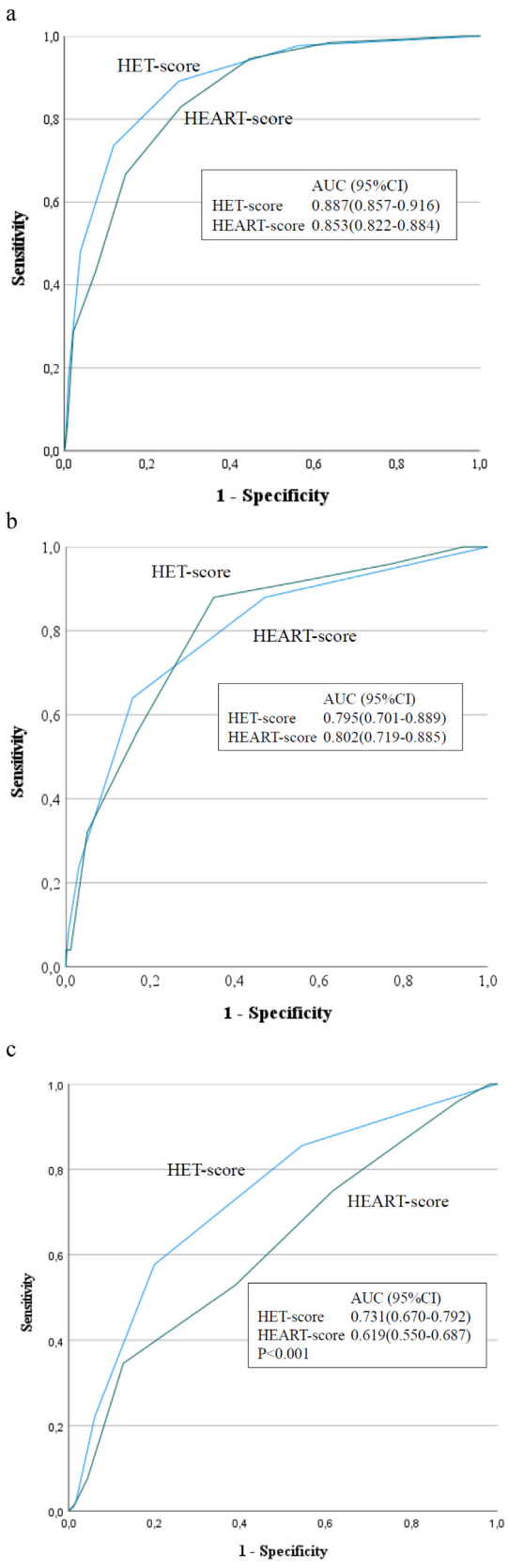

Fig. 3. Receiver operating characteristic (ROC) curve for HEART- and HET-score to detect cardiovascular event: (a) all patients, (b) patients with and (c) without normal troponins.

risk patients with 30-day risk of 6.2%, whereas 2 out of 10 were identified as high-risk patients with a 30-day risk of 43.2%.

The HEART-score was initially introduced by Six et al. [21] and variables were selected on clinical grounds rather than on an optimization of a prediction model. The score has, thereafter, been validated in several studies, including prospective multicenter studies and meta-analyses [8,9,22,23]. In a previous report from the present study, we demonstrated that a clinical implementation of a 1-h high-sensitive troponin algorithm in combination with the HEART-score could safely reduce admission rate and other measures of the health-care burden [10].

The assessment of patients with chest pain at the ED is often performed by less experienced physicians and there is a need for guidance to support their clinical decisions. Simple and well-validated scores without need for a calculator or a scoring card are useful in a busy ED. Although HEART-score is simple, a further simplification of the score would therefore be of great value. The score has also been criticized for identifying all elderly with risk factors to be of increased risk regardless of symptoms, ECG and troponin level [24]. The use of age in risk scores may also lead to less focus on younger patients where the overall consequences of a missed diagnosis and subsequent treatment may be greater.

In the present study, all variables included in the HEART-score were associated with the short-term risk of cardiovascular events in the univariable analyses and there was an increased risk for cardiovascular events with increasing HEART-score. But in the multivariable analysis, there was no independent association between age-class and risk of cardiovascular events (OR [95%CI]: 1.01 [0.66–1.56]) and for risk factors there was a trend towards a lower risk of cardiovascular events (0.72 [0.52–1.00], $p = 0.051$). Our finding is supported by older studies by Panju et al. [25] but also by more recent studies by Melki et al. and Backus et al. who both showed that there was no significant association between age-class, risk factors and outcome when adjusting for the other HEART-score variables [11,12]. In the stratified adjusted analyses, history and ECG were significantly associated with a higher cardiovascular risk in both troponin-negative and positive patients, whereas increasing age and risk factors were associated with a lower risk of cardiovascular events in troponin-positive patients. A possible reason for this is that young age and no risk factors indicate serious causes for troponin elevation, whereas higher age and more risk factors may indicate more benign causes.

In a previous publication by Smith et al., [26] the authors presented a modified variant of HEART-score without troponin testing, (HEAR-score), and sought to identify a population that would not benefit from troponin testing. However, only 9% (447 patients) were classified as low-risk, (subsequent major adverse cardiac event in this group was 0.9%) which supports the rationale of troponin testing. Indeed, our data supports the crucial role of troponin measurements in patients with chest pain. Only in troponin-negative patients, HEART- and HET-score could identify a substantial number of low-risk patients, and only in troponin-positive patients, the scores could identify a substantial number of high-risk patients.

The clinical implication of our findings may be substantial. The use of HET-score can simplify decision algorithms. Patients with negative troponin can have either a history of some typical features (1 point) or non-specific ECG-changes (1 point), but not both, and still be considered as a low risk patients and should be considered for early discharge. However, to reach a negative predictive value >99%, which many clinicians consider as acceptable, HET-score could not be above 0 in those with negative troponin in the present study. Patients with typical history (2 points) or ST-segment deviations (2 points) have at least an intermediate risk and many of these need further testing and evaluation. In troponin-positive patients, on the other hand, it will not be

possible to identify low-risk patients, and if the patient has more than some typical features in the history or non-specific ECG changes, he/she will be considered as a high-risk individual that should be admitted for further diagnostic work-up.

The strength of this study is the pre-specified research question where most data were prospectively collected, and all sites were closely monitored, and all MI events were adjudicated by two independent cardiologists and the composite endpoint was limited to specific and well-defined outcome data. Endpoints like unstable angina or need for unplanned revascularization are softer and may be driven by risk stratification measures. Also, the multi-center approach increases the generalizability and the external validity of our findings. But the present study also has limitations. During phase 1 HEART-scoring for symptoms was performed retrospectively using medical records. This may introduce a bias since symptom severity may be underestimated in patients that were discharged and overestimated in those who were admitted [27]. However, in a sensitivity analysis, including only patients from phase 2, in which all scoring was performed prospectively, the results were similar to the overall results. Although not small, the size of the study was still limited, and larger studies are needed to really claim that the HET-score can replace HEART-score in the early assessment of patients with chest pain. This is an observational study before and after implementing a combination of a troponin-based algorithm and HEART-score. To truly compare the effects of implementing different risk scores a randomized study is needed. The study was performed at six sites in Stockholm and Uppsala. Any score must be validated and if needed recalibrated in the population in which it will be used.

In conclusion, HET-score is a simplification of HEART-score and appears to have similar ability to risk stratify patients presenting to the ED with chest pain.

Presented

Poster at European Society of Cardiology annual meeting, Munich, Aug 2017.

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CRediT authorship contribution statement

Henrik Löfmark: Writing – original draft, Methodology, Data curation, Conceptualization. **Josephine Muhrbeck:** Writing – review & editing, Supervision, Methodology. **Kai M. Eggers:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Rickard Linder:** Writing – review & editing. **Lina Ljung:** Writing – review & editing. **Arne Martinsson:** Writing – review & editing. **Dina Melki:** Writing – review & editing. **Nondita Sarkar:** Writing – review & editing. **Per Svensson:** Writing – review & editing. **Bertil Lindahl:** Writing – review & editing. **Tomas Jernberg:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2023.09.037.

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