HEART Score Recalibration Using Higher Sensitivity Troponin T

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Study objective: We examined the diagnostic performance of a recalibrated History, Electrocardiogram, Age, Risk factors, Troponin (HEART), and Thrombolysis in Myocardial Infarction (TIMI) score in patients with suspected acute cardiac syndrome (ACS). Recalibration of troponin thresholds was performed, including shifting from the 99th percentile to the limit of detection (LOD) or to the limit of quantification (LOQ) We compared the discharge potential and safety of the recalibrated composite scores using a single presentation high-sensitivity cardiac troponin (hs-cTn) T to the conventional scores and with a LOD/LOQ troponin strategy alone.

Methods: We undertook a 2-center prospective cohort study in the United Kingdom (UK) (2018) (Clinicaltrials.gov NCT03619733) to specifically assess recalibrated risk scores (shifting the troponin subset scoring from 99th percentile to LOD [UK]) and combined the results of this with secondary analyses of 2 prospective cohort studies in the UK (2011) and the United States (2018, using LOQ rather than LOD). The primary outcome was major adverse cardiovascular events (MACE), defined as adjudicated type 1 myocardial infarction (MI), urgent coronary revascularization, and all-cause death, at 30 days. We evaluated the original scores using hs-cTn below the 99th percentile and recalibrated scores using hs-cTn <LOD/LOQ and compared these composite scores with a single hs-cTnT less than LOD/LOQ combined with a nonischemic ECG. For each discharge strategy, an assessment of clinical effectiveness was also made, defined as the proportion of patients eligible for discharge from the emergency department without the need for further inpatient testing.

Results: We studied 3,752 patients (3,003 in the UK and 749 in the United States). Median age was 58 years, and 48% were female. At 30 days, 330/3,752 (8.8%) experienced MACE. The sensitivities of the original HEART less or equal to 3 and recalibrated HEART less or equal to 3 scores for rule-out were 96.1% (95% confidence interval [CI], 93.4 to 97.9) and 98.6% (95% CI, 96.5 to 99.5) respectively; the original TIMI less or equal to 1 and recalibrated TIMI less or equal to 1 scores' sensitivities were 79.7% (95% CI, 74.9 to 83.9) and 96.1% (95% CI, 93.4 to 97.9) respectively; and nonischemic ECG with hs-cTn T below the 99th percentile and hs-cTn T less than LOD/LOQ was 79.7% (95%CI, 0.749 to 0.839) and 99.1% (95% CI, 0.974 to 0.998), respectively. Recalibrated HEART less or equal to 3 was projected to discharge 14% more patients than hs-cTn T less than LOD/LOQ. The improved sensitivity of rule-out for recalibrated HEART less than or equal to 3 came at the cost of reduced specificity (50.8% versus 53.8% for recalibrated HEART and conventional HEART respectively).

Conclusion: This study indicates that recalibrated HEART score of less or equal to 3 is a feasible and safe early discharge strategy using a single presentation hs-cTnT. This finding should be further tested using competitor hs-cTn assays in independent prospective cohorts before implementation. [Ann Emerg Med. 2023;■:1-15.]

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INTRODUCTION

Background

Patients with suspected acute coronary syndrome (ACS) constitute 10% of patients presenting to emergency departments,[1] though less than 15% are suffering from acute myocardial infarction (MI).[2,3] Early, safe discharge for those not suffering from MI or other serious pathology remains a challenge. Several strategies for early discharge have been proposed, including a low-risk Thrombolysis In Myocardial Infarction (TIMI)[4,5] score, a low-risk History, Electrocardiogram, Age, Risk factors, Troponin (HEART)[2] score, and a single high sensitive cardiac troponin (hs-cTn) below the limit of detection (LOD) either alone or in combination with a normal electrocardiogram (ECG).[6,7] Presentation LOD

Editor's Capsule Summary

What is already known on this topic

Troponin measurements with risk tools help detect those at higher risk for adverse events and possible acute coronary syndrome (ACS).

What question this study addressed

Does recalibration of an ACS risk score tool using newer, higher sensitivity troponin in emergency department (ED) patients improve performance?

What this study adds to our knowledge?

In 3773 patients from 3 samples, a single high-sensitivity troponin below the level of detection with a nonischemic ECG increased sensitivity and lowered specificity to assess for major adverse cardiac events while increasing the proportion of patients deemed safe for discharge home as part of the HEART score.

How this is relevant to clinical practice

If validated, this approach could inform rapid discharge strategies of more low-risk ED patients with potential ACS.

troponin levels form part of the pathways recommended by the European Society of Cardiology for excluding MI in patients with suspected ACS.[8] Despite the emergence of hs-cTn with quantifiable levels of troponin below the 99th percentile or upper limit of normal, it is noteworthy that both HEART and TIMI scores do not differentiate between levels below the 99th percentile and below the LOD or limit of quantification (LOQ) in their scoring. The LOD is the lowest hs-cTn value reported to clinicians in Europe, and the LOQ is the lowest reported in the United States. Patients with a hs-cTn level above the LOD but below the 99th percentile are at a higher risk of MACE than those with a hs-cTn below the LOD.[3] One large prospective cohort study in Scotland estimated, during medium-term follow-up, a greater than 5 times risk of MI or all-cause death for suspected ACS patients presenting with hs-cTn between 5ng/l and 99th percentile, compared with <5ng/l.[3]

Adapting risk scores for hs-cTn values below the 99th percentile, such as LOD or LOQ, could provide an alternative predictive algorithm for ruling out MI[9,10] and longer-term (1-year outcome) reassurance than the use of low-level hs-cTn levels alone.[11]

In a prospective observational cohort, the original HEART score using hs-cTn was as effective as LOD in early rule out of ACS.[2] However, one other study estimated a major adverse cardiac event (MACE) miss rate of 3.3% for a low-risk HEART score of less or equal to 3, raising concerns about the safety of this approach.[12] We examined the diagnostic performance of a modified (recalibrated) HEART and TIMI score incorporating a very low cut off threshold for the HstnT (high sensitivity troponin T) (Figure 1). We compared this to

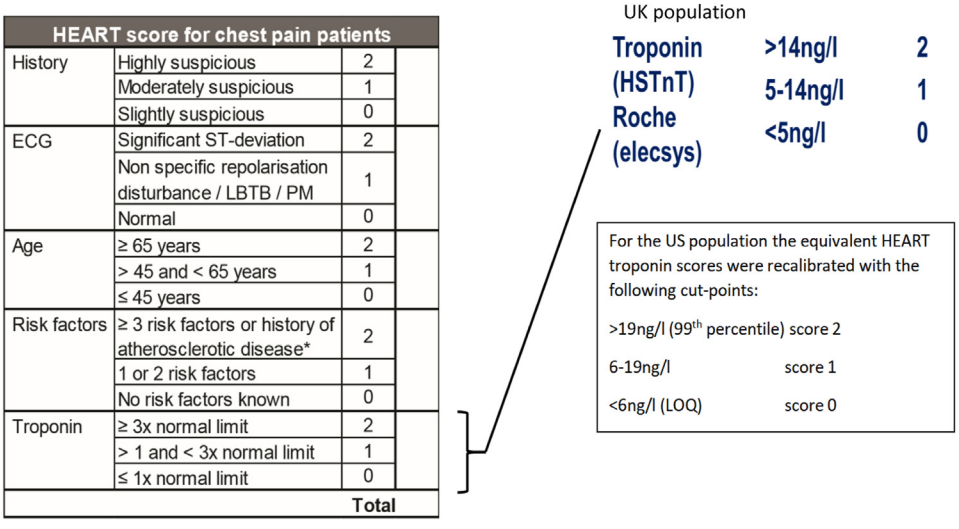

Figure 1. Derivation of Recalibrated (LOD) HEART and TIMI score from respective conventional scores (see TIMI Risk Score for UA/NSTEMI - MDCalc for TIMI score calculation). The troponin thresholds are different for UK and USA due to differences in the patient population (and therefore 99th percentile) but also due to differences in the reporting of the lowest numerical troponin values (LOD for UK and LOQ for USA) (see TIMI Risk Score for UA/NSTEMI - MDCalc for TIMI score calculation).

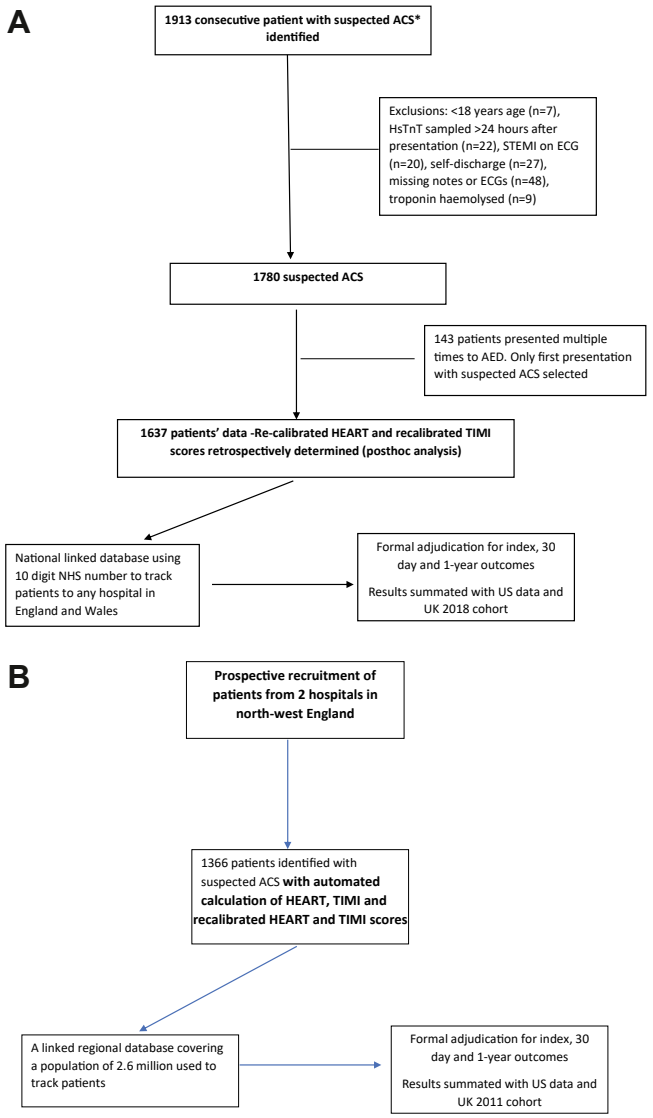

Figure 2. *A*, UK COHORT 2011: Consecutive patients with suspected ACS, prospectively identified, in one large Accident and emergency department in Northwest England. *B*, UK COHORT 2018: Consecutive patients with suspected ACS from 2 large Accident and emergency departments in Northwest England. Study designed specifically to assess recalibrated risk scores. *C*, United States cohort 2018: prospectively identified with consent for diagnostic reclassification study in a single tertiary care center. *AED*, automated external defibrillator.

conventional risk scores and the use of LOD/LOQ rule-out, using a single presentation troponin, as advocated in European Society of Cardiology guidelines.[8]

METHODS

This study adheres to STARD reporting.[13] We prespecified, for clinical acceptability, a minimum sensitivity and negative predictive value to rule-out of 98% and 99.5%, respectively, consistent with notions of acceptable risks of discharge by one survey of ED clinicians.[14]

Study Design and Setting (Figure 1)

We conducted a two-center prospective cohort study (n=1366) in 2018, evaluating the use of hs-cTn T below LOD in the HEART and TIMI scores (validation cohort) (Clinicaltrials.gov NCT03619733). We combined this data with secondary analyses of 2 prospective cohort studies of patients with suspected ACS. One was a UK cohort (n=1637) conducted in 2011, with post hoc analysis demonstrating the promise of combining LOD with HEART score as a discharge strategy (derivation cohort),[15] and the second was a prospective cohort study in the United States (external validation, n=749).[16] For the latter, we defined a subset of the patients with suspected ACS (Figure 1).

Selection of Participants

UK cohort 2011. We undertook a secondary analysis of this prospective cohort study with retrospective computation of recalibrated HEART and TIMI scores (Figure 2, A-C). The original study was an assessment of the diagnostic performance of a number of conventional risk scores (low-risk HEART, GRACE, TIMI) compared with the LOD troponin (combined with a nonischemic ECG).[2] It was undertaken at a single center in 2011 with consecutive identification of patients with suspected ACS. The suspected ACS patient was defined as an ED presentation with predominant symptom of chest pain, who had both an ECG and at least one blood sample for HSTnT check**.** Patients with ST-segment elevation on ECG directed for primary percutaneous intervention were excluded. There were 5 patients who presented with marginal ST shift on ECG (not fulfilling criteria for primary percutaneous coronary intervention or thrombolysis) and therefore were not excluded in the original study. For the purposes of this study, to harmonize patient selection between cohorts, we excluded these patients. Therefore, of the 1642 patients in this original cohort study, we included 1637 for this secondary analysis. All data were entered prospectively, but the History component of the HEART score was determined retrospectively by researchers, with reference to ED notes and dedicated chest pain proforma. Using a national linked database, and a unique 10-digit National Health Service (NHS) code, we tracked all patients nationally for 1 year primarily for adjudication for possible MI using ICD-10 codes (including a range of codes for ischemic heart disease). Previously interobserver variation for

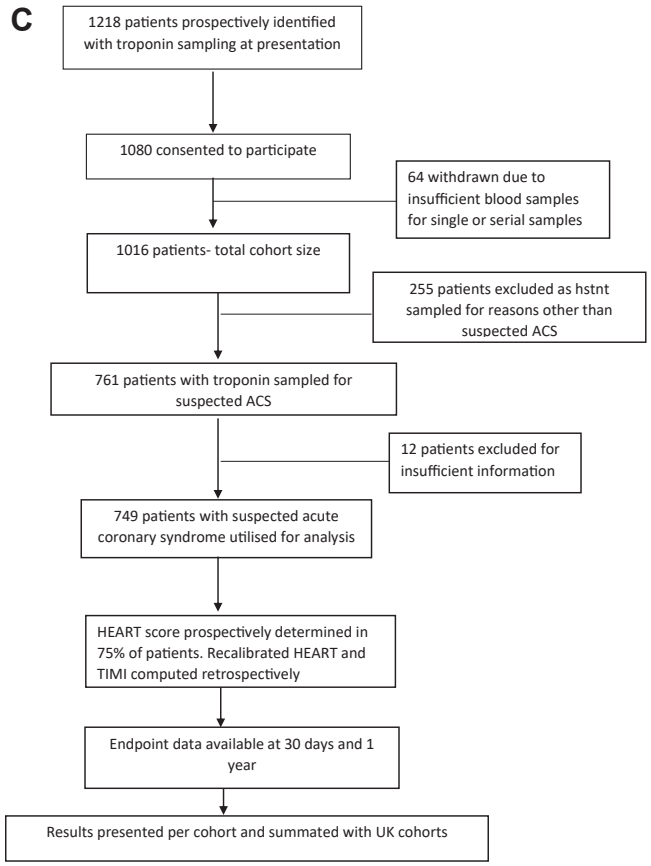

Figure 2. Continued.

determination of HEART scores (retrospective evaluation of History component) had been undertaken for this cohort and published as a supplementary file.[2] Interobserver variation for an absolute score for HEART was 89%, and for the risk category, 100%.

UK cohort 2018. This study was an assessment of diagnostic performance. It was specifically undertaken and designed to address the primary research question of the value of recalibrated risk scores as an early rule-out for MACE. Recruitment was from 2 large secondary care hospitals and included consecutive patients with a primary symptom of chest pain in whom the attending clinician decided to sample troponin and undertake an electrocardiogram. We established in the 2011 cohort, with patients tracked nationally, that no subsequent adjudicated MI, to one year, presented out with the local region. We tracked the 2018 validation cohort regionally rather than nationally. The HEART, TIMI, recalibrated HEART, and TIMI scores were computed automatically from prospectively collected data. The History component of the HEART score was, though, retrospectively assessed by reference to a scoring chart (Figure E1, available at http://www.annemergmed.com).

US cohort 2018. This study was an assessment of diagnostic performance. It included a convenience sample of the adult (≥18 years old) ED patients with suspected ACS and excluded those with ST-segment elevation undergoing emergency cardiac catheterization.[16] The US study was a prospective single center, before and after study, investigating the diagnostic reclassification of MI between conventional troponin and hs-cTn. We undertook a secondary analysis of this cohort. Although the primary study included ED patients undergoing troponin testing for any reason, only those undergoing troponin testing for suspected ACS (749/1,016) were included in the current analysis (Figure 1C). Details of methodology in the US cohort are available in the respective primary publication.[16] The HEART scores were collected during the index encounter from the treating emergency physician. If the treating emergency physician was unavailable, the HEART score was calculated retrospectively by the research team. Seventy-five percent of the HEART score was computed prospectively, and 25% was retrospectively scored by researchers. A blinded comparison of prospective and retrospective HEART scoring indicated in the most subjective part of HEART scoring (History) that just over 90% of the time there was no difference or a difference of 1. In terms of the overall score, almost 80% had the same score or a difference of 1 between prospective, physician scoring, and retrospective scoring. A similar structured guide, to the UK cohorts, for the History sub score to interpret the documentation in the electronic medical record was used.

Combining Data from the 3 Cohort Studies for Aggregate Results

Table E1 (available at http://www.annemergmed.com) illustrates the commonality and differences between the UK and US cohorts. There were a number of similarities between the cohorts: the same hs-cTn (Roche, elecsys), similar gold standard adjudication with 2 experienced clinicians, and a third acting as a tiebreaker for MI adjudication and details of individual end-points allowing data to be collated on an individual patient basis. The History component of the HEART score was scored from emergency department notes and chest pain proforma in the UK cohorts but prospectively in three-quarters of patients in the US cohort. Internal quality control from the US cohort revealed consistency of results. There were differences in the patient population between the UK and US cohorts, as denoted by the 99th percentile of the populations. However, hs-cTns, allowed exploration in the context of the concept of lowering the troponin threshold, from the 99th percentile,

for both TIMI and HEART scores, using values relevant to the population in question. Clinical data and risk scores were visible and available to the researchers entering the data but not the adjudicators for type 1 MI.

Calculation of Scores Incorporating LOD/LOQ Troponins

The LOD and LOQ represent the lowest quantifiable troponin values reported to clinicians in the UK and the United States, respectively. The LOD value for hs-cTn T is 5 ng/L in the UK, and the LOQ value for hs-cTnT is 6 ng/L in the United States. In the troponin sub scores for both HEART and TIMI, the troponin value thresholds were shifted down from the 99th percentile to the LOD in the UK cohorts and to LOQ for the US cohort. For the recalibrated TIMI score, hs-cTn T values equal to or greater than the LOD/LOQ scored 1, and those less than LOD/LOQ scored 0. For the recalibrated HEART score, the troponin sub score was 0 if the initial hs-cTn T was less than LOD/LOQ, 1 for hs-cTn between the LOD/LOQ and 99th percentile thresholds, and 2 for hs-cTn above the 99th percentile threshold. For hs-cTn T, the 99th percentile threshold is 14 ng/L in the UK and 19 ng/L in the US population (Figure 1). To evaluate rule-in, we used a HEART score of 7-10 and a TIMI score of 6-7 (for both conventional and recalibrated scores, respectively). The TIMI score rule-in was used as it has been used in a confirmed ACS population to indicate high risk. For comparison with the risk scores, we assessed rule-in by a single value of hs-cTn T of 52ng/l alone, based on the European Society of Cardiology recommended 0/1 hour pathway.[17] For patients in each algorithm or strategy not fulfilling rule-out or rule-in, we present in all results tables the gray zone (or observation group). The results of the gray zone are presented as an absolute number, percentage of the overall cohort, and the incidence rate of the studied endpoint. The size of the gray zone conventionally is one indicator of the value of a specific risk score or algorithm: the smaller the gray zone, the less challenging the overall triage and management of patients.

Hs-cTn T Assay

In the UK cohorts, the hs-cTn T assay was performed in-house on COBAS e601 (Roche Elecsys) analyzers. The 99th percentile for the assay is 14 ng/L. Monthly external quality assurance by the National External Quality Assessment Service revealed an interhospital coefficient of variance of 10% for a sample concentration of 6 ng/l. Quality control of assay (in-house) at the Liverpool Clinical laboratories revealed a coefficient of variance of 11% at values of 4.5 ng/L.

In the US cohort, the hs-cTn T assay was performed in-house on the COBAS e411 (Roche Elecsys) analyzers. The LOQ is 6ng/L, and the 99th percentile upper reference limit, exhibiting less than 10% coefficient of variance, is 19 ng/L.

Adjudication of Possible MI

In the 2011 and 2018 UK cohorts, any presentation with hs-cTn T above the 99th percentile in the index or subsequent presentations underwent review and adjudication for the outcome of MI, using the third universal definition of MI. Two physicians (emergency physicians and cardiologists) independently reviewed relevant notes, laboratory results, ECGs, cardiac imaging, and procedure reports to determine whether no MI, type 1 MI, or type 2 MI was present. In cases of disagreement, an experienced cardiologist reviewed the case and served as a tiebreaker.

Contentious outcomes based on urgent coronary revascularizationn, without antecedent troponin elevation, or where there was insufficient information for type 1 MI adjudication underwent adjudication by an endpoint committee (AK, LM, FF, MC).

The review and adjudication process for the US cohort was similar, with 2 independent reviewers and a tiebreaker using the Fourth Universal Definition of MI.[16]

Ethics

The 2018 UK validation cohort was undertaken as a quality improvement program, and therefore, the requirement of consent for each identified patient was waived. This allowed the extraction of data from regional hospitals (circa population of 2.6 million). For the US cohort, the study was approved by the local Institutional Review Board.

MACE

The primary outcome was MACE at 30 days, defined as the composite of type 1 MI, unplanned coronary revascularizationn, and all-cause death. Unplanned coronary revascularization was defined as admission for unstable angina or MI necessitating same-day or same-admission coronary revascularization. Secondary outcomes included type 1 MI at 30 days and MACE at 1 year. For each outcome, we compared the original HEART score, original TIMI score, recalibrated HEART score, recalibrated TIMI score, hs-cTn T less than LOD/LOQ with a nonischemic ECG, and hs-cTn T below the 99th percentile with a nonischemic ECG. We also investigated

Table 1. Descriptive demographics for pooled cohort (UK and US combined).

	N	All	Type 1 MI (30 days)	Type 1+2 MI (30 days)	MACE (30 days)*
Totals	3752	3752	263	283	330
Age (median, IQR) (y)	3752	58(46, 71)	73(61, 82)	74(63, 82)	72(61, 82)
Male	3752	1941 (52)	161 (61)	170 (60)	197 (60)
TIMI (mean, sd)	3752	1.3(1.35)	2.7(1.34)	2.7(1.33)	2.7(1.35)
HEART (mean, sd)	3752	3.4(2.22)	6.8(1.58)	6.8(1.57)	6.5(1.75)
Hypertension	3749	1715 (46)	178 (68)	193 (68)	222 (67)
Diabetes mellitus	3749	657 (18)	63 (24)	71 (25)	84 (26)
Dyslipidemia	3750	1054 (28)	112 (43)	121 (43)	139 (42)
Previous MI	3751	658 (18)	85 (32)	95 (34)	102 (31)
Previous PCI/CABG	3747	386 (10)	43 (16)	43 (15)	58 (18)
Previous stroke	3742	272 (7)	27 (10)	29 (10)	36 (11)
Creatinine (median, IQR)	3742	86(72, 102)	97(80, 118)	97(80, 116)	96(78, 118)
Time of chest pain to presentation	3709				
≤3 hours		1031 (28)	106 (41)	120 (43)	125 (38)
>3 hours		2678 (71)	153 (5)	159 (57)	200 (62)
Presentation to 1st Tn check (median, IQR)	3749	1.7(0.9, 3.1)	2.3(1.2, 4.6)	2.4(1.2, 4.8)	2.0(1.0, 4.2)
Time of peak CP to 1st Tn	2958				
≤6 hours		652 (22)	74 (31)	90 (32)	86 (31)
>6 hours		2306 (61)	167 (69)	188 (68)	191 (69)
ECG	3726				
Ischemic		1486 (40)	155 (59)	176 (62)	196 (60)
Nonischemic**		2240 (60)	107 (41)	106 (38)	133 (40)
Current aspirin use	3746	1125 (30)	149 (57)	157 (55)	179 (54)

CP, chest pain.
*MACE 30 days excludes type 2 MI.
**Nonischemic ECG: sinus rhythm (or atrial fibrillation or atrial flutter with ventricular rate<110) and absence of the following: LBBB, paced rhythm, ST-segment elevation, ST-segment depression, T wave inversion or T wave flattening or biphasic T waves in 2 contiguous leads.

the interaction of early presentation (equal or less than 3 hours versus greater than 3 hours from chest pain onset to presentation) with outcomes in the UK cohorts.

Eligibility for Discharge

Eligibility for discharge was defined as follows for each strategy: original HEART score equal or less than 3, original TIMI score equal or less than 1, recalibrated HEART score equal or less than 3, recalibrated TIMI score equal or less than 1, hs-cTn T below the 99th percentile with nonischemic ECG, and hs-cTnT<LOD/LOQ with nonischemic ECG. We determined the proportion of the cohort that would have been eligible for discharge using each of these strategies.

Analysis

All analyses were performed using the Stata version 14. (StataCorp LLC, College Station, TX, USA).

Summary statistics were presented as n (%) for categorical data and as median (interquartile range [IQR]) for continuous data. We took an interval likelihood ratio approach for each original and recalibrated algorithm using 2 test thresholds: one to rule-out and one to rule-in disease. This resulted in 3 possible test result zones, including rule-out, central non-predictive gray zone, and rule-in. We calculated standard diagnostic test statistics (sensitivity, specificity, negative predictive value, and positive predictive value) for each of the 2 test thresholds for each diagnostic algorithm.[18] The gray zone is also denoted in the tables and is simply the difference between the sum of patients either ruled in or out and the total cohort. The size of the gray zone and the event rate (of the relevant metric, either MI or MACE) is presented for this group for each diagnostic algorithm.

Confidence intervals for positive predictive value and negative predictive value were calculated using exact

Table 2. Performance of rule-out and rule-in protocols at 30 days for global data (US and UK combined), n=3752.

		MACE (MI, unplanned coronary revasc and all-cause death) Type 1 MI only 30 days										
Rule-out protocol	**Discharge potential n (%)**	**Sensitivity (95%CI)**	**Specificity (95% CI)**	**NPV (95% CI)**	**PPV (95% CI)**	***Gray Zone, n(% cohort size) -n events (%)**	**Rule- in**	**N (%)†**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**NPV (95% CI)**	**PPV (95% CI)**
TIMI≤1	2258 (60.)	79.7 (75,84)	64.0 (62,66)	97 (96,98)	17.6 (16,20)	1487 (39.) - 259 (17.4)	TIMI 6-7	7 (0.2%)	1.2 (0,3)	99.9 (99.7,100)	91.3 (90,92)	57.1 (18,90)
Recal. TIMI≤1	1783 (47.5%)	91.5 (88,94)	51.3 (50,53)	98.4 (98,99)	15.3 (14,17)	1930 (51.4) - 286 (14.8)	Recal TIMI 6-7	39 (1.0%)	4.8 (3,8)	99.3 (99,100)	91.5 (91,92)	41 (26,58)
HEART≤3	1820 (48.8)	96.1 (93,98)	53.1 (51,55)	99.3 (99,100)	16.6 (15,18)	1558 (41.7) - 145 (9.3)	HEART 7-10	355 (9.5%)	52.1 (47,58)	94.7 (94,95)	95.3 (95,96)	48.5 (43,54)
Recal. HEART≤3	1743 (46.5)	98.5 (97,100)	50.8 (49,53)	99.7 (99,100)	16.2 (15,18)	1450 (38.6) - 122 (8.4)	Recal HEART 7-10	559 (14.9%)	61.5(56-67)	89.6 (89,91)	96 (95,97)	36.3 (32,41)
HSTnT<LOD/LOQ + ECG nonischemic	1221 (32.6)	99.1 (97,100)	35.7 (34,37)	99.8 (99,100)	13 (12,14)	2217 (59.1) - 175 (7.9)	HsTnT>52ng/l	303 (8.1%)	46.1 (41,52)	95.6 (95,96)	94.8 (94,96)	50.2 (44,56)
HSTnT<99th percentile, ECG nonischemic	2282 (61.2)	89.4 (86,93)	66.1 (64,68)	98.5 (98,99)	20.4 (18,23)	1146 (30.5) - 143 (12.5)						

		MI (Type 1 MI only 30 days)										
Rule-out protocol	**Discharge potential (%)**	**Sensitivity (95%)**	**Specificity (95% CI)**	**NPV (95% CI)**	**PPV (95% CI)**	***Gray Zone, n(% cohort size) -n events (%)**	**Rule-in**	**N (%)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**NPV (95% CI)**	**PPV (95% CI)**
TIMI≤1	2258 (60.2)	81.4 (76,86)	63.3 (62,65)	97.8 (97,98)	14.3 (13,16)	1487 (39.6) - 211 (14.2)	TIMI 6-7	7 (0.2)	1.1 (0,3)	99.9 (99.7,100)	93.1 (92,94)	42.9 (10,82)
Recal. TIMI≤1	1783 (47.5)	92.0 (88,95)	50.5 (49,52)	98.8 (98,99)	12.3 (11,14)	1930 (51.4) - 229 (11.9)	Recal TIMI 6-7	39 (1.0)	4.9 (3,8)	99.3 (99,100)	93.3 (92,94)	33.3 (19,50)
HEART≤3	1820 (48.8)	98.1 (96,99)	52.3 (51,54)	99.7 (99,100)	13.5 (12,15)	1558 (41.7) - 101 (6.5)	HEART 7-10	355 (9.5)	59.7 (54,66)	94.3 (94,95)	96.9 (96,97)	44.2 (39,50)
Recal. HEART≤3	1743 (46.5)	99.6 (98,100)	49.9 (48,52)	99.9 (99,100)	13 (12,15)	1450 (38.6) - 83 (5.7)	Recal HEART 7-10	559 (14.9)	68.1 (62,74)	89.1 (88,90)	0.97.4 (97,98)	32 (28,36)
HSTnT<LOD/LOQ + ECG nonischemic	1221 (32.6)	99.2 (97,100)	35 (34,37)	99.8 (99,100)	10.4 (9,12)	2217 (59.1) - 125 (5.6)	HSTnT>52ng/l	303 (8.1)	51.7 (46,58)	95.2 (95,96)	96.3 (96,97)	44.9 (39,51)
HSTnT<99th percentile, ECG nonischemic	2282 (61.2)	92.8 (89,96)	65.3 (64,67)	99.2 (99,100)	16.8 (15,19)	1146 (30.5) - 108 (9.4)						

NPV, negative predictive value; *PPV*, positive predictive value, *Recal.*, recalibrated.

Recalibrated HEART: scoring of presentation (first) single troponin component is altered so that <LOD/LOQ hs-ctn scores 0, between LOD/LOQ and 99th percentile scores 1 and >99th percentile scores 2. Recalibrated TIMI score troponin component scoring changed so that 0 score reserved for single presentation troponin <LOD/LOQ and 1 for any value greater than or equal to LOD/LOQ. 95% Confidence intervals rounded to whole numbers except where there there is makes upper and lower range identical.

*Gray Zone is rule-in minus rule-out. The percentage relates to the total cohort size. The subsequent n represents the number of events in the gray zone (and the percentage reflects the gray zone size).

†N for is absolute number of cohort fulfilling rule-in and % is this number as a percentage of total cohort size.

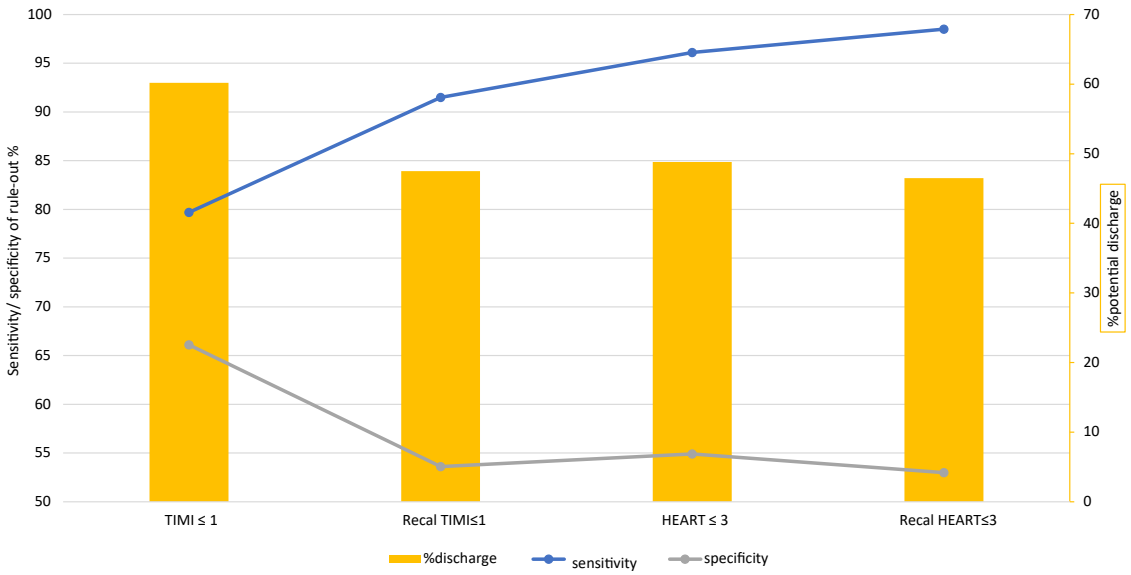

Figure 3. Performance metrics for rule-out for risk scores with HSTnT dichotomy at 99th percentile vs LOD/LOQ (US and UK combined data, n=3752). HSTnT, high sensitivity troponin T.

binomial proportions. The primary results in terms of diagnostic performance (positive predictive value, negative predictive value, sensitivity, and specificity) are presented as point estimates with CIs.

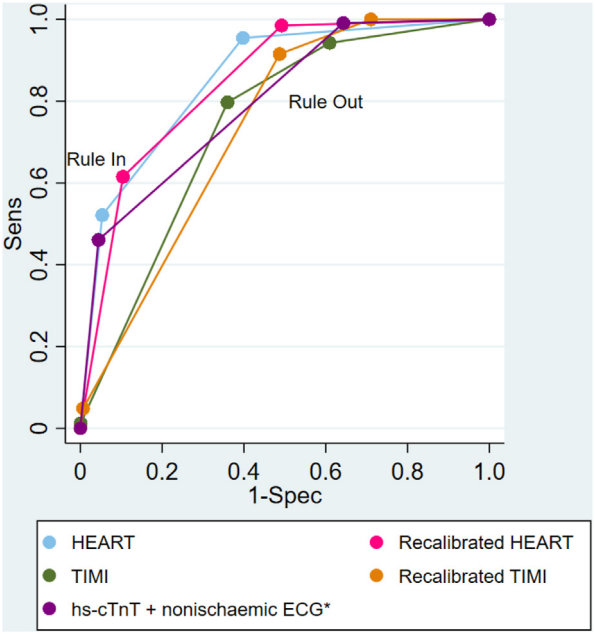

Figure 4. Simplified receiver operator characteristic curve for risk scores and hs-cTnT *hs-cTnT>52ng/l Rule-in and hs-cTnT<LOD/LOQ Rule-out, Cut-points for conventional and recalibrated HEART are 3 for rule-out and 7 for rule-in, corresponding points for TIMI and recalibrated TIMI are 1 and 6.

RESULTS

Overall Cohort

The overall cohort comprised 1637 patients from the 2011 UK cohort, 1366 from the 2018 UK cohort, and 749 from the US cohort. Overall, the median age was 58 years (IQR 46-71). Nearly half of patients (46%; 1714/3749) had a history of hypertension, and 18% (658/3751) had sustained a prior MI. A minority, 28% (1031/3709), presented within 3 hours of symptom onset (Table 1). The 2011 (UK) derivation cohort, was older by 3 years with greater overall risk scores than the later 2018 validation cohort. Twenty percent of patients in the 2011 cohort had suffered a previous MI compared with 6% in the 2018 UK validation cohort, thus, reflecting a higher burden of disease in the earlier 2011 derivation cohort. Tables E2-E5 (available at http://www.annemergmed.com) detail individual cohort characteristics.

MACE at 30 days

In the overall cohort, 330/3752 (8.8%) experienced the primary outcome of 30-day MACE; 202/1637 (12.3%) in the 2011 UK cohort, 81/1366 (5.9%) in the 2018 UK cohort, and 47/749 (6.3%) in the US cohort. The diagnostic performance of all metrics for rule-out and rule-in, and the gray zone for each of the 3 cohorts are detailed in Tables E6-E8 (available at http://www.annemergmed.com). Corresponding performance in the global cohort is detailed in Table 2. In addition, for all tables, the size and event rate in the gray zone (patients not in rule-in or rule-out) are detailed. Both recalibrated

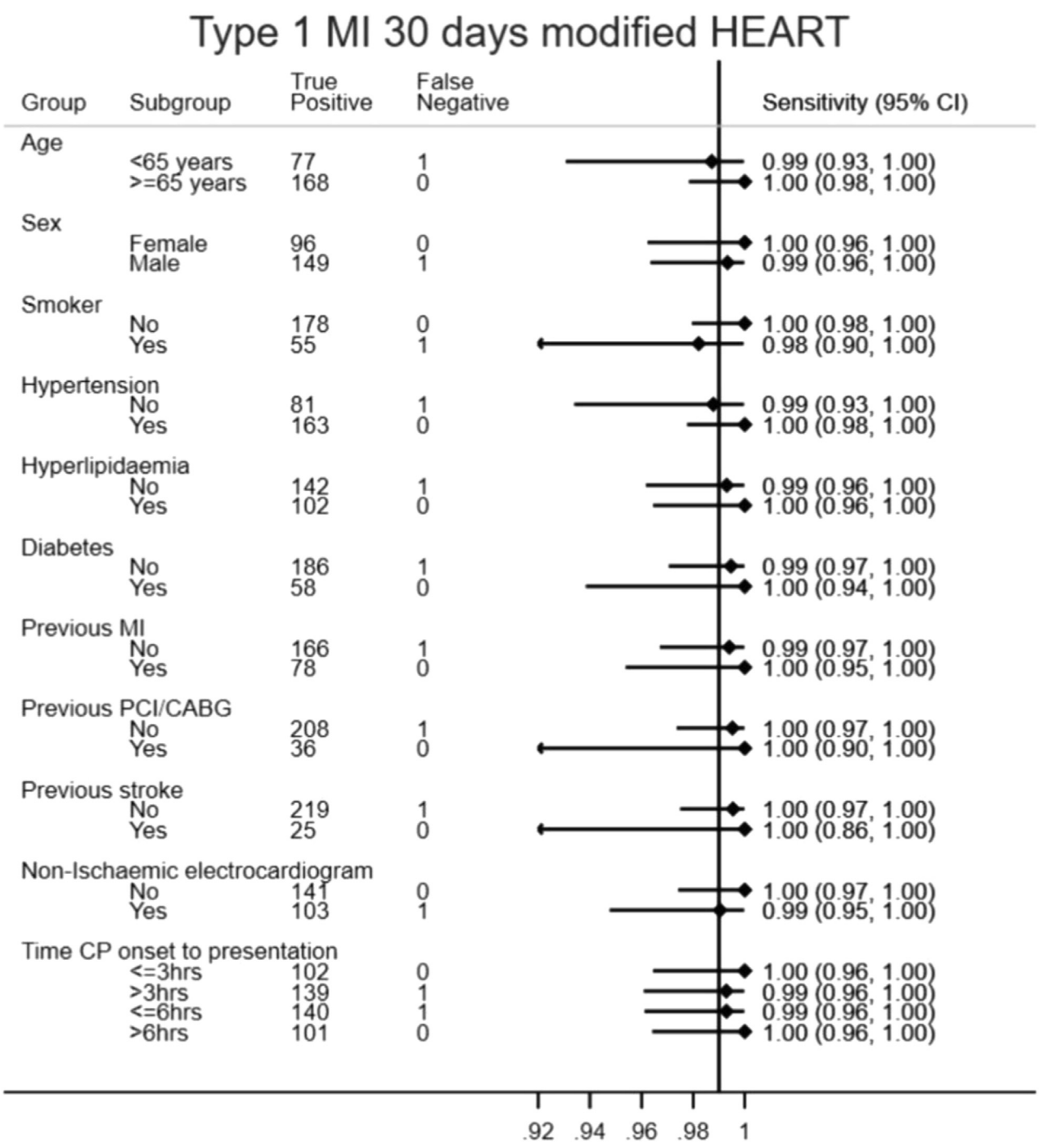

Figure 5. Subgroups with associated sensitivities for type 1 MI rule-out using recalibrated HEART≤3 (from combined UK cohort, n=3003).

HEART scores equal to or less than 3 and recalibrated TIMI scores equal to or less than 1 achieved greater point estimate negative predictive value and sensitivity than conventional HEART scores equal or less than 3 and original TIMI score equal or less than 1, respectively, in all 3 individual cohorts and in the overall cohort. In the overall cohort, sensitivity of rule-out by recalibrated HEART score equal to or less than 3 was 98.5% (with 5 MACE events missed, 3 of which were noncardiac deaths.) There was variation between the 3 cohorts for the sensitivity of rule-out MACE. Except in the US cohort, the sensitivity of recalibrated HEART score equal or less than 3 rule-out strategy was greater than the 98% prespecified target for sensitivity. There

were 3 noncardiac deaths in the US cohort that resulted in a lower sensitivity; when these were excluded, sensitivity increased to 100%. Figure 3 illustrates sensitivity, specificity, and percentage discharge for all 4 risk scores. Only recalibrated HEART scores less than 3 and hs-cTn T less than LOD/LOQ with a nonischemic ECG discharge strategies achieved the prespecified 30-day MACE sensitivity and negative predictive value target in the overall cohort and, thus, form the principal comparison in rule-out strategies (Table E5). There was no statistically significant difference in sensitivity or negative predictive value between the 2 strategies. Figure 4 is a simplified receiver operating characteristic (ROC) curve of all risk scores for MACE at 30 days inclusive of recalibrated and conventional scores and also details the performance of rule-out by hs-cTn T less than LOD/LOQ with a non-ischemic ECG and hs-cTn T greater than 52 ng/l for rule-in. The ROC curves focus on cut-points for rule-out and rule-in and illustrate greater sensitivity for rule-out with recalibrated HEART score, compared with conventional HEART score, at the cost of reduced specificity for rule-in. Pair-wise comparisons were undertaken for all 6 discharge strategies; hs-cTn T less than LOD/LOQ and recalibrated HEART scores equal, or less than 3 were superior to all strategies for rule-out, and by Mcnemar's test, there was no difference between these 2 strategies.

An analysis was also undertaken to determine variation in important subsets in terms of sensitivity for recalibrated HEART scores equal to or less than 3 rule-out performance. There was consistent sensitivity for the rule-out of MI at 30 days in a wide number of subsets derived from the combined UK cohorts (n=3003) (Figure 5), including early presenters. Table E9 (available at http://www.annemergmed.com) represents a more detailed illustration of the lack of variation of the primary outcome with early (less than 3 hours) versus later presentation with chest pain. The increased sensitivity of rule-in for recalibrated HEART score was at the cost of specificity, which was slightly lower for recalibrated HEART score equal to or less than 3 compared with conventional HEART score equal to or less than 3. Interestingly rule-in proportions were greater with recalibrated HEART score compared with conventional HEART score but with lower positive predictive value and specificity for rule-in. The gray zone cohort size was in fact smaller for recalibrated HEART score compared with the HEART score but with similar event rates. The TIMI score rule-in had small numbers with wide CIs. For a numerical rule-in value of hs-cTn T greater than 52 ng/l, the positive predictive value and specificity were fairly similar to the conventional HEART score and greater than recalibrated HEART score. The gray zone, between LOD/LOQ and hs-cTn T greater than 52 ng/l, was greater than with HEART or recalibrated HEART score.

Type 1 MI at 30 Days

In the overall cohort, the secondary outcome of type 1 MI at 30 days occurred in 7% (263/3752). In the 2011 UK cohort, 2018 UK cohort, and US cohort 10.8% (177/1637), 5.1% (69/1366), and 2.3% (17/749) sustained a type 1 MI, respectively (Table 2, Tables E6-E8.) Compared with the original risk scores, the point estimates for sensitivity and negative predictive value for type 1 MI, for each individual cohort and in the overall cohort, were greater for the recalibrated HEART score equal or less than 3 and recalibrated TIMI score equal to or less than 1 score. Secondly, hs-cTn T less than LOD/LOQ with nonischemic ECG rule-out point estimates for sensitivity and negative predictive value were superior to hs-cTn T below the 99th with nonischemic ECG percentile rule-out in all 3 cohorts and in the overall cohort. The results remained consistent when type 2 MI was included. Recalibrated HEART score equal to or less than 3 and hs-cTn T less than LOD/LOQ with a nonischemic ECG were the only 2 rule-out algorithms that consistently achieved (in all 3 individual cohorts and in the overall cohort) prespecified criteria for rule-out for type 1 MI (negative predictive value $\leq$ 99.5%, sensitivity score $\leq$ 98%). The recalibrated TIMI equal to or less than 1 score achieved 100% sensitivity and negative predictive value for exclusion of type 1 MI at 30 days in the US cohort but not in the UK cohorts. In the combined cohort, recalibrated TIMI scores equal or less than 1 did not achieve prespecified negative predictive value and sensitivity for type 1 MI nor MACE (Table 2).

MACE and Type 1 MI at 1 Year

In the overall cohort, the secondary outcome of MACE at 1 year occurred in 14.0% (527/3752); 268/1637 (16.4%) in the 2011 UK cohort, 144/1366(10.5%) in the 2018 UK cohort, and 115/749 (15.3%) in the US cohort (Table E10, available at http://www.annemergmed.com).

An additional 31 events occurred between 30 days and 1 year for patients with recalibrated HEART score of equal to or less than 3 in the overall cohort. These were mostly deaths (n=24) with only 3 further type 1 MIs between 30 days and 1 year. Sensitivity and negative predictive value for recalibrated HEART score equal or less than 3 for MACE at 1 year was 93.2% and 97.9%, respectively. By

comparison, in the subgroup of hs-cTn T<LOD/LOQ with a nonischemic ECG, there were an additional 20 MACE events between 30 days and 1 year in the overall cohort: 11 additional all-cause deaths and 2 additional MIs. The sensitivity and negative predictive value for hs-cTn<LOD/LOQ with nonischemic ECG were 95.7% and 98.1%, respectively.

The 1-year incidence of type 1 MI in the overall cohort at 1 year was 7.6% (284/3752); 11.5% in the 2011 UK cohort (188/1637), 5.0% in the 2018 UK cohort (69/1366), and 3.6% in the US cohort (27/749). Sensitivity for both recalibrated HEART scores equal or less than 3 and hs-cTn T less than LOD/LOQ for type 1 MI at 1 year in the overall cohort was greater than 98%, indicating acceptable medium-term results for a cardiovascular outcome.

Potential Early ED Discharge

A recalibrated HEART score equal or less than 3 identified 46.5% (1743/3752) patients for potential early discharge; recalibrated TIMI score equal or less than 1 identified 47.5% (1783/3752), whereas hs-cTn T less than LOD/LOQ with a nonischemic ECG identified 32.5%% (1221/3752). An original HEART score equal or less than 3 and original TIMI score equal or less than 1 identified 48.5% (1820/3752) and 60.1% (2258/3752) as suitable for discharge, respectively. A hs-cTn T equal to or below the 99th percentile combined with a nonischemic ECG identified 60.2% for potential early discharge. Potential discharge proportion by recalibrated HEART score equal or less than 3 was consistent in all 3 cohorts and superior to hs-cTnT less than LOD/LOQ. However, in the US cohort, the difference was greater; potential discharge was 29.6% and 8.9% for the recalibrated HEART score equal to or less than 3 and hs-cTnT less than LOQ strategy, respectively, a difference of 20.7%. Figure 4 summarizes rule-out safety and potential discharge.

Limitations

There are limitations inherent to any observational study. The event rates for MI were low in the UK 2018 and the US cohort. Thus, the sample size might be insufficient to tease out true sensitivity for rule-out, particularly for early presenters. However, the summative performance of the entire population (Table 2) and subgroup analysis (Figure 5) suggests no interaction between early presenters and primary or secondary outcome. The time from presentation to the first sampling of troponin was long in the 2011 UK cohort, improved in the 2018 UK cohort but remained suboptimal. This could bias the outcomes and falsely reassure the performance of any clinical decision rule for early presenters. The 2011 UK derivation study was also a higher risk cohort, indicating that there has been a lowering of the threshold for troponin sampling and ECG for suspected ACS in the 2018 validation cohort. Although other evidence supports hs-cTn below the LOD,[19] current guidelines apply only to those presenting at least 3 hours from chest pain and recommend a second hs-cTn sample for patients presenting within 3 hours of symptom onset. It is possible to have a recalibrated HEART score equal to or less than 3 but with a very high troponin (troponin score of 2 (ie, greater than the 99th percentile) in the absence of risk factors in a young person with a normal ECG. This could, in the absence of clinical assessment, lead to false reassurance. This occurred in 30 cases in the UK and 9 in the US population. Not one of these cases was adjudicated as an MI.

In the UK cohorts, the third universal definition was chosen for adjudication of type 1 MI, with the US cohort being adjudicated by the fourth universal definition. It is unlikely this would confound the frequency of type 1 MI diagnosis between the cohorts, but it could have influenced the frequency of type 2 MI. Finally, we could not reliably differentiate cardiac from noncardiac death in the UK cohorts and therefore chose all-cause mortality as a MACE endpoint. This would, in fact, falsely lower the performance of intended algorithms as hs-cTns do not predict noncardiac deaths. Therefore, the diagnostic performance of all algorithms tested is an underestimate. We did not test other algorithms that are used, such as Troponin-only Manchester Acute Coronary Syndromes[20] and Emergency Department Assessment of Chest Pain Score.[10] This study has not tested competitor laboratory-based or point-of-care troponins and, in particular, troponin I with this concept. The performance of assays is subject to quality controls and may also be influenced by the analyzer. It is important for each laboratory to have estimates of precision at the low end (below the 99th percentile) as well as near the 99th percentile to apply these algorithms/risk scores with confidence.

DISCUSSION

Our study contains novel findings. Firstly, recalibrated HEART score equal to or less than 3, with a single presentation hs-cTn T, can safely exclude 30-day MACE in ED patients with suspected ACS. Secondly, the point estimates for negative predictive value and sensitivity of rule-out with recalibrated HEART score equal or less than 3 and recalibrated TIMI score equal or less than 1, for

MACE and MI, are consistently higher than those for original HEART score and original TIMI score in all 3 cohorts (Tables E6-E8). Thirdly, there was no signal for harm or decline in predictive performance for early presenters with suspected ACS (Table E9). Fourthly, recalibrated HEART score equal to or less than 3 allowed the potential discharge of 14% more patients than LOD/LOQ hs-cTn T with a nonischemic ECG as a strategy for ruling out 30-day MACE. Finally, medium-term data for cardiovascular outcomes are reassuring when using recalibrated HEART scores equal to or less than 3 as a discharge strategy. For the outcome of type 1 MI at one year, recalibrated HEART score equal to or less than 3 had a negative predictive value of 99.8% and sensitivity of 98.8% for the UK pooled cohort (n=3003), and 99.5% and 96.3%, for negative predictive value and sensitivity respectively, for the US cohort. The type 1 MI event rate, though, was similarly low and impressive at 1 year with the use of hs-cTn T <LOD/LOQ with a nonischemic ECG.

There are several advantages to our work compared with previous work in this area.[11,21] In each cohort, quality control was undertaken at the lower end of the high troponin assays used. The 2011 derivation and 2018 validation UK cohorts included a consecutive series of patients with suspected ACS, and the US cohort included a representative convenience sample so that the population is representative of clinical practice. There was standardization of outcomes with independent adjudication to the third or fourth Universal Definition of MI. Adjudications for MI were coordinated centrally in the 2018 UK cohort and in the US cohort with no access by the adjudicators to the clinical diagnoses or risk scores, thus minimising bias.

There was a difference in index MI and 30-day MACE rates between the 3 cohorts, despite similar demographics and risk factors, implying differing thresholds for testing (Tables E2-E5). The incidence of MI and MACE were higher in the 2011 UK cohort than in the 2018 UK cohort and the US cohort. However, considering the consistent direction of the outcomes for each discharge rule, these results are potentially meaningful for clinical practice using the Roche hs-cTn T assay. It is also important to note the familiarity and simplicity of the HEART score and likely ease if introduced in clinical practice. A substantially greater percentage of the suspected ACS population can be discharged at equivalent short-term safety to the more established LOD/LOQ below the 99th percentile with a nonischemic ECG strategy. These results extended to 1 year with only slight reductions in point estimates of sensitivity and negative predictive value. These results do not challenge the necessity for repeat high-sensitivity sampling to determine rule-in, as the decision aids tested are focused on early rule-out and discharge. They do not imply either that these algorithms could replace serial testing of hs-cTns for either exclusion or prediction of MI. However, they do imply that for a subset of patients, rule-out by recalibrated HEART score equal to or less than 3 could improve on a strategy of single presentation troponin sample using LOD/LOQ. Replacement of LOD hs-cTn T with recalibrated HEART score equal to or less than 3 as a single sample rule-out could enhance early, safe discharge rates with no compromise to safety compared with the LOD strategy currently advocated in most algorithms, including the European Society of Cardiology 0/1 hour pathway.[8] The recent HISTORIC trial has confirmed the real-world effectiveness and safety of an accelerated discharge strategy (HIGH-STEACS pathway).[22] However, it is important to note that the use of recalibrated HEART score equal to or less than 3 reduced specificity, although this effect was small. This indicates the value of rule-out but not of rule-in with a single presentation hs-cTn T allied to HEART score using very low levels (sub 99th percentile) as cut-of points for scoring.

Combining Low hs-cTn With Clinical Decision Rules

As a rule-out strategy, the combination of clinical risk assessment and low (sub 99th percentile) hs-cTn at presentation is attractive. The HEART, as well as other clinical decision rules such as Emergency Department Assessment of Chest Pain Score[20] and Troponin-only Manchester Acute Coronary Syndromes,[20] also focus on the assessment of chest pain and baseline risk (age, risk factors). High-sensitivity troponins near the 99th percentile or above may reflect a high burden of "nonculprit" plaque as well other causes.[23] Recalibrating existing risk stratification scores to lower levels of hs-cTn reduces the risk of subsequent MACE events further when combined with clinical decision rules. Very low troponin values are associated with a very low probability of underlying cardiac disease and even atherosclerosis in the absence of overt cardiac disease.[24,25]

This strategy has been tested in the 2018 UK validation cohort, in a posthoc analysis,[15] and in a number of other studies with mixed results.[10,21] Mark et al[10] undertook a retrospective analysis in a regional database of both HEART and Emergency Department Assessment of Chest Pain Score with a 60-day outcome. The optimized value for troponin was derived from a statistical technique termed reclassification yield. This value (Beckmann-Coulter assay), combined with the HEART or Emergency Department Assessment of Chest Pain score, was much lower than the 99th percentile. However, this study included only patients with troponins less than the 99th percentile and reported negative predictive

value, and not sensitivity, to decrease the spectrum bias to results. By contrast, the study by Body et al[21] demonstrated poor performance of HEART score equal to or less than 3, calibrated to LOQ in a nested study of the BEST trial (n=999). However, one-eighth of patients in this study had incomplete data for HEART score calculation.

In conclusion, recalibrated HEART score equal to or less than 3, with the use of a single presentation hs-cTnT at less than LOD/LOQ, appears an effective rule-out strategy for suspected ACS and potentially discharges considerably more patients than a strategy of LOD/LOQ below the 99th percentile with a nonischemic ECG. However, testing in further independent cohorts is required, particularly with other high-sensitivity troponin assays, to further assess the external validity of this finding.

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