ORIGINAL RESEARCH ARTICLE

Assessment of the 2016 National Institute for Health and Care Excellence high-sensitivity troponin rule-out strategy

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ABSTRACT

Objective We aimed to evaluate the limit of detection of high-sensitivity troponin (hs-cTn) and Thrombolysis In Myocardial Infarction (TIMI) score combination rule-out strategy suggested within the 2016 National Institute for Health and Care Excellence (NICE) Chest Pain of Recent Onset guidelines and establish the optimal TIMI score threshold for clinical use.

Methods A pooled analysis of adult patients presenting to the emergency department with chest pain and a non-ischaemic ECG, recruited into six prospective studies, from Australia, New Zealand and the UK. We evaluated the sensitivity of TIMI score thresholds from 0 to 2 alongside hs-cTnT or hs-cTnI for the primary outcome of major adverse cardiac events within 30 days.

Results Data were available for 3159 patients for hs-cTnT and 4532 for hs-cTnI, of these 376 (11.9%) and 445 (9.8%) had major adverse cardiac events, respectively. Using a TIMI score of 0, the sensitivity for the primary outcome was 99.5% (95% CI 98.1% to 99.9%) alongside hs-cTnT and 98.9% (97.4% to 99.6%)%) alongside hs-cTnI, identifying 17.9% and 21.0% of patients as low risk, respectively. For a TIMI score ≤1 sensitivity was 98.9% (97.3% to 99.7%)%) alongside hs-cTnT and 98.4% (96.8% to 99.4%)%) alongside hs-cTnI, identifying 28.1% and 35.7% as low risk, respectively. For TIMI≤2, meta-sensitivity was <98% with either assay.

Conclusions Our findings support the rule-out strategy suggested by NICE. The TIMI score threshold suggested for clinical use is 0. The proportion of patients identified as low risk (18%–21%) and suitable for early discharge using this threshold may be sufficient to encourage change of practice.

Trial registration numbers ADAPT observational study/IMPACT intervention trial ACTRN12611001069943. ADAPT-ADP randomised controlled trial ACTRN12610000766011. EDACS-ADP randomised controlled trial ACTRN12613000745741. TRUST observational study ISRCTN no. 21109279.

INTRODUCTION

The 2016 update to the National Institute for Health and Care Excellence (NICE) CG95 Chest Pain of Recent Onset guidelines proposes a step change in the use of biomarkers for the diagnosis of acute coronary syndrome (ACS).[1] For the first time in the UK, a rule-out strategy using a single high-sensitivity cardiac troponin (hs-cTn) test taken at presentation to the emergency department (ED) is recommended. NICE suggest that clinicians

'consider performing a hs-cTn test only at presentation to rule-out non-ST elevation myocardial infarction (NSTEMI) if the test is below the limit of detection (LoD)' and 'the patient is low-risk as indicated by a validated tool'.

Numerous observational studies have evaluated the limit of detection (LoD) (lowest analyte concentration at which detection is feasible) of hs-cTn assays alone at presentation to ED.[2–7] This cut-off concentration of the hs-cTnT assay, when combined with a non-ischaemic ECG, is potentially safe. In a meta-analysis of >9000 patients, pooled sensitivity for 30-day major adverse cardiac events (MACEs) was 98.0% (95% CI 94.7% to 99.3%).[8]

However, the strategy suggested by NICE mandates that a risk stratification tool is used alongside the LoD cut-off on a single troponin sample to identify patients suitable for discharge after a single hs-cTn test. The Thrombolysis In Myocardial Infarction (TIMI) score[9] or the Global Registry of Acute Cardiac Events (GRACE) score[10] are suggested for clinical use.[1] The GRACE score has been shown to have limited efficacy in combination with presentation hs-cTn testing.[11] Prior evaluations of the TIMI score in combination with hs-cTn assay results in ED patients with chest pain have demonstrated that between 20% and 40% of patients will be low risk.[11–13] Yet, these studies have incorporated cut-offs at the 99th percentile rather than the LoD and most have used serial hs-cTn sampling. Furthermore, NICE recommends that TIMI score thresholds of 0–2 are applied to define a patient as low risk.[1] This approach has not been validated; therefore, how best to apply the NICE recommendations in a clinical environment remains unknown.

The use of hs-cTn cut-offs between the LoD and the 99th percentile to maximise the proportion of patients suitable for discharge after a single hs-cTn result has also been explored.[7 14] It may be possible that by incorporating the TIMI score with low cut-off concentrations of hs-cTn will increase the proportion of patients suitable for discharge after a single hs-cTn result.

We aimed to validate the LoD and TIMI score combination strategy suggested by NICE, in prospectively recruited ED patients with suspected cardiac chest pain, using the two commercially available hs-cTn assays and establish which TIMI score cut-off should be implemented in clinical practice. In addition, we aimed to explore the safety and efficacy of low hs-cTn cut-offs above the LoD in combination with the TIMI score using simulation modelling.

METHODS
Study design and participants
The study population consisted of eligible patients presenting to the ED with chest pain, recruited into six prospective studies, from three countries: the Brisbane, Australia, and Christchurch, New Zealand, cohorts of the Accelerated Diagnostic Protocol to Assess Patients with Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker (ADAPT) observational study,[12] the Brisbane, Australia cohort of the Improved Assessment of Chest pain Trial (IMPACT) intervention trial,[15] the Christchurch ADAPT-ADP randomised controlled trial,[16] the Christchurch Emergency Department of Chest Pain Score (EDACS-ADP) randomised controlled trial,[13] and the Poole, UK, Triage Rule-out Using high-Sensitivity Troponin.(TRUST) observational study.[5] Inclusion and exclusion criteria, assessment of ECG, preparation of samples and assays used for diagnosis of Acute Myocardial Infarction (AMI) have been reported in detail in each study.[5 12 13 15 16] All patients recruited in the trials were eligible for enrolment if they presented with chest pain symptoms suggestive of cardiac ischaemia and investigation for ACS with serial biomarker tests was planned. Detailed exclusion criteria are included in the online supplementary material. Specific to this analysis, participants in whom hs-cTn results taken at presentation to the ED were not available were excluded. In addition, patients with new onset ECG changes diagnostic of ischaemia (ST segment depression ≥1 mm or T-wave inversion consistent with ischaemia) were excluded. These patients are high-risk independent of hs-cTn results or TIMI score and therefore not suitable for early discharge.

Written informed consent was obtained from all patients and the study protocols were approved by the respective local ethics committees. Recruitment was undertaken from 1 November 2007 to 1 January 2015.

Clinical processes
All participants had laboratory troponin concentrations measured at presentation and at least 2 hours later. The assays in use for routine clinical care at the time of recruitment and serial testing time points are detailed in online supplementary table 2. All clinical management was at the discretion of the treating clinician.

Laboratory measurement
Testing was undertaken using both commercially available hs-cTn (T and I) assays. One study (TRUST) used the Elecsys hs-cTnT assay (Roche, Basel, Switzerland) and one study (EDACS-ADP) used the Architect hs-cTnI assay (Abbott Diagnostics, Chicago, Illinois, USA) in routine clinical care (online supplementary table 2), where analysis was undertaken in real time. In remaining studies, research samples taken on presentation were centrifuged and serum stored frozen at ≤−70°C for later analysis. The LoD for hs-cTnT is 5 ng/L.[17] For hs-cTnI, a range of 1.2–1.9 ng/L for the LoD is quoted,[17] we rounded this value to 2 ng/L as is common laboratory practice.[18] Prior analysis of

applying the LoD at 2 ng/L, rather than 1.2 ng/L, for hs-cTnI, has demonstrated an improved efficacy (patients eligible for early discharge; 25.6% vs 18.8%) but with a reduction in diagnostic sensitivity (99.0% vs 97.9%).[7]

Patient data and TIMI risk scores
Patient data were recorded according to standardised data collection forms using a published data dictionary.[19] TIMI risk scores (box 1) were calculated from clinical data recorded by research staff. Follow-up events were monitored by dedicated research staff through a combination of telephone contact, corroboration by review of hospital online patient management systems and query to the national death registries at least 6 months after index presentation.

Outcomes
Given the focus of NICE Guideline CG95 on the rule-out of ACS, we deemed that the most appropriate primary outcome for this analysis was the sensitivity (as a measure of safety) of each strategy for MACE occurring within 30 days of hospital attendance. MACE included death due to ischaemic heart disease, cardiac arrest, unplanned symptom-induced revascularisation, cardiogenic shock, ventricular arrhythmia, high-degree atrioventricular block needing intervention and AMI. This outcome was adjudicated by researchers with knowledge of the troponin assay results in clinical use, ECGs and all other clinical information available up to 30 days after presentation. Methods for the adjudication of MACE by study site are detailed in online supplementary table 1.

The presence of AMI was defined according to the Third Universal Definition, which states that a rise and/or fall in troponin, with at least one value above the 99th percentile value in a patient with ischaemic symptoms or signs, would satisfy the diagnosis.[20] AMI was adjudicated using presentation and late troponin results, according to assays in use at each institution at the time of recruitment (online supplementary table 2).

The secondary outcome was the proportion of patients potentially suitable for early discharge using each algorithm as an estimate of efficacy.

Statistical analysis

Data were analysed using Stata V.12 and R V.3.3.2.[21] Baseline characteristics of the study population were analysed with conventional group descriptive statistics. Results were pooled for calculation of sensitivity, specificity, negative predictive value (NPV) and positive predictive value for each hs-cTn assay and each TIMI score threshold from 0 to 2. All CIs based on the 2×2 diagnostic matrices for each troponin assay are exact binomial 95% CIs. To provide a meta-estimate of sensitivity, we used a random-effects bivariate model to obtain the summary estimates of sensitivity and its 95% CIs.[22] We quantified heterogeneity with the I^2 statistic, which reflects the proportion of variation in point estimates among studies beyond that expected by chance. I^2 values <25%, 25% to <75% and ≥75% were considered to represent low, moderate and high heterogeneity, respectively.[23]

To estimate the optimal combinations of hs-cTn concentration with TIMI score to safely rule-out MACE within 30 days, we calculated the sensitivity and proportion low risk for every combination of hs-cTn from the LoD to 20 ng/L in steps of 1 ng/L with TIMI score from 0 to 5. To improve the generalisability of the estimates, we used bootstrapping, whereby we created 500 bootstrap cohorts (replicates) and repeated the analysis on each cohort and averaged the resultant sensitivity, specificity and proportion low risk and used averaged values to construct contour plots of sensitivity on the TIMI score. Bootstrapping selects a cohort of the same size as the initial cohort by drawing subjects at random from the initial cohort (replacing them each time) and then repeating the analysis.[24]

RESULTS

Of 5316 patients eligible for analysis, for the hs-cTnT assay, data were available for 3159 patients, including 704 from Australia, 1534 from New Zealand and 921 from the UK (figure 1). Of these, 1866 (59.1%) were male. Mean age was 59.3 (SD 13.3)

years and 376 (11.9%) had a 30-day MACE. For the hs-cTnI assay, data were available for 4532 patients, including 1761 from Australia, 1904 from New Zealand and 867 from the UK (figure 1). Of these, 2964 (59.4%) were male. Mean age was 57.2 (SD 13.0) years and 445 (9.8%) had a 30-day MACE. Baseline characteristics classified by hs-cTn assay are shown in table 1.

Across all cohorts, 2157 and 784 patients were excluded because hs-cTnT and hs-cTnI results were not available, respectively. There were no missing data for calculation of TIMI scores. No patients were lost to follow-up. Other exclusions from the primary studies are detailed in figure 1. Of note, 438 patients were excluded due to the presence of ischaemia on the initial ECG.

Validation of the NICE guideline

LoD of hs-cTnT and TIMI 0 strategy

Two patients (0.5%) with 30-day MACE were incorrectly classified as low risk, yielding a sensitivity of 99.5% (95% CI 98.1% to 99.9%) and NPV of 99.6% (98.7% to 100%) (table 2). The meta-estimate for sensitivity was 98.7% (96.5% to 99.6%: I^2 15.3). This strategy identified 17.9% (16.6% to 19.3%) of patients as low risk and potentially suitable for discharge.

LoD of hs-cTnI and TIMI 0 strategy

Five patients (1.1%) with 30-day MACE were incorrectly classified as low risk, yielding a sensitivity of 98.9% (97.4% to 99.6%) and NPV of 99.5% (98.8% to 99.8%) (table 2). The meta-estimate for sensitivity was 98.5% (95.4% to 99.5%: I^2 73.7) This strategy identified 21.0% (19.9% to 22.2%) of patients as low risk.

The hs-cTnI assay in combination with TIMI 0 identified a greater proportion of patients potentially suitable for early
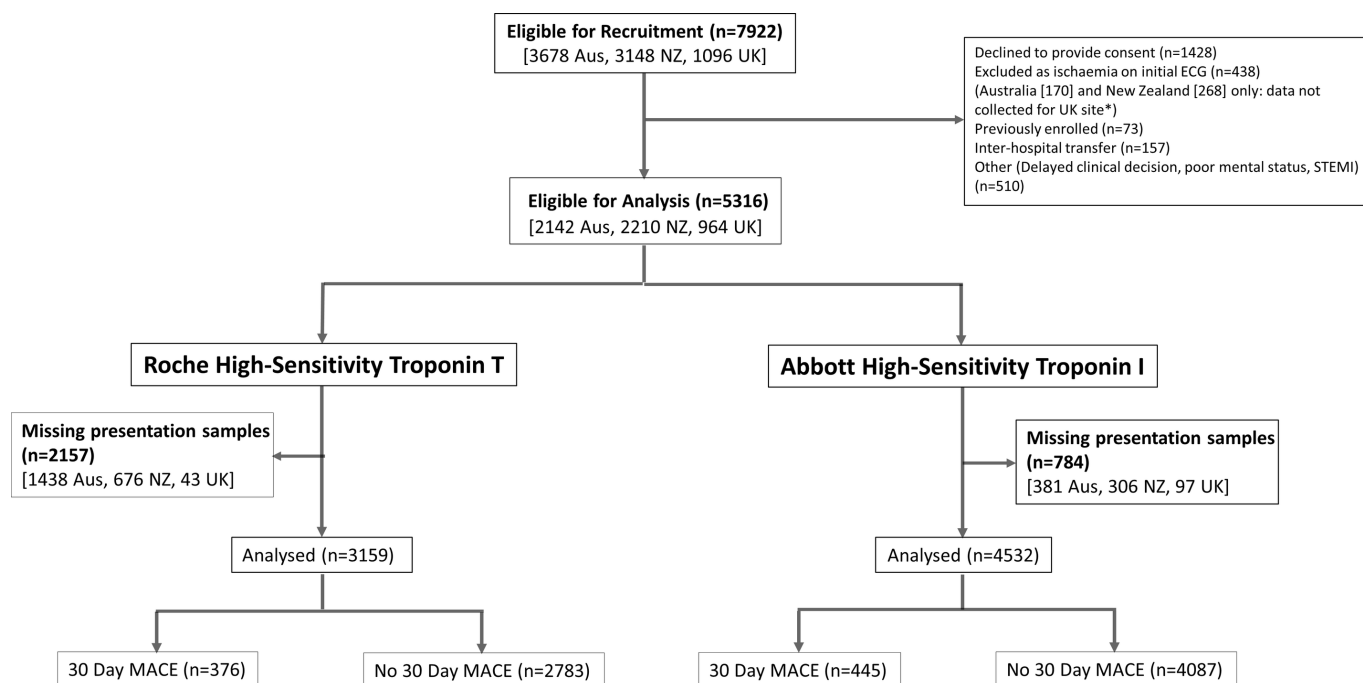

Figure 1 Participant recruitment flow chart. *The local ethics committee for the UK site did not approve data collection for patients with ischaemia on initial ECG as these patients were deemed not relevant to the primary study. Aus, Brisbane, Australia; NZ, Christchurch, New Zealand; UK, Poole, UK; 30-Day MACE, 30-day major adverse cardiac events (death due to ischaemic heart disease, cardiac arrest, unplanned symptom-induced revascularisation, cardiogenic shock, ventricular arrhythmia, high-degree atrioventricular block needing intervention and acute myocardial infarction).

Table 1 Characteristics of patients classified by high-sensitivity troponin assay

	hs-cTnT cohort (n=3159)	hs-cTnI cohort (n=4532)
Age, years; mean (SD)	59.3 (13.3)	57.2 (13.0)
Sex (% male)	1866 (59.1)	2694 (59.4)
Ethnicity (% Caucasian)	2745 (87.5)*	3917 (86.9)
Risk factors, n (%)		
Hypertension	1667 (52.8)	2233 (49.3)
Diabetes	476 (15.1)	643 (14.2)
Dyslipidemia	1773 (56.1)	2319 (51.2)
Smoking current	657 (20.8)	1000 (22.1)
Family history of CAD	1570 (49.7)	2087 (46.1)
Medical history, n (%)		
Angina	960 (30.4)	1129 (24.9)
Myocardial infarction	734 (23.2)	916 (20.2)
Percutaneous coronary intervention	544 (17.2)	701 (15.5)
Congestive cardiac failure	162 (5.1)	175 (3.9)
Stroke/TIA	203 (6.4)	261 (5.8)
CABG	223 (7.1)	267 (5.9)
TIMI risk score		
Age≥65	1117 (35.4)	1322 (29.2)
≥3 Risk factors for coronary artery disease	1046 (33.1)	1344 (29.7)
Significant coronary stenosis	907 (28.7)	1109 (24.5)
Severe angina	951 (30.1)	1483 (32.7)
Aspirin use in the past 7 days	1278 (40.5)	1583 (34.9)
MACE within 30 days, n (%)	376 (11.9)	445 (9.8)

*Data missing for ethnicity in 21 cases for hs-cTnT and 23 cases for hs-cTnI.
CABG, Coronary Artery Bypass Graft; CAD, Coronary Artery Disease; MACE, major adverse cardiac event; TIA, Transient Ischaemic Attack.

discharge; difference 3.1% (1.3% to 4.9%) in comparison to the hs-cTnT assay, with no difference in missed event rates; 0.6% (−0.9% to 2.1%).

LoD of hs-cTnT and TIMI ≤1 strategy
Four patients (1.1%) with 30-day MACE were incorrectly classified as low risk using this strategy, yielding a sensitivity of 98.9% (97.3% to 99.7%) and NPV of 99.5% (98.8% to 99.9%) (table 2). The meta-estimate for sensitivity was 98.4% (95.7% to 99.4%: I^2 0). This strategy identified 28.1% (26.5% to 29.7%) of patients as low risk and potentially suitable for discharge.

LoD of hs-cTnI and TIMI ≤1 strategy
Seven patients (1.6%) with 30-day MACE were incorrectly classified as low risk, yielding a sensitivity of 98.4% (96.8% to 99.4%) and NPV of 99.6% (99.1% to 99.8%) (table 2). The meta-estimate for sensitivity was 98.2% (94.5% to 99.4: I^2 74.4). This strategy identified 35.7% (34.3% to 37.1%) of patients as low risk.

The hs-cTnI assay in combination with TIMI ≤1 identified a greater proportion as potentially suitable for discharge; difference 7.6% (5.5% to 9.7%) in comparison to the hs-cTnT assay, with no difference in missed event rates; 0.5% (−1.3% to 2.3%).

LoD of hs-cTnT or I and TIMI≤2 strategy
Using either hs-cTn assay in combination with TIMI ≤2 yielded a meta-estimate for sensitivity for 30-day MACE of <98% (table 2).

Early presenters
Patients presented between a median time of 2.3 hours (the UK) and 4.8 hours (New Zealand) after chest pain onset (online supplementary table 3). Subgroup analysis of patients presenting early (within 3 hours of chest pain onset) is included in online supplementary table 4.

For hs-cTnT, 1988/3159 patients (62.9%) presented early. The LoD of hs-cTnT and TIMI 0 strategy yielded a sensitivity of 99.3% (97.3% to 99.9%) in this subgroup.

For hs-cTnI, 2658/4532 patients (58.6%) presented early. The LoD of hs-cTnI and TIMI 0 strategy yielded a sensitivity of 99.3% (97.6% to 99.9%) in this subgroup.

Variation between sites
Characteristics of patients classified by hs-cTn assay separated by country are reported in the supplement (online supplementary table 3). The proportion of patients classified as having 30-day MACE ranged from 6.1% (Australia) to 15.6% (New Zealand) for the hs-cTnT cohort and 4.8% (Australia) to 14.6% (New Zealand) for hs-cTnI. The Forest plot (figure 2) demonstrates how the sensitivity for 30-day MACE for each strategy varied between countries.

Exploration of 0 hour cut-off concentrations of high-sensitivity troponin above the LoD in combination with the TIMI score
For hs-cTnT at presentation, the contour plot based on the average sensitivities of the 500 bootstrapped replicates (figure 3) demonstrates a high range of cut-off values (<15 ng/L) at which the sensitivity for 30-day MACE remains >99% in conjunction with a TIMI score of 0. A greater proportion of patients will be classified as low risk by adopting a cut-off concentration above the LoD (6 or 7 ng/L) in combination with a TIMI score of ≤1, with good sensitivity (>99%).

For hs-cTnI at presentation, the contour plot (figure 4) shows a narrow range of <5 ng/L in conjunction with a TIMI score of 0 or at the LoD with a TIMI score of ≤1 where there was a very good sensitivity (>99%) for 30-day MACE.

DISCUSSION
Using both hs-cTn assays, with a TIMI score threshold of 0, the rule-out strategy advocated by NICE Guideline CG95 has a sensitivity of approximately 99% for 30-day MACE, a safety level most frequently identified by ED physicians as acceptable.[25] The proportion of patients identified as low risk (18%–21%) maybe sufficient to encourage change of practice. Diagnostic accuracy of this TIMI score threshold is maintained in early presenters. An additional 10%–15% of patients are identified as low risk if the TIMI score threshold is increased to 1. This is at the cost of increased numbers of false negatives, although the point estimate of sensitivity for both assays was >98%. Using a TIMI score threshold of 2, approximately 30%–40% of patients would be classed as low risk; however, the meta-estimate for sensitivity falls to <98%. While the additional benefit of potentially discharging more patients early is tempting, clinicians should consider the lower bounds of the CIs and consider if they would be satisfied with the safety of the strategy if the true sensitivity was around this lower bound. Given the potential implications of missing MACE, we would encourage clinicians to adopt a more cautious approach. We therefore recommend that a TIMI score of 0 is used to identify low-risk patients, in combination with the LoD cut-off of either hs-cTn assay, when applied to clinical practice.

Table 2 Summary statistics of the suggested National Institute for Health and Care Excellence algorithm according to high-sensitivity troponin assay and Thrombolysis In Myocardial Infarction (TIMI) score threshold

	Hs-cTnT		Hs-cTnI	
TIMI score 0 2×2	MACE	No MACE	MACE	No MACE
Test positive: hs-cTn>LoD or TIMI>0	374	2219	440	3140
Test negative (rule-out): hs-cTn≤LoD and TIMI=0	2	564	5	947
Sensitivity (95% CI)	99.5% (98.1% to 99.9%)		98.9% (97.4% to 99.6%)	
Meta-estimate of sensitivity (95% CI)	98.7% (96.5% to 99.6)		98.5% (95.4% to 99.5%)	
Negative predictive value (95% CI)	99.6% (98.7% to 100%)		99.5% (98.8% to 99.8%)	
Specificity (95% CI)	20.3% (18.8% to 21.8%)		23.2% (21.9% to 24.5%)	
Positive predictive value (95% CI)	14.4% (13.1% to 15.8%)		12.3% (11.2% to 13.4%)	
Proportion of patients potentially suitable for early discharge (95% CI)	17.9% (16.6% to 19.3%)		21.0% (19.9% to 22.2%)	
TIMI score≤1 2×2	MACE	No MACE	MACE	No MACE
Test positive: hs-cTn>LoD or TIMI>1	372	1900	438	2477
Test negative (rule-out): hs-cTn≤LoD and TIMI≤1	4	883	7	1610
Sensitivity (95% CI)	98.9% (97.3% to 99.7%)		98.4% (96.8% to 99.4%)	
Meta-estimate of sensitivity (95% CI)	98.4% (95.7% to 99.4%)		98.2% (94.5% to 99.4%)	
Negative predictive value (95% CI)	99.5% (98.8% to 99.9%)		99.6% (99.1% to 99.8%)	
Specificity (95% CI)	31.7% (30.0% to 33.5%)		39.4% (37.9% to 40.9%)	
Positive predictive value (95% CI)	16.4% (14.9% to 18.0%)		15.0% (13.7% to 16.4%)	
Proportion of patients potentially suitable for early discharge (95% CI)	28.1% (26.5% to 29.7%)		35.7% (34.3% to 37.1%)	
TIMI score≤2 2×2	MACE	No MACE	MACE	No MACE
Test positive: hs-cTn>LoD or TIMI>2	369	1736	433	2216
Test negative (rule-out): hs-cTn≤LoD and TIMI≤2	7	1047	12	1871
Sensitivity (95% CI)	98.1% (96.2% to 99.2%)		97.3% (95.3% to 98.6%)	
Meta-estimate of sensitivity (95% CI)	97.4% (94.7% to 98.8%)		97.7% (92.4% to 99.3%)	
Negative predictive value (95% CI)	99.3% (98.6% to 99.7%)		99.4% (98.9% to 99.7%)	
Specificity (95% CI)	37.6% (35.8% to 39.5%)		45.8% (44.2% to 47.3%)	
Positive predictive value (95% CI)	17.5% (15.9% to 19.2%)		16.3% (15.0% to 17.8%)	
Proportion of patients potentially suitable for early discharge (95% CI)	33.4% (31.7% to 35.0%)		40.5% (39.0% to 41.9%)	

MACE, major adverse cardiac event; Hs-cTn: high-sensitivity cardiac troponin T or I; TIMI, thrombolysis inmyocardial infarction.

Beyond the explicit recommendations of NICE, our simulation modelling demonstrates that higher cut-off concentrations of both hs-cTnT and hs-cTnI may be used in combination with the TIMI score to identify a higher proportion of patients potentially eligible for early discharge with a sensitivity >99%. Given the higher range of cut-off values at which the sensitivity remains >99%, this effect is likely to be greater with the hs-cTnT assay. For example, a conservative threshold of around 7 ng/L in conjunction with TIMI 0 may enable even more patients to be treated as low risk than the use of the LoD alone. In this case, the sensitivity for 30-day MACE of hs-cTnT ≤7 ng/L and TIMI 0 was 99.4% (99.2%–99.7%), resulting in 23.3% (22.8%–23.7%) of patients identified as low risk and potentially suitable for early discharge. Notably, in both contour graphs, even with the large numbers available and the bootstrapping technique used, the contours are not smooth and so it is appropriate to interpret them cautiously.

Because the LoD cut-off is both assay and manufacturer specific, it is important to recognise that this analysis (and the recommendations of NICE) applies to the specific assays tested. Also, the analytic reliability of the LoD as a cut-off is vulnerable to variation in batches, set-up, calibration and operation of analysers in laboratories at individual sites. Therefore, expecting these assays to universally perform well and consistently at such low values may be optimistic.[8]

The TIMI risk score was designed to predict mortality in patients with confirmed ACS rather than to risk stratify undifferentiated ED patients with chest pain. Consequently, the original derivation included the variable of ST-segment deviation.[9] Irrespective of hs-cTn results and TIMI scores, in an ED environment, patients with ST-segment deviation will not be discharged. Ours and prior analyses have therefore classified these patients as high risk, yet we demonstrate that the TIMI score can still be successfully applied to an undifferentiated ED population.[11–13] However, given that prior analyses have demonstrated that the combination of the LoD cut-off and ECG testing, in the absence of a risk score such as TIMI, is potentially safe,[5–8] the additional benefits of using the TIMI score remain uncertain.[26]

Furthermore, scores designed with the specific purpose of evaluating ED patients with chest pain, such as the HEART score,[27] T-MACS rule[28] or EDACS,[13] may improve risk stratification. Most studies evaluating risk scores are observational, meaning no patient is physically discharged according to the rule-out strategy tested. Importantly, the HEART score in combination with a single hs-cTn result has been shown to lead to no significant increase in early discharges compared with usual care within an interventional trial.[29] Therefore, further data from interventional trials to establish the clinical and cost-effectiveness of strategies that use a single hs-cTn result to facilitate early discharge are needed.

Group	TP	FP	FN	TN
hs-cTnT <= LoD and TIMI=0				
UK	93	634	1	193
AU	39	549	1	115
NZ	242	1036	0	256
Combined	374	2219	2	564
hs-cTnI <= LoD and TIMI=0				
UK	81	531	2	253
AU	77	1251	3	433
NZ	282	1358	0	264
Combined	440	3140	5	947
hs-cTnT <= LoD and TIMI <= 1				
UK	92	575	2	252
AU	39	405	1	259
NZ	241	920	1	372
Combined	372	1900	4	883
hs-cTnI <= LoD and TIMI <= 1				
UK	79	419	4	365
AU	77	804	3	877
NZ	282	1254	0	368
Combined	438	2477	7	1610
hs-cTnT <= LoD and TIMI <= 2				
UK	91	547	3	280
AU	38	372	2	292
NZ	240	817	2	475
Combined	369	1736	7	2783
hs-cTnI <= LoD and TIMI <= 2				
UK	77	336	6	448
AU	77	804	3	80
NZ	282	1162	0	460
Combined	433	2216	12	1871
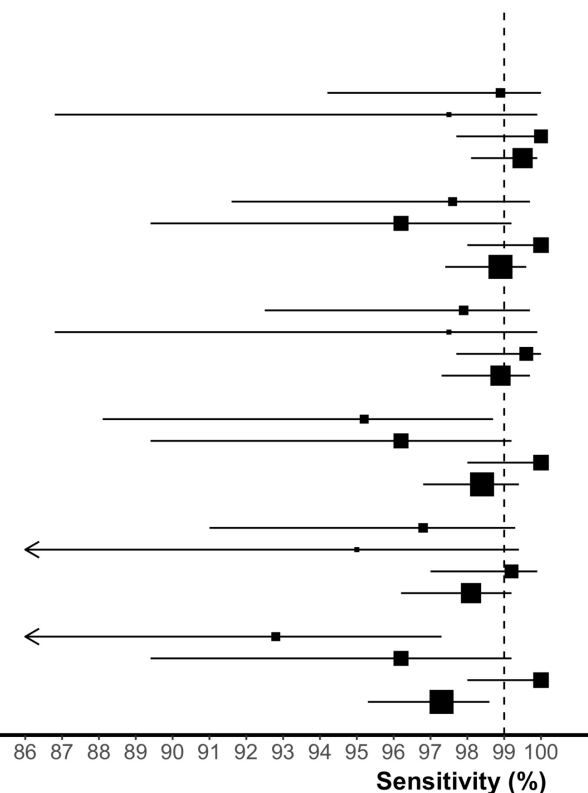
Figure 2 Forest plots of the sensitivity (95% CI) for major adverse cardiac events occurring within 30 days separated by rule-out strategy and study site. FN, false negatives; FP, false positives; LoD, limit of detection; TN, true negatives; TP, true positives; TIMI, Thrombolysis In Myocardial Infarction.

LIMITATIONS

The processes and troponin assays used to adjudicate MACE at each site were not identical. While this variance may reflect the subjectivity of real-world clinical assessment, it is possible that this methodology may have led to misclassification bias.

The timing of serial troponin sampling varied across sites, with some patients being discharged without a 6-hour sample. It is possible that a small proportion of events may have been missed in those patients having early (2-hour) sampling. However, given this testing strategy was in clinical use at the time of recruitment and the missed event rate using this approach has been shown to be <0.8%,[12] the impact of this methodology is likely to be negligible.

For this analysis, a large number of participants were excluded because troponin results were not available. Importantly, the hs-cTnT group has a higher mean age and a higher prevalence of comorbidities. These exclusions may therefore bias the reported diagnostic accuracy statistics and the proportions suitable for early discharge demonstrated between assays.
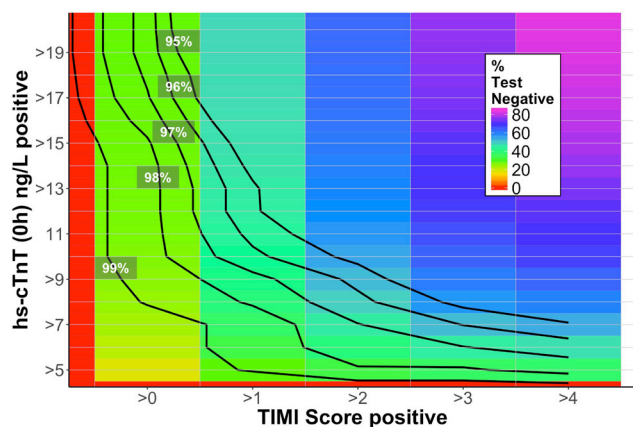

Figure 3 Sensitivity contours and percentages who tested negative for combinations of hs-cTnT and Thrombolysis In Myocardial Infarction (TIMI) score. A positive test is if either the troponin or the TIMI score exceeds a specified value. Note that within each TIMI score the change in contour represent the change in sensitivity at different hs-cTnT concentrations only.
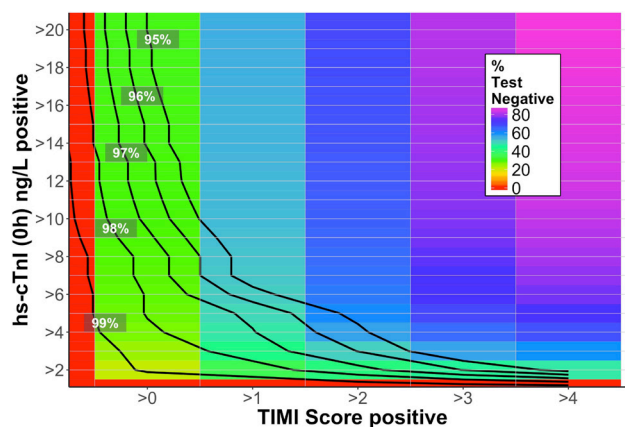

Figure 4 Sensitivity contours and percentages who tested negative for combinations of hs-cTnI and Thrombolysis In Myocardial Infarction (TIMI) score. A positive test is if either the troponin or the TIMI score exceeds a specified value. Note that within each TIMI score the change in contour represent the change in sensitivity at different hs-cTnI concentrations only.

CONCLUSIONS

Our findings support the NICE strategy incorporating the LoD of hs-cTn with the TIMI score for the rule-out of ACS. The TIMI score threshold suggested for clinical use for identifying low-risk patients is 0. The optimal strategy for identifying patients suitable for discharge after a single hs-cTn result in combination with the TIMI score may include cut-off concentrations above the LoD.

Key questions

What is already known on this subject?
For the first time in the UK a rule-out strategy for patients with chest pain using a single cardiac troponin test has been recommended by the National Institute for Health and Care Excellence (NICE). NICE recommends the Thrombolysis in Myocardial Infarction (TIMI) risk score should be used in combination with a single undetectable high-sensitivity troponin result. However, this approach has not been validated.

What might this study add?
We assessed TIMI score thresholds for the identification of low-risk patients, alongside high-sensitivity cardiac troponin T and I assays in prospectively recruited emergency department patients with suspected cardiac chest pain and a non-ischaemic ECG from six studies, from three countries. We established a TIMI score threshold of 0 in combination with an undetectable troponin identified 18%–21% of patients potentially suitable for safe discharge after a single blood test with a sensitivity for 30-day major adverse cardiac events of approximately 99%.

How might this impact on clinical practice?
Strategies that incorporate a risk score with high-sensitivity troponin results at presentation are ready for clinical implementation, yet further work is needed to define the optimum strategy. The strategy suggested by NICE is conservative and will allow early discharge of around 20% of patients.

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Correction notice Since this paper was first published online the author affiliations have been updated.

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