Diagnostic Accuracy of High-Sensitivity Cardiac Troponin T at Presentation Combined With History and ECG for Ruling Out Major Adverse Cardiac Events

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Study objective: We evaluate the diagnostic accuracy of a high-sensitivity cardiac troponin T (hs-cTnT) level less than 5 ng/L or less than or equal to 14 ng/L at emergency department (ED) presentation, combined with the emergency physician's assessment of history and ECG, for ruling out major adverse cardiac events within 30 days.

Methods: This prospective observational study enrolled consecutive ED chest pain patients. Emergency physicians' assessments of patient history and ECG were collected. The primary outcome was 30-day major adverse cardiac events, defined as acute myocardial infarction, unstable angina, cardiogenic shock, ventricular arrhythmia, atrioventricular block, cardiac arrest, or death of cardiac or unknown cause.

Results: A total of 1,138 patients were included in the final analysis. The combination of hs-cTnT less than 5 ng/L, a nonischemic ECG result, and a nonhigh risk history was present for 29.2% of all patients and had a sensitivity of 99.2% (95% confidence interval [CI] 95.6% to 100%), negative predictive value (NPV) of 99.7% (95% CI 98.3% to 100%), and a negative likelihood ratio of 0.02 (95% CI 0 to 0.17) for 30-day major adverse cardiac events. The same combination with hs-cTnT less than or equal to 14 ng/L was present in 66.7% of the patients and had a sensitivity of 92% (95% CI 85.8% to 96.1%), NPV of 98.7% (95% CI 97.6% to 99.4%), and negative likelihood ratio of 0.11 (95% CI 0.06 to 0.20).

Conclusion: A single hs-cTnT result of less than 5 ng/L at ED presentation when combined with a nonischemic ECG result and a nonhigh risk history identified 29% of chest pain patients at a very low risk of 30-day major adverse cardiac events. A similar strategy with hs-cTnT less than or equal to 14 ng/L was associated with a higher miss rate. [Ann Emerg Med. 2016;68:649-658.]

Please see page 650 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Acute coronary syndrome, ie, acute myocardial infarction or unstable angina, is one of the main diagnostic concerns in emergency department (ED) chest pain patients. The principal methods used in clinical practice to assess the likelihood of acute coronary syndrome are patient history, ECG result, and blood troponin levels.

Several studies indicate that a single high-sensitivity cardiac troponin T (hs-cTnT) result below the limit of detection (<5 ng/L) at ED presentation can accurately rule out acute myocardial infarction.[1-3] However, our routine evaluation of ED chest pain patients focuses not only on the risk of acute myocardial infarction but also on the risk of unstable angina and major adverse cardiac events. An hs-cTnT level less than 5 ng/L alone does not safely rule out acute coronary syndrome.[4,5] Clinical management of ED chest pain patients is, however, not only based on troponin levels but also on assessment of the history and ECG. It is unknown whether an hs-cTnT level less than 5 ng/L, when combined with a low pretest probability based on history and ECG, is able to rule out acute coronary syndrome and major adverse cardiac events.

Furthermore, one study has suggested that a safe rule-out might be achieved by combining hs-cTnT level less than or equal to 14 ng/L (99th percentile upper reference limit), ECG, and physician gestalt,[6] but these results have yet to be validated.

Editor's Capsule Summary

What is already known on this topic

Higher-sensitivity troponin assays have shortened the time required to rule out acute myocardial infarction.

What question this study addressed

Whether nonhigh-risk clinical gestalt, nonischemic ECG result, and a single high-sensitivity troponin value less than 5 ng/mL at presentation could identify a group of patients at very low risk for 30-day events.

What this study adds to our knowledge

In this 1,138-patient study, this combination had a sensitivity of 99.2% (95% confidence interval 95.6% to 100%) and negative predictive value of 99.7% (95% confidence interval 98.3% to 100%).

How this is relevant to clinical practice

The ability to rule out acute myocardial infarction with a single high-sensitivity troponin value would be significant; however, one should not generalize from one troponin assay to another.

Importance

The majority of chest pain patients do not have acute coronary syndrome, yet many undergo lengthy assessments with serial troponin analyses, admission for observation, imaging, or stress testing.[7-9] If the combination of history, ECG, and a single hs-cTnT level at presentation can identify patients with a very low risk of major adverse cardiac events who are suitable for discharge, this could potentially reduce ED crowding, hospital admissions, and further diagnostic testing, with clear benefits for both patients and the health care system.

Goals of This Investigation

Our aim was to evaluate the diagnostic accuracy of an hs-cTnT level less than 5 ng/L or less than or equal to 14 ng/L at ED presentation, combined with the emergency physician's assessment of the history and ECG result, for ruling out major adverse cardiac events within 30 days.

MATERIALS AND METHODS

Study Design and Setting

The present study was a prospective observational study, and the methods have been described elsewhere.[10] The study enrolled patients presenting between February 2013 and April 2014 to the ED of Skåne University Hospital in Lund, a tertiary care center with an annual ED census of 65,000. This study was approved by the regional ethical review board in Lund, and all patients provided written informed consent.

Selection of Participants

Consecutive patients aged 18 years or older, with a primary symptom of nontraumatic chest pain, and for whom hs-cTnT was ordered at presentation (0 hours) were enrolled during weekdays between 9 AM and 9 PM. We did not enroll patients with severe communication barriers, eg, not speaking Swedish or English, or with dementia, and other patients who were unable to provide written informed consent. We also did not enroll patients with ST-segment elevation myocardial infarction because this diagnosis is not based on biomarkers. Patients with ST-segment elevation myocardial infarction at the index visit who were erroneously enrolled were excluded. We also excluded patients with missing physician assessments of history or ECG result and those with 0-hour samples with significant hemolysis (H-index $\geq$100, the level recommended by the manufacturer) because this can cause falsely low hs-cTnT results. In cases in which a sample without hemolysis was available 1 hour after the 0-hour sample, these hs-cTnT samples replaced the 0-hour sample to reflect actual practice in which a new test is commonly ordered in case of hemolysis.

Methods of Measurement

Clinical data and physician assessments were collected by research assistants using a custom-made data form. Our ED is staffed mainly by emergency physicians. Physicians making the initial assessments in this study were interns, residents, or attending physicians. In Sweden, interns have 0 to 2 years of clinical experience after medical graduation; residents, 2 to 7 years of experience; and attending physicians, greater than or equal to 7 years of experience. Physicians were approached shortly after consulting with the patient to obtain their assessment of the likelihood of acute coronary syndrome according to the patient history and ECG result before hs-cTnT results were available. The patient history was assessed as high, intermediate, low, or very low risk of acute coronary syndrome. To obtain the physician's unbiased impression ("gestalt"), the questionnaire provided no guidance on how to differentiate the different risk levels. The physicians also assessed whether the ECG showed signs of acute ischemia. We similarly did not provide a definition of signs of acute ischemia, but the questionnaire included the definitions of significant ST elevation, ST depression, T-wave inversion,

and Q waves, as defined by the universal acute myocardial infarction guidelines.[11]

Samples for hs-cTnT, which was the assay in clinical use during the study period, were collected in lithium heparin tubes and analyzed with the Roche Cobas e602 (Roche Diagnostics, Basel, Switzerland), as in routine care. This assay has a limit of blank of 3 ng/L and a limit of detection of 5 ng/L, and the coefficient of variation is less than 10% at the 99th percentile cutoff point of 14 ng/L.[12]

Patients were subsequently managed at the discretion of the responsible physician, as in routine care.

The primarily evaluated 2 index tests were hs-cTnT less than 5 ng/L and less than or equal to 14 ng/L at ED presentation, combined with a physician assessment of a nonischemic ECG result and a nonhigh risk history (history assessed as intermediate, low, or very low risk of acute coronary syndrome). Emergency physicians' dichotomous assessment of history and ECG result in chest pain patients has previously been shown to have good interobserver reliability, with κ values of 0.75 and 0.85, respectively, and has been associated with adverse cardiac events independently of troponin levels in multivariable analysis.[6,13] We also evaluated an isolated hs-cTnT level less than 5 ng/L or less than or equal to 14 ng/L at presentation, and when combined with only a nonischemic ECG result. Additionally, we studied a presentation hs-cTnT level in the setting of a high pretest probability, defined as either an ischemic ECG and/or a high-risk history. All analyses were prespecified.

Outcome Measures

The primary outcome was major adverse cardiac events within 30 days, including the index visit. Major adverse cardiac events were defined as an adjudicated diagnosis of acute myocardial infarction, unstable angina, cardiac arrest, cardiogenic shock, ventricular arrhythmia requiring intervention, high-degree atrioventricular block requiring intervention, or death from a cardiac or unknown cause. The secondary outcome was major adverse cardiac events without unstable angina within 30 days.

The reference standard was a final adjudicated diagnosis of 30-day major adverse cardiac events, as decided by independent reviews by 2 cardiologists, and in case of disagreement, by a third cardiologist. The cardiologists were unaware of the study hypothesis and blinded to the data form. A detailed account of the adjudication process is provided in a previous publication.[10]

Medical records from all hospitals and all diagnostic examinations in the region were accessed, including those ordered by primary care physicians. To not miss hospital visits outside the region, data from the National Patient Register were also obtained, which include all admissions for inhospital care in Sweden. Medical records were retrieved for patients who sought care outside our region but inside Sweden. The adjudicators were then provided with all available clinical information from all hospitals in Sweden within 60 days from the index visit, including complete medical records, results of blood samples and radiologic investigations, ECGs, echocardiograms, stress tests, and coronary angiographies.

Deaths and causes of death were obtained from medical records, the Swedish population registry, and the national cause-of-death registry.

Acute myocardial infarction was defined according to the universal definition, requiring a significant increase or decrease of hs-cTnT levels, with at least 1 value above the 99th percentile, combined with symptoms or signs of cardiac ischemia.[11] Because the literature is unclear in regard to the optimal definition of significant troponin dynamics, we provided the adjudicators with the following definitions based on a literature review: an absolute change greater than 7 ng/L within 2 to 3 hours or greater than or equal to 9 ng/L within 6 hours,[14-17] or a change greater than 20% if the 0-hour hs-cTnT level was greater than 14 ng/L.[17] To avoid misclassification of patients presenting in a troponin plateau phase, an acute myocardial infarction diagnosis could still be adjudicated in patients with increased hs-cTnT levels in the absence of a significant increase or decrease, if considered to be the most likely diagnosis based on all available information.[11,18]

The diagnosis of unstable angina required normal or slightly increased hs-cTnT levels without a significant increase or decrease and a history consistent with unstable angina, defined as rest angina, new-onset angina of Canadian Cardiovascular Society class greater than or equal to 3, or increasing angina, and at least 1 of the following: stenosis greater than or equal to 70% in a vessel on coronary angiography, positive stress test result if no angiography was performed, or new ischemic ECG changes in patients managed without stress test or angiography. An unstable angina diagnosis could also be adjudicated in patients who were discharged after acute myocardial infarction was ruled out and who subsequently received a diagnosis of acute myocardial infarction or experienced death of cardiac or unknown cause within 30 days from the index visit.

The other components of the 30-day major adverse cardiac events outcome were defined according to published standardized data definitions.[19]

Primary Data Analysis

For descriptive data, continuous variables are described with mean and SD or median with interquartile range, and

categorical variables are described with proportions. Sensitivity, specificity, negative predictive values (NPVs), and negative likelihood ratios (LR–) and corresponding 95% confidence intervals (CIs) were calculated for the different diagnostic strategies.

It has been estimated that the test threshold for acute coronary syndrome is approximately 2%,[20] meaning that when the risk of acute coronary syndrome is below 2%, patients are more likely to derive harm than benefit from further testing. In general, emergency physicians will, however, accept only a less than 1% risk of 30-day major adverse cardiac events (not including unstable angina) in discharged patients, and a majority only a less than or equal to 0.5% risk.[21] In this study, we postulated that for a rule-out to be deemed safe and acceptable, patients should have a less than 2% risk of 30-day major adverse cardiac events (including unstable angina), thereby ensuring a risk of acute coronary syndrome below the test threshold, and preferably a less than or equal to 0.5% risk of 30-day major adverse cardiac events without unstable angina.

Five prespecified subgroup analyses (patient sex, <65 versus ≥65 years, time of chest pain onset to 0-hour hs-cTnT sample ≤3 versus >3 hours, intern/resident versus specialist physician, and ongoing versus abated chest pain) were performed for both primary index tests.

This study was a planned secondary analysis of this database, and there was no formal sample size calculation.

All tests were 2-tailed and $P<.05$ was considered significant. IBM SPSS (version 21; IBM, Armonk, NY) and MedCalc Statistical Software (version 14.8.1; MedCalc Software bvba, Ostend, Belgium) were used for all statistical analyses.

RESULTS

Characteristics of Study Subjects

A total of 1,167 patients were enrolled in the study, with 1,138 patients included in the final analyses (Figure 1). Three patients had an ST-segment elevation myocardial infarction that was initially missed, leading to erroneous enrollment, and were therefore excluded. All 3 had an increased hs-cTnT level at presentation (mean 1,032 ng/L) and so would not have been identified for rule-out by either index test. Ten patients with hemolysis (H-index ≥100) in their 0-hour sample had an hs-cTnT sample at 1 hour and were included. None of these patients had a 30-day major adverse cardiac event.

As shown in Table 1, the median age of included patients was 63.2 years (range 18 to 98 years), 54.6% were men, and 19.9% had a previous acute myocardial infarction. At least 2 hs-cTnT samples were analyzed during the index visit for 1,094 (96.1%) patients. A final diagnosis of 30-day major adverse cardiac events was adjudicated for 125 patients (11%), and 30-day major adverse cardiac events without unstable angina for 87

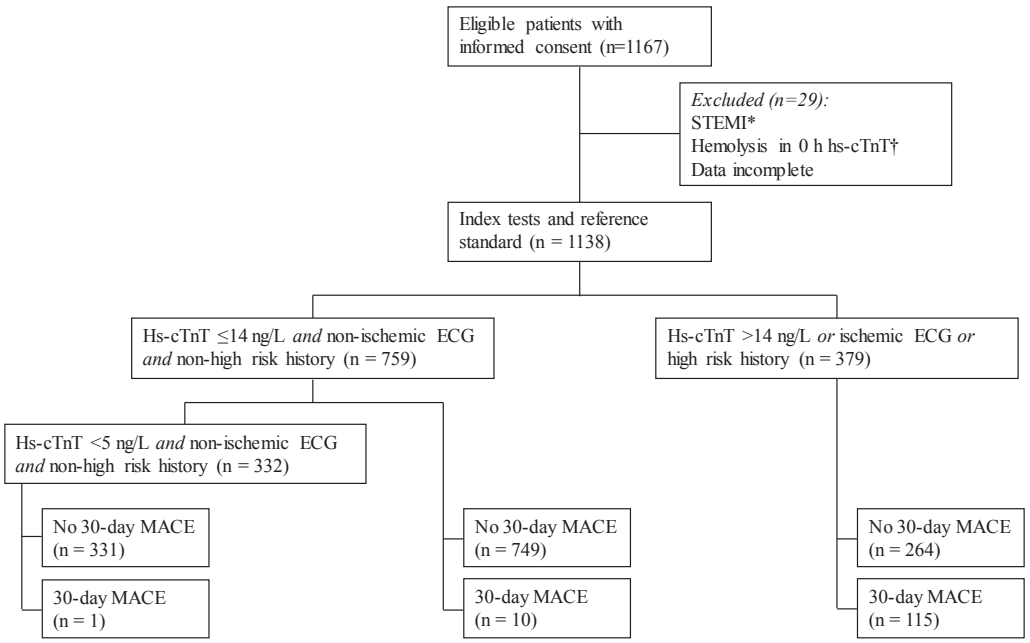

Figure 1. Flow diagram of patient inclusion and exclusion. *STEMI*, ST-segment elevation myocardial infarction; *MACE*, major adverse cardiac event. *Patients with STEMI at the index visit who were erroneously enrolled. †Only patients without an available replacement sample at 1 hour were excluded.

Table 1. Patient characteristics.*

Characteristics	All Patients (n=1,138)	30-Day MACE (n=125)	No MACE (n=1,013)
Age, y	63.2 (49.1–73.7)	70 (61.2–78.6)	62.3 (47.4–72.6)
Male sex	621 (54.6)	90 (72.0)	531 (52.4)
Arrival by ambulance	462 (40.6)	66 (52.8)	396 (39.1)
Referred by PCP	250 (22.0)	48 (38.4)	202 (19.9)
Medical history			
Diabetes	158 (13.9)	43 (34.4)	115 (11.4)
Hypertension	495 (43.5)	85 (68.0)	410 (40.5)
Hypercholesterolemia	259 (22.8)	46 (36.8)	213 (21.0)
Previous AMI	226 (19.9)	41 (32.8)	185 (18.3)
Previous revascularization	231 (20.3)	46 (36.8)	185 (18.3)
Stable angina	233 (20.5)	50 (40.0)	183 (18.1)
Previous stroke/TIA	102 (9.0)	19 (15.2)	83 (8.2)
Other risk factors			
Family history of CAD†	257 (22.6)	31 (24.8)	226 (22.3)
Current or past smoker	641 (56.3)	86 (68.8)	555 (54.8)
Previous medication			
Aspirin	325 (28.6)	65 (52.0)	260 (25.7)
β-Blocker	346 (30.4)	59 (47.2)	287 (28.3)
Nitrates	262 (23.0)	52 (41.6)	210 (20.7)
Statin	339 (29.8)	59 (47.2)	280 (27.6)
Clinical findings			
Systolic BP, mm Hg	145 (24)	152 (28)	144 (23)
Diastolic BP, mm Hg	85 (14)	85 (15)	84 (14)
Symptom onset to 0 h hs-cTnT, h‡			
≤3	344 (30.7)	48 (38.4)	296 (29.2)
>3	777 (68.3)	74 (59.2)	703 (69.3)
0-h hs-cTnT level, ng/L			
<5	343 (30.1)	4 (3.2)	339 (33.5)
5–14	496 (43.6)	28 (22.4)	468 (46.2)
>14	299 (26.3)	93 (74.4)	206 (20.3)
High-risk history	153 (13.4)	81 (64.8)	72 (7.1)
Acute ischemia on ECG	69 (6.1)	38 (30.4)	31 (3.1)
Physician experience			
Intern	407 (35.8)	34 (27.2)	373 (36.8)
Resident	487 (42.8)	65 (52.0)	422 (41.7)
Attending	244 (21.4)	26 (20.8)	218 (21.5)

PCP, Primary care physician; *AMI*, acute myocardial infarction; *TIA*, transient ischemic attack; *CAD*, coronary artery disease; *BP*, blood pressure.
*Values are mean (SD), median (interquartile range), or No. (%).
†Defined as close relative with AMI, angina, or cardiac death before aged 55 years.
‡n=1,121.

patients (7.6%). The number of subjects with each component of the major adverse cardiac events outcome is shown in Table 2. Of the 80 patients with an index visit acute myocardial infarction, 14 had a 0-hour hs-cTnT level measured less than or equal to 2 hours from symptom onset, of whom 3 had an initial hs-cTnT level between 5 and 14 ng/L. The final adjudicated diagnoses during the index visit are shown in Table E1 (available online at http://www.annemergmed.com).

Among patients assessed as having a nonischemic ECG result, 8.1% had a major adverse cardiac event within 30 days, and among those with both a nonhigh risk history and a nonischemic ECG result, 3.4% had a 30-day major adverse cardiac event. Patients assessed as having a nonhigh risk history were generally younger, were more often women, and less often had a history of previous acute myocardial infarction or cardiac risk factors (Table E2, available online at http://www.annemergmed.com). They also less often described their pain as similar to previous ischemia, radiating to the left or right arm, or worse with exertion but more often as pleuritic.

Main Results

With a criterion of hs-cTnT level less than 5 ng/L, 343 (30.1%) of all patients were identified for rule-out, and when a nonischemic ECG result and a nonhigh risk history were added, 332 (29.2%) were ruled out. Table 3 shows that hs-cTnT level less than 5 ng/L alone had a sensitivity of 96.8% (95% CI 92% to 99.1%), LR– of 0.10 (95% CI 0.04 to 0.25), and an NPV of 98.8%

Table 2. 30-Day outcomes.*

Outcomes	All Patients (n=1,138)	Hs-cTnT ≤14 ng/L and Negative ECG Result† and History‡ (n=759)	Hs-cTnT Level <5 ng/L and Negative ECG Result† and History‡ (n=332)
30-day MACE§	125 (11.0)	10 (1.3)	1 (0.3)
AMI during index visit	80 (7.0)	4 (0.5)	0
AMI during follow-up‖	4 (0.4)	0	0
Unstable angina	41 (3.6)	5 (0.7)	1 (0.3)
Cardiogenic shock	0	0	0
Cardiac arrest	1 (0.1)	1 (0.1)	0
Ventricular arrhythmia¶	0	0	0
High-grade AV block¶	1 (0.1)	0	0
Cardiac death	4 (0.4)	1 (0.1)	0
Death of unknown cause	0	0	0
30-day MACE without UA	87 (7.6)	5 (0.7)	0

UA, Unstable angina.
*Values are No. (%).
†Defined as ECG showing no signs of acute ischemia.
‡Defined as a history assessed as nonhigh risk.
§Patients could have more than 1 event.
‖No AMI during index visit.
¶Requiring intervention.

(95% CI 97% to 99.7%) for 30-day major adverse cardiac events, giving a post-test probability of 1.2% and missing 4 patients (2 acute myocardial infarction and 2 unstable angina). When supplemented with a nonischemic ECG result, the resulting sensitivity was 97.6% (95% CI 93.2% to 99.5%), the LR– 0.07 (95% CI 0.02 to 0.22), and the NPV 99.1% (95% CI 97.4% to 99.8%), missing 1 acute myocardial infarction and 2 unstable angina cases. When a nonhigh risk history was further added, it yielded a sensitivity of 99.2% (95% CI 95.6% to 100%), LR– of 0.02 (95% CI 0 to 0.17), and an NPV of 99.7% (95% CI 98.3% to 100%). Only a single case of unstable angina (described in Table E3, available online at http://www.annemergmed.com) was then missed. This combination had a high NPV across all subgroups (Figure E1, available online at http://www.annemergmed.com), except for among patients aged 65 years or older. Only 30 (5.8%) of the 521 patients aged 65 years or older were identified for rule-out by this strategy, and the NPV was only 96.7% (95% CI 82.8% to 99.9%), the sensitivity 98.8% (95% CI 93.5 to 100), and LR– 0.18 (95% CI 0.02 to 1.30).

Table 3 also shows that for the outcome 30-day major adverse cardiac events without unstable angina, hs-cTnT level less than 5 ng/L combined with ECG and history resulted in a sensitivity of 100% (95% CI 95.9% to 100%), LR– of 0 (95% CI 0 to 0.15), and NPV of 100% (95% CI 98.9% to 100%).

Eleven patients had an hs-cTnT level less than 5 ng/L, combined with a high pretest probability (acute ischemia on ECG and/or a high-risk history). Among these patients, 3 had a major adverse cardiac event (2 acute myocardial infarction and 1 unstable angina) within 30 days (NPV 72.7%), all at the index visit.

As shown in Table 4, hs-cTnT level was less than or equal to 14 ng/L at presentation in 839 patients (73.7%),

Table 3. Diagnostic accuracy of hs-cTnT level less than 5 ng/L at presentation in combination with ECG result and history.

	Sensitivity, % (95% CI)	Specificity, % (95% CI)	NPV, % (95% CI)	LR– (95% CI)
30-day MACE				
Hs-cTnT level <5 ng/L (n=343)	96.8 (92.0–99.1)	33.5 (30.6–36.5)	98.8 (97.0–99.7)	0.10 (0.04–0.25)
Hs-cTnT level <5 ng/L+negative ECG result* (n=340)	97.6 (93.2–99.5)	33.3 (30.4–36.3)	99.1 (97.4–99.8)	0.07 (0.02–0.22)
Hs-cTnT level <5 ng/L+negative ECG result* and history† (n=332)	99.2 (95.6–100)	32.7 (29.8–35.7)	99.7 (98.3–100)	0.02 (0.00–0.17)
30-day MACE without UA				
Hs-cTnT level <5 ng/L	97.7 (91.9–99.7)	32.5 (29.6–35.4)	99.4 (97.9–99.9)	0.07 (0.02–0.28)
Hs-cTnT level <5 ng/L+negative ECG result*	98.9 (93.8–100)	32.3 (29.4–35.2)	99.7 (98.4–100)	0.04 (0.01–0.25)
Hs-cTnT level <5 ng/L+negative ECG result* and history†	100 (95.9–100)	31.6 (28.8–34.5)	100 (98.9–100)	0 (0–0.15)

LR, Likelihood ratio.
*Defined as ECG showing no signs of acute ischemia.
†Defined as a history assessed as nonhigh risk.

Table 4. Diagnostic accuracy of hs-cTnT less than or equal to 14 ng/L at presentation in combination with ECG result and history.

	Sensitivity, % (95% CI)	Specificity, % (95% CI)	NPV, % (95% CI)	LR– (95% CI)
30-day MACE				
Hs-cTnT ≤14 ng/L (n=839)	74.4 (65.8–81.8)	79.7 (77.1–82.1)	96.2 (94.7–97.4)	0.32 (0.24–0.43)
Hs-cTnT ≤14 ng/L+negative ECG result* (n=811)	79.2 (71.0–85.9)	77.5 (74.8–80.0)	96.8 (95.3–97.9)	0.27 (0.19–0.38)
Hs-cTnT ≤14 ng/L+negative ECG result* and history† (n=759)	92.0 (85.8–96.1)	73.9 (71.1–76.6)	98.7 (97.6–99.4)	0.11 (0.06–0.20)
30-day MACE without UA				
Hs-cTnT ≤14 ng/L	86.2 (77.2–92.7)	78.7 (76.1–81.1)	98.6 (97.5–99.3)	0.18 (0.10–0.30)
Hs-cTnT ≤14 ng/L+negative ECG result*	89.7 (81.3–95.2)	76.3 (73.6–78.9)	98.9 (97.9–99.5)	0.14 (0.07–0.25)
Hs-cTnT ≤14 ng/L+negative ECG result* and history†	94.3 (87.1–98.1)	71.7 (68.9–74.5)	99.3 (98.5–99.8)	0.08 (0.03–0.19)

*Defined as ECG showing no signs of acute ischemia.
†Defined as a history assessed as nonhigh risk.

with a sensitivity of 74.4% (95% CI 65.8% to 81.8%), LR– of 0.32 (95% CI 0.24 to 0.43), and NPV of 96.2% (95% CI 94.7% to 97.4%) for 30-day major adverse cardiac events. When hs-cTnT level less than or equal to 14 ng/L, a nonischemic ECG result, and a nonhigh risk history were combined, 759 patients (66.7%) were identified for rule-out, with a sensitivity of 92% (95% CI 85.8% to 96.1%), LR– 0.11 (95% CI 0.06 to 0.20), and NPV 98.7% (95% CI 97.6% to 99.4%), missing 10 patients with 30-day major adverse cardiac events (described in Table E3, available online at http://www.annemergmed.com). In the subgroup analyses for this strategy (Figure E2, available online at http://www.annemergmed.com), the NPV was highest in patients with ongoing pain.

For the outcome 30-day major adverse cardiac events without unstable angina, hs-cTnT level less than or equal to 14 ng/L combined with a nonischemic ECG and a nonhigh risk history had a sensitivity of 94.3% (95% CI 87.1% to 98.1%), LR– of 0.08 (95% CI 0.03 to 0.19), and NPV of 99.3% (95% CI 98.5% to 99.8%).

The performance of the different diagnostic strategies in relation to our prespecified thresholds is depicted in Figure 2.

LIMITATIONS

We did not enroll patients during all hours of the day or during weekends, and this study was performed at a single university hospital. As previously shown,[22] there were, however, no important differences between included patients and patients seeking care outside of inclusion hours. Our acute myocardial infarction and unstable angina prevalence was also similar to that in previous studies with a continuous patient inclusion at our ED,[23,24] suggesting that there was no significant selection bias and that the

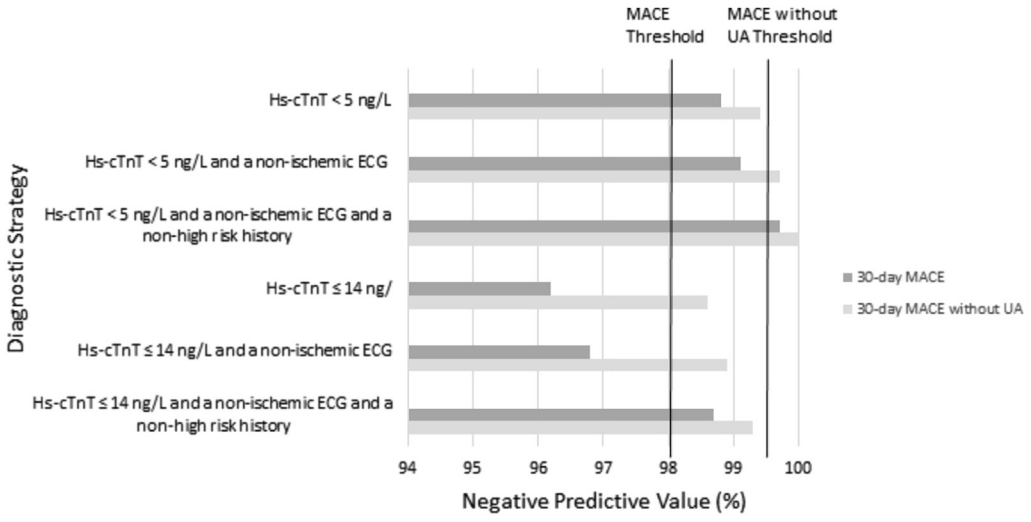

Figure 2. Performance of diagnostic strategies, using a presentation hs-cTnT level less than 5 or less than or equal to 14 ng/L, with and without a nonischemic ECG and a nonhigh-risk history. The negative predictive values for the different strategies are depicted for both the outcome of 30-day MACE (dark grey bars) and 30-day MACE without UA (light grey bars). Vertical lines represent the lowest acceptable negative predicitive value for the 2 outcomes.

present sample was representative of our entire ED chest pain population. Furthermore, our acute myocardial infarction prevalence was similar to that at several other centers,[7,9,13] and our acute coronary syndrome prevalence was similar to the reported average ED acute coronary syndrome rate.[25] We find it reasonable to believe that our results are applicable to other centers.

The findings in the present study should be validated in other settings before clinical implementation. However, because the lower bound of the 95% CI for the NPV of hs-cTnT level less than 5 ng/L combined with a nonischemic ECG result and a nonhigh risk history was 98.3% for 30-day major adverse cardiac events, it seems reasonable to assume that the true risk will be below the test threshold in settings with a similar acute coronary syndrome and major adverse cardiac event prevalence.

Patients with a missing assessment of the history or ECG were excluded. This might introduce a risk of selection bias, but because these cases were few, any such bias is likely to be of limited importance.

We used the Roche hs-cTnT assay, and our results do not necessarily apply to troponin I assays. However, single troponin rule-out strategies with high-sensitivity cardiac troponin I have also performed well,[26,27] and it seems reasonable to believe that combining high-sensitivity cardiac troponin I with clinical information will yield results similar to those obtained with hs-cTnT.

The adjudicators were not blinded to the 0-hour hs-cTnT level, which introduces a risk of incorporation bias. This is difficult to avoid because troponins are obligatory for the acute myocardial infarction diagnosis according to universal guidelines.[11] The acute myocardial infarction diagnoses in our study were, however, usually based on a significant hs-cTnT increase or decrease in a proper clinical context and on all clinical information within 60 days. The adjudicating cardiologists were also blinded to the study hypothesis, as well as the data form.

DISCUSSION

In this prospective observational study, we evaluated the diagnostic accuracy for major adverse cardiac events of a single hs-cTnT at ED presentation with and without the addition of ECG result and patient history.

Our main finding was that hs-cTnT level less than 5 ng/L at presentation in combination with a nonischemic ECG result and a nonhigh-risk history identified patients with a very low risk of major adverse cardiac events within 30 days, and almost no risk of major adverse cardiac events without unstable angina. These patients had a risk of acute coronary syndrome clearly below the test threshold and a risk of major adverse cardiac events without unstable angina below the threshold acceptable to most emergency physicians. To our knowledge, this is the first study to evaluate a strategy based on the combination of hs-cTnT level less than 5 ng/L, ECG result, and patient history, which we believe is representative of actual clinical practice. Two previous studies have shown that hs-cTnT level less than 5 ng/L by itself does not rule out acute coronary syndrome.[4,5] Our study, however, shows that if used in patients with a low pretest probability based on history and ECG result, it may indeed identify patients at a very low risk of acute coronary syndrome. This emphasizes the importance of interpreting hs-cTnT in conjunction with other clinical information, which was also evident from the large proportion of 30-day major adverse cardiac events among the patients with hs-cTnT level less than 5 ng/L and a high pretest probability.

The strategy of ruling out patients with an hs-cTnT level less than 5 ng/L combined with a nonhigh-risk history and a nonischemic ECG result could allow safe discharge of approximately 30% of ED chest pain patients after a single hs-cTnT test result at presentation. Because their risk of acute coronary syndrome was clearly below the test threshold, ruled-out patients will not need further evaluation for acute coronary syndrome, and additional investigations such as stress testing or admission for diagnostic assessment are more likely to be harmful than beneficial.[20,28]

Concerns have, however, been raised about the safety of rapid rule-out strategies in patients when troponin sampling is performed within 2 hours after symptom onset.[29,30] Even though the combined strategy using hs-cTnT level less than 5 ng/L performed well also in these patients, acute myocardial infarction patients who had an hs-cTnT measurement within 2 hours from symptom onset were few. Because of the possible risk of false-negative results for these patients,[30] we recommend serial hs-cTnT testing for very early presenters.

Most patients identified for rule-out were younger than 65 years. Previous studies have also shown that patients with hs-cTnT level less than 5 ng/L are commonly younger and have fewer cardiovascular comorbidities, which might in part explain their low risk.[1,2,4] For patients aged 65 years or older who were ruled out by our strategy, the risk of 30-day major adverse cardiac events was 3.3% and thereby above the test threshold. These patients were, however, few and the CI very wide, which is why these results should be interpreted with caution. Our results are nonetheless in line with the findings of Body et al,[31] who showed that 4.3% of patients aged 65 years or older and with an hs-cTnT level less than 5 ng/L and a nonischemic ECG result had a 30-day major adverse cardiac event.

An hs-cTnT level less than or equal to 14 ng/L at presentation, used in conjunction with both a nonischemic ECG result and a nonhigh-risk history, would have resulted in a higher miss rate than the strategy using hs-cTnT level less than 5 ng/L. Body et al[6] reported an NPV of 100% with this combination for ruling out acute myocardial infarction. The strategy did not perform as well in our study, and our results are more comparable to those of Freund et al,[32] who found a 1% risk of AMI in patients with hs-cTnT level less than or equal to 14 ng/L and a low to moderate pretest probability, according to clinical assessment and ECG result. The risk of 30-day major adverse cardiac events without unstable angina in the present study thus exceeded the 0.5% risk that most emergency physicians find acceptable.[21] This rule-out strategy might therefore not gain clinical acceptance in all settings, but because the risk tolerance varies between countries,[21] the miss rate might be considered acceptable by some. At many centers, a 0.7% risk for major adverse cardiac event without unstable angina for discharged patients might be lower than in the current routine care.[8,33]

There are several other validated diagnostic strategies for rule-out, such as the 1-hour algorithm,[10,34] accelerated diagnostic pathways using the Thrombolysis in Myocardial Infarction score[35] and the HEART Pathway.[36,37] These protocols, however, require serial troponin testing, and none have been shown to identify patients at a lower risk of 30-day major adverse cardiac events than hs-cTnT level less than 5 ng/L used in conjunction with history and ECG result. On the other hand, they will likely identify patients with a lower risk of major adverse cardiac events without unstable angina than the strategy with hs-cTnT level less than or equal to 14 ng/L.[10,35] For patients with a presentation hs-cTnT level of greater than or equal to 5 ng/L, we would therefore recommend a subsequent 1- to 3-hour hs-cTnT test, which would decrease the miss rate while allowing a rapid rule-out. This is also the approach recommended by the European Society of Cardiology.[38]

In summary, among ED chest pain patients, a single hs-cTnT level less than 5 ng/L at presentation in combination with a nonischemic ECG result and a nonhigh risk history identifies approximately 30% of patients at a very low risk of major adverse cardiac events within 30 days. These patients do not seem to need further assessment for acute coronary syndrome and are likely suited for immediate discharge. A similar strategy with hs-cTnT level less than or equal to 14 ng/L identified patients at a slightly higher risk of 30-day major adverse cardiac events, for whom we would recommend additional hs-cTnT testing. Our results should undergo prospective external validation before clinical implementation.

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Table E1. Final adjudicated diagnoses at index visit.

Final Diagnosis	Hs-cTnT Level ≤14 ng/L + Negative ECG Result* and History,† N = 759	Hs-cTnT Level <5 ng/L + Negative ECG Result* and History,† N = 332
AMI	4 (0.5)	0
UA	5 (0.7)	1 (0.3)
Non-ACS cardiovascular	63 (8.3)	15 (4.5)
Aortic dissection	0	0
Myocarditis	0	0
Pericarditis	7 (0.9)	5 (1.5)
Arrhythmia	33 (4.3)	10 (3.0)
Other cardiac‡	23 (3.0)	0
Noncardiac§	687 (90.5)	316 (95.2)
PE	5 (0.7)	3 (0.9)
Pneumothorax	3 (0.4)	1 (0.3)

ACS, Acute coronary syndrome; *PE*, pulmonary embolism.
Data are presented as No. (%).
*Defined as ECG showing no signs of acute ischemia.
†Defined as a history assessed as nonhigh risk.
‡Such as heart failure, aortic stenosis, or stable angina.
§Includes pulmonary, gastrointestinal, chest wall, psychiatric and unspecified causes of chest pain.

Table E2. Patient characteristics dependent on physician assessment of patient history.

Characteristics	High-Risk History (n = 153)	Nonhigh-Risk History (n = 985)
Age, y	69.6 (60.2–77.6)	62 (47.2–72.4)
Male sex	109 (71.2)	512 (52.0)
Medical history		
Diabetes	37 (24.2)	121 (12.3)
Hypertension	95 (62.1)	400 (40.6)
Hypercholesterolemia	60 (39.2)	199 (20.3)
Previous AMI	55 (35.9)	171 (17.4)
Previous revascularization	64 (41.8)	167 (17.0)
Stable angina	65 (42.5)	168 (17.1)
Previous stroke/TIA	16 (10.5)	86 (8.7)
Other risk factors		
Family history of CAD	42 (27.5)	215 (21.8)
Current or past smoker	106 (69.3)	535 (54.3)
Chest pain characteristics		
Radiation left arm*	71 (46.4)	309 (31.4)
Radiation right arm*	32 (20.9)	109 (11.1)
Radiation neck*	37 (24.2)	184 (18.7)
No pain radiation*	55 (35.9)	402 (40.8)
Described as pressure†	90 (58.8)	467 (47.4)
Relieved by nitrates†	60 (39.2)	129 (13.1)
Pleuritic†	27 (17.6)	325 (33.0)
Worse with exertion†	92 (60.1)	293 (29.7)
Similar to previous AMI or angina‡	63 (41.2)	158 (16.0)

Values are median (IQR) or No. (%).
*n=1,100.
†n=1,108.
‡n=1,099.

Table E3. Patients missed. All patients described were missed by the strategy of hs-cTnT less than or equal to 14 ng/L at presentation combined with a nonhigh-risk history and nonischemic ECG. The last patient was the only patient missed by the strategy of hs-cTnT level less than 5 ng/L at presentation combined with a nonhigh risk history and nonischemic ECG.

Age, Sex	Medical History	Details of Presentation	30-Day MACE
66 y, male	Stable angina, previous PCI and CABG	Described worsening of his usual angina with increased duration and intensity of chest pain episodes. Assessed by an attending physician. Hs-cTnT 9–9 ng/L. Discharged. Returned within 30 days with increasing symptoms and had a positive stress test result. Underwent PCI.	UA
79 y, male	AMI×2, previous CABG, previous smoker	Referred by primary care physician on suspicion of UA. Described worsening episodic chest pains since several weeks. Assessed by a resident. Hs-cTnT 13-13-13 ng/L. Underwent angiography and subsequent PCI.	UA
61 y, female	Hypertension, smoker	Described episodic chest pain not related to exertion. Assessed by an attending physician. Hs-cTnT 11-23-33-30 ng/L. Coronary angiography without significant stenoses.	AMI
45 y, female	No previous illnesses, previous smoker	Complained of chest pain radiating to shoulders and jaw. Assessed by a resident. Hs-cTnT 13-22-55-325 ng/L. Coronary angiography without significant stenoses.	AMI
78 y, male	Stable angina, hypertension, stroke	Chest pain with associated nausea. Assessed by a resident. Hs-cTnT 13-17-19 ng/L. Underwent PCI.	UA
69 y, male	Atrial fibrillation, Hypertension, PE	One-week duration of chest pain episodes during exertion, radiating to both arms. Assessed by a resident. Hs-cTnT 11-17-47-51 ng/L. Underwent PCI.	AMI
41 y, male	Ulcerous colitis	One-and-a-half weeks' duration of chest pain associated with coughing. Presented after episode of central chest pain radiating to left arm when walking flight of stairs. Assessed by an attending physician. Hs-cTnT 6-11-14 ng/L. Discharged with noncardiac diagnosis. Cardiac arrest at home 27 days later.	Cardiac arrest/cardiac death
48 y, male	GERD, previous smoker	Central chest pain radiating to left arm, worsened by breathing and body movements. Assessed by a resident. Hs-cTnT 14-18-28-55-123 ng/L. Underwent PCI.	AMI
78 y, male	AMI, hypertension, stroke	Episodic chest pain during last few days. Pain described as burning and lasting minutes to hours, not correlated to exertion. Assessed by a resident. Hs-cTnT 9-9-8-9 ng/L. Positive stress test result. Underwent PCI.	UA
72 y, female	Diabetes, hypertension, hypercholesterolemia, family history of CAD	Referred by primary care physician on suspicion of UA. Described episodic pressing chest pain radiating to her left arm and back, lasting minutes with concomitant diaphoresis. Assessed by an attending physician. Hs-cTnT <5–<5–<5–<5 ng/L. Coronary angiography showed a significant stenosis, and PCI was performed.	UA

PCI, Percutaneous coronary intervention; *CABG*, coronary artery bypass graft; *GERD*, gastroesophageal reflux disease.

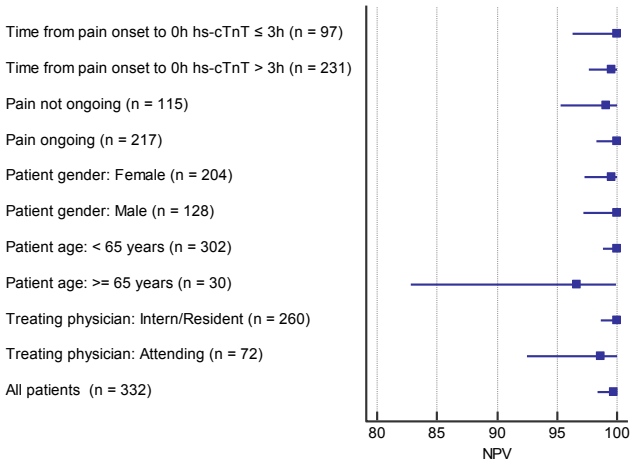

Figure E1. Differences in NPV for 30-day major adverse cardiac events between subgroups in patients with hs-cTnT level less than 5 ng/L and nonischemic ECG and nonhigh risk history.

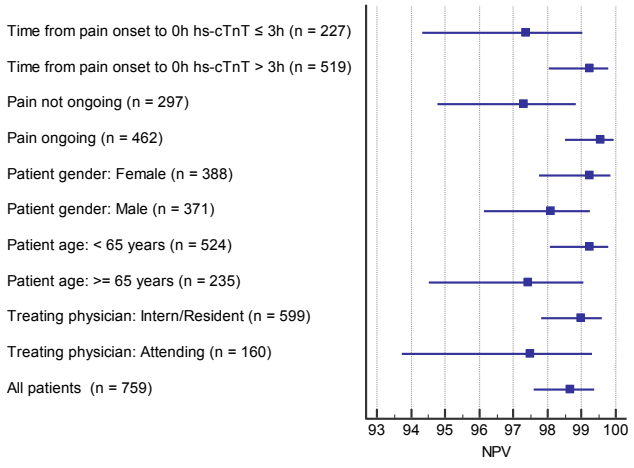

Figure E2. Differences in NPV for 30-day major adverse cardiac events between subgroups in patients with hs-cTnT less than or equal to 14 ng/L and nonischemic ECG and nonhigh risk history.