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Association of High-Sensitivity Cardiac Troponin I Concentration With Cardiac Outcomes in Patients With Suspected Acute Coronary Syndrome

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IMPORTANCE High-sensitivity cardiac troponin I testing is widely used to evaluate patients with suspected acute coronary syndrome. A cardiac troponin concentration of less than 5 ng/L identifies patients at presentation as low risk, but the optimal threshold is uncertain.

OBJECTIVE To evaluate the performance of a cardiac troponin I threshold of 5 ng/L at presentation as a risk stratification tool in patients with suspected acute coronary syndrome.

DATA SOURCES Systematic search of MEDLINE, EMBASE, Cochrane, and Web of Science databases from January 1, 2006, to March 18, 2017.

STUDY SELECTION Prospective studies measuring high-sensitivity cardiac troponin I concentrations in patients with suspected acute coronary syndrome in which the diagnosis was adjudicated according to the universal definition of myocardial infarction.

DATA EXTRACTION AND SYNTHESIS The systematic review identified 19 cohorts. Individual patient-level data were obtained from the corresponding authors of 17 cohorts, with aggregate data from 2 cohorts. Meta-estimates for primary and secondary outcomes were derived using a binomial-normal random-effects model.

MAIN OUTCOMES AND MEASURES The primary outcome was myocardial infarction or cardiac death at 30 days. Performance was evaluated in subgroups and across a range of troponin concentrations (2-16 ng/L) using individual patient data.

RESULTS Of 11 845 articles identified, 104 underwent full-text review, and 19 cohorts from 9 countries were included. Among 22 457 patients included in the meta-analysis (mean age, 62 [SD, 15.5] years; n = 9329 women [41.5%]), the primary outcome occurred in 2786 (12.4%). Cardiac troponin I concentrations were less than 5 ng/L at presentation in 11 012 patients (49%), in whom there were 60 missed index or 30-day events (59 index myocardial infarctions, 1 myocardial infarction at 30 days, and no cardiac deaths at 30 days). This resulted in a negative predictive value of 99.5% (95% CI, 99.3%-99.6%) for the primary outcome. There were no cardiac deaths at 30 days and 7 (0.1%) at 1 year, with a negative predictive value of 99.9% (95% CI, 99.7%-99.9%) for cardiac death.

CONCLUSIONS AND RELEVANCE Among patients with suspected acute coronary syndrome, a high-sensitivity cardiac troponin I concentration of less than 5 ng/L identified those at low risk of myocardial infarction or cardiac death within 30 days. Further research is needed to understand the clinical utility and cost-effectiveness of this approach to risk stratification.

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Supplemental content

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Chest pain is one of the most common reasons for presentation to hospitals worldwide.[1] Despite the majority of patients not having myocardial infarction,[2] hospital admission for observation and serial cardiac troponin testing is required in many patients to identify those with and without myocardial infarction.[3] Novel strategies to identify low-risk patients at presentation have been proposed to reduce hospital admissions, serial testing, and resource utilization as well as to improve care for patients.[4,5]

High-sensitivity assays are able to quantify cardiac troponin at low concentrations and provide an opportunity to rule out myocardial infarction at an earlier stage. In a prospective study of consecutive patients with suspected acute coronary syndrome, a risk stratification threshold was defined using a high-sensitivity cardiac troponin I assay. In 4870 patients, a threshold of less than 5 ng/L had a negative predictive value (NPV) of 99.6%, misclassifying less than 1 myocardial infarction for every 200 patients tested.[6] This threshold identified more than half of all patients with suspected acute coronary syndrome as low risk, reducing the proportion of patients who require admission for serial testing.[7]

Recent studies have questioned whether 5 ng/L is the optimal threshold to risk-stratify patients and have proposed alternative thresholds that may miss fewer patients with myocardial infarction.[8-11] To investigate these concerns, a systematic review of all studies of high-sensitivity cardiac troponin I testing in patients with suspected acute coronary syndrome was undertaken and individual patient-level data were obtained. Across multiple cohorts with varying prevalence of myocardial infarction, the aim was to evaluate the performance of this threshold, to evaluate other risk stratification thresholds, and to determine the association with other clinical risk characteristics.

Key Points

Question What is the optimal high-sensitivity cardiac troponin I concentration at presentation to risk-stratify patients with suspected acute coronary syndrome?

Findings In an individual patient-level meta-analysis of 22 457 patients from 9 countries, troponin I concentrations were less than 5 ng/L in 49%, among whom 5 per 1000 patients had a myocardial infarction or cardiac death at 30 days.

Meaning Among patients with suspected acute coronary syndrome, a high-sensitivity cardiac troponin I threshold of less than 5 ng/L identified patients at low risk of cardiac events; further research is needed to assess the clinical utility of this test.

Methods

Search Strategy and Selection of Articles

A systematic search of the MEDLINE, EMBASE, Cochrane, and Web of Science databases was performed without language restriction from January 1, 2006, to March 18, 2017, using detailed search terms for *chest pain*, *acute coronary syndrome*, *acute myocardial infarction*, *troponin*, *high sensitive/sensitivity*, and *emergency department* (**Figure 1**; eAppendix 1 in the Supplement contains the full search strategy). Studies were included if they met the following prespecified eligibility criteria: (1) were prospective studies of patients investigated in the emergency department for suspected acute coronary syndrome; (2) measured cardiac troponin using the Abbott ARCHITECT$_{STAT}$ high-sensitive cardiac troponin I assay (Abbott Laboratories) at presentation; and (3) had an adjudicated end point of myocardial infarction on index hospitalization (eAppendixes 2 and 3 in the Supplement). All findings are reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis of Individual Participant Data (PRISMA-IPD).[12]

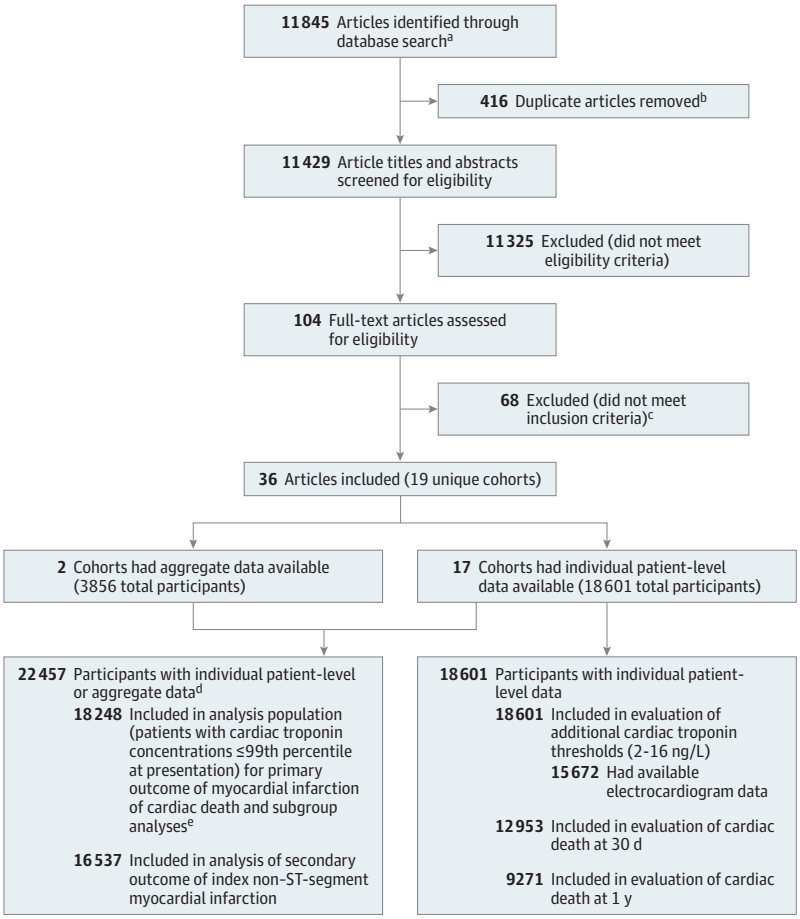
Data Extraction

Two investigators (A.R.C. and K.K.L.) performed the initial screening of titles and abstracts. Full-text reports of potentially relevant articles were obtained and assessed by both investigators using a prespecified protocol (PROSPERO register CRD42017059128). A third investigator (A.S.V.S.) adjudicated all disagreements. When there were multiple articles describing the same cohort, the article that included the largest number of participants was included. The corresponding authors of each eligible cohort were contacted with a request for anonymized data including cardiac troponin concentrations, adjudicated diagnosis, outcomes, and prespecified covariates (age, sex, chest pain, time from symptom onset to presentation sample, myocardial ischemia on electrocardiogram, cigarette smoking, diabetes mellitus, hypertension, hyperlipidemia, known angina, previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, and stroke). All studies were prospective and conducted in accordance with the Declaration of Helsinki with approval from the regional ethics committee or institutional review board, and written consent was obtained where required. This approval permitted each contributor to share individual-level data or aggregate data for inclusion in this meta-analysis. Bias was assessed by 2 investigators independently, with consensus from a third, using the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) framework (eAppendix 4 in the Supplement).

Analysis Population and Primary Outcome

The analysis population comprised patients with cardiac troponin concentrations at or below the 99th percentile at presentation (those above the 99th percentile have evidence of myocardial injury and are not eligible for risk stratification at presentation). Patients with ST-segment elevation myocardial infarction and those who presented in cardiac arrest were excluded from this analysis. The prespecified primary outcome was a composite of type 1 myocardial infarction or cardiac death at 30 days. The prespecified secondary outcomes were recurrent myocardial infarction and cardiac death at 1 year. In addition, we evaluated the performance of cardiac troponin thresholds for the

Figure 1. Flow of the Study Population and Data Analysis



Flow diagram illustrating the systematic database review and screening of articles, level of exclusion, the number of articles included, and the individual patient-level data or aggregate data available for each analysis, based on the PRISMA-IPD guidelines.[12]

[a] Articles identified through a systematic database search: MEDLINE = 2078; EMBASE = 7116; Cochrane = 390; Web of Science = 2261.

[b] Any identical publications were removed, but articles from the same cohorts were retained at this stage.

[c] Articles excluded after full-text review because they evaluated a contemporary cardiac troponin I assay (n = 36), a different high-sensitivity cardiac troponin I assay (n = 14), a high-sensitivity cardiac troponin T assay (n = 5), a different patient population (n = 4), or a different outcome measure (n = 9).

[d] Authors who did not provide individual patient-level data provided aggregate data for the primary outcome, subgroup analyses, and secondary outcome when available.

[e] Subgroup analyses were prespecified, with the following data available per group: age (n = 18 248), sex (n = 18 248), diagnosis of ischemic heart disease (n = 14 160), time from symptom onset to troponin sample time (n = 13 404), and electrocardiogram (n = 15 887).

diagnosis of type 1 or type 2 myocardial infarction on index presentation. The number of patients available for each analysis is shown in Figure 1.

Statistical Analysis

Baseline characteristics are summarized as mean (standard deviation) or median (interquartile range) as appropriate. The primary outcome measure was the NPV of a high-sensitivity cardiac troponin I concentration of less than 5 ng/L at presentation. All cardiac troponin concentrations were rounded to integer values in line with clinical standards for reporting. When individual patient-level data were available, this was checked for consistency and completeness, and cohort-level summary counts of patients with and without the primary outcome were derived for a high-sensitivity cardiac troponin I concentration of less than 5 ng/L at presentation. In cohorts in which raw data were not available, the corresponding authors were asked to provide these summaries. The NPV was calculated at a cohort level using a Bayesian approach, with a binomial likelihood and beta prior (a noninformative Jeffreys prior with both shape parameters equal to 0.5), as this produces confidence intervals with better coverage when proportions are close to 0 or 1.[13] Heterogeneity is reported using the I^2 statistic.[14] Survival free from cardiac death at 30 days and at 1 year is reported for patients with cardiac troponin I concentrations of less than 5 ng/L, 5 ng/L to the 99th percentile, and greater than the 99th percentile at presentation.

Prespecified Subgroup Analyses

For the primary outcome, the NPV was evaluated in prespecified subgroups stratified by age (≤65 or >65 years), sex, history of ischemic heart disease, time since symptom onset (≤2 or >2 hours), and presence of myocardial ischemia on electrocardiogram. Most cohorts defined myocardial ischemia as at least 2-mm ST-segment depression in 2 consecutive leads or new T-wave inversion. To explore the clinical implications of differences in performance between subgroups, we undertook these subgroup analyses in patients without myocardial ischemia on electrocardiogram. Studies have demonstrated imperfect calibration between high-sensitivity cardiac troponin I and T assays, with up to 17.5% of patients greater than the 99th percentile on the T assay shown to be less than the 99th percentile on the I assay.[15] Therefore, a further analysis evaluated whether the assay used to adjudicate the index diagnosis affected the performance of the risk stratification threshold. In addition, we determined whether the assessed risk of bias and site of patient recruitment affected the NPV.

Derivation of Meta-estimates

Meta-estimates of the NPV were derived in the analysis population for all primary and secondary outcomes by modeling cohort-level proportions (true negative/[true negative + false negative]) in a binomial-normal random-effects model, with an additional term when cohort-level characteristics (adjudication assay, assessment of bias or location of recruitment) were compared. We estimated odds ratios for the difference in NPV between prespecified subgroups, meta-analyzing this across cohorts to obtain the mean odds ratio and a *P* value for the null hypothesis of no association. For cohorts in which individual patient-level data were available, the cardiac troponin threshold that would identify the highest proportion of patients as at low risk for an NPV at or above 99.5% was determined. For this analysis, we prespecified an NPV of 99.5% as being clinically acceptable and equivalent to a miss rate of 5 per 1000 low-risk patients.[16] To evaluate how the inclusion of a risk stratification threshold would affect the overall diagnosis in all patients with suspected acute coronary syndrome, meta-estimates of NPV, positive predictive value (PPV), and sensitivity were derived for risk stratification thresholds alone (2-16 ng/L) and in conjunction with a nonischemic electrocardiogram result at presentation. At each threshold, the proportion of the total population classified as low risk and the miss rate per 1000 patients was reported. All analyses were performed in R version 3.2.2, with the meta-analyses performed using the metafor package.[17] The analysis code is available online (eAppendix 5 in the Supplement).

Results

Systematic Review

The initial search identified 11 845 articles, of which 104 articles underwent full-text review. A total of 36 articles met inclusion criteria, reporting observations from 19 individual cohorts across 9 different countries (Figure 1). Five articles reported outcomes for a high-sensitivity cardiac troponin I concentration of less than 5 ng/L.[6,8-10,18]

Study Population

All corresponding authors from the 19 individual cohorts identified in the systematic review agreed to provide data for the meta-analysis. Individual patient-level data were obtained from 17 cohorts[6-9,11,18-29] and aggregate data from 2 cohorts,[10,30] for a total study population of 22 457 patients with suspected acute coronary syndrome (mean age, 62 [SD, 16] years; 41.5% women) (**Table 1**, **Table 2**, and **Table 3**). In 11 cohorts, data were available for the prespecified primary outcome of type 1 myocardial infarction or cardiac death at 30 days (**Table 4**). In the remainder, the outcome was index type 1 myocardial infarction (n = 1) or non-ST-segment elevation myocardial infarction on index presentation (n = 5) or at 30 days (n = 2). The assessed risk of bias was high in 11 cohorts because of patient selection or use of a contemporary reference standard (eAppendixes 3 and 4 in the Supplement). Across all cohorts, the proportion with the primary outcome was 12.4% (range, 2.4%-24.0%). The analysis population comprised 18 248 of 22 457 patients in which high-sensitivity cardiac troponin I concentrations were below the 99th percentile at presentation, and the prevalence of the primary outcome was 3.5% (range, 0.6%-6.1%).

Meta-estimate of the Risk Stratification Threshold

High-sensitivity cardiac troponin I concentrations were less than 5 ng/L at presentation in 11 012 patients (49%), with an NPV of 99.5% (95% CI, 99.3%-99.6%) (**Figure 2** and Table 2) for the primary outcome and a total of 60 missed index or 30-day events (59 index myocardial infarctions, 1 myocardial infarction at 30 days, and no cardiac deaths at 30 days) (eTable 1 in the Supplement). The NPV was similar across cohorts with varying prevalence of myocardial infarction. The estimate of heterogeneity (I^2) was 31.9%. Cohort-level 2×2 summary tables are provided for the analysis population in eTable 2 in the Supplement. When data were available in the analysis population (n = 16 537 [90.6%]), we estimated the NPV for the secondary outcome of index non-ST-segment elevation myocardial infarction (type 1 or type 2 myocardial infarction). Cardiac troponin I concentrations were less than 5 ng/L at presentation in 9574 patients (48%), with an NPV of 99.4% (95% CI, 99.2%-99.6%) and a total of 58 missed events.

Subgroup Analysis

Meta-estimates of NPV were obtained in a number of prespecified subgroups (**Figure 3**). The NPV was lower in those with (98.2%; 95% CI, 96.4%-99.1% [n = 2178]) compared with those without (99.7%; 95% CI, 99.4%-99.8% [n = 13 709]) myocardial ischemia on electrocardiogram ($P < .001$) and in those who presented within 2 hours of symptom onset (99.0% [95% CI, 97.7%-99.5%] [n = 2303] vs 99.6% [95% CI, 99.4%-99.8%] [n = 11 101]; $P = .003$). Differences in the NPV were also observed between patients older

Table 1. Baseline Characteristics of All Study Patients and High-Sensitivity Cardiac Troponin I Cohorts

Characteristics	All Patients (N = 22 457)	High STEACS-V[6] (n = 4701)	UTROPIA[10] (n = 1630)	High STEACS-P[19] (n = 1064)	High STEACS-S[7] (n = 756[a])	EDACS[20] (n = 558)
Age, mean (SD), y	62 (15.5)[b]	63.7 (16.3)	57.5 (15.3)	65.6 (15.9)	62 (14.2)	59.2 (11.9)
Male, No. (%)	13 128 (58.5)	2651 (56.4)	911 (55.9)	579 (54.4)	462 (61.1)	340 (60.9)
Chest pain, No. (%)	16 760 (80.2)	3917 (83.3)	835 (51.2)	880 (82.9)	651 (86.1)	558 (100)
Time from symptom onset to troponin sample, median (IQR), min	355 (172-794)	454 (255-814)	352 (114-590)	NA	244 (146-644)	210 (115-501)
Myocardial ischemia on ECG, No. (%)	3663 (18.8)	795 (19.5)	126 (7.7)	326 (31.6)	84 (12.3)	25 (4.5)
Cardiovascular risk factors, No. (%)						
Hypertension	11 018 (54.3)	1376 (33.3)	1074 (65.9)	570 (53.6)	327 (45.0)	290 (52)
Hyperlipidemia	9270 (45.7)	1113 (27.0)	696 (42.7)	484 (45.7)	291 (40.3)	284 (50.9)
Smoker	6093 (32.6)	842 (32.1)	592 (36.3)	255 (26.2)	149 (20.3)	84 (15.1)
Diabetes	3703 (18.3)	661 (16.0)	505 (31.0)	173 (16.2)	115 (15.6)	78 (14)
Known angina	4299 (28.7)	1379 (33.3)	264 (16.2)	451 (42.5)	220 (29.8)	139 (24.9)
Previous myocardial infarction	4319 (21.3)	785 (19.0)	190 (11.7)	284 (26.7)	161 (21.9)	130 (23.3)
Previous PCI	2521 (15.6)	439 (10.6)	150 (9.2)	162 (15.2)	132 (18.1)	NA
Previous CABG surgery	1536 (8.4)	242 (5.9)	73 (4.5)	83 (7.8)	37 (5.1)	26 (4.7)
Previous stroke	1603 (8.1)	333 (8.1)	153 (9.4)	136 (12.8)	40 (5.6)	NA
High-sensitivity cardiac troponin percentile at presentation, No. (%)						
≤99th	18 248 (81.3)	3781 (80.4)	1326 (81.3)	828 (77.8)	617 (81.6)	494 (88.5)
>99th	4209 (18.7)	920 (19.6)	304 (18.7)	236 (22.1)	139 (18.4)	64 (11.5)

Abbreviations: CABG, coronary artery bypass graft; ECG, electrocardiogram; EDACS, Emergency Department Assessment of Chest Pain Score; High STEACS-P, High-Sensitivity Cardiac Troponin in the Evaluation of Patients With Suspected Acute Coronary Syndrome–Pilot; High STEACS-S; High-Sensitivity Cardiac Troponin in the Evaluation of Patients With Suspected Acute Coronary Syndrome–Substudy; High STEACS-V; High-Sensitivity Cardiac Troponin in the Evaluation of Patients With Suspected Acute Coronary Syndrome–Validation; IQR, interquartile range; NA, data not available; PCI, percutaneous coronary intervention; UTROPIA, Use of Abbott High Sensitivity Cardiac Troponin I Assay in Acute Coronary Syndromes.

[a] Only unique patients from the High STEACS-S cohort are included.

[b] Summary estimates for age and sample time exclude UTROPIA and APACE (Advantageous Predictors of Acute Coronary Syndromes Evaluation) because only aggregate data were available.

than 65 years (NPV, 99.1%; 95% CI, 98.5%-99.5% [n = 6818]) compared with those aged 65 years or younger (99.6%; 95% CI, 99.4%-99.8% [n = 11 430]; *P* = .02) and in those with (NPV, 98.8%; 95% CI, 98.1%-99.3% [n = 3990]) compared with those without (NPV, 99.6%; 95% CI, 99.4%-99.7% [n = 10 170]) a history of ischemic heart disease (*P* = .03). When this analysis was restricted to patients without myocardial ischemia on electrocardiogram, estimates of NPV were higher than 99% for all subgroups (eFigure 1 in the Supplement). Performance of the risk stratification threshold was similar regardless of the assay used for adjudication (high-sensitivity cardiac troponin I: NPV, 99.6% [95% CI, 99.3%-99.7%] [n = 7046]; contemporary cardiac troponin I or T: NPV, 99.6% [95% CI, 99.3%-99.7%] [n = 5907]; high-sensitivity cardiac troponin T: NPV, 99.2% [95% CI, 98.6%-99.6%] [n = 5295]; *P* = .27), the assessed risk of bias (high risk of bias: NPV, 99.5% [95% CI, 99.1%-99.7%] [n = 7043]; low risk of bias: NPV, 99.3% [95% CI, 99.3%-99.6%] [n = 11 205]; *P* = .37), and the site of patient recruitment (Europe: NPV, 99.5% [95% CI, 99.1%-99.7%] [n = 11 714]; North America: NPV, 99.5% [95% CI, 99.0%-99.8%] [n = 2999]; Asia-Pacific: NPV, 99.5% [95% CI, 99.1%-99.7%] [n = 3535]; *P* = .30) (eFigure 2 in the Supplement).

Short- and Long-term Outcomes According to the Risk Stratification Threshold

Follow-up data for cardiac death at 30 days and at 1 year were available in 12 953 patients (57.7%) and 9271 patients (41.3%), respectively (eTables 3 and 4 in the Supplement). In patients with cardiac troponin concentrations of less than 5 ng/L at presentation (n = 6956), there were no cardiac deaths at 30 days (NPV, 100% [95% CI, 99.9%-100%]; sensitivity, 99.4% [95% CI, 97.7%-100%]) and 7 cardiac deaths (0.1%) at 1 year (NPV, 99.9% [95% CI, 99.7%-99.9%]; sensitivity, 96.1% [95% CI, 92.9%-98.3%]). In patients with cardiac troponin concentrations between 5 ng/L and the 99th percentile at presentation (n = 3817), there were 19 cardiac deaths at 30 days (0.5%) and 58 (2.1%) at 1 year. In comparison, in those with troponin concentrations above the 99th percentile (n = 2180), there were 62 cardiac deaths at 30 days (2.8%) and 125 (8.2%) at 1 year. In patients with troponin concentrations of less than 5 ng/L at presentation and an index or 30-day myocardial infarction, there were no cardiac deaths at 30 days or at 1 year. Because the majority of studies did not adjudicate recurrent myocardial infarction events at 1 year, we were not able to conduct this prespecified analysis.

Table 2. Baseline Characteristics of Contemporary Cardiac Troponin I and T Cohorts

Characteristics	Keller et al[21] (n = 1598)	ADAPT-B[22] (n = 804)	IMPACT[23] (n = 1127)	ROMI[18] (n = 1137)	Korley et al[24] (n = 808)	ADAPT-C[25] (n = 1106)	ADAPT-RCT[26] (n = 474)	RING[27] (n = 144)
Age, mean (SD), y	61.3 (13.6)	55.2 (15.2)	51.2 (12.6)	66.7 (16.5)	56.6 (13.3)	65.3 (13.0)	60.7 (12.6)	59.7 (13.7)
Male, No. (%)	1046 (65.5)	482 (60.0)	676 (60.0)	535 (47.1)	381 (47.2)	659 (59.6)	297 (62.7)	93 (64.6)
Chest pain, No. (%)	833 (52.1)	690 (85.8)	844 (74.9)	651 (57.3)	479 (59.3)	1106 (100)	474 (100)	134 (93.1)
Time from symptom onset to troponin sample, median (IQR), min	295 (150-833)	330 (130-1275)	216 (110-676)	NA	669 (348-750)	390 (210-785)	300 (180-525)	210 (140-275)
Myocardial ischemia on ECG, No. (%)	855 (54.1)	51 (6.3)	36 (3.2)	NA	NA	188 (17.0)	21 (4.4)	NA
Cardiovascular risk factors, No. (%)								
Hypertension	1190 (74.5)	403 (50.1)	447 (39.7)	804 (71.2)	509 (63)	679 (61.4)	214 (45.1)	92 (64.3)
Hyperlipidemia	1178 (73.7)	386 (48)	427 (37.9)	676 (60.6)	340 (42.1)	636 (57.5)	243 (51.3)	79 (56.4)
Smoker	362 (22.8)	188 (23.4)	276 (24.5)	700 (61.6)	290 (35.9)	161 (14.6)	85 (17.9)	95 (66.4)
Diabetes	246 (15.7)	107 (13.3)	141 (12.5)	333 (29.7)	240 (29.7)	178 (16.1)	70 (14.8)	36 (25.9)
Known angina	NA	188 (23.4)	125 (11.1)	305 (27.5)	168 (20.8)	527 (47.6)	100 (21.1)	60 (41.7)
Previous MI	363 (23.2)	138 (17.2)	130 (11.5)	408 (36.6)	153 (18.9)	334 (30.2)	121 (25.5)	52 (36.4)
Previous PCI	335 (25.8)	87 (10.8)	85 (7.5)	251 (22.4)	112 (13.9)	NA	NA	NA
Previous CABG surgery	165 (14.7)	55 (6.8)	44 (3.9)	251 (22.4)	61 (7.5)	122 (11.0)	37 (7.8)	46 (32.2)
Previous stroke	87 (5.5)	74 (9.2)	46 (4.1)	190 (17.0)	117 (14.5)	65 (5.9)	47 (9.9)	11 (7.7)
Cardiac troponin concentration percentile at presentation, No. (%)								
≤99th	1193 (74.7)	720 (89.6)	1083 (96.1)	915 (80.5)	636 (78.7)	838 (75.8)	400 (84.4)	122 (84.7)
>99th	405 (25.3)	84 (10.4)	44 (3.9)	222 (19.5)	172 (21.3)	268 (24.2)	74 (15.6)	22 (15.3)

Abbreviations: ADAPT, 2-h Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker; CABG, coronary artery bypass graft; ECG, electrocardiogram; IMPACT, Improved Assessment of Chest Pain Trial; IQR, interquartile range; MI, myocardial infarction; NA, data not available; PCI, percutaneous coronary intervention; RCT, randomized clinical trial; RING, Reducing the Time Interval for Identifying New Guideline; ROMI, Rule Out of Myocardial Infarction.

Table 3. Baseline Characteristics of High-Sensitivity Cardiac Troponin T Cohorts

Characteristics	TI-AMO[11] (n = 1552)	APACE[30] (n = 2226)	BACC[9] (n = 1496)	TRUST[8] (n = 867)	Body et al[28] (n = 229)	Body et al[29] (n = 180)
Age, mean (SD), y	67.2 (16.0)	62 (16.0)	62.6 (15.7)	57.9 (13.1)	65.4 (15.6)	57.2 (14.5)
Male, No. (%)	781 (50.3)	1512 (67.9)	955 (63.8)	515 (59.4)	137 (59.8)	116 (64.4)
Chest pain, No. (%)	NA	2226 (100)	1206 (80.7)	867 (100)	229 (100)	180 (100.0)
Time from symptom onset to troponin sample, median (IQR), min	NA	300 (120-720)	NA	179 (119-349)	189 (96-513)[a]	197 (84-333)[a]
Myocardial ischemia on ECG, No. (%)	156 (10.5)	476 (21.4)	430 (29.4)	0	48 (21.0)	46 (25.6)
Cardiovascular risk factors, No. (%)						
Hypertension	NA	1383 (62.1)	1015 (68.2)	477 (55.0)	93 (40.6)	75 (41.9)
Hyperlipidemia	NA	1111 (49.9)	592 (39.6)	583 (67.2)	91 (39.7)	60 (33.3)
Smoker	NA	1370 (61.5)	352 (23.6)	210 (24.2)	36 (15.7)	46 (26.9)
Diabetes	NA	405 (18.2)	201 (13.6)	145 (16.7)	42 (18.3)	27 (15.0)
Known angina	NA	NA	NA	223 (25.7)	97 (42.4)	53 (29.6)
Previous myocardial infarction	NA	514 (23.1)	240 (16.1)	190 (21.9)	78 (34.1)	48 (27.0)
Previous PCI	NA	527 (23.7)	NA	168 (19.4)	34 (14.8)	39 (21.8)
Previous CABG surgery	NA	211 (9.5)	NA	41 (4.7)	30 (13.1)	12 (6.8)
Previous stroke	NA	122 (5.5)	102 (6.8)	57 (6.6)	20 (8.7)[b]	3 (1.7)[b]
High-sensitivity cardiac troponin percentile at presentation, No. (%)						
≤99th	1156 (74.5)	1801 (80.9)	1202 (80.3)	810 (93.4)	179 (78.2)	147 (81.7)
>99th	396 (25.5)	425 (19.1)	294 (19.7)	57 (6.6)	50 (21.8)	33 (18.3)

Abbreviations: APACE, Advantageous Predictors of Acute Coronary Syndromes Evaluation; BACC, Biomarkers in Acute Cardiovascular Care; CABG, coronary artery bypass graft; ECG, electrocardiogram; IQR, interquartile range; NA, data not available; PCI, percutaneous coronary intervention; TRUST, Triage Rule-Out Using High-Sensitivity Troponin.

[a] Only symptom to presentation time available.

[b] Includes patients with transient ischemic attack.

Table 4. Summary of Cohort Size, End Points, and Prevalence of Myocardial Infarction

Cohorts	Cohort Size, No.	Primary Outcome	Prevalence of Primary Outcome, No. (%)		Assay Used for MI Adjudication	NPV, % (95% CI)	hs-cTnI <5 ng/L at Presentation, No. (%) of Total Cohort
			Total Cohort	≤99th Percentile[a]			
High-Sensitivity Cardiac Troponin I Cohorts							
High STEACS-V[6]	4701	Type 1 MI or cardiac death (30 d)	662 (14.1)	141 (3.7)	Abbott hs-cTnI	99.6 (99.3-99.8)	2292 (48.8)
UTROPIA[10]	1630	Type 1 MI or cardiac death (30 d)	70 (4.3)	22 (1.4)	Abbott hs-cTnI	99.5 (99.0-99.9)	774 (47.5)
High STEACS-P[19]	1064	Type 1 MI or cardiac death (30 d)	201 (18.9)	46 (5.6)	Abbott hs-cTnI	99.7 (99.0-100)	469 (44.1)
High STEACS-S[7]	756	Type 1 MI or cardiac death (30 d)	115 (15.2)	25 (4.1)	Abbott hs-cTnI	99.4 (98.5-99.9)	428 (56.6)
EDACS[20]	558	Type 1 MI or cardiac death (30 d)	66 (11.8)	17 (3.4)	Abbott hs-cTnI	99.1 (97.9-99.8)	378 (67.7)
Contemporary Cardiac Troponin I and T Cohorts							
Keller et al[21]	1598	Index NSTEMI	268 (16.8)	29 (2.4)	Roche cTnT	99.9 (99.7-100)	563 (35.2)
ADAPT-B[22]	804	Type 1 MI or cardiac death (30 d)	48 (6.0)	8 (1.1)	Beckmann Accu-cTnI	99.7 (99.1-100)	532 (66.2)
IMPACT[23]	1127	Type 1 MI or cardiac death (30 d)	49 (4.3)	26 (2.4)	Beckmann Accu-cTnI	99.5 (99.0-99.9)	923 (81.9)
ROMI[18]	1137	Index NSTEMI	133 (11.7)	40 (4.4)	Abbott cTnI	99.1 (98.1-99.7)	503 (44.2)
Korley et al[24]	808	Index type 1 MI	19 (2.4)	4 (0.6)	Abbott cTnI	99.4 (98.3-100)	266 (32.9)
ADAPT-C[25]	1106	Type 1 MI or cardiac death (30 d)	265 (24.0)	42 (5.0)	Abbott cTnI	99.1 (98.0-99.7)	475 (42.9)
ADAPT-RCT[26]	474	Type 1 MI or cardiac death (30 d)	75 (15.8)	20 (5.0)	Abbott cTnI	99.3 (98.0-100)	228 (48.1)
RING[27]	144	Index NSTEMI	9 (6.2)	1 (0.8)	Roche c-TnT	99.4 (97.8-100)	88 (61.1)
High-Sensitivity Cardiac Troponin T Cohorts							
TI-AMO[11]	1552	Index NSTEMI	90 (5.8)	18 (1.6)	Roche hs-cTnT	99.8 (99.2-100)	613 (39.5)
APACE[30]	2226	Index NSTEMI	399 (17.9)	117 (6.1)	Roche hs-cTnT	99.2 (98.6-99.7)	1801 (49.8)
BACC[9]	1496	Type 1 MI or cardiac death (30 d)	181 (12.0)	47 (3.9)	Roche hs-cTnT	98.9 (97.8-99.6)	567 (37.9)
TRUST[8]	867	Type 1 MI or cardiac death (30 d)	66 (7.6)	28 (3.5)	Roche hs-cTnT	98.3 (97.2-99.1)	664 (76.6)
Body et al[28]	229	NSTEMI (30 d)	43 (18.8)	9 (5.0)	Roche hs-cTnT	99.0 (96.1-100)	48 (21.0)
Body et al[29]	180	NSTEMI (30 d)	27 (15.0)	5 (3.4)	Roche hs-cTnT	98.4 (95.1-99.9)	93 (51.7)
Summary	22 457		2786 (12.4)	645 (3.5)		99.5 (99.3-99.6)	11 012 (49.0)

Abbreviations: ADAPT, 2-h Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker; APACE, Advantageous Predictors of Acute Coronary Syndromes Evaluation; BACC, Biomarkers in Acute Cardiovascular Care; cTnI, cardiac troponin I; cTnT, cardiac troponin T; EDACS, Emergency Department Assessment of Chest Pain Score; High STEACS-P, High-Sensitivity Cardiac Troponin in the Evaluation of Patients With Suspected Acute Coronary Syndrome–Pilot; High STEACS-S; High-Sensitivity Cardiac Troponin in the Evaluation of Patients With Suspected Acute Coronary Syndrome–Substudy; High STEACS-V; High-Sensitivity Cardiac Troponin in the Evaluation of Patients With Suspected Acute Coronary Syndrome–Validation; hs, high sensitivity; IMPACT, Improved Assessment of Chest Pain Trial; MI, myocardial infarction; NPV, negative predictive value; NSTEMI, non–ST-segment elevation myocardial infarction; RCT, randomized clinical trial; RING, Reducing the Time Interval for Identifying New Guideline; ROMI, Rule Out of Myocardial Infarction; TRUST, Triage Rule-Out Using High-Sensitivity Troponin; UTROPIA, Use of Abbott High Sensitivity Cardiac Troponin I Assay in Acute Coronary Syndromes.

[a] Indicates patients with cardiac troponin concentrations ≤99th percentile at presentation.

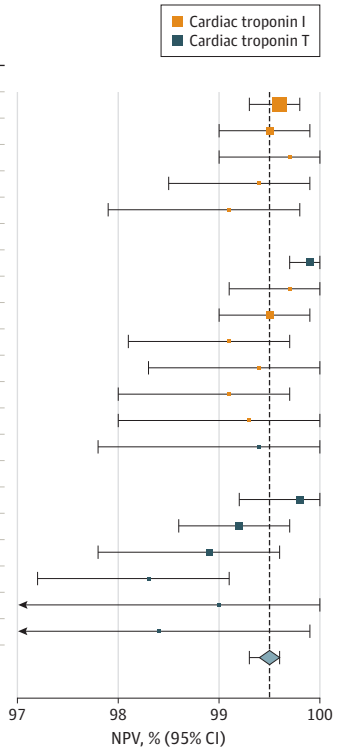
Risk Stratification Thresholds and Diagnosis of Myocardial Infarction

In all patients with suspected acute coronary syndrome for whom individual patient-level data were available (n = 18 601 [82.8%]), we evaluated how different risk stratification thresholds would affect the NPV and sensitivity for the primary outcome. When used in isolation, a troponin I concentration of less than 5 ng/L gave an NPV of 99.5% (95% CI, 99.3%-99.7%) and a sensitivity of 98.0% (95% CI, 96.4%-98.9%), identifying 49.1% of patients as low risk with a miss rate of 5.4 (95% CI, 4.0-7.0) per 1000 patients. At a threshold of less than 2 ng/L, the NPV was 99.8% (95% CI, 99.0%-100%) and the sensitivity was 100% (95% CI, 98.9%-100%), but the proportion of patients identified as low risk was lower at 13.7%. Although the absolute number of missed cases was lower, the miss rate was similar at 4.1 (95% CI, 2.0-6.9) per 1000 patients (eTable 5 in the Supplement).

In a subgroup analysis combining risk stratification thresholds and a nonischemic electrocardiogram result (**Figure 4**), a cardiac troponin I concentration of less than 5 ng/L gave an NPV of 99.7% (95% CI, 99.4%-99.8%) and a sensitivity of 99.0% (95% CI, 97.3%-99.6%), identifying

Figure 2. Negative Predictive Value of an hs-cTnI Concentration of Less Than 5 ng/L at Presentation by Cohort for Primary Outcome (Index Myocardial Infarction or Cardiac Death at 30 Days) by Assay Used for Adjudication

Cohort	False Negatives, No.	True Negatives, No.	Total No. of Patients With Cardiac Troponin Concentrations ≤99th Percentile at Presentation	NPV, % (95% CI)
hs-cTnI assay				
High STEACS-V[6]	9	2283	3781	99.6 (99.3-99.8)
UTROPIA[10]	3	771	1326	99.5 (99.0-99.9)
High STEACS-P[19]	1	468	828	99.7 (99.0-100)
High STEACS-S[7]	2	426	617	99.4 (98.5-99.9)
EDACS[20]	3	375	494	99.1 (97.9-99.8)
cTnI or cTnT assay				
Keller et al[21]	0	563	1193	99.9 (99.7-100)
ADAPT-B[22]	1	531	720	99.7 (99.1-100)
IMPACT[23]	4	919	1083	99.5 (99.0-99.9)
ROMI[18]	4	499	915	99.1 (98.1-99.7)
Korley et al[24]	1	265	636	99.4 (98.3-100)
ADAPT-C[25]	4	471	838	99.1 (98.0-99.7)
ADAPT-RCT[26]	1	227	400	99.3 (98.0-100)
RING[27]	0	88	122	99.4 (97.8-100)
hs-cTnT assay				
TI-AMO[11]	1	612	1156	99.8 (99.2-100)
APACE[30]	8	1100	1801	99.2 (98.6-99.7)
BACC[9]	6	561	1202	98.9 (97.8-99.6)
TRUST[8]	11	653	810	98.3 (97.2-99.1)
Body et al[28]	0	48	179	99.0 (96.1-100)
Body et al[29]	1	92	147	98.4 (95.1-99.9)
Summary	60	10952	18248	99.5 (99.3-99.6)



Data markers indicate the central estimate of negative predictive value (NPV) (orange markers for cardiac troponin I [cTnI] and black markers for cardiac troponin T [cTnT] assays) with size of the data markers corresponding to the number of patients per cohort (large, >3000 patients; medium, ≥1000 patients; small, <1000 patients) and error bars indicating 95% CIs. Dotted line indicates central estimate of NPV at 99.5%. ADAPT indicates 2-h Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker; APACE, Advantageous Predictors of Acute Coronary Syndromes Evaluation; BACC, Biomarkers in Acute Cardiovascular Care; EDACS, Emergency Department Assessment of Chest Pain Score; High STEACS-P, High-Sensitivity Cardiac Troponin in the Evaluation of Patients With Suspected Acute Coronary Syndrome–Pilot; High STEACS-S; High-Sensitivity Cardiac Troponin in the Evaluation of Patients With Suspected Acute Coronary Syndrome–Substudy; High STEACS-V; High-Sensitivity Cardiac Troponin in the Evaluation of Patients With Suspected Acute Coronary Syndrome–Validation; hs, high sensitivity; IMPACT, Improved Assessment of Chest Pain Trial; RCT, randomized clinical trial; RING, Reducing the Time Interval for Identifying New Guideline; ROMI, Rule Out of Myocardial Infarction; TRUST, Triage Rule-Out Using High-Sensitivity Troponin; UTROPIA, Use of Abbott High Sensitivity Cardiac Troponin I Assay in Acute Coronary Syndromes.

45.9% of patients as low risk, with 4.4 (95% CI, 3.0-6.0) false negatives per 1000 patients and a PPV of 24.5% (95% CI, 20.3%-29.2%). The combination of a cardiac troponin I concentration of less than 2 ng/L and a nonischemic electrocardiogram result gave a similar NPV of 99.9% (95% CI, 98.5%-100%) and a sensitivity of 100% (95% CI, 96.6%-100%) but identified just 13.1% of patients as low risk, with 4.1 (95% CI, 1.8-7.3) false negatives per 1000 patients and a lower PPV of 14.2% (95% CI, 11.3%-17.6%).

Discussion

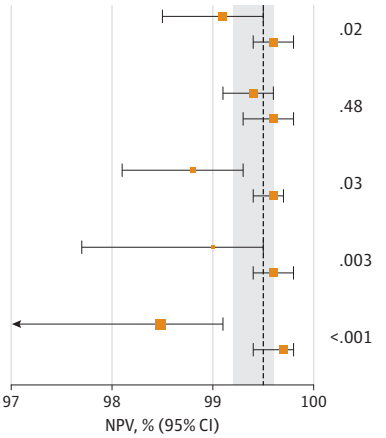
In 19 cohorts across 9 countries and encompassing more than 22 000 patients, a cardiac troponin I concentration of less than 5 ng/L at presentation identified half of all patients with suspected acute coronary syndrome as at low risk of myocardial infarction or cardiac death at 30 days, with 5 false negatives per 1000 patients tested.

There are a number of strengths to the analysis. This was a prespecified systematic review and meta-analysis that included individual patient-level data from all cohorts identified. The findings were consistent across a range of health care settings and geographic regions with considerable differences in the prevalence of myocardial infarction. Individual patient-level data were included from more than 22 000 patients, allowing a meaningful analysis of important subgroups. All studies were prospective, and in all studies the final diagnosis was adjudicated according to the universal definition of myocardial infarction.

Two recent meta-analyses have suggested an approach to risk stratification using the limit of detection of the high-sensitivity cardiac troponin T assay, which identifies up to 31% of patients with an NPV of 99.3%.[31,32] The limit of detection of the high-sensitivity cardiac troponin I assay identifies 19% to 27% of patients as low risk with an NPV of 99.5% or greater.[8-10] The major limitation of this approach for both assays is analytical, with biases and analytical variation at the

Figure 3. Negative Predictive Value of an hs-cTnI Concentration of Less Than 5 ng/L at Presentation for Primary Outcome (Index Myocardial Infarction or Cardiac Death at 30 Days) by Prespecified Subgroup

Prespecified Subgroup	False Negatives, No.	True Negatives, No.	Total No. of Patients With Cardiac Troponin Concentrations ≤99th Percentile at Presentation	NPV, % (95% CI)	*P* Value
Age, y					
>65	26	2571	6818	99.1 (98.5-99.5)	.02
≤65	34	8381	11430	99.6 (99.4-99.8)	
Sex					
Male	38	6043	10920	99.4 (99.1-99.6)	.48
Female	22	4909	7328	99.6 (99.3-99.8)	
Ischemic heart disease					
Known[a]	22	1834	3990	98.8 (98.1-99.3)	.03
None known	31	7035	10170	99.6 (99.4-99.7)	
Time from symptom onset to troponin sample collection, h					
≤2[b]	20	1540	2303	99 (97.7-99.5)	.003
>2	26	6851	11101	99.6 (99.4-99.8)	
Myocardial ischemia on electrocardiogram					
Yes[c]	15	818	2178	98.2 (96.4-99.1)	<.001
No	39	8899	13709	99.7 (99.4-99.8)	



hs-cTnI indicates high-sensitivity cardiac troponin I; NPV, negative predictive value. Data markers indicate the central estimate of NPV with size corresponding to the number of patients per cohort (large, >3000 patients; medium, ≥1000 patients; small, <1000 patients) and error bars indicating 95% CIs. Dotted line and shaded areas represent the central estimate and 95% CIs for the full analysis population. All 19 cohorts were included in analyses unless otherwise specified.

[a] Ischemic heart disease status available in 16 of 19 cohorts.

[b] Time from symptom onset to troponin sample collection available in 15 of 19 cohorts.

[c] Electrocardiogram findings available in 15 of 19 cohorts.

limit of detection associated with rates of misclassification that are twice that observed at 5 ng/L.[33,34]

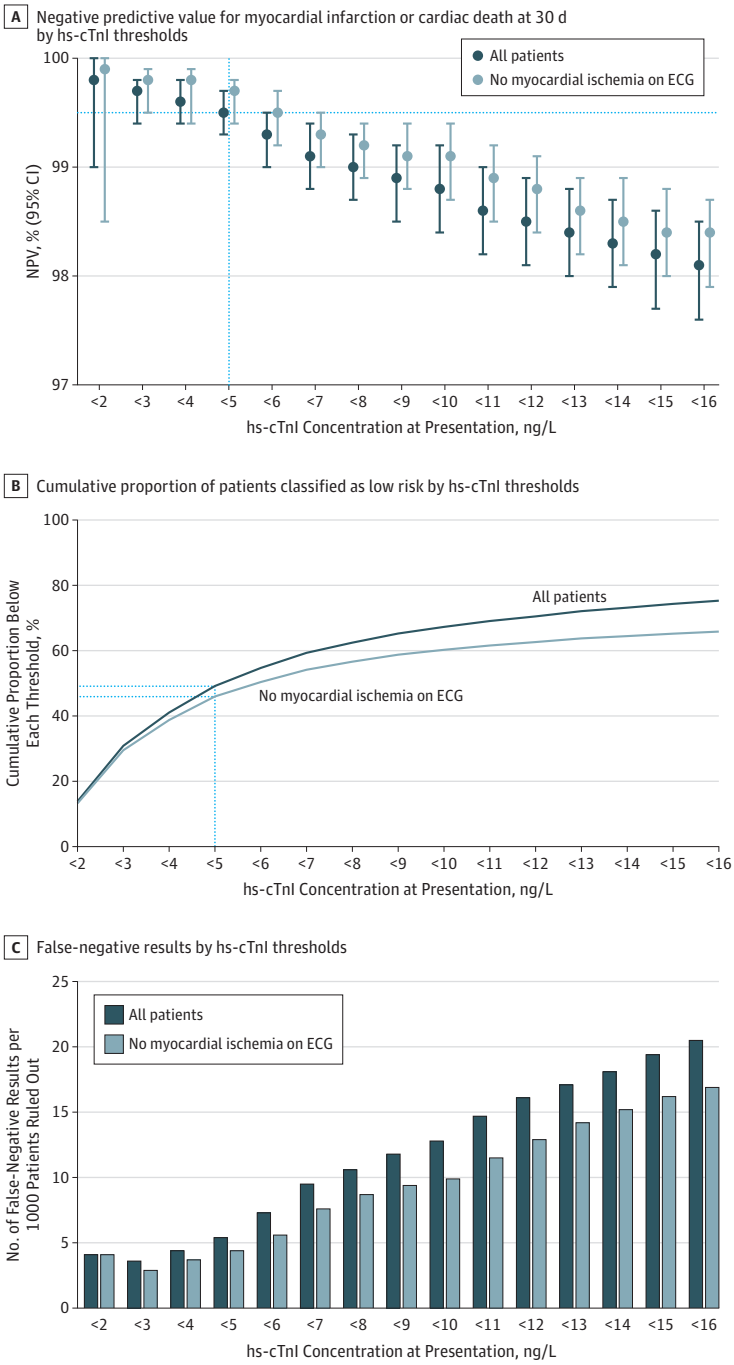
In clinical practice, cardiac troponin concentrations are interpreted in conjunction with the electrocardiogram and clinical assessment. When a risk stratification threshold of less than 5 ng/L was evaluated in the subgroup of patients without myocardial ischemia on electrocardiogram, the NPV and sensitivity were excellent. To ensure that safety estimates were conservative, performance was evaluated not just for an index diagnosis but for a composite end point that included events up to 30 days. Although there were 81 cardiac deaths at 30 days, none occurred in the 6956 patients with cardiac troponin I concentrations less than 5 ng/L. Furthermore, performance was similar for both spontaneous type 1 and secondary type 2 myocardial infarction. This is relevant because the diagnosis of type 2 myocardial infarction is more challenging and is associated with a worse prognosis.[35-37]

At a threshold of 5 ng/L, the analytical performance of the high-sensitivity cardiac troponin I assay is excellent.[6,38] The use of lower thresholds did not improve diagnostic accuracy. A miss rate of 5 per 1000 patients was observed when applying less than 5 ng/L as the risk stratification threshold, with a miss rate of 4 per 1000 patients observed at a threshold of less than 2 ng/L. Although the true risk of missing an individual patient with myocardial infarction is the same at both thresholds, lower thresholds reduce the proportion of patients classified as at low risk; only 1 in 10 patients had a troponin I concentration of less than 2 ng/L compared with 5 in 10 patients a with concentration of less than 5 ng/L. Use of lower thresholds would result in more patients without myocardial infarction being admitted for serial testing and further investigation, with an increase in health care expenditures.

Despite recent changes to guidelines,[5] the majority of clinicians continue to rely on the 99th percentile to rule in and rule out myocardial infarction.[39] A pathway incorporating a risk stratification threshold of less than 5 ng/L alongside nonischemic electrocardiogram findings misses 5-fold fewer index myocardial infarctions or 30-day events than guideline-approved pathways based exclusively on the 99th percentile.[7] This limitation of the 99th percentile has now been demonstrated in multiple studies.[25,40] This approach to risk stratification using low high-sensitivity cardiac troponin concentrations has major potential to improve both the efficiency of health care delivery and patient safety and is being formally evaluated in a prospective multicenter clinical trial (NCT03005158).

This study has several limitations. First, not all cohorts used identical protocols, with differences both in the inclusion criteria and the diagnostic criteria used for adjudication (eAppendix 3 in the Supplement). However, no significant differences in NPV were observed when stratified by adjudicating assay, and the NPV was high across individual cohorts, suggesting that these findings are generalizable. Second, the percentage of patients who presented early after onset of

Figure 4. Optimal Threshold of hs-cTnI at Presentation to Risk-Stratify Patients With Suspected Acute Coronary Syndrome for Myocardial Infarction or Cardiac Death at 30 Days



hs-cTnI indicates high-sensitivity cardiac troponin I; NPV, negative predictive value. In all panels, performance of hs-cTnI thresholds are shown for all patients (dark blue) and when applied to patients with nonischemic electrocardiogram (ECG) findings at presentation (light blue). All estimates of NPV are derived from a binomial-normal random-effects model using individual patient-level data (available in 17 cohorts) for each hs-cTnI threshold (n = 18 601; eTable 5 in the Supplement).[6-9,11,18-29] A, NPV across a range of hs-cTnI concentrations. Error bars indicate 95% CIs. Horizontal dotted line indicates prespecified target NPV of 99.5% and vertical dotted line indicates hs-cTnI concentration of less than 5 ng/L. B, Cumulative proportion of all patients with suspected acute coronary syndrome classified as low risk. Dotted vertical line indicates proportion of patients with hs-cTnI concentration of less than 5 ng/L. C, Number of false negatives per 1000 patients tested across a range of hs-cTnI thresholds. Electrocardiogram data were not available for 2929 patients (15.7%).

symptoms was low at just 10% of the study population. Despite observing an NPV of 99% in this subgroup, inconsistencies in the documentation of symptom onset across cohorts may affect the analysis, and until further research is available, serial testing is recommended in patients presenting within 2 hours of symptom onset.[5] The greatest number of false negatives was observed in the cohort with the shortest median symptom onset to sample time (179 [interquartile range, 119-349] minutes), which may explain the lower NPV and sensitivity reported at this threshold in a previous study.[8] Third, while it is reassuring that patients with troponin I concentrations of less than 5 ng/L had a much lower rate of cardiac death at 1 year than did patients with concentrations between 5 ng/L and the 99th percentile, this observation needs to be verified in prospective studies in which patient care is guided by this approach.

Conclusions

Among patients with suspected acute coronary syndrome, a high-sensitivity cardiac troponin I concentration of less than 5 ng/L at presentation identified those at low risk of myocardial infarction or cardiac death within 30 days. Further research is needed to understand the clinical utility and cost-effectiveness of this approach to risk stratification.

ARTICLE INFORMATION

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