Troponin in early presenters to rule out myocardial infarction

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CLINICAL RESEARCH
Ischaemic heart disease

Troponin in early presenters to rule out myocardial infarction

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Abstract

Aims Whether a single cardiac troponin measurement can safely rule out myocardial infarction in patients presenting within a few hours of symptom onset is uncertain. The study aim was to assess the performance of troponin in early presenters.

Methods and results In patients with possible myocardial infarction, the diagnostic performance of a single measurement of high-sensitivity cardiac troponin I at presentation was evaluated and externally validated in those tested ≤3, 4–12, and >12 h from symptom onset. The limit-of-detection (2 ng/L), rule-out (5 ng/L), and sex-specific 99th centile (16 ng/L in women; 34 ng/L in men) thresholds were compared. In 41 103 consecutive patients [60 (17) years, 46% women], 12 595 (31%) presented within 3 h, and 3728 (9%) had myocardial infarction. In those presenting ≤3 h, a threshold of 2 ng/L had greater sensitivity and negative predictive value [99.4% (95% confidence interval 99.2%–99.5%) and 99.7% (99.6%–99.8%)] compared with 5 ng/L [96.5% (96.2%–96.8%) and 99.3% (99.1%–99.4%)]. In those presenting ≥3 h, the sensitivity and negative predictive value were similar for both thresholds. The sensitivity of the 99th centile was low in early and late presenters at 71.4% (70.6%–72.2%) and 92.5% (92.0%–93.0%), respectively. Findings were consistent in an external validation cohort of 7088 patients.

Conclusion In early presenters, a single measurement of high-sensitivity cardiac troponin I below the limit of detection may facilitate the safe rule out of myocardial infarction. The 99th centile should not be used to rule out myocardial infarction at presentation even in those presenting later following symptom onset.

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Structured Graphical Abstract

Key Question

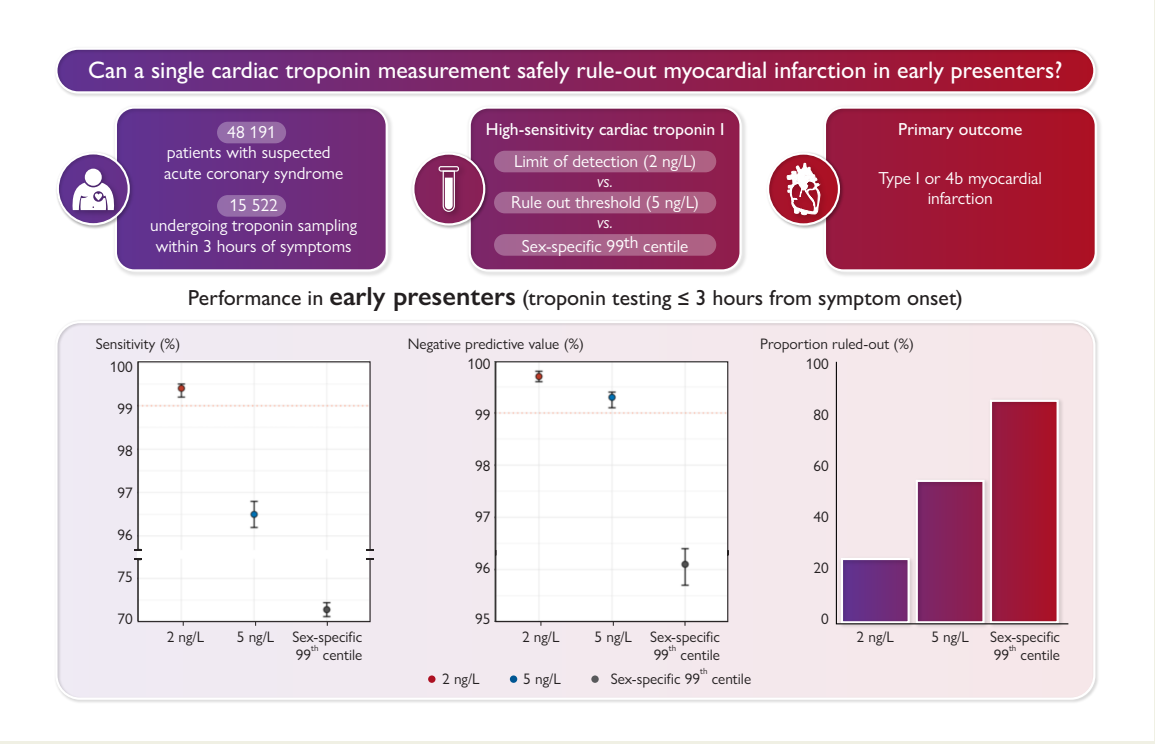
Can a single measurement of high-sensitivity cardiac troponin below the limit of detection facilitate the safe rule-out of myocardial infarction in patients presenting early following symptom onset?

Key Finding

In patients undergoing troponin sampling at or within 3 hours of symptom onset, a single measurement of high-sensitivity cardiac troponin below the limit of detection had a sensitivity and negative predictive value of 99.4% [95% confidence interval 99.2–99.5%] and 99.7% [99.6–99.8%] for myocardial infarction, respectively.

Take Home Message

In early presenters, a single measurement of high-sensitivity cardiac troponin I below the limit of detection may facilitate the safe rule-out of myocardial infarction.



Three panel plot showing the sensitivity (left), negative predictive value (middle) and proportion of patients (right) with cardiac troponin concentrations below 2 ng/L (red), 5 ng/L (blue), and the sex-specific 99th centile (grey) at presentation in patients presenting at or within 3 h of the onset of symptoms of myocardial infarction.

Keywords Symptoms • Myocardial infarction • Cardiac troponin

Introduction

High-sensitivity cardiac troponin assays are able to quantify low levels of cardiac troponin in the majority of presumably healthy individuals.[1,2] This has led to accelerated diagnostic pathways that use a single measurement of cardiac troponin at presentation to rule out myocardial infarction.[3–5] Such approaches are safe and effective in patients presenting more than 2 or 3 h after symptom onset.[6,7] However, concerns remain about the use of a single test strategy in early presenters, and it is unclear how the performance of cardiac troponin changes with time following symptom onset.

Early rule-out thresholds use low levels of cardiac troponin to identify patients at presentation who are low risk and may not require serial testing.[8–11] Studies have used either the limit of detection of a high-sensitivity assay[12–14] or have defined the optimal rule-out threshold as the highest cardiac troponin concentration measurable that enables the greatest proportion of patients to be ruled out with a negative predictive value of ≥99.5% for myocardial infarction or cardiac death at 30 days.[15] However, concerns remain that cardiac troponin elevations may not be recognised if testing is performed within a few hours of symptom onset. Indeed, an increase in the proportion of false negatives has been observed in patients presenting within 2 or 3 h.[15–18] As such, international guidelines recommend serial sampling in early presenters,[3–5,19] which adds complexity to patient assessment and reduces the proportion of

patients eligible for a single test rule out, and therefore the effectiveness of these strategies.

In consecutive patients with suspected myocardial infarction, we aimed to evaluate and to validate externally the diagnostic performance of a single measurement of cardiac troponin I at presentation stratified according to the time of symptom onset.

Methods

Study design and population

Initial evaluation was performed as a secondary analysis of the High-Sensitivity Troponin in the Evaluation of patients with suspected Acute Coronary Syndrome (High-STEACS) randomised controlled trial[20] (NCT01852123) with external validation performed in the Advantageous Predictors of Acute Coronary Syndromes Evaluation (APACE) Study (NCT00470587).[21,22]

Patients presenting with symptoms of suspected acute coronary syndrome were eligible for inclusion. Patients were excluded if the time from symptom onset to troponin sampling was not known; they had an adjudicated diagnosis of ST-elevation myocardial infarction, missing presentation high-sensitivity cardiac troponin measurement, or there was insufficient clinical information to adjudicate the diagnosis (*Figure 1*).

Derivation cohort

The High-STEACS trial evaluated the implementation of a high-sensitivity cardiac troponin I assay in consecutive patients with suspected acute coronary syndrome across 10 secondary and tertiary care hospitals in Scotland. All patients attending the emergency department between June 2013 and March 2016 in whom the attending clinician suspected acute coronary syndrome and underwent cardiac troponin sampling were considered eligible for inclusion in the trial. Patients were excluded from the trial if they had been admitted previously during the trial period or were not resident in Scotland. The time from patient reported symptom onset to troponin sampling was recorded by the attending physician in whole hours using an electronic form integrated into the clinical care pathway that was completed at the time of troponin sampling. Defining the onset of symptoms was based on patient history and clinical judgement (see Supplementary data online, *Materials*).

Cardiac troponin testing was performed at presentation and repeated 6 or 12 h after symptom onset at the discretion of the attending clinician in accordance with international guidelines in use during enrolment.[20] High-sensitivity cardiac troponin was measured using the ARCHITECT$_{STAT}$ high-sensitivity troponin I assay (Abbott Laboratories, Abbott Park, IL, USA). This assay has an inter-assay coefficient of variation of <10% at 4.7 ng/L, a limit of detection of 1.9 ng/L, and a 99th centile upper reference limit of 34 ng/L in men and 16 ng/L in women.[23]

The High-STEACS trial was approved by the Scotland Research Ethics Committee, the Public Benefit and Privacy Panel for Health and Social Care and by each National Health Service Health Board. Individual patient consent was not required, and data from consecutive patients were collected prospectively from the electronic record, de-identified, and linked within secure National Health Service Safe Havens.

External validation

External validation was performed using data from the APACE study (NCT00470587).[21,22] APACE is a prospective international multicentre study recruiting adult patients (≥18 years) presenting to the emergency department with symptoms suggestive of myocardial infarction with the aim of improving the diagnosis of myocardial infarction. The time from patient reported first symptom onset to presentation and the time from maximal symptom severity to presentation were recorded in hours by a member of the research team. The interval between presentation and the first troponin sample and the time from symptom onset to presentation were combined to produce the time in whole hours from symptom onset to troponin sampling (see Supplementary data online, *Materials*).

Cardiac troponin testing was performed at presentation and repeated at 1, 2, 3, and 6 h from presentation. Serial sampling was discontinued when a patient was discharged or transferred to the catheterization laboratory. Cardiac troponin was measured using the ARCHITECT$_{STAT}$ high-sensitivity troponin I assay (Abbott Laboratories). Analysis was performed using the ARCHITECT$_{STAT}$ high-sensitivity troponin I assay unless otherwise stated.

In addition, presentation cardiac troponin was measured using the following high-sensitivity cardiac troponin I assays: Beckman Access (Beckman Coulter); Ortho VITROS (Ortho Clinical Diagnostics); ADVIA Centaur, Dimension EXL, and Dimension Vista (Siemens Healthineers); Singulex Clarity (Singulex); and LSI Medience PATHFAST POC (LSI Medience Corporation). Detailed information about cardiac troponin testing in the APACE study is provided in the Online Supplement. In accordance with international guidance, we assessed cardiac troponin values rounded up to the nearest whole number.[24]

The APACE study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. Written informed consent was obtained from all patients.

Adjudication of myocardial infarction

All patients with a high-sensitivity cardiac troponin concentration above the 99th centile were adjudicated and classified according to the Fourth Universal Definition of Myocardial Infarction.[25] In both cohorts, two physicians independently reviewed all clinical information, including all available serial cardiac troponin measurements, with discordant diagnoses resolved by an independent third physician. Adjudication was performed using the ARCHITECT$_{STAT}$ high-sensitivity troponin I assay.

Study outcomes

The primary outcome was type 1 or 4b myocardial infarction during the index presentation. The secondary outcome was type 1 or 4b myocardial infarction or cardiovascular death within 30 days of the index presentation. Regional and national registries were used to ensure complete follow-up in both trial populations.[20]

Statistical analysis

Baseline characteristics are summarised as number (%) for categorical variables, and continuous variables are summarised as mean (standard deviation) or median (25th–75th centile) when not normally distributed. Comparisons were performed using Wilcoxon rank sum test, Kruskal–Wallis rank sum test, and Pearson's chi-squared test where appropriate. The study population was stratified into three groups based on the time in hours from symptom onset to troponin sampling: ≤3 h (early presenters), 4–12 h (reference group), and >12 h (late presenters). Further evaluation was performed by stratifying patients according to the number of hours from symptom onset to troponin sampling (1–12 h) with patients grouped if they presented >12 h from symptom onset (see Supplementary data online, *Figure S1*).

In patients with an index diagnosis of type 1 or 4b myocardial infarction, we compared the distribution between the cardiac troponin concentration at presentation and the maximal concentration on serial measurements. A single measurement of cardiac troponin at presentation was evaluated using sensitivity and negative predictive value for the primary and secondary diagnostic outcome with performance compared when applying the limit of detection (2 ng/L), the optimised rule-out threshold (5 ng/L), or the sex-specific 99th centile (16 ng/L in women; 34 ng/L in men). The 95% confidence intervals (CIs) were calculated using 1000 bootstrapped samples.

In the external cohort, we assessed the primary and secondary outcome when using both the time from initial symptom onset to troponin sampling and the time from maximal severity of symptoms to troponin sampling.

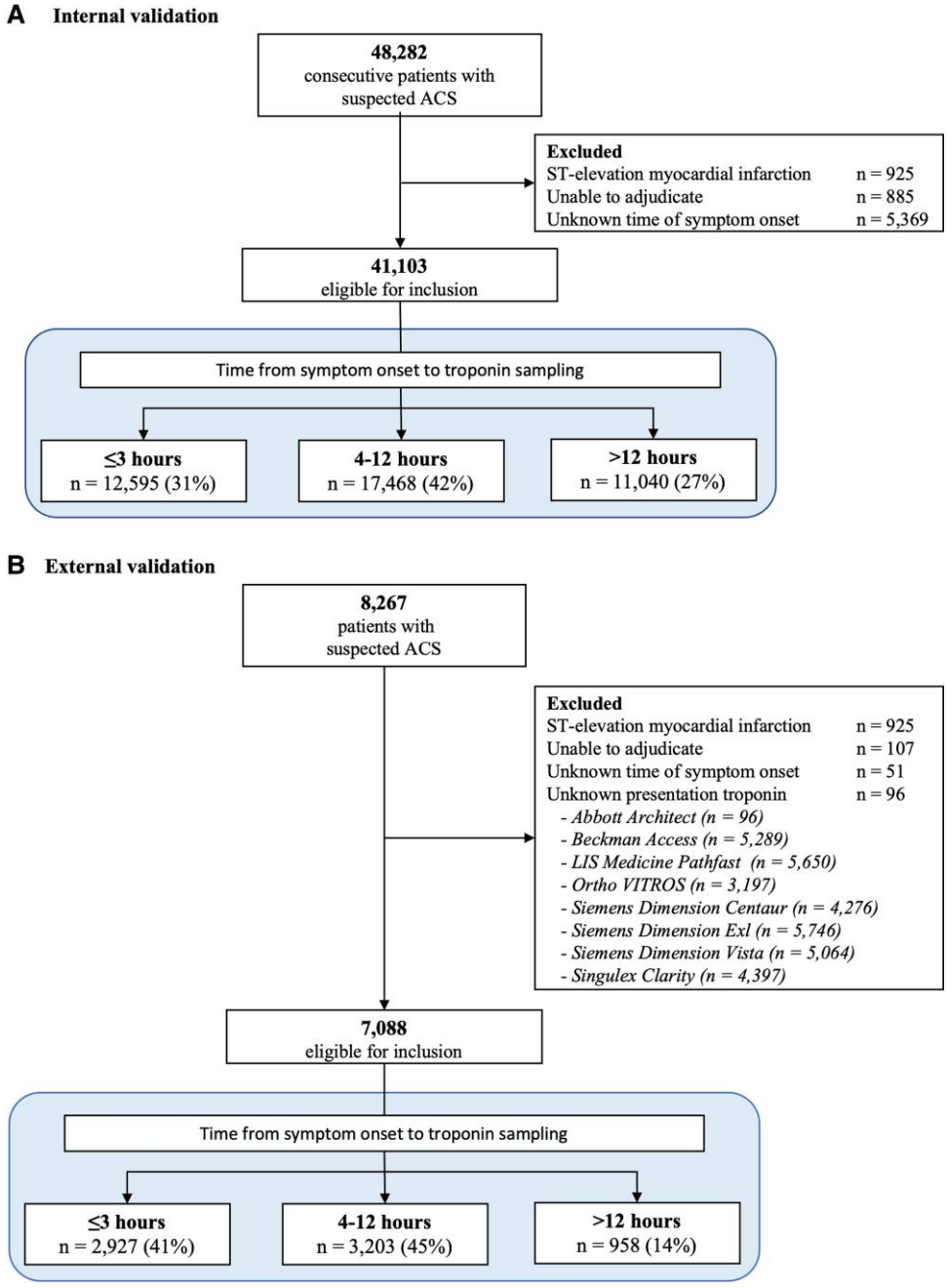


Figure 1 Consort diagram. This flow diagram shows the derivation of the study (*A*) and external validation (*B*) populations. ACS, acute coronary syndrome.

Where additional cardiac troponin I assay measurements were available, we assessed the primary outcome restricted to patients undergoing sampling ≤3 h from maximal symptom severity.

In sensitivity analyses, we compared diagnostic performance by age (under 75 years vs. 75 years and over), sex, presenting symptom, and the presence or absence of cardiovascular comorbidities (ischaemic heart disease, diabetes mellitus, heart failure, and chronic renal impairment). We evaluated performance restricted to patients undergoing serial troponin sampling, those without evidence of myocardial ischaemia on 12-lead electrocardiogram, by the Global Registry of Acute Coronary Events (GRACE) risk score (<140 vs. ≥140),[3] and for a broader diagnostic outcome measure that included patients with an adjudicated diagnosis of type 2 myocardial infarction. We further evaluated performance by GRACE category (low risk ≤104, medium risk 104–140, and high risk ≥140) in the external cohort.[26]

All analysis was conducted using R (version 4.2.0).

Results

Clinical characteristics of study population

A total of 41 103 [60 (17) years, 46% women] of the 48 282 patients enrolled in the High-STEACS trial were eligible for inclusion (*Figure 1*). Of the

included patients, 12 595 (31%) underwent troponin sampling ≤3 h, 17 468 (42%) within 4–12 h, and 11 040 (27%) >12 h from symptom onset (*Table 1*). Of the 12 595 patients who underwent troponin sampling ≤3 h, 2469 (20%), 5303 (42%), and 4823 (38%) had troponin samples taken at 1, 2, and 3 h after the onset of symptoms, respectively (see Supplementary data online, *Table S1*).

Compared with patients undergoing sampling ≤3 or 4–12 h from symptom onset, those undergoing sampling >12 h from symptom onset were younger and had fewer comorbidities (*Table 1*). The adjudicated diagnosis was myocardial infarction in 3692 (9%) in whom 1418 (38%) underwent troponin testing ≤3 h, 1541 (42%) within 4–12 h, and 733 (20%) >12 h from symptom onset. Patients undergoing troponin testing ≤3 h from symptom onset were more likely to have myocardial infarction or acute myocardial injury compared with those undergoing sampling later ($P < 0.001$ for all) (see Supplementary data online, *Figure S2*). In patients with myocardial infarction, cardiac troponin concentrations were lowest at presentation in those undergoing testing ≤3 h and highest in those undergoing testing >12 h after symptom onset [62 (23–260) vs. 182 (47–1437) ng/L, $P < 0.001$] (see Supplementary data online, *Figure S3*).

Rule out of index type 1 or 4b myocardial infarction

For the rule out of myocardial infarction, the sensitivity and negative predictive value for all thresholds evaluated at presentation were lower in patients undergoing testing ≤3 h compared with later time points (*Table 2* and *Figure 2*). In patients undergoing testing ≤3 h from symptom onset, a threshold of 2 ng/L resulted in a sensitivity of 99.4% (95% CI 99.2%–99.5%) and negative predictive value of 99.7% (95% CI 99.6%–99.8%), compared with a threshold of 5 ng/L that resulted in a sensitivity of 96.5% (95% CI 96.2%–96.8%) and negative predictive value of 99.3% (95% CI 99.1%–99.4%). Both were superior to the sex-specific 99th centile diagnostic threshold, which at presentation gave a sensitivity and negative predictive value of 71.4% (95% CI 70.6%–72.2%) and 96.1% (95% CI 95.7%–96.4%), respectively.

In patients undergoing testing ≤1 h from symptom onset, a threshold of 2 ng/L resulted in a sensitivity of 99.6% (95% CI 99.3%–99.8%) and negative predictive value of 99.8% (95% CI 99.6%–99.9%) (*Figure 3*). In contrast, the sensitivity and negative predictive value for a threshold of 5 ng/L in patients presenting ≤1 h were 92.6% (95% CI 91.5%–93.6%) and 98.4% (95% CI 97.8%–98.8%), respectively (see Supplementary data online, *Table S2*).

For all thresholds, sensitivity increased with time from symptom onset. In patients undergoing sampling >12 h from symptom onset, the sensitivity and negative predictive value of 2 and 5 ng/L thresholds were >99.0% and 99.5%, respectively (*Table 2*). In contrast, sensitivity of the sex-specific 99th centile to rule out myocardial infarction in those undergoing testing >12 h after symptom onset was 92.5% (95% CI 92.0–93.0%).

In those undergoing testing ≥ 4 h from symptom onset, a threshold of 5 ng/L ruled out myocardial infarction in a greater proportion of patients compared with a threshold of 2 ng/L [60% (17 055/28 509) vs. 29% (8316/28 509)] whilst maintaining a similar negative predictive value (*Figure 2*). Applying a 2 ng/L threshold in patients presenting ≤3 h would rule out an additional 3020 patients. Assigning rule out on the basis of a presentation sample <2 ng/L in early presenters and <5 ng/L in those undergoing sampling more than 3 h from symptom onset increased the proportion of patients ruled out at presentation compared with the use of the single measurement rule-out threshold of 5 ng/L alone in those undergoing troponin measurement more than 3 h from symptom onset [20 075 (49%) vs. 17 055 (42%)].

Cardiovascular death or myocardial infarction within 30 days

For a more conservative secondary outcome of type 1 or 4b myocardial infarction or cardiovascular death within 30 days of the index presentation, in patients undergoing testing ≤3 h from symptom onset, the sensitivity and negative predictive value of a 2 ng/L threshold were 99.2% (95% CI 99.0%–99.3%) and 99.6% (95% CI 99.4%–99.7%), respectively. A 5 ng/L threshold had both a lower sensitivity of 95.9% (95% CI 95.6%–96.3%) and negative predictive value of 99.0% (95% CI 98.8%–99.2%) (see Supplementary data online, *Figure S4* and *Table S3*).

External validation

A total of 7088 (60 [17] years, 34% women) of the 8267 eligible patients in the APACE study were included in the external validation cohort (*Figure 1*). The adjudicated diagnosis of type 1 or 4b myocardial infarction was 14% (975/7088) (see Supplementary data online, *Table S4*). When applying the time from maximal symptom severity to cardiac troponin testing, 2927 (41%) patients underwent troponin testing ≤3 h, 3203 (46%) 4–12 h, and 958 (14%) > 12 h from symptom onset. For the primary outcome of index type 1 or 4b myocardial infarction, a threshold of 2 ng/L gave a sensitivity of 100% (95% CI 99.8%–100%) and negative predictive value of 100% (95% CI 99.8%–100%), compared with a threshold of 5 ng/L where the sensitivity was 98.4% (95% CI 97.8%–98.8%) and negative predictive value was 99.6% (95% CI 99.3%–99.8%) in patients undergoing testing ≤3 h symptom onset (see Supplementary data online, *Table S5*, Supplementary data online, *Figure S5*). The 2 ng/L threshold achieved a sensitivity and negative predictive value of more than 99.5% in the 467 patients presenting ≤1 h of symptom onset (see Supplementary data online, *Table S6*). For the secondary outcome of type 1 or 4b myocardial infarction or cardiovascular death at 30 days, a threshold of 2 ng/L gave a sensitivity of 100% (95% CI 99.8%–100%) and negative predictive value of 100% (95% CI 99.8%–100%), in patients undergoing testing ≤3 h from symptom onset (see Supplementary data online, *Table S7*).

Defining symptom onset as the interval in hours from first onset to troponin sampling resulted in a decrease in the proportion of patients classified as early presenters [27% (1880/7088) vs. 41% (2927/7088)] and an increase in the proportion classified as late presenters [32% (2244/7088) vs. 14% (958/7088)] (see Supplementary data online, *Table S8*). Sensitivity and negative predictive value for the rule out of type 1 or 4b myocardial infarction were comparable when using either definition (see Supplementary data online, *Tables S9* and *S10*).

The availability of troponin measurements was varied by assay type (*Figure 1*). Baseline characteristics were broadly similar between assay groups (see Supplementary data online, *Table S11*). The limit of detection for the Beckman Coulter Access, Siemens ADVIA Centaur, Siemens Dimension Vista, Siemens Dimension EXL, and Ortho VITROS high-sensitivity cardiac troponin I assays consistently achieved a sensitivity and negative predictive value of >99.5% for the diagnosis of type 1 or 4b myocardial infarction in patients undergoing troponin testing ≤3 h (*Figure 4* and Supplementary data online, *Table S12*). The proportion of patients with presentation values below the limit of detection was varied by assay with the Beckman Coulter Access assay ruling out the greatest proportion of patients presenting ≤3 h from symptom onset (40%).

Sensitivity analyses

Excluding patients with evidence of myocardial ischaemia on 12-lead electrocardiogram or restricting analysis to patients undergoing serial

Table 1 Baseline characteristics of the population stratified by time from symptom onset

		Hours from symptom onset			
	Overall	≤3 h	4–12 h	>12 h	*P*-value
Number of participants	41 103	12 595 (31)	17 468 (42)	11 040 (27)	
Age, years	60 (17)	62 (17)	61 (17)	58 (17)	<0.001
Sex					<0.001
Women	19 077 (46%)	5480 (44%)	8424 (48%)	5172 (47%)	
Men	22 027 (54%)	7115 (56%)	9044 (52%)	5868 (53%)	
Presenting complaint					<0.001
Chest pain[a]	33 492 (81%)	9747 (77%)	14 674 (84%)	6156 (86%)	
Time from symptom onset to troponin sampling (hours)	7.2 (4.5)	2.2 (0.7)	7.1 (2.9)	n/a	<0.001
Previous medical conditions					
Ischaemic heart disease	9968 (24%)	3383 (27%)	4388 (25%)	2197 (20%)	<0.001
Myocardial infarction	3478 (8%)	1242 (9.9%)	1530 (8.8%)	706 (6.4%)	<0.001
Heart failure	3474 (8.5%)	1194 (9.5%)	1480 (8.5%)	800 (7.2%)	<0.001
Cerebrovascular disease	2407 (6%)	817 (6.5%)	1082 (6.2%)	508 (4.6%)	<0.001
Diabetes mellitus	2903 (7%)	973 (7.7%)	1302 (7.5%)	628 (5.7%)	<0.001
Chronic renal disease	7798 (19%)	2568 (20%)	3694 (21%)	1536 (14%)	<0.001
Previous revascularisation					
Percutaneous coronary intervention	3169 (8%)	653 (8.4%)	1338 (7.7%)	733 (6.6%)	<0.001
Coronary artery bypass grafting	663 (2%)	129 (1.7%)	288 (1.6%)	145 (1.3%)	0.005
Medications at presentation					
Aspirin	10 998 (27%)	3713 (29%)	4762 (27%)	2523 (23%)	<0.001
P2Y12 inhibitor	3834 (9.3%)	1313 (10%)	1690 (9.7%)	831 (7.5%)	
Dual anti-platelet therapy[b]	1301 (3%)	456 (3.6%)	565 (3.2%)	280 (2.5%)	<0.001
Statin	16 313 (40%)	5407 (43%)	7047 (40%)	3859 (35%)	<0.001
ACE inhibitor or ARB	13 222 (32%)	4391 (35%)	5678 (33%)	3153 (29%)	<0.001
Beta-blocker	11 012 (27%)	3710 (29%)	4743 (27%)	2559 (23%)	<0.001
Oral anticoagulant[c]	2664 (6%)	859 (6.8%)	1171 (6.7%)	634 (5.7%)	0.001
Physiological parameters on presentation[d]					
Heart rate, b.p.m.	86 (27)	86 (28)	85 (25)	87 (27)	0.037
Systolic blood pressure, mmHg	139 (29)	138 (30)	141 (29)	140 (28)	<0.001
GRACE score	142 (37)	145 (39)	140 (35)	141 (39)	<0.001
Ischaemia on ECG	1646 (26%)	686 (29%)	609 (24%)	351 (25%)	<0.001
Haematology and clinical chemistry measurements					
Haemoglobin, g/L	138 (21)	136 (22)	136 (21)	138 (20)	<0.001
Estimated glomerular filtration, mL/min	82 (24)	79 (24)	82 (24)	85 (24)	<0.001
Presentation high-sensitivity cardiac troponin I, ng/L	3 [1–11]	4 [2–13]	3 [1–11]	3 [1–9]	<0.001
Serial troponin[e] measurement	18 913 (46%)	7704 (61%)	8599 (49%)	2610 (24%)	<0.001
Adjudicated diagnosis					
Type 1 myocardial infarction	3692 (9%)	1418 (11%)	1541 (8.8%)	733 (6.6%)	<0.001
Type 2 myocardial infarction	1026 (2.5%)	408 (3.2%)	417 (2.4%)	201 (1.8%)	<0.001

Continued

Table 1 ***Continued***

	Overall	Hours from symptom onset			*P*-value
		≤3 h	4–12 h	>12 h	
Type 4b myocardial infarction	36 (<0.1%)	21 (0.2%)	12 (<0.1%)	<5 (<0.1%)	<0.001
Acute myocardial injury	1495 (3.6%)	545 (4.3%)	572 (3.3%)	378 (3.4%)	<0.001
Chronic myocardial injury	1131 (2.8%)	338 (2.7%)	459 (2.6%)	334 (3.0%)	0.12
No myocardial injury	33 716 (82%)	9863 (78%)	14 463 (83%)	9389 (85%)	<0.001
Outcome at 30 days					
Type 1 or 4b myocardial infarction	217 (0.5%)	80 (0.6%)	83 (0.5%)	54 (0.5%)	0.14
Cardiovascular death	413 (1.0%)	211 (1.7%)	133 (0.8%)	69 (0.6%)	<0.001

Values are mean (SD) and median (25th–75th centile); *n* (%).
ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers.
[a]Presenting symptom was missing in 2264 (11%).
[b]Two medications from aspirin, clopidogrel, prasugrel, or ticagrelor.
[c]Includes warfarin or novel oral anticoagulants.
[d]Electrocardiographic and physiological data reported for the 83% (6762/8179) patients with myocardial infarction or myocardial injury who had electrocardiographic data available.
[e]Serial testing defined as two or more tests within 24 h of presentation.

troponin testing at 6–12 h from presentation resulted in a sensitivity and negative predictive value of >99% for the rule out of type 1 or 4b myocardial infarction across time groups when applying a 2 ng/L threshold. When the assessment of the 99th centile was limited to patients with a GRACE score of <140, sensitivity remained poor, even in those patients presenting more than 12 h from symptom onset [92.8% (95% CI 92.3%–93.3%)]. A 2 ng/L threshold maintained excellent sensitivity and negative predictive value regardless of the GRACE risk category (see Supplementary data online, *Tables S13–S16*).

The negative predictive value for myocardial infarction when applying a presentation cardiac troponin measurement of 2 or 5 ng/L by subgroup in patients with troponin testing ≤3 h from symptom onset is shown in *Figure 5*. The central estimate for the negative predictive value was <99% for both thresholds in patients with prior ischaemic heart disease and diabetes mellitus and those with an estimated glomerular filtration rate of <60 mL/min. The proportion of patients with a presentation troponin value below each threshold was lower in patients aged ≥75 years compared with those <75 years (see Supplementary data online, *Table S17*). Sensitivity was varied by age across time groups and thresholds with the overall sensitivity for each threshold lower in patients aged <75 years compared with those ≥75 years. Regardless of age, in patients who underwent sampling within 3 h, a threshold of 2 ng/L resulted in a sensitivity and a negative predictive value of ≥ 99% and was superior to a threshold of 5 ng/L.

When assessing performance for an outcome of type 1, type 2, or type 4b myocardial infarction, the sensitivity and negative predictive value for the 2 and 5 ng/L threshold across all groups stratified by time of symptom onset were comparable with those when using a diagnostic outcome of type 1 or 4b myocardial infarction only (see Supplementary data online, *Table S18*).

Discussion

In 48 191 patients with suspected myocardial infarction, of whom one-third underwent testing at or within 3 h of symptom onset, we assessed the impact of time from the onset of symptoms to troponin sampling on the performance of a single measurement of high-sensitivity cardiac troponin I to rule out myocardial infarction. We report four main findings that are relevant to clinical practice.

First, the guideline-recommended rule-out threshold of 5 ng/L had excellent sensitivity and negative predictive value in patients presenting >3 h from symptom onset. Furthermore, it identified twice as many patients as low risk compared with the limit of detection. However, the sensitivity and negative predictive value were reduced in patients presenting ≤3 h of symptom onset. This is consistent with prior observations[15,18] and supports the current recommendation in practice guidelines to perform serial measurements in early presenters.[3,4,19]

Second, a lower threshold of 2 ng/L based on the limit of detection of the high-sensitivity cardiac troponin I assay achieved a sensitivity of >99% and a negative predictive value of >99.5% in all patients regardless of the time from symptom onset for both the index diagnosis of type 1 myocardial infarction; a composite of type 1, type 2, or type 4b myocardial infarction; and for 30-day events.

Third, the sensitivity of the sex-specific 99th centile to rule out myocardial infarction at presentation was low at 81.3%, and even in patients presenting with symptom onset >12 h prior to testing, the sensitivity was just 92.5%. When the 99th centile was combined with a normal electrocardiogram or an established risk score, the sensitivity remained insufficient for use in practice at 91.3% and 92.8%, respectively. Our study shows that the 99th centile should not be used to rule out myocardial infarction at presentation even in those presenting late who are considered to be at low risk by other measures.

Finally, our findings were consistent in an international external validation cohort and in multiple sensitivity analyses, suggesting our findings are robust and generalisable. This included assessing performance by different methods of defining the onset of symptoms, stratification by risk score category, and the assessment of the limit of detection of multiple high-sensitivity cardiac troponin I assays (*Structured Graphical Abstract*).

Implementation of clinical decision pathways that include a single high-sensitivity cardiac troponin measurement to rule out myocardial

Table 2 Diagnostic performance of rule-out thresholds for type 1 or 4b myocardial infarction by time from symptom onset

Hours from symptom onset	Presentation high-sensitivity cardiac troponin I								
	TN	FN	TP	FP	Sensitivity (95% CI)	NPV (95% CI)	Specificity (95% CI)	PPV (95% CI)	Proportion ruled out (%)
2 ng/L									
≤3 h	3020	9	1430	8136	99.4% (99.2%–99.5%)	99.7% (99.6%–99.8%)	27.1% (26.3%–27.9%)	14.9% (14.3%–15.6%)	24%
4–12 h	4764	6	1547	11 151	99.6% (99.5%–99.7%)	99.9% (99.8%–99.9%)	29.9% (29.3%–30.6%)	12.2% (11.7%–12.7%)	27%
>12 h	3552	1	734	6752	99.9% (99.8%–99.9%)	100% (99.9%–100%)	34.5% (33.6%–35.4%)	9.8% (9.3%–10.4%)	32%
Overall	11 336	16	3712	26 039	99.6% (99.5%–99.6%)	99.9% (99.8%–99.9%)	30.3% (29.9%–30.8%)	12.5% (12.2%–12.8%)	28%
5 ng/L									
≤3 h	6668	50	1389	4488	96.5% (96.2%–96.8%)	99.3% (99.1%–99.4%)	59.8% (58.9%–60.6%)	23.6% (22.9%–24.4%)	53%
4–12 h	10 148	20	1533	5767	98.7% (98.5%–98.9%)	99.8% (99.7%–99.9%)	63.8% (63.0%–64.5%)	21.0% (20.4%–21.6%)	58%
>12 h	6907	6	730	3397	99.2% (99.0%–99.3%)	99.9% (99.8%–100%)	67.0% (66.1%–67.9%)	17.7% (17.0%–18.4%)	63%
Overall	23 723	76	3652	13 652	98.0% (97.8%–98.1%)	99.7% (99.6%–99.7%)	63.5% (63.0%–63.9%)	21.1% (20.7%–21.5%)	58%
Sex-specific 99th centile									
≤3 h	10 107	411	1028	1049	71.4% (70.6%–72.2%)	96.1% (95.7%–96.4%)	90.6% (90.1%–91.1%)	49.5% (48.6%–50.4%)	84%
4–12 h	14 616	232	1321	1299	85.1% (84.5%–85.6%)	98.4% (98.2%–98.6%)	91.8% (91.4%–92.2%)	50.4% (49.7%–51.2%)	85%
>12 h	9416	55	681	888	92.5% (92.0%–93.0%)	99.4% (99.3%–99.5%)	91.4% (90.8%–91.9%)	43.4% (42.5%–44.3%)	86%
Overall	34 139	698	3030	3236	81.3% (80.9%–81.7%)	98.0% (97.9%–98.1%)	91.3% (91.1%–91.6%)	48.4% (47.9%–48.8%)	85%

Presented as number or % (95% confidence intervals) as appropriate. Number of patients in each time group: ≤3 h = 12 595; 4–12 h = 17 468; >12 h = 11 040; overall = 41 103.
FN, false negatives; ARCHITECT$_{STAT}$, high-sensitivity cardiac troponin I assay; NPV, negative predictive value; TN, true negatives.
Sex-specific 99th centile = 34 ng/L in men and 16 ng/L in women.

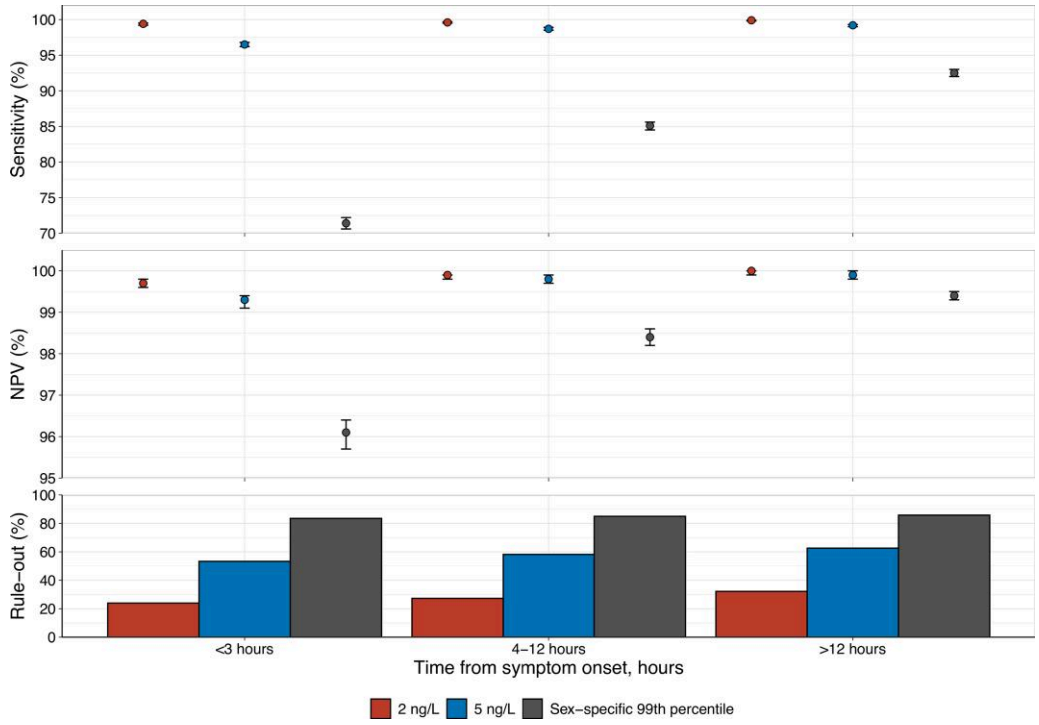


Figure 2 Performance of presentation cardiac troponin I to rule out myocardial infarction. Combined scatter and bar plot showing the sensitivity, negative predictive value, and proportion of patients with cardiac troponin concentrations below 2 ng/L, 5 ng/L, and the sex-specific 99th centile at presentation stratified by time from symptom onset, respectively. NPV, negative predictive value.

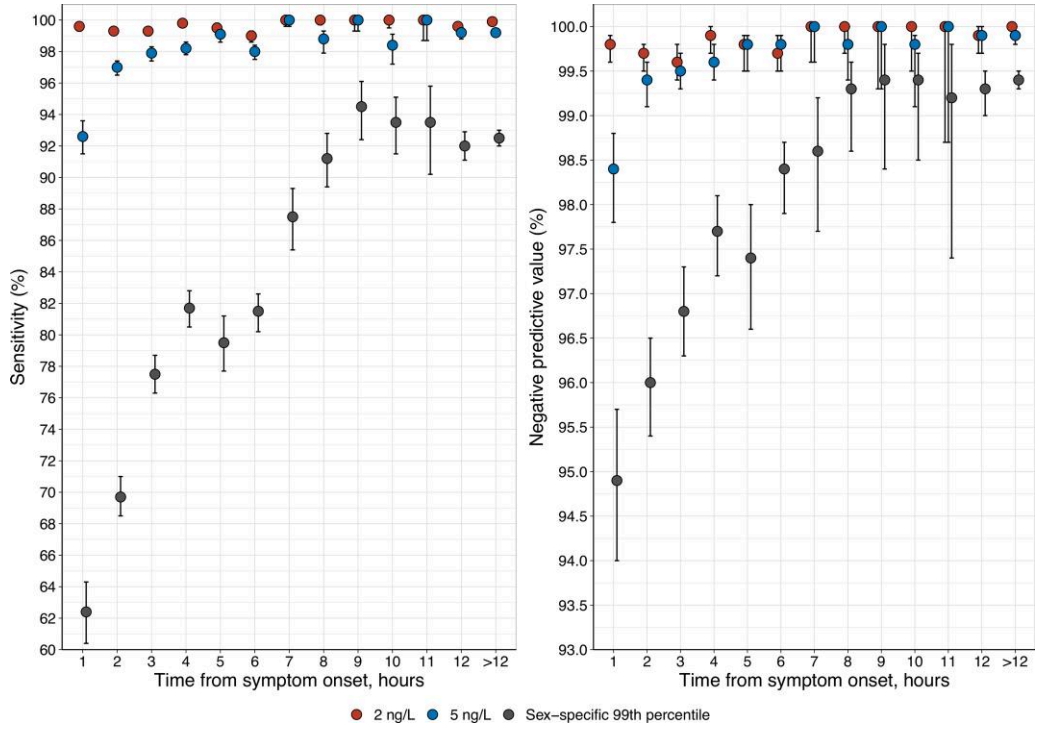


Figure 3 Impact of time on the rule out of myocardial infarction using presentation cardiac troponin I. Scatter plot with 95% confidence intervals showing the sensitivity and negative predictive value for patients with cardiac troponin concentrations at presentation below 2 ng/L, 5 ng/L, and the sex-specific 99th centile per hour from symptom onset for the diagnosis of type 1 or type 4b myocardial infarction.

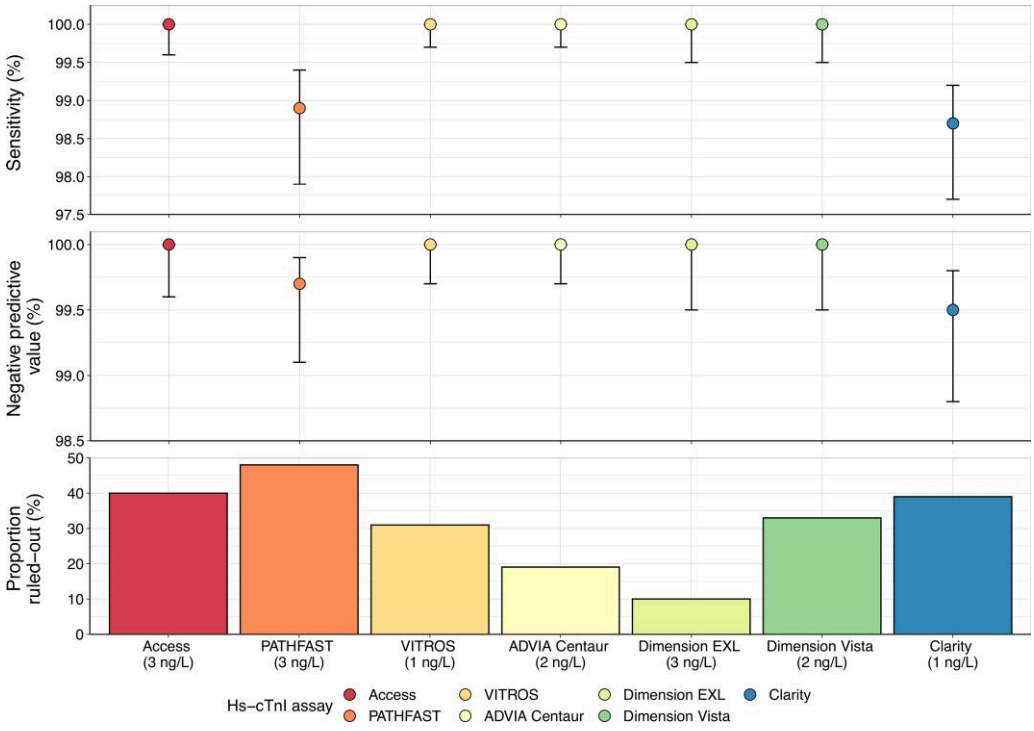


Figure 4 Diagnostic performance of the limit of detection of additional cardiac troponin I assays. Combined scatter and bar plot showing the sensitivity, negative predictive value for the rule out of type 1 or 4b myocardial infarction, and proportion of patients with cardiac troponin I concentrations below the assay specific limit of detection at presentation restricted to patients undergoing troponin testing at or within 3 h of maximal symptom severity.

infarction at presentation decreases the duration of hospital stay by more than 3 h and improves the odds of avoiding hospital admission by more than 50%.[6,7] However, these approaches are not applicable to around a third of all patients as they present within 3 h of symptom onset and therefore require additional investigation or observation with associated increased length of hospital stay and healthcare costs.[12,27,28] Solutions able to safely rule out myocardial infarction in early presenters could substantially reduce resource utilization as well as improve patient experience. In the USA alone, more than 20 million patients attend the emergency department each year with possible myocardial infarction.[29] At an average cost of $1200 per patient for admission to an observation ward, an increase in the proportion of patients directly discharged from the emergency department of just 5% would result in a cost saving of >$1.2 billion in bed occupancy alone.[30]

In our study, we showed that a single high-sensitivity cardiac troponin I measurement below 2 ng/L had excellent sensitivity and negative predictive value irrespective of the time of symptom onset or prevalence of myocardial infarction. This was informed by over 15 000 consecutive patients where testing was performed ≤3 h of symptom onset and 5000 where it was performed ≤1 h. The superior performance of a threshold of 2 ng/L compared with 5 ng/L in patients presenting very early after the onset of symptoms is intuitive and supported by recent experimental studies demonstrating that changes in cardiac troponin concentration within the normal reference range are detectable within 30 min of induced myocardial ischaemia.[31–34] Whilst only one in four patients tested ≤3 h from symptom onset had an undetectable cardiac troponin concentration, when this threshold was combined with the guideline-recommended threshold of 5 ng/L in those presenting later, the single measurement rule-out strategy could be applied to an additional 3020 patients, increasing the proportion eligible for immediate discharge from 42% to 49%.

Our findings are consistent with smaller studies that have evaluated the impact of time from symptom onset on the diagnostic performance of high-sensitivity cardiac troponin. Andersen *et al.* assessed the performance of a cardiac troponin I concentration below 3 ng/L at presentation using the Siemens Centaur assay. In 1370 patients, in which 134 had a diagnosis of myocardial infarction, they reported a sensitivity of 100% (95% CI 92.1%–100%) and a negative predictive value of 100% (95% CI 97.3%–100%) in those presenting ≤3 h ($n = 470$).[12] Sandoval *et al.*[11] observed comparable sensitivity and negative predictive value for the same assay and threshold in 2212 patients [99.2% (95% CI 98.2%–100%) and 99.8% (95% CI 99.5%–100%)], with no difference in performance between early and late presenters. Our analysis provides additional evidence to support the use of thresholds based on the limit of detection of a high-sensitivity cardiac troponin I assay to rule out myocardial infarction at presentation in early presenters.

We observed consistent performance of the limit of detection across multiple high-sensitivity cardiac troponin I assays. However, sensitivity was <99% in early presenters when assessing the Singulex clarity or LSI Medience POC Pathfast assay using a threshold of 1 or 3 ng/L, respectively. Of note, the Singulex clarity assay has a manufacturer reported limit of detection of 0.08 ng/L, more than a factor of 10 below the 1 ng/L limit we tested. Our use of the 1 ng/L threshold is to reflect current recommendations on the reporting of troponin values to the nearest whole number and in recognition of the 'very low' early rule-out threshold in the current European Society of Cardiology guidelines,

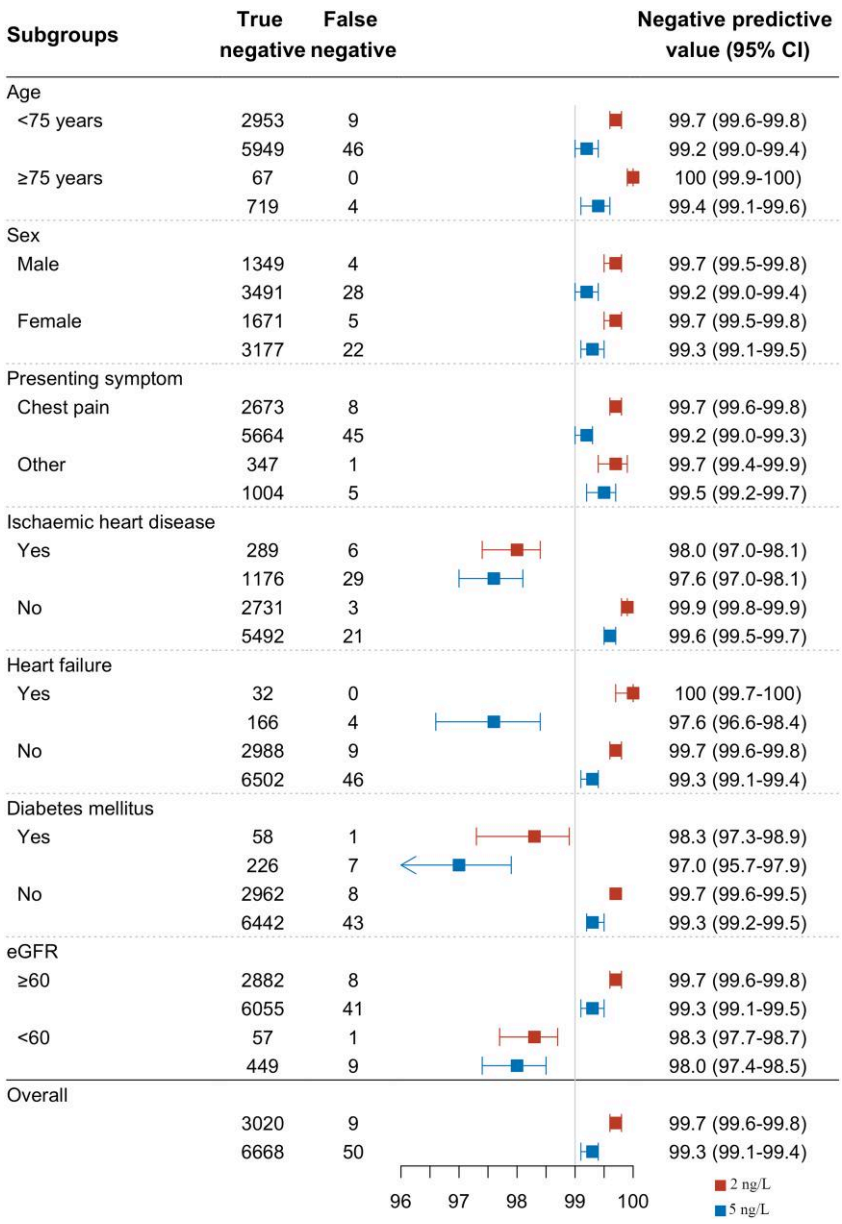


Figure 5 Safety of rule-out thresholds in early presenters by sub-groups. Forest plot showing negative predictive value of presentation cardiac troponin concentrations below 2 and 5 ng/L across sub-groups of patients presenting within 3 h of symptom onset. Grey horizontal line marks the target negative predictive value of 99.5%. CI, confidence interval; eGFR, estimated glomerular filtration rate.

without findings supporting the recommendation that this threshold should not be employed to rule out myocardial infarction in early presenters.[3] The LSI Medience POC Pathfast assay is a point-of-care assay that achieves the analytical and clinical performance characteristics to be classified as high sensitivity. Whilst it has been shown to be safe and efficient in patients presenting more than 3 h after symptom onset, our findings are consistent with previous diagnostic evaluations that showed reduced performance in early presenters.[35] Point-of-care assays offer the potential for testing of troponin in the pre-hospital setting, an approach likely to result in more patients being classified as 'early presenters', and for which our results are pertinent.

Our finding that the 99th centile has poor sensitivity to rule out myocardial infarction even in those presenting late after symptom onset adds to prior work illustrating this approach is inferior to pathways using lower thresholds.[36–39] Indeed, despite the widespread use of the 99th centile as an approach to rule out myocardial infarction in practice, based on these studies the European Society of Cardiology downgraded their recommendations favouring pathways using multiple lower thresholds in 2020.[3] More recently an expert consensus statement from the American College of Cardiology went further and no longer recommend a 0-/3-h approach using the 99th centile to rule out myocardial infarction.[19] Our observations would support these changes to clinical guidelines, adding that the sensitivity of the 99th centile is insufficient to rule out myocardial infarction at presentation even in those who present late following symptom onset and who are considered low risk by other conventional measures. In addition, when

testing coincided with the expected peak in cardiac troponin concentration, the specificity and positive predictive value of the sex-specific 99th centile to rule in myocardial infarction remained poor. Acute myocardial injury and sub-types of myocardial infarction share similar kinetic profiles,[25,40,41] and therefore a single troponin measurement at presentation cannot reliably distinguish between causes of myocardial injury or infarction irrespective of the timing of symptom onset.

Are we now able to rule out myocardial infarction at presentation in patients with very recent onset symptoms if cardiac troponin I levels are undetectable? There are several considerations. First, our findings are only applicable to the high-sensitivity cardiac troponin I assays tested here, and additional data are needed in similarly large cohorts to determine whether the same approach could be applied for other assays. In contrast to cardiac troponin I, for cardiac troponin T, the guideline-recommended rule-out threshold of 5 ng/L is based on the limit of detection, and on most platforms, the current assay is not able to measure troponin below this threshold.[42] Second, we demonstrate heterogeneity in the sensitivity and negative predictive value of a threshold of 2 ng/L in sub-groups of patients who presented within 3 h of symptom onset. In particular, the negative predictive value was <99% in those with known ischaemic heart disease, diabetes mellitus, and renal impairment, although this may in part reflect the extremely small number of patients with these conditions who have undetectable values. This variation was not seen in patients presenting at later time points, suggesting that these factors influence the release kinetics of cardiac troponin or the perception of the onset of symptoms. Further research on the kinetics of cardiac troponin in patients with these conditions is required, and clinicians should exercise caution and clinical judgement when applying the limit of detection to rule out those who present early. Third, our findings are not applicable to patients who present with ST-elevation myocardial infarction. Patients with ST-elevation myocardial infarction have a distinct kinetic profile with up to half having either an undetectable presentation troponin concentration or one below the 99th centile.[43–45] Finally, no patients presenting ≤3 h of symptom onset were discharged based on the 2 ng/L threshold, and prospective studies are needed to demonstrate the safety of this approach in practice.

Establishing and accurately recording the exact time of the onset of symptoms of myocardial infarction are challenging, particularly in patient groups who may experience atypical symptoms or in cases where symptoms remit or relapse. As such, there are several additional limitations that merit consideration. First, we were reliant on the attending clinician to accurately complete the time from symptom onset based on the patient's history when requesting cardiac troponin. No guidance on what constituted the onset of symptoms was provided, and this was left to clinician judgement. Whilst this approach reflects current clinical practice, it is likely this has introduced variation in the recording of the onset of symptoms and misclassification. However, our findings were validated in an external cohort where the time of symptom onset was standardised and recorded by researchers directly from the patient at the time of enrolment. Second, we lack detailed information on symptom course and are unable to assess safety in patients with recurrent chest pain. Third, we recorded the time from symptom onset to testing at hourly intervals with all presentations >12 h being recorded as >12 h. This limits our ability to evaluate shorter time intervals and performance in those presenting beyond 12 h from symptom onset. This also introduces a degree of inaccuracy and potential misclassification in cases where the symptom onset lay between integers: we do not know how such cases have been classified by clinicians.

To address these limitations, we evaluated three methods by which the time from symptom onset to troponin sampling could be defined and employed clinically. In the High-STEACS trial, the time from symptom onset was recorded by the treating physician in whole hours, an approach that reflects current clinical practice.[3,5,37] In the APACE study, we evaluated rule-out performance using two pre-defined definitions of symptom onset: the interval between the initial onset of symptoms and troponin sampling and the interval between peak symptom severity and troponin sampling. Although we cannot exclude a degree of misclassification in the time of symptom onset, we have demonstrated consistent findings across cohorts and multiple definitions of what constitutes the onset of symptoms of suspected myocardial infarction.

In conclusion, the time from symptom onset to testing strongly influences the diagnostic performance of high-sensitivity cardiac troponin I to rule out myocardial infarction. A single measurement below the limit of detection enables myocardial infarction to be ruled out at presentation in those undergoing troponin testing within a few hours of symptom onset. In contrast, the 99th centile diagnostic threshold should not be used to rule out myocardial infarction at presentation even in those presenting 12 h after symptom onset.

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

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Data Availability

The High-STEACS trial makes use of several routine electronic health care data sources that are linked, de-identified, and held in our national safe haven, which is accessible by approved individuals who have undertaken the necessary governance training. Summary data can be made available upon request to the corresponding author.

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Ethical Approval

The study was approved by the Scotland Research Ethics Committee, the Public Benefit and Privacy Panel for Health and Social Care, and each National Health Service Health Board. Individual patient consent was not required and data from consecutive patients was collected prospectively from the electronic record, de-identified, and linked within secure National Health Service Safe Havens.

Pre-registered Clinical Trial Number

The pre-registered clinical trial number is NCT01852123 (Clinical Trials.gov).

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