

High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study



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Summary

Background Suspected acute coronary syndrome is the commonest reason for emergency admission to hospital and is a large burden on health-care resources. Strategies to identify low-risk patients suitable for immediate discharge would have major benefits.

Methods We did a prospective cohort study of 6304 consecutively enrolled patients with suspected acute coronary syndrome presenting to four secondary and tertiary care hospitals in Scotland. We measured plasma troponin concentrations at presentation using a high-sensitivity cardiac troponin I assay. In derivation and validation cohorts, we evaluated the negative predictive value of a range of troponin concentrations for the primary outcome of index myocardial infarction, or subsequent myocardial infarction or cardiac death at 30 days. This trial is registered with ClinicalTrials.gov (number NCT01852123).

Findings 782 (16%) of 4870 patients in the derivation cohort had index myocardial infarction, with a further 32 (1%) re-presenting with myocardial infarction and 75 (2%) cardiac deaths at 30 days. In patients without myocardial infarction at presentation, troponin concentrations were less than 5 ng/L in 2311 (61%) of 3799 patients, with a negative predictive value of 99.6% (95% CI 99.3–99.8) for the primary outcome. The negative predictive value was consistent across groups stratified by age, sex, risk factors, and previous cardiovascular disease. In two independent validation cohorts, troponin concentrations were less than 5 ng/L in 594 (56%) of 1061 patients, with an overall negative predictive value of 99.4% (98.8–99.9). At 1 year, these patients had a lower risk of myocardial infarction and cardiac death than did those with a troponin concentration of 5 ng/L or more (0.6% vs 3.3%; adjusted hazard ratio 0.41, 95% CI 0.21–0.80; $p < 0.0001$).

Interpretation Low plasma troponin concentrations identify two-thirds of patients at very low risk of cardiac events who could be discharged from hospital. Implementation of this approach could substantially reduce hospital admissions and have major benefits for both patients and health-care providers.

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Introduction

Chest pain is a common cause of hospital admission worldwide and is a major burden on health-care resources.¹ In the UK, chest pain is responsible for roughly 1 million visits to emergency departments each year.² Although many of these patients might be suitable for direct discharge from the emergency department,³ current care pathways are unable to rule out myocardial infarction at presentation, and guidelines recommend serial troponin tests requiring hospital admission in most patients.⁴ Because most of these patients do not have myocardial infarction, this approach leads to a large number of potentially avoidable hospital admissions.^{2,5,6}

High-sensitivity cardiac troponin assays with high precision at very low concentrations enable accurate quantification of troponin in most healthy people.^{7,8} These assays could transform the assessment of patients with chest pain through the development of safe and effective strategies to exclude myocardial infarction in

the emergency department.⁹ Although international guidelines¹⁰ recommend that cardiac troponin concentrations above the 99th centile be used for the diagnosis of myocardial infarction, some studies suggest that patients with undetectable troponin concentrations are at low risk.^{10–15}

In a prospective study of the use of a high-sensitivity cardiac troponin I assay, we aimed to define a threshold that identifies patients with suspected acute coronary syndrome at presentation who are at low risk of myocardial infarction and potentially suitable for immediate discharge.

Methods

Study design and participants

For the derivation cohort, we prospectively identified consecutive patients with suspected acute coronary syndrome presenting to emergency departments of secondary care hospitals (St John's Hospital, Western General Hospital) and a tertiary care hospital (Royal

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Research in context**Evidence before this study**

Patients with suspected acute coronary syndrome are admitted to hospital for serial cardiac troponin testing to rule out myocardial infarction at the 99th centile upper limit. Cohort studies and a recent systematic review and meta-analysis suggest that patients with undetectable plasma troponin concentrations at presentation are at low risk of myocardial infarction. However, the optimal approach and threshold of cardiac troponin to identify low-risk patients who would be suitable for immediate discharge is unknown.

Added value of this study

We prospectively and systematically assessed a range of troponin concentrations using a high-sensitivity cardiac

troponin I assay in consecutive unselected patients with suspected acute coronary syndrome across different health-care settings. We established a threshold (<5 ng/L) that identified a large proportion of patients at very low risk of cardiac events who were admitted to hospital but could have been safely discharged.

Implications of all the available evidence

Low plasma cardiac troponin I concentrations at presentation can enable the immediate and safe discharge of up to two-thirds of patients with suspected acute coronary syndrome. This approach could have major benefits for both patients and health-care providers.

Infirmery of Edinburgh) in the southeast of Scotland between June 1, 2013, and Jan 31, 2014, enrolled in the standard care arm of a stepped-wedge cluster randomised trial (ClinicalTrials.gov number NCT01852123). All patients who had cardiac troponin requested by the attending clinician and an electrocardiogram done were included. Patients were excluded if they had been admitted previously during the study period, were pregnant, or did not live in Scotland (appendix).

We then assessed the threshold in two independent validation cohorts (n=1434). The first validation cohort included 1126 consecutively enrolled patients with suspected acute coronary syndrome presenting to the Royal Infirmery of Edinburgh, Edinburgh, UK (appendix).¹² The second included 308 consecutively enrolled patients from the UTROPIA study (ClinicalTrials.gov number NCT02060760) who presented to Hennepin County Medical Center. The inclusion and exclusion criteria for the validation cohort were the same as for the deviation cohort.

The study was approved by the national research ethics committee, and in accordance with the Declaration of Helsinki.

Procedures

Attending clinicians reviewed all patients at presentation and included those with suspected acute coronary syndrome. The clinicians screened all patients for suspected acute coronary syndrome using an electronic form that was integrated into the clinical care pathway before measurement of plasma cardiac troponin I concentration at presentation. Troponin testing was repeated 6 h or 12 h after the onset of symptoms at their discretion. All patients who met the inclusion criteria were assigned a study code and additional data from the electronic patient record were collected prospectively and linked in real time with a unique patient identifier.

We collected baseline clinical characteristics and investigations from a standardised electronic patient

record (TrakCare; InterSystems Corporation, Cambridge, MA, USA).^{11,12,16} Hyperlipidaemia and hypertension were defined as a history of the condition, or by the use of lipid-lowering or antihypertensive drugs, respectively. We calculated Global Registry of Acute Coronary Events (GRACE) risk scores and stratified patients as low risk (<1% risk of in-hospital mortality) or intermediate-high risk (\geq 1% risk of in-hospital mortality).¹⁷

As standard of care, a sensitive cardiac troponin I assay (ARCHITECT_{STAT} troponin I assay; Abbott Laboratories, Abbott Park, IL, USA) was used for clinical decision making and the result declared to the patients' clinicians. This assay has been validated.^{11,16} According to the manufacturer, the limit of detection is 10 ng/L and the upper reference limit (99th centile) of a normal reference population is 28 ng/L. The inter-assay coefficient of variation was less than 10 % at 50 ng/L under local laboratory conditions and this concentration is used as the diagnostic threshold.

In parallel, a high-sensitivity assay (ARCHITECT_{STAT} high-sensitive troponin I assay; Abbott Laboratories) was used to remeasure cardiac troponin I concentrations on plasma excess to clinical requirements but the results were not reported on the health record systems or communicated to clinicians responsible for patients' care. This assay has a limit of detection of 1.2 ng/L, and an upper reference limit (99th centile) of 34 ng/L in men and 16 ng/L in women.^{12,18} It has a coefficient of variation of 23% at the limit of detection (1.2 ng/L) and less than 10% at 6 ng/L.^{19,20} Assay precision was further evaluated across all laboratories under routine working conditions at regular intervals during the study by the independent United Kingdom National External Quality Assurance Scheme for cardiac biomarkers (Glasgow), which reported that the interlaboratory coefficient of variation was 12.6% at 3.5 ng/L across 33 instruments (appendix).

All patients with evidence of myocardial necrosis (troponin concentration >99th centile using sex-specific upper reference limit on presentation or subsequent testing) were identified. Two investigators (AS, AA)

See Online for appendix

independently reviewed all clinical information, including non-invasive and invasive investigations, and outcomes from presentation to 30 days. Patients were classified as having type 1 or type 2 myocardial infarction, or having myocardial injury according to the universal definition of myocardial infarction.^{10,21} Type 1 myocardial infarction was defined as myocardial necrosis at an isolated presentation with suspected acute coronary syndrome with chest pain or evidence of myocardial ischaemia on an electrocardiogram. Patients with symptoms or signs of myocardial ischaemia due to increased oxygen demand or decreased supply (eg, tachyarrhythmia, hypotension, or anaemia) and myocardial necrosis were classified as type 2 myocardial infarction. Myocardial injury was defined as evidence of myocardial necrosis in the absence of any clinical features of myocardial ischaemia. Any discrepancies were resolved by the adjudication of a third independent reviewer (NLM). Index myocardial infarction was defined as any type 1 myocardial infarction arising during the first clinical episode. Agreement for an adjudicated diagnosis of type 1 myocardial infarction was excellent (κ 0·83, 95% CI 0·80–0·86).

We used regional and national registries to ensure that follow-up was complete for the entire study population. TrakCare (InterSystems; Cambridge, MA, USA) is a regional electronic patient record system, which provides data on all hospital admissions to both tertiary or secondary care hospitals in southeast Scotland. When assessing readmissions with myocardial infarction, all patients were re-adjudicated and classified after review of all clinical notes and investigations, and according to the same criteria used for their index admission. All in-hospital and community deaths are recorded in a comprehensive national database, the General Register of Scotland. Cardiac death was defined as any death due to myocardial infarction, arrhythmia, or heart failure. Cardiac death was defined with ICD-10 codes I20–25, I34–37, I42, I43, I46, and I48–51.

Outcomes

The primary outcome was a composite of index type 1 myocardial infarction, or type 1 myocardial infarction or cardiac death at 30 days. The secondary outcome was 1-year survival from myocardial infarction or cardiac death following the index presentation.

Statistical analysis

We established the negative predictive values for the primary outcome across a range of troponin concentrations starting at 1 ng/L. Patients with ST-segment elevation myocardial infarction and troponin concentrations above the 99th centile on presentation were not included in this analysis. Previous analyses of high-sensitivity cardiac troponin T assay have used a threshold based on the lowest detectable concentration. However, the precision of the high-sensitivity cardiac troponin I assay at low concentrations is sufficient to enable the assessment of a

	All patients (n=4870)	<99th centile at presentation* (n=3799)
Age (years)	64 (16)	62 (16)
Women	2061 (43%)	1580 (42%)
Presenting complaint	n=4870	n=3799
Chest pain	4043 (83%)	3251 (86%)
Dyspnoea	269 (6%)	141 (4%)
Palpitations	127 (3%)	102 (3%)
Syncope	181 (4%)	134 (4%)
Other	250 (5%)	171 (5%)
≤2 h since onset of chest pain	657/4043 (16%)	482/3251 (15%)
Medical history	n=4277	n=3317
Diabetes	669 (16%)	513 (16%)
Hypertension	1393 (33%)	1033 (31%)
Hyperlipidaemia	1123 (27%)	870 (26%)
Cerebrovascular accident	337 (8%)	236 (7%)
Myocardial infarction	796 (19%)	606 (18%)
Ischaemic heart disease	1391 (33%)	1058 (32%)
Previous revascularisation	n=4269	n=3289
Percutaneous coronary intervention	447 (11%)	360 (11%)
Coronary artery bypass graft	245 (6%)	178 (5%)
Current drugs†	n=3004	n=2370
Statin	1124 (38%)	881 (37%)
Aspirin	926 (32%)	720 (30%)
Clopidogrel	336 (11%)	248 (10%)
ACE inhibitor or ARB	962 (33%)	745 (31%)
β blockers	772 (26%)	584 (25%)
Oral anticoagulant	211 (7%)	159 (7%)
Cardiac troponin concentrations		
At presentation (ng/L)	5 (2–19)	5 (3–11)
Peak (ng/L)	6 (2–26)	4 (2–8)
Electrocardiograph results	n=4244	n=3279
Bundle branch block	278 (7%)	164 (5%)
ST-segment elevation	143 (3%)	93 (3%)
ST-segment depression	302 (7%)	153 (5%)
T-wave inversion	515 (13%)	341 (10%)
Heart rate (beats per min)	82 (23)	80 (22)
Systolic blood pressure (mm Hg)	138 (26)	138 (25)
Adjudicated diagnosis	n=4870	n=3799
Non-ST-elevation type 1 myocardial infarction	651 (13%)	132 (3%)
ST-elevation type 1 myocardial infarction	131 (3%)	0 (0%)
Type 2 myocardial infarction	173 (4%)	33 (1%)
Myocardial injury	301 (6%)	21 (1%)
Admitted to hospital	2978 (61%)	2015 (53%)
Outcome at 30 days	n=4870	n=3799
Readmission with myocardial infarction	32 (1%)	13 (0%)
Cardiac death	75 (2%)	13 (0%)
Index type 1 myocardial infarction, readmission with type 1 myocardial infarction or cardiac death	814 (17%)	145 (4%)

Data are mean (SD), n (%), or median (IQR). ACE=angiotensin converting enzyme. ARB=angiotensin receptor blocker. *Excludes patients presenting with ST-segment elevation myocardial infarction. †Drugs patients were already taking at presentation.

Table 1: Baseline characteristics of the derivation cohort

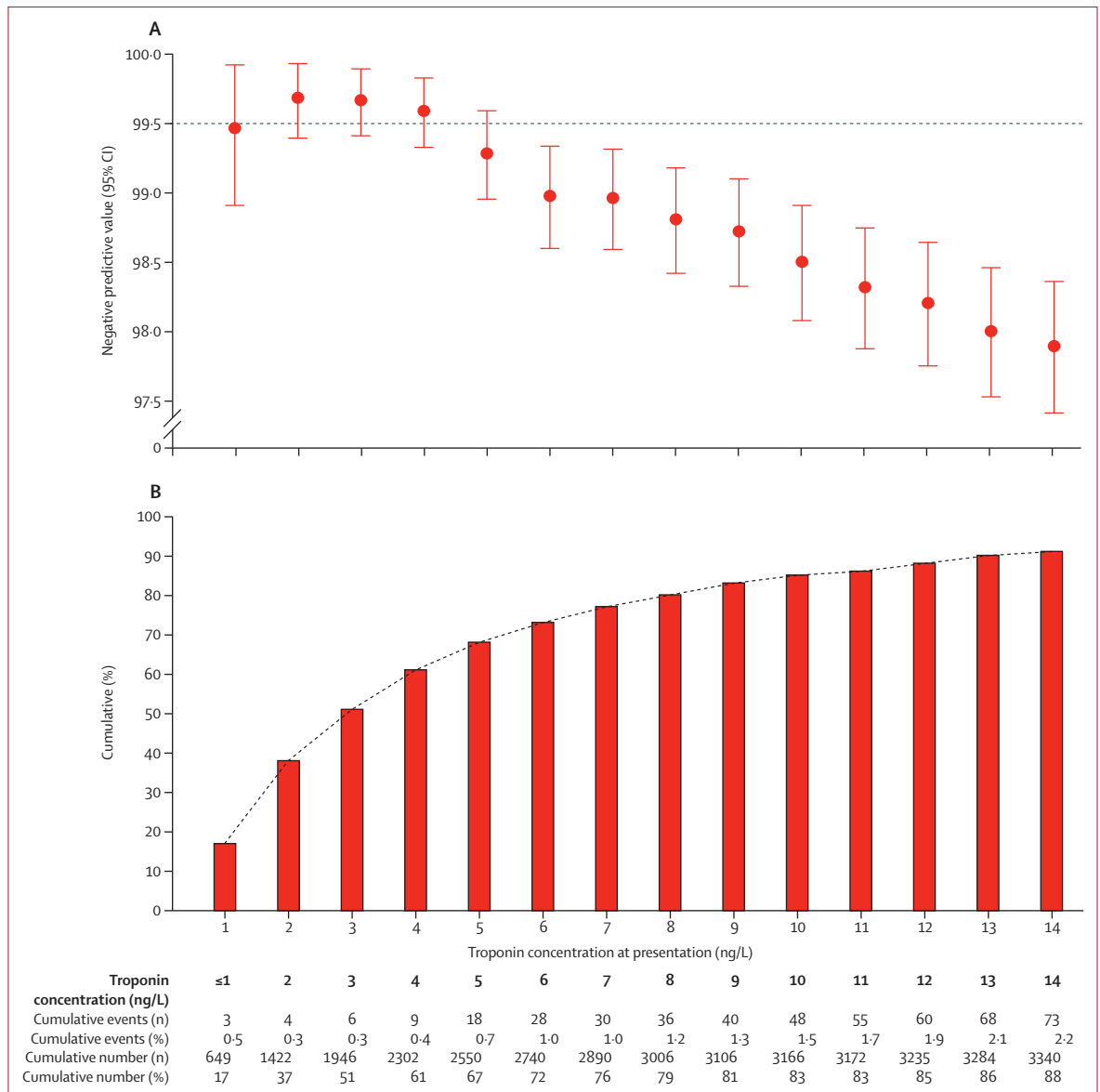


Figure 1: Cardiac troponin I concentration at presentation and risk of myocardial infarction
 (A) Negative predictive value of a range of troponin I concentrations at presentation for the composite outcome of index myocardial infarction, and myocardial infarction or cardiac death at 30 days. (B) Cumulative proportion of patients with suspected acute coronary syndrome with troponin concentrations below each threshold.

range of thresholds.¹⁰⁻¹⁵ As such, we selected a threshold on the basis of clinical need rather than assay performance. The trial steering committee prespecified that the cardiac troponin threshold on presentation should achieve a negative predictive value of at least 99.5% for the primary outcome. In sample size calculations, we estimated that 3500 patients would enable us to estimate a negative predictive value of 99.5% with a 95% CI of 99.2-99.7, and that we had 92% power for an α of 0.05 to test the null hypothesis that the negative predictive value was less than 99%.

We assessed the proportion of patients with troponin concentrations below each threshold who reached the

primary outcome. We did subgroup analyses to estimate the negative predictive value, stratifying by age, sex, duration of symptoms, cardiovascular risk factors, history of cardiovascular disease, and presence of myocardial ischaemia on the presenting electrocardiogram. We expected the negative predictive value to be close to 100%; therefore, we estimated the proportion by sampling from a binomial likelihood with a Jeffrey's prior (β distribution shape parameters both equal to 0.5) because intervals produced with this approach have good coverage for proportions close to 0 or 1.²² We compared survival free from myocardial infarction or cardiac death between patients with troponin

concentrations above and below the threshold using Cox proportional hazard models adjusted for age and sex. For the validation cohort, we estimated the proportion of patients with troponin concentrations below the threshold determined in the derivation cohort who reached the primary outcome, using the same method. We did the analyses with R (version 3.2.2).

Role of the funding source

The funder had no role in study design, data collection, analysis, or interpretation, or the writing of the report. The trial steering committee and NLM were responsible for the decision to submit the report for publication.

Results

We enrolled 6304 patients with suspected acute coronary syndrome: 4870 in the derivation cohort (table 1, appendix), 1126 in the internal validation cohort (appendix), and 308 in the external validation cohort (appendix).

In the derivation cohort, most patients presented with chest pain that began more than 2 h before troponin testing (table 1, appendix p 10). The median time from arrival in the emergency department to blood sampling for measurement of cardiac troponin was 54 min (IQR 33–85; appendix p 11). Repeat testing was done for 1608 (42%) of 3799 patients with troponin concentrations at presentation of below the 99th centile. Troponin concentrations were above the limit of detection in 4304 (88%) of 4870 patients and were above the 99th centile in 1253 (26%) of 4870 patients, with 782 (16%) judged to have type 1 myocardial infarction and 173 (4%) to have type 2 myocardial infarction. A further 301 (6%) of 4870 patients were classified as having myocardial injury. At 30 days, 32 (1%) patients re-presented with myocardial infarction, and 75 (2%) died from cardiac causes.

In the derivation cohort, low plasma troponin concentrations at presentation gave excellent negative predictive value for the composite endpoint of index type 1 myocardial infarction, or type 1 myocardial infarction or cardiac death at 30 days. A troponin concentration <5 ng/L was present in 2311 (61%) of 3799 patients below the 99th centile at presentation, giving a negative predictive value of 99.6% (95% CI 99.3–99.8; figure 1, appendix p 4). The negative predictive value decreased at higher troponin concentrations and was less than 99.5% at concentrations of 5 ng/L or more.

The negative predictive value of a troponin concentration less than 5 ng/L was similar in men and women and when stratified by age, cardiovascular risk factors, previous cardiovascular disease, or the presence of myocardial ischaemia on the presenting electrocardiogram (figure 2). In 2017 patients with a troponin concentration of less than 5 ng/L and an available electrocardiogram, 1833 (91%) had no evidence of ischaemia. The negative predictive value was similar across groups stratified by GRACE risk score (low risk 99.7%, 95% CI 99.4–100% vs intermediate–high risk

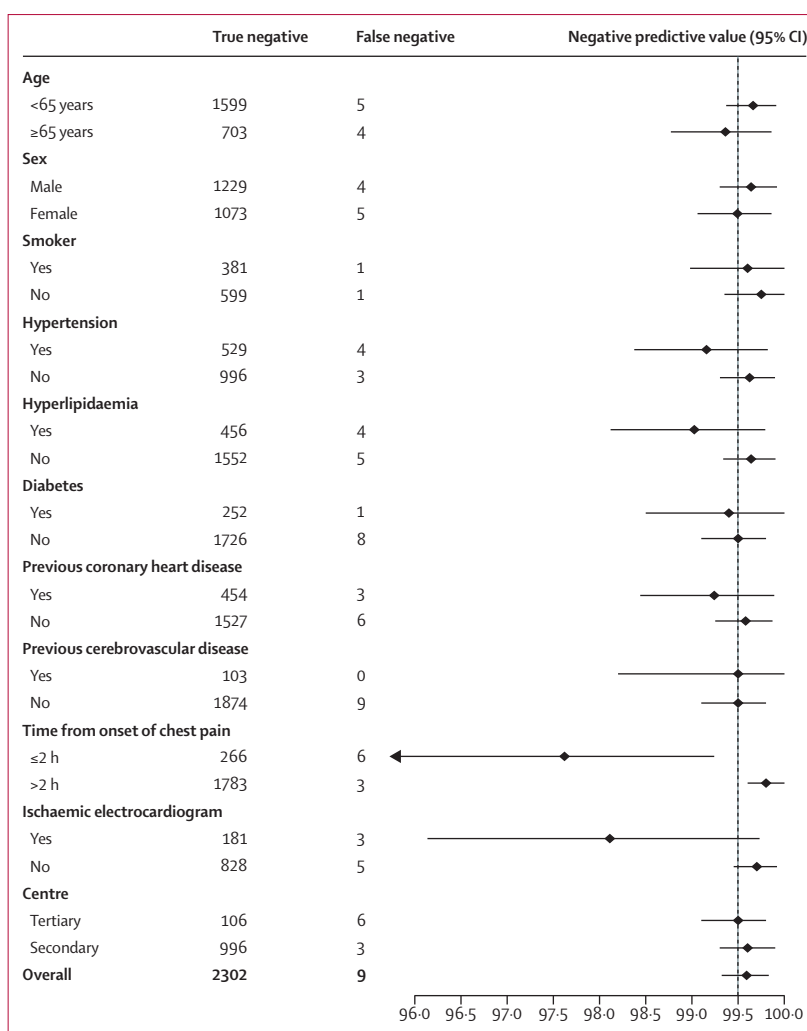


Figure 2: Negative predictive value of troponin concentrations <5 ng/L at presentation, stratified by subgroups For the composite outcome of index myocardial infarction, and myocardial infarction or cardiac death at 30 days. Dashed line is the prespecified negative predictive value of 99.5%.

98.4%, 97.0–99.7). The negative predictive value was lower in the 482 (15%) of 3251 patients who were tested for troponin within 2 h of the onset of chest pain (97.6%, 95% CI 95.8–99.2) than in the 2769 (85%) who had had chest pain for more than 2 h (99.8%, 95% CI 99.6–100.0). In a post-hoc sensitivity analysis in which type 2 myocardial infarction and myocardial injury were incorporated into the primary outcome (a troponin concentration >99th centile irrespective of clinical presentation), a troponin concentration of less than 5 ng/L gave a negative predictive value of 99.4% (95% CI 99.0–99.7).

In the two validation cohorts, a troponin concentration less than 5 ng/L was present in 470 (57%) of 829 and 124 (54%) of 232 patients without myocardial infarction at presentation, and had a negative predictive value of 99.3% (95% CI 98.5–99.9) and 99.8% (98.0–100.0), respectively. Overall troponin concentrations were less

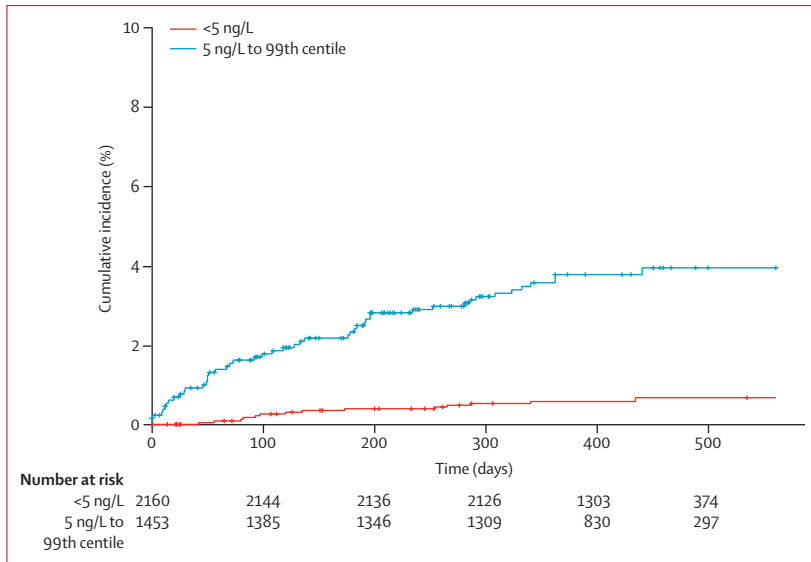


Figure 3: Cumulative incidence of myocardial infarction or cardiac death in patients with troponin concentrations less than the 99th centile
 Patients without index myocardial infarction were stratified into two groups based on the troponin concentration at presentation. Compared to patients with troponin concentrations ≥ 5 ng/L, patients with troponin concentrations < 5 ng/L were less likely to have a myocardial infarction or cardiac death at 1 year (0.6% vs 3.3%; hazard ratio 0.41, 95% CI 0.21–0.80; log-rank $p < 0.0001$).

	<5 ng/L (n=2160)	5 ng/L to 99th centile (n=1453)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Myocardial infarction				
30 days	0 (0.0%)	6 (0.4%)		
1 year	6 (0.3%)	19 (1.3%)	0.21 (0.08–0.51)	0.36 (0.13–0.99)
Cardiac death				
30 days	0 (0.0%)	6 (0.4%)		
1 year	6 (0.3%)	32 (2.2%)	0.14 (0.06–0.31)	0.41 (0.17–0.98)
Myocardial infarction or cardiac death				
30 days	0 (0.0%)	12 (0.8%)		
1 year	12 (0.6%)	48 (3.3%)	0.17 (0.09–0.31)	0.41 (0.21–0.80)

Data are n (%) unless stated otherwise. The hazard ratios are derived from a Cox regression model using all follow-up data. The median follow up was 427 days (IQR 371–489 days).

Table 2: Subsequent myocardial infarction or cardiac death in patients with troponin concentrations below the 99th centile in the derivation cohort

than 5 ng/L in 594 patients (56%) with a negative predictive value of 99.4% (98.8–99.9). Across all derivation and validation cohorts, 12 (0.4%) of 2905 patients with troponin concentrations less than 5 ng/L at presentation met the primary endpoint (appendix pp 5–6).

In the derivation cohort, 2978 (61%) patients were admitted to hospital for further investigation (table 1). In the 2272 patients admitted to hospital who were not diagnosed with type 1 myocardial infarction, 1009 (44%) had troponin concentrations less than 5 ng/L at

presentation and might have been suitable for immediate discharge.

In the derivation cohort, patients with troponin concentrations less than 5 ng/L at presentation, myocardial infarction or cardiac death were rare at a median follow-up of 427 days (IQR 371–489; figure 3). Compared with patients with peak troponin concentrations between 5 ng/L and the 99th centile (appendix p 7), patients with troponin concentrations of less than 5 ng/L at presentation were less likely to have myocardial infarction or cardiac death at 1 year ($p = 0.0001$; table 2). This association persisted after adjustment for differences in age and sex ($p < 0.0001$; table 2).

Discussion

In more than 6000 patients with suspected acute coronary syndrome, we have defined a cardiac troponin threshold at presentation that identifies almost two-thirds of patients as being at very low risk of myocardial infarction or cardiac death, and who could potentially be safely discharged from the emergency department. Implementation of this approach would reduce avoidable hospital admission and have major benefits for both patients and health-care providers.

Our study has several strengths that distinguish it from previous studies. First, we prospectively identified all consecutive unselected patients presenting to both secondary and tertiary care hospitals, including patients admitted out of hours. As such, we believe our findings to be both representative and generalisable, and that this approach will be widely applicable across different health-care settings. Second, our study population exceeded the combined number of patients in a meta-analysis,³ which enabled us to analyse clinically important subgroups, such as patients who present early or have previous cardiovascular disease. Third, we have systematically assessed a range of troponin concentrations to identify a threshold that maximised the proportion of patients to be safely discharged. Finally, we used an assay with the necessary precision under routine laboratory conditions to report troponin concentrations at this threshold and to use this approach to guide patient care.

One of the main limitations was that we did not test the implementation of this threshold in routine clinical practice. Although we determined the number of patients who could be safely discharged, whether clinicians can effectively implement this threshold in clinical practice and whether this will substantially improve rates of discharge, is unknown. Conversely, this threshold should not be implemented in isolation and without regard to appropriate clinical assessment. One in 200 patients still had an index or 30-day event and many had other evidence of myocardial ischaemia. Finally, we had no data about later investigations and treatments. Implementation of this threshold is expected to reduce health-care costs but these benefits might be lost if recurrent presentations or additional outpatient consultations increase.

A troponin concentration of less than 5 ng/L met our prespecified criteria for a negative predictive value of at least 99.5%. At this threshold, almost two-thirds of patients with suspected acute coronary syndrome could have been discharged with very few cardiac events. Indeed, implementation of this threshold could double the number of patients discharged directly from the emergency department. Lower thresholds did not improve the negative predictive value, and would identify fewer patients suitable for discharge. Increasing the threshold to less than 6 ng/L would identify an additional 6% of patients suitable for discharge, but would double the number of adverse events. Moreover, we have internally and externally validated this threshold, and a troponin concentration less than 5 ng/L seems to be the best threshold for our study populations.

The negative predictive value of our approach was 99.6% across the entire study population, and was similar for men and women, between age groups, and in patients with previous cardiovascular disease. The use of risk scores to stratify patients with suspected acute coronary syndrome is common, but few scores have been developed or validated in this population, in which most patients did not have myocardial infarction. Stratification by GRACE score did not significantly improve the negative predictive value. The negative predictive value remained high in patients with a high pre-test probability of myocardial infarction, suggesting that this approach is probably valid even in higher risk populations. The only factor that seemed to affect the negative predictive value was the time from onset of chest pain to troponin testing. The negative predictive value of patients presenting within 2 h of chest pain was 97.6% but such patients were a small proportion of the overall population and could be addressed by repeat testing.

Of the 2905 patients with troponin concentrations of less than 5 ng/L at presentation, only 12 had an adverse event, of whom ten had an index myocardial infarction with five having clear diagnostic evidence of myocardial ischaemia on the presenting electrocardiograph. Two further patients were in cardiac arrest at presentation and did not survive. We included all consecutive patients without selection to make our safety estimates conservative. However, most of these adverse events would have been identified at presentation and therefore these patients would probably not have been discharged from hospital. This finding also shows the importance of not applying this threshold in isolation and that all available information should be used for clinical decision making.

Our observations complement previous studies of the use of cardiac troponins to triage patients with suspected acute coronary syndrome in emergency departments. The limit of detection and the limit of blank of a high-sensitivity cardiac troponin T assay both show promise for the assessment of patients at presentation.^{10–12} These studies

were included in a systematic review and meta-analysis⁵ showing that cardiac troponin T concentrations below the limit of detection had a false negative rate of 1.5% and identified 25% of patients as low risk. However, half of the studies used a contemporary troponin assay as a reference and would have missed smaller myocardial infarctions that could only be detected with a high-sensitivity assay, which will inflate the negative predictive value. In our analysis, we judged the final diagnosis using a high-sensitivity assay to ensure robust case ascertainment. Unlike previous studies of the cardiac troponin T assay, our analysis was the first to use a high-sensitivity cardiac troponin I assay, which has greater precision and reproducibility at low concentrations and at the proposed threshold. This will ensure the application of this approach is consistent across sites, analysers, and reagent batches: a prerequisite for use in clinical practice. Furthermore, use of cardiac troponin I at our threshold identifies two-to-three-times more low-risk patients than do previous approaches,^{10–12,23} which would avoid the need for repeat testing in most patients, or the incorporation of clinical risk scores used in accelerated diagnostic pathways.^{24–26} Studies are needed assess the clinical and cost-effectiveness of our approach in routine clinical practice.

Contributors

The High-STEACS investigators contributed to the conception or design of the work, or the acquisition, analysis, or interpretation of data. They were all involved in drafting and revising the report.

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Declaration of interests

ASVS has acted as a consultant for Abbott Laboratories. FSA has acted as a consultant for Philips Incubator and has received research funding (non-salaried) from Abbott Laboratories, Alere, Siemens, Ortho-Clinical Diagnostics, Beckman Coulter, and Roche Diagnostics. NLM has acted as a consultant for Abbott Laboratories, Beckman-Coulter, Roche, and Singulex. The other authors declare no competing interests.

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