Circulation

ORIGINAL RESEARCH ARTICLE

Rapid Exclusion of Acute Myocardial Injury and Infarction With a Single High-Sensitivity Cardiac Troponin T in the Emergency Department: A Multicenter United States Evaluation

Yader Sandoval, MD; Bradley R. Lewis, MS; Ramila A. Mehta, MS; Olatunde Ola, MD, MPH; Jonathan D. Knott, MD; Laura De Michieli, MD; Ashok Akula, MD; Ronstan Lobo, MB, BCH, BAO; Eric H. Yang, MD; S. Michael Gharacholou, MD; Marshall Dworak, BS; Erika Crockford, DO; Nicholas Rastas, BS; Eric Grube, DO; Swetha Karturi, MD; Scott Wohlrab, MBA; David O. Hodge, MS; Tahir Tak, MD, PhD; Charles Cagin, DO; Rajiv Gulati, MD, PhD; Allan S. Jaffe, MD

BACKGROUND: There are good data to support using a single high-sensitivity cardiac troponin T (hs-cTnT) below the limit of detection of 5 ng/L to exclude acute myocardial infarction. Per the US Food and Drug Administration, hs-cTnT can only report to the limit of quantitation of 6 ng/L, a threshold for which there are limited data. Our goal was to determine whether a single hs-cTnT below the limit of quantitation of 6 ng/L is a safe strategy to identify patients at low risk for acute myocardial injury and infarction.

METHODS: The efficacy (proportion identified as low risk based on baseline hs-cTnT<6 ng/L) of identifying low-risk patients was examined in a multicenter (n=22 sites) US cohort study of emergency department patients undergoing at least 1 hs-cTnT (CV Data Mart Biomarker cohort). We then determined the performance of a single hs-cTnT<6 ng/L (biomarker alone) to exclude acute myocardial injury (subsequent hs-cTnT >99th percentile in those with an initial hs-cTnT<6 ng/L). The clinically intended rule-out strategy combining a nonischemic ECG with a baseline hs-cTnT<6 ng/L was subsequently tested in an adjudicated cohort in which the diagnostic performance for ruling out acute myocardial infarction and safety (myocardial infarction or death at 30 days) were evaluated.

RESULTS: A total of 85 610 patients were evaluated in the CV Data Mart Biomarker cohort, among which 24 646 (29%) had a baseline hs-cTnT<6 ng/L. Women were more likely than men to have hs-cTnT<6 ng/L (38% versus 20%, $P<0.0001$). Among 11 962 patients with baseline hs-cTnT<6 ng/L and serial measurements, only 1.2% developed acute myocardial injury, resulting in a negative predictive value of 98.8% (95% CI, 98.6–99.0) and sensitivity of 99.6% (95% CI, 99.5–99.6). In the adjudicated cohort, a nonischemic ECG with hs-cTnT<6 ng/L identified 33% of patients (610/1849) as low risk and resulted in a negative predictive value and sensitivity of 100% and a 30-day rate of 0.2% for myocardial infarction or death.

CONCLUSIONS: A single hs-cTnT below the limit of quantitation of 6 ng/L is a safe and rapid method to identify a substantial number of patients at very low risk for acute myocardial injury and infarction.

Key Words: myocardial infarction ■ myocardial ischemia ■ troponin T

Correspondence to: Yader Sandoval, MD, Department of Cardiovascular Diseases, Mayo Clinic, 200 1st Street SW, Rochester, MN 55415. Email yadersandoval@gmail.com

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.122.059235.

For Sources of Funding and Disclosures, see page 1717.

Circulation is available at www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- Data for excluding acute myocardial infarction with a single high-sensitivity cardiac troponin relies largely on the limit of detection. This threshold cannot be reported in the United States per the US Food and Drug Administration, where the lowest reportable concentration is the limit of quantitation.
- This is the largest study evaluating a single high-sensitivity cardiac troponin T below the limit of quantitation of 6 ng/L to identify patients at low risk for acute myocardial injury and infarction.
- Among 11 962 patients with high-sensitivity cardiac troponin T <6 ng/L and serial measurements, only 1.2% developed acute myocardial injury. In an adjudicated cohort, among those with a nonischemic ECG, only 0.2% had myocardial infarction or death at 30 days.

What Are the Clinical Implications?

- The latest American Heart Association/American College of Cardiology clinical practice guidelines recommend the use of a single high-sensitivity cardiac troponin below the limit of detection to exclude myocardial injury. This concentration threshold, however, is not available for clinical use in the United States.
- For high-sensitivity cardiac troponin T, this is a particular issue, because there are limited data about exclusion of myocardial injury and infarction on the basis of the limit of quantitation of 6 ng/L.
- The present study demonstrates that a single high-sensitivity cardiac troponin T below the limit of quantitation of 6 ng/L is a safe and rapid method to identify a substantial number of patients at very low risk for acute myocardial injury and infarction.

Nonstandard Abbreviations and Acronyms

ESC	European Society of Cardiology
FDA	Food and Drug Administration
Hs-cTn	high-sensitivity cardiac troponin
ICD	Internal Classification of Diseases
LoD	limit of detection
LoQ	limit of quantitation
NPV	negative predictive values

There are >6.5 million emergency department visits for symptoms that are suspicious for acute myocardial infarction yearly across the United States.[1] High-sensitivity cardiac troponin (hs-cTn) assays permit earlier evaluation of these patients.[2,3] Studies indicate that a single hs-cTn measurement with a concentration below the limit of detection (LoD), or for some assays at higher optimized concentrations, is safe to exclude acute myocardial infarction.[4–13] Since 2015, European Society of Cardiology (ESC) guidelines have endorsed algorithms that allow single-sample rule-out of acute myocardial infarction with class I recommendations when the initial hs-cTn is very low.[14,15] For high-sensitivity cardiac troponin T (hs-cTnT), these guidelines[14,15] recommend rule-out in those with a baseline hs-cTnT below the LoD of 5 ng/L. There are good data[4,6,11–13] from outside the United States supporting the approach. These include meta-analyses[4,6] and 2 randomized trials[11,12] using hs-cTnT. Most studies in this field have been designed to exclude acute myocardial infarction rather than myocardial injury. In the United States, however, the LoD cannot be reported for clinical use per the US Food and Drug Administration (FDA)[16,17] despite recent guidelines[1] from the American Heart Association/American College of Cardiology that support this approach to exclude myocardial injury with a class 2a recommendation (level of evidence B, nonrandomized) for patients with suspected acute coronary syndrome with symptom onset at least 3 hours before presentation.

In the United States, hs-cTn assays were FDA cleared for clinical use to report down to the limit of quantitation (LoQ) where imprecision is ≤20%,[16,17] which for high-sensitivity assays is a concentration threshold above the LoD. For hs-cTnT, this means that results can only be reported to hs-cTnT<6 ng/L.[17] Whether a single-sample rule-out approach using the LoQ is safe for clinical use is unclear.

A few small studies have evaluated hs-cTnT below the LoQ threshold of 6 ng/L. They often use investigational samples[18,19] or are secondary analyses from outside the United States.[20,21] Some of these studies have been inconclusive and lack an adequate gold-standard assay[18,19] for acute myocardial infarction diagnosis, including some data suggesting that a single hs-cTnT <6 ng/L may not be safe.[22] In the United States, hs-cTn testing is used more broadly[23,24] than in Europe, so European data from more selected chest pain populations[21] may not be as informative for US practice, and validation of the LoQ approach is needed. Concerns exist surrounding the analytic performance of hs-cTnT, especially below the LoQ.[25,26] Despite these uncertainties and a paucity of definitive data, some US centers have implemented this approach.[27–29] Thus, there is an urgent need for more data to inform whether the single-sample rule-out strategy using a hs-cTnT<6 ng/L is an efficient and safe strategy to identify patients at low risk for acute myocardial infarction.

To address this unmet need, we examined our multicenter US experience with hs-cTnT. Our goals were 2-fold. First, we examined the efficacy (proportion of patients identified as low risk) and safety of a single hs-cTnT<6 ng/L to identify low-risk patients on the basis of its ability to rule out acute myocardial injury in a large

multicenter biomarker cohort. Second, to evaluate the clinical use of this approach to identify patients at low risk for acute myocardial infarction, we examined the combined use of a nonischemic ECG with a hs-cTnT<6 ng/L in an adjudicated cohort to assess the diagnostic performance for index acute myocardial infarction and 30-day safety (myocardial infarction or death).

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

CV Data Mart Biomarker Cohort: Efficacy of a Single hs-cTnT<6 ng/L LoQ for Identifying Low-Risk Patients by Excluding Acute Myocardial Injury

The CV Data Mart Biomarker cohort is a multicenter, observational, biomarker study involving consecutive, adult patients who presented to one of the Mayo Clinic emergency departments (Rochester, Florida, and Arizona campuses or the 19 Mayo Clinic Health System emergency departments across Minnesota and Wisconsin) in whom at least 1 hs-cTnT measurement was obtained within 12 hours of presentation from the date of site-specific hs-cTnT implementation until December 8, 2020. It does not include electrocardiographic data. Eligible patients including their baseline characteristics and outcomes were identified using the Mayo Clinic CV Data Mart platform. The CV Data Mart is a collection of cardiology databases that facilitates analyses of existing data from the clinical systems. Patients without a required Minnesota Research Authorization form, those that did not present through the emergency department, those aged <18 years old, with ST-segment–elevation myocardial infarction, cardiac arrest, and pregnancy were excluded (Figure S1). In patients with multiple presentations, the earliest was used. The study was approved by the Institutional Review Board (ID 20-009951).

In the CV Data Mart Biomarker cohort, the efficacy of a single hs-cTnT<6 ng/L to identify low-risk patients was examined. Efficacy was defined as the proportion of patients with a baseline hs-cTnT<6 ng/L that qualified as low risk among the entire CV Data Biomarker cohort, and such proportions were examined across major sites, in patients with chest pain, and according to sex. The safety of a single hs-cTnT<6 ng/L to reliably identify these low-risk patients was evaluated by examining the frequency of acute myocardial injury[30] (defined as any subsequent hs-cTnT increase above the sex-specific 99th percentile during the initial 24 hours) among those with a baseline hs-cTnT<6 ng/L with serial measurements. Analyses were also performed using an overall 99th percentile threshold of 14 ng/L. Given that acute myocardial infarction diagnoses were not adjudicated in the large CV Data Mart Biomarker cohort, acute myocardial injury served as an objective measure because it is a central criterion necessary to make any acute myocardial infarction diagnosis.[30] Previous hs-cTnT and hs-cTnI studies have evaluated single-sample rule-out strategies using this approach.[31,32] Subgroup evaluations included analyses according to age, sex, chest pain, comorbidities, and site were performed. Given concerns[25,26] surrounding the analytic performance and imprecision of hs-cTnT at the LoQ, among patients with an initial hs-cTnT<6 ng/L with 0/2-hour serial measurements, we also examined whether the second sample concentration remained at <6 ng/L.

To further corroborate the safety of identifying low-risk patients, secondary analyses evaluated the proportion of index presentation deaths and acute myocardial infarction diagnoses on the basis of International Classification of Diseases, 10th Revision (ICD-10) among patients with baseline hs-cTnT<6 ng/L as have commonly been used in other rule-out studies.[22,33] Because ICD-10 codes have limitations,[34,35] they were not the primary focus of analyses addressing acute myocardial infarction, which are addressed in the adjudicated cohort. ICD-10 codes are summarized in Table S1.

Adjudicated Cohort: Diagnostic Performance and Safety for Ruling Out Acute Myocardial Infarction

The ACTION study (Mayo Southwest Wisconsin 5th Gen Troponin T Implementation) was used to evaluate the diagnostic performance and safety of ruling out acute myocardial infarction. The study was approved by the Institutional Review Board (ID 19-002668). The primary results and methods have been described.[36] This is a multicenter (n=2), retrospective, observational cohort study across the Southwest Mayo Clinic Health System that evaluated consecutive encounters of adult patients presenting to these emergency departments in whom at least 1 cTnT measurement was obtained. Data were abstracted and reviewed from the electronic health records by trained study staff following a standardized data collection process and entered in Research Electronic Data Capture. For the present study, analyses addressed unique patients on the basis of their first presentation during the hs-cTnT study period and excluded patients aged <18 years old, those without a 12-lead ECG, with ischemic ST-segment elevation on the presenting ECG, or in whom hs-cTnT was not measured within 12 hours of emergency department presentation (Figure S1). All cases with at least 1 hs-cTnT above the sex-specific 99th percentile upper-reference limit were adjudicated using the Fourth Universal Definition of Myocardial Infarction[30] criteria by trained physicians. Details regarding the adjudication are included in the Supplemental Material.

This adjudicated cohort permitted the evaluation of the intended clinical rule-out pathway that combines a nonischemic ECG with a baseline hs-cTnT<6 ng/L and allowed analyses that examined diagnostic performance and safety for ruling out acute myocardial infarction, including subgroup analyses according to sex, chest discomfort, early presenters (<3 hours), electrocardiographic findings, and risk strata based on History, Electrocardiography, Age, Risk Factors (HEAR) scores.[37] Given the robust follow-up (median follow-up of 23.3 months available in 1866 patients), it also allowed 30-day safety outcomes analyses on the basis of a composite of myocardial infarction or death, and 2-year outcomes, as well. Following guidance from the 2018 American College of Emergency Physicians clinical policy[38] and other survey[39] analyses on acceptable missed rates, we established that patients identified to be low risk on the basis of their nonischemic ECG and baseline hs-cTnT<6 ng/L should have

no more than 1% to 2% adverse event rates during 30-day follow-up to consider the rule-out pathway acceptable.

Hs-cTnT Assay

hs-cTnT was measured by using the Elecsys Troponin T Gen 5 STAT assay (Roche Diagnostics). Per FDA clearance,[17] concentrations are reported down to the LoQ of <6 ng/L. For results <6 ng/L, the laboratory inputs a concentration of 5 ng/L for delta calculations. Sex-specific 99th percentile upper-reference limits of 10 ng/L for women and 15 ng/L for men are used.[17,40–43] Results are reported as whole units (no decimals) in ng/L. The 0/2-hour hs-cTnT protocol for the evaluation of patients with suspected acute myocardial infarction has been described[17,36,43] and is summarized in Figure S2. Except for patients with symptom onset >6 hours in whom myocardial injury is considered ruled out if the initial hs-cTnT is below the sex-specific 99th percentile, a single-sample rule-out strategy was not recommended by institutional protocols.

Statistical Analysis

Continuous variables are presented as means (standard deviations) or medians (interquartile range). Between-group comparisons were performed using the Kruskal-Wallis test. Discrete variables are summarized as frequency (percentage) and between-groups comparisons were analyzed with the χ^2 test. Negative predictive values (NPVs) and sensitivities with corresponding 95% CIs were calculated using exact binomial methods.[44] Diagnostic performance for acute myocardial infarction and 30-day safety were determined in the adjudicated cohort. False omission rates defined as false negatives among those with a negative test result (ie, baseline hs-cTnT<6 ng/L) are considered missed events. Forest plots evaluated NPVs across subgroups. Kaplan-Meier curves compared hs-cTnT groups. The time to event was defined as the arrival date of the index hospitalization to the time of first event. Long-term event rates were calculated using Kaplan-Meier methods. Analyses were conducted using SAS version 9.4 and R version 4.0.3.

RESULTS

CV Data Mart Biomarker Cohort: Efficacy of a Single hs-cTnT<6 ng/L LoQ for Identifying Low-Risk Patients by Excluding Acute Myocardial Injury

A total of 85 610 patients were included in the CV Data Mart Biomarker cohort. Baseline characteristics are shown in Table 1 and Tables S2 through S4. The mean age was 63 (18) years and women represented 50% of the cohort. A total of 24 646 (29%) patients had baseline hs-cTnT<6 ng/L. Similar proportions of patients with baseline hs-cTnT<6 ng/L were observed across major sites (range, 28%–30%; Figure 1). Among the 24 646 patients with a baseline hs-cTnT<6 ng/L, 49 (0.2%) acute myocardial infarction diagnoses based on ICD-10 codes and 19 (0.1%) deaths occurred during the index presentation. Among 27 198 patients with chest pain, a total of 11 725 (43%) had baseline hs-cTnT<6 ng/L. Similar proportions were observed across sites (range, 41%–44%; Figure 1). In 11 725 patients with chest pain and a baseline hs-cTnT<6 ng/L, 24 (0.2%) acute myocardial infarction diagnoses based on ICD-10 codes and 3 (0.03%) deaths were identified during the index presentation.

Baseline characteristics according to baseline hs-cTnT (Table 1) demonstrated that patients with an initial hs-cTnT<6 ng/L were younger, more often women, and less likely to have comorbidities compared with those with quantifiable hs-cTnT and those with increased concentrations above the sex-specific 99th percentile. Sex-specific analyses demonstrated that women were more likely than men to have baseline hs-cTnT<6 ng/L (38% versus 20%, $P<0.0001$). Compared with men with hs-cTnT<6 ng/L, except for previous myocardial infarction and coronary artery disease that were more frequent in men, women with hs-cTnT<6 ng/L were older and more likely to have comorbidities (Table S4).

Baseline hs-cTnT<6 ng/L With Serial Measurements for Acute Myocardial Injury Exclusion

The ability of identifying low-risk patients by excluding acute myocardial injury was evaluated among 11 962 patients with a baseline hs-cTnT<6 ng/L with serial measurements (Table 2). Patients with baseline hs-cTnT<6 ng/L and serial measurements were older and had more comorbidities than those without serial measurements (Table S3). Among these patients, the 2-hour hs-cTnT remained at <6 ng/L in 85% of cases, whereas 2-hour hs-cTnT concentrations where within the reference range in 14% of cases. Patients with quantifiable 2-hour hs-cTnT concentrations within the reference range were older and had more comorbidities than those with 2-hour hs-cTnT<6 ng/L (Table S5).

Acute myocardial injury (any subsequent hs-cTnT increase above the sex-specific 99th percentile during the initial 24 hours) occurred in 146 (1.2%) of the 11 962 patients with a baseline hs-cTnT<6 ng/L, which resulted in a NPV of 98.8% (95% CI, 98.6–99.0) and sensitivity of 99.6% (95% CI, 99.5–99.6; Table 2 and Table S6). Similar findings were observed among patients with chest pain. Among patients that developed acute myocardial injury, maximum hs-cTnT concentrations were 20 (14–43) ng/L. Adjudication of the 146 false-negative cases (117 were women and 29 men) that developed acute myocardial injury demonstrated that most diagnoses (111, 76%) were attributable to isolated nonischemic acute myocardial injury, with the remaining 35 cases (25 women and 10 men) classified as acute myocardial infarction; most (20/35) were type 2 myocardial infarctions, and 15 cases were adjudicated as type 1 myocardial infarction.

Table 1. Baseline Characteristics for the CV Data Mart Biomarker Cohort and According to Baseline High-Sensitivity Cardiac Troponin T Concentrations

Characteristics	Total (n=85 610)	<LoQ (n=24 646)	LoQ-99th percentile (n=25 200)	>99th percentile (n=35 764)
Age, mean (SD)	63 (18)	47 (15)	63 (15)	74 (14)
Women, n (%)	43 043 (50)	16 143 (66)	9281 (37)	17 619 (49)
Chest pain, n (%)	27 198 (32)	11 725 (48)	8281 (33)	7192 (20)
Coronary artery disease, n (%)	23 636 (28)	1891 (7.7)	6361 (25)	15 384 (43)
Previous myocardial infarction, n (%)	9114 (11)	665 (2.7)	2257 (9.0)	6192 (17)
Hypertension, n (%)	48 717 (57)	7088 (29)	14 230 (57)	27 399 (77)
Diabetes, n (%)	30 213 (35)	4604 (19)	8385 (33)	17 224 (48)
Chronic kidney disease, n (%)	17 070 (20)	693 (2.8)	2939 (12)	13 438 (38)
Dialysis, n (%)	1459 (1.7)	26 (0.1)	112 (0.4)	1321 (3.7)
Peripheral vascular disease, n (%)	21 394 (25)	1483 (6)	5050 (20)	14 861 (42)
Heart failure, n (%)	14 986 (18)	625 (2.5)	2589 (10)	11 772 (33)
Atrial fibrillation, n (%)	15 298 (18)	851 (3.5)	3406 (14)	11 041 (31)
Liver cirrhosis, n (%)	10 547 (12)	2152 (8.7)	3296 (13)	5099 (14)
Index presentation death, n (%)	775 (0.9)	19 (0.1)	57 (0.2)	699 (2.0)

LoQ indicates limit of quantitation.

In men, acute myocardial injury occurred in 0.7% (29/4264) of those with a baseline hs-cTnT<6 ng/L with serial measurements, with a corresponding NPV of 99.3% (95% CI, 99.0–99.6) and sensitivity of 99.8% (95% CI, 99.8–99.9). Among men that developed acute myocardial injury, maximum hs-cTnT concentrations were 40 (21–71) ng/L. Similar findings were observed among men with chest pain. Subgroup analyses in men demonstrated no heterogeneity across NPVs (Figure S3).

In women, acute myocardial injury occurred in 1.5% (117/7698) of those with a baseline hs-cTnT<6 ng/L with serial measurements, with a corresponding NPV of 98.5% (95% CI, 98.2–98.7) and sensitivity of 99.3% (95% CI, 99.1–99.4). Among women that developed acute myocardial injury, maximum hs-cTnT concentrations were 16 (13–33) ng/L. Similar findings were observed among women with chest pain. Subgroup analyses in women demonstrated lower NPVs, primarily among older adults and those with coronary artery disease (Figure S4).

Analyses using an overall 99th percentile of 14 ng/L upper-reference limit to define myocardial injury showed that, among those with a baseline hs-cTnT<6 ng/L, acute myocardial injury occurred in 0.9%, with a NPV of 99.1% (95% CI, 99.0–99.3) and sensitivity of 99.6% (95% CI, 99.6–99.7). In men, acute myocardial injury occurred in 0.8%, with a NPV of 99.2% (95% CI, 98.9–99.5) and sensitivity of 99.8% (95% CI, 99.7–99.9) and no heterogeneity was observed among subgroups (Figure S5). In women, acute myocardial injury occurred in 0.9%, with a NPV of 99.1% (95% CI, 98.9–99.3) and sensitivity of 99.4% (95% CI, 99.3–99.6). Lower NPVs were again observed among the older adults and those with coronary artery disease (Figure S6).

Adjudicated Cohort: Diagnostic Performance and Safety for Ruling Out Acute Myocardial Infarction

A total of 1979 emergency department patients who met inclusion criteria were evaluated. Baseline characteristics are presented in Tables S7 through S9. The incidence of acute myocardial infarction (including both type 1 and 2 myocardial infarctions) was 7.1% (n=141). Overall, 624 (32%) patients had a baseline hs-cTnT<6 ng/L. With the use of a single baseline hs-cTnT<6 ng/L in isolation (biomarker alone), the NPV and sensitivity for acute myocardial infarction were 99.8% (95% CI, 99.1–100) and 99.3% (95% CI, 96.1–100), respectively (Table 3 and Table S10). At 30 days after discharge, including index events, 0.3% (2/624) had an event. False negatives are summarized in Table S11. Sex-specific analyses showed similar diagnostic and safety performance. Subgroup analyses demonstrated no differences in rule-out performance (Figure S7).

Among those with a nonischemic ECG (n=1849), 610 (33%) patients had a baseline hs-cTnT<6 ng/L. In this group, the NPV and sensitivity for acute myocardial infarction were 100%, and there were no missed diagnoses of acute myocardial infarction during the index hospitalization (Table 3). At 30 days after discharge, including index events, 0.2% (1/610) had an event. In early presenters (symptom onset <3 hours) with a baseline hs-cTnT<6 ng/L and a nonischemic ECG (145/420, 35%), NPV and sensitivity were 100% with no missed diagnoses at index presentation or during 30-day follow-up (Table S12). Sensitivity analyses in those with chest pain showed similar results (Table S13). At 1 and 2 years, myocardial infarction or death occurred in 2.1% and

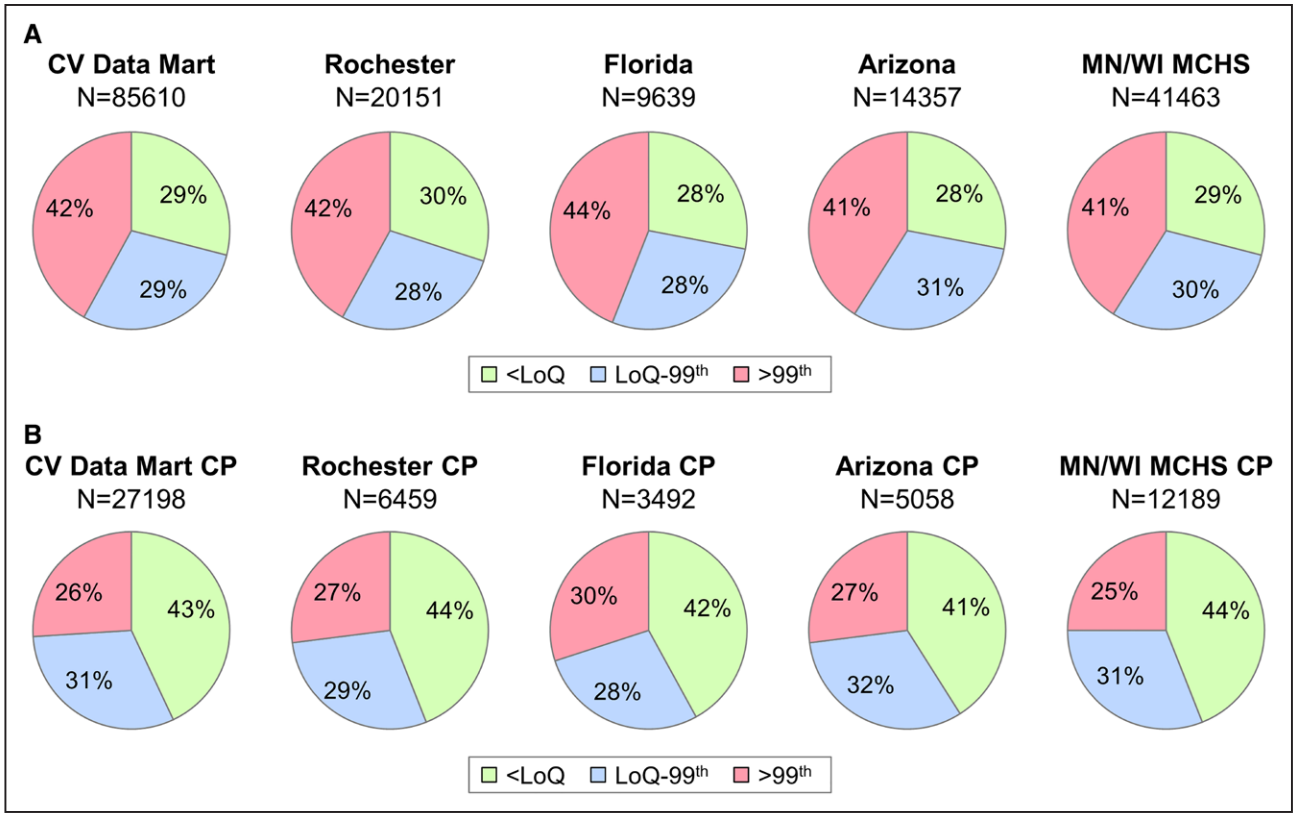

Figure 1. Proportion of patients with baseline high-sensitivity cardiac troponin T<6 ng/L across the CV Data Mart Biomarker overall cohort (A) and in those with chest pain (B) for the entire population and per site.
CP indicates chest pain; LoQ, limit of quantitation; MCHS, Mayo Clinic Health System; MN, Minnesota; and WI, Wisconsin.

2.6% of patients with baseline hs-cTnT<6 ng/L (Figure S8), and 2.0% and 2.3% in those with a baseline hs-cTnT<6 ng/L and a nonischemic ECG (Figure 2).

Among the 624 patients with a baseline hs-cTnT<6 ng/L, 206 (33%) had serial hs-cTnT measurements. In those with a 2-hour serial measurement, concentrations remained <6 ng/L in 84% (173/206). Within 24 hours of the initial baseline hs-cTnT<6 ng/L, 2 patients (0.97%) developed acute myocardial injury. Among patients with baseline hs-cTnT<6 ng/L, there were no differences in myocardial infarction or death between those with 2-hour hs-cTnT that remained <6 ng/L in comparison

Table 2. Diagnostic Performance of a Single Baseline hs-cTnT Below the LoQ of 6 ng/L for Acute Myocardial Injury (Defined as Any hs-cTnT Increase Above the Sex-Specific 99th Percentiles Within 24 Hours of Presentation) in Patients With a Baseline hs-cTnT<6 ng/L With Serial Measurements in the CV Data Mart Biomarker Cohort

	Baseline hs-cTnT<6 ng/L (LoQ) with serial hs-cTnT measurements					
	All-comers			Chest pain subgroup		
CV Data Mart Biomarker Cohort	All	Men	Women	All	Men	Women
Patients with baseline hs-cTnT<6 ng/L (LoQ) and serial measurements, n (%)	11 962	4264	7698	5840	2219	3621
Patients with baseline hs-cTnT<6 ng/L with 2-h hs-cTnT<6 ng/L (LoQ), n (%)	10 184 (85)	3469 (81)	6715 (87)	5085 (87)	1865 (84)	3220 (89)
Negative predictive value of hs-cTnT<6 ng/L for acute myocardial injury (hs-cTnT>99th percentile), % (95% CI)	98.8 (98.6–99.0)	99.3 (99.0–99.6)	98.5 (98.2–98.7)	98.9 (98.6–99.1)	99.4 (99.0–99.7)	98.6 (98.1–98.9)
Sensitivity of hs-cTnT<6 ng/L for acute myocardial injury (hs-cTnT>99th percentile), % (95% CI)	99.6 (99.5–99.6)	99.8 (99.8–99.9)	99.3 (99.1–99.4)	99.0 (98.8–99.2)	99.6 (99.4–99.8)	98.4 (97.9–98.8)
Acute myocardial injury (hs-cTnT >99th percentile) among patients with a baseline hs-cTnT<6 ng/L (LoQ), %	1.2% (146/11 962)	0.7% (29/4264)	1.5% (117/7698)	1.1% (65/5840)	0.6% (13/2219)	1.4% (52/3621)
Maximum hs-cTnT concentrations in those with acute myocardial injury (ng/L), median (Q1–Q3)	20 (14–43)	40 (21–71)	16 (13–33)	25 (14–48)	40 (24–70)	21 (14–47)

hs-cTnT indicates high-sensitivity cardiac troponin T; and LoQ, limit of quantitation.

Table 3. Diagnostic Performance, Efficacy, and Safety of a Single Baseline hs-cTnT Below the LoQ of 6 ng/L for Index Acute Myocardial Infarction Rule-out in Patients in the Adjudicated Cohort

	Total cohort			Total cohort with nonischemic ECG		
Adjudicated cohort	Total	Men	Women	Total	Men	Women
Population and incidence of acute myocardial infarction						
Total patients, n	1979	949	1030	1849	895	954
Incidence of myocardial infarction, n (%)	141 (7.1)	70 (7.4)	71 (6.9)	95 (5.0)	51 (5.7)	44 (4.6)
Efficacy: number (percentage) of patients identified as low risk						
Patients with baseline hs-cTnT <LoQ (efficacy), n (%)	624 (32)	214 (23)	410 (40)	610 (33)	210 (23)	400 (42)
Diagnostic performance of baseline hs-cTnT<LoQ for ruling out index presentation acute myocardial infarction						
Negative predictive value, % (95% CI)	99.8 (99.1–100)	100 (98.3–100)	99.8 (98.7–100)	100 (99.4–100)	100 (98.3–100)	100 (99.1–100)
Sensitivity, % (95% CI)	99.3 (96.1–100)	100 (94.9–100)	98.6 (92.4–100)	100 (96.2–100)	100 (93.0–100)	100 (92.0–100)
Negative likelihood ratio (95% CI)	0.02 (0.00–0.15)	0	0.03 (0.00–0.23)	0	0	0
Missed myocardial infarction rate among those with a negative test	0.2% (1/624)	0% (0/214)	0.2% (1/410)	0% (0/610)	0% (0/210)	0% (0/400)
Safety of baseline hs-cTnT<LoQ based on acute myocardial infarction or death within 30 days						
Negative predictive value, % (95% CI)	99.7 (98.9–100)	100 (98.3–100)	99.5 (98.3–99.9)	99.8 (99.1–100)	100 (98.3–100)	99.8 (98.6–100)
Sensitivity, % (95% CI)	99.0 (96.4–99.9)	100 (96.3–100)	98.0 (92.8–99.8)	99.3 (96.2–100)	100 (95.2–100)	98.6 (92.3–100)
Negative likelihood ratio (95% CI)	0.03 (0.01–0.12)	0	0.05 (0.01–0.18)	0.02 (0.00–0.14)	0	0.03 (0.00–0.22)
Missed acute myocardial infarction or death within 30 days among those with a negative test	0.3% (2/624)	0% (0/214)	0.5% (2/410)	0.2% (1/610)	0% (0/210)	0.3% (1/400)

hs-cTnT indicates high-sensitivity cardiac troponin T; and LoQ, limit of quantitation.

with those with 2-hour hs-cTnT>6 ng/L but below the sex-specific 99th percentile (Figure S9).

DISCUSSION

This multicenter study is the largest to evaluate the role of a single hs-cTnT below the LoQ of 6 ng/L to identify patients at very low risk for acute myocardial injury and infarction. Although extensive data support single-sample rule-out when hs-cTnT concentrations are below the LoD of 5 ng/L, this concentration threshold is not available for clinical use in the United States, and limited data exist for the LoQ, which is the lowest reportable concentration for hs-cTnT per the FDA.[17] Our data therefore provide important and timely information to US clinicians because they demonstrate that a single hs-cTnT below the LoQ of 6 ng/L is a safe method to rapidly triage and identify patients at very low risk for acute myocardial injury and infarction.

This approach identifies a substantial number of low-risk patients that may be eligible for early discharge, which likely would be associated with important reductions in length of stay, emergency department overcrowding, and costs. Our study demonstrates that the proportions of patients identified as low risk on the basis of hs-cTnT below the LoQ of 6 ng/L were similar across sites, which underscores the generalizable benefits of this approach. In all-comers, our study showed that 28% to 30% of patients can be rapidly identified as low risk with the use of a single hs-cTnT measurement. It is critical to note that the efficacy of this approach is augmented when applied to patients with chest discomfort, with 41% to 44% of such patients identified as low risk across sites.

The safety of a single hs-cTnT<6 ng/L to identify low-risk patients was comprehensively examined in multiple ways. In the large CV Data Mart Biomarker cohort, we evaluated the ability of a baseline hs-cTnT<6 ng/L to reliably identify low-risk patients. First, on the basis of analyses performed in 11 962 patients with a baseline hs-cTnT<6 ng/L and serial measurements, we demonstrated that acute myocardial injury is unlikely to occur when the initial hs-cTnT<6 ng/L, with only 1.2% of patients identified to have increases in hs-cTnT above the sex-specific 99th percentiles. This is a robust and objective metric because it is the central criterion for the diagnosis of acute myocardial infarction.[30–32] Second, in this same subset of patients, we demonstrated that the subsequent 2-hour hs-cTnT measurement remained <6 ng/L in 85% of cases. These findings confirm that these results are reliable for clinical decision-making and attenuate concerns about analytic performance.[25,26] Third, secondary

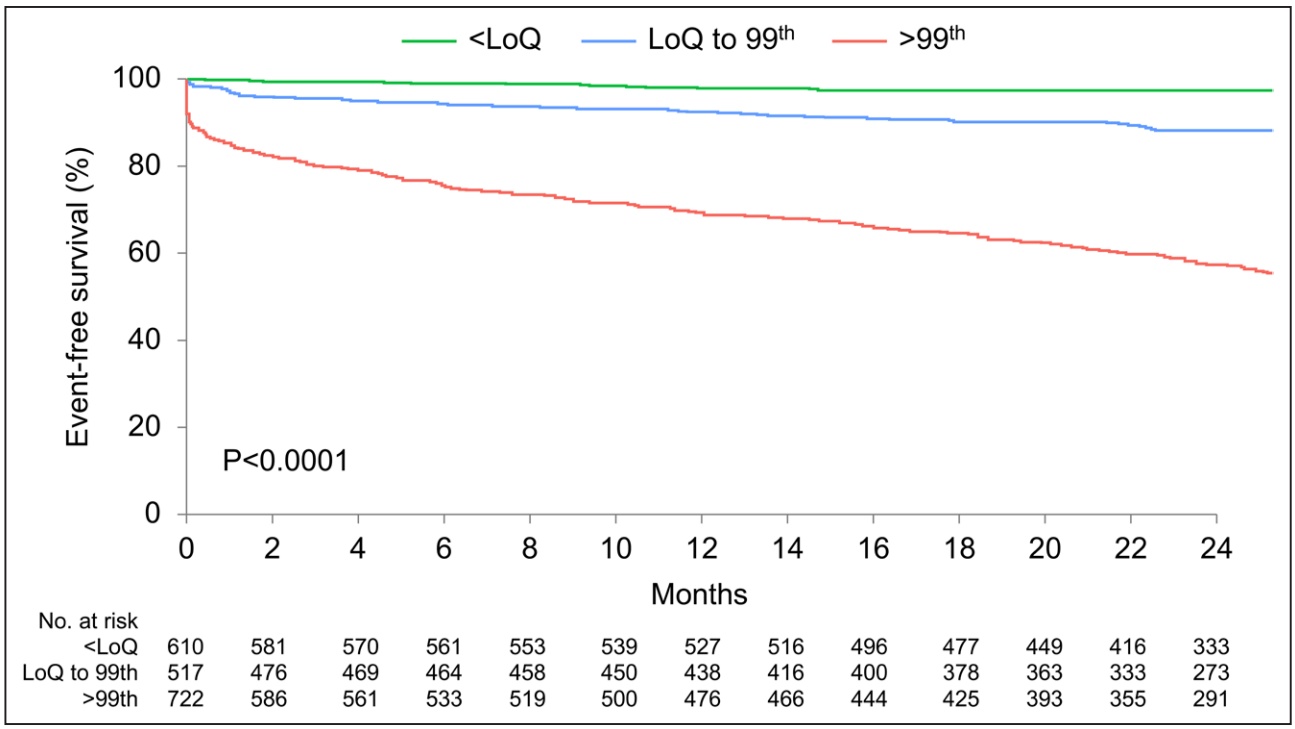

Figure 2. Kaplan-Meier curves for survival free of myocardial infarction or death according to baseline high-sensitivity cardiac troponin T groups in patients with a nonischemic ECG from the adjudicated cohort.
LoQ indicates limit of quantitation.

analyses addressing the entire CV Data Biomarker cohort involving 24 646 patients with a baseline hs-cTnT<6 ng/L further corroborated the safety of this approach, with only 0.2% acute myocardial infarction diagnoses based on ICD-10 codes and only 0.1% deaths occurring in such patients during the index presentation. Although ICD-10 codes have recognized limitations,[34,35] they provided another complementary layer of safety because they allowed us to evaluate whether any acute myocardial infarction diagnoses were coded among patients with a baseline hs-cTnT<6 ng/L. Last, and most importantly, we validated the safety of this approach in an adjudicated cohort where the combination of nonischemic ECG with a baseline hs-cTnT<6 ng/L resulted in a NPV of 99.8% and sensitivity of 99.3% for acute myocardial infarction or death at 30 days (including index events). These data support the observations from the CV Data Mart using ICD-10 codes. Patients with a nonischemic ECG and a baseline hs-cTnT<6 ng/L had favorable short- and long-term outcomes, with only ≈2% having myocardial infarction or death at 1 and 2 years, which further corroborates the safety of this approach. These findings underscore how a nonischemic ECG with a baseline hs-cTnT<6 ng/L allows the reliable identification of very low-risk patients in whom, in most circumstances, hospital admission or observation is often unwarranted for ischemic evaluation purposes, and in whom additional testing during the index presentation can be avoided or, if clinically needed, deferred to the outpatient setting.

Our data complement the extensive data on the safety of a single hs-cTnT below the 5 ng/L LoD. There are randomized data[11,12] using the LoD of hs-cTnT<5 ng/L which demonstrate that this approach is safe. The RAPID-TNT trial[12] (Rapid Assessment of Possible ACS in the Emergency Department with High-Sensitivity Troponin T) was a prospective, randomized, noninferiority evaluation of the ESC 0/1-hour protocol that involved rule-out when baseline hs-cTnT was <5 ng/L at >3 hours after the onset of symptoms. The trial demonstrated noninferiority compared with standard care, with a NPV for the 0/1-hour hs-cTnT protocol for 30-day death or myocardial infarction of 99.6%.[12] The LoDED trial[11] (Limit of Detection and ECG Discharge) enrolled patients with chest pain across 8 UK hospitals with a nonischemic ECG; no patient with an undetectable hs-cTnT had a major adverse event within 30 days.[11] There are also large meta-analyses[4,6] documenting that this approach is safe. In a collaborative meta-analysis of 9241 patients, Pickering et al[4] demonstrated that low-risk patients defined as those with a nonischemic ECG and a hs-cTnT<5 ng/L had a pooled sensitivity of 98.7% for acute myocardial infarction and 98.0% for 30-day major adverse cardiac events and no low-risk patients died. In another recent international collaborative meta-analysis,[6] both the ESC 0/1-hour and 0/2-hour hs-cTnT

protocols incorporating single-sample rule-out using hs-cTnT<5 ng/L were evaluated. The ESC 0/1-hour protocol was evaluated in 13 899 patients across 12 cohorts and demonstrated a sensitivity of 99.2% and NPV of 99.8%.[6] The ESC 0/2-hour protocol was evaluated in 2488 patients across 5 cohorts and demonstrated a sensitivity of 99.0% and NPV of 99.5%.[6] Implementation data[13] from Scotland also confirm safety with cardiovascular death occurring in only 0.1% at both 30 days and 1 year in those with hs-cTnT<5 ng/L in the intervention group. Our data complement the vast experience on the LoD of hs-cTnT<5 ng/L and demonstrate that the LoQ of hs-cTnT<6 ng/L is also safe.

Limited data exist for hs-cTnT below the LoQ of 6 ng/L as used across the United states. Small studies often using investigational samples[18,19] or performed outside the United States[20,21] have probed the performance of hs-cTnT<6 ng/L, but no robust data exist. Allen et al[19] evaluated initial hs-cTnT measurements in 1462 participants in a prospective multicenter observational cohort in which treating clinicians were blinded to the investigational hs-cTnT results and patient care and adjudications were based on local contemporary cTn results, which is a less sensitive gold standard biomarker for the detection of myocardial injury and diagnosis of myocardial infarction than the hs-cTnT assay used in our study. This has been a common limitation in US studies probing this approach with hs-cTnT.[18,19] Many either use a less sensitive assay for adjudication or higher 99th percentile upper-reference limits than we used. Like our findings, Allen et al[19] demonstrated that 32% of patients had a baseline hs-cTnT<6 ng/L and a nonischemic ECG, with a NPV of 99.1% and 98.9%, respectively, for index myocardial infarction and 30-day cardiac death and myocardial infarction. They demonstrated that the approach associated with the highest NPV required the combination of hs-cTnT<6 ng/L with a low HEAR score.[19] Our adjudicated cohort analyses showed an excellent performance for acute myocardial infarction rule-out using a baseline hs-cTnT<6 ng/L in combination with a nonischemic ECG. Subgroup analyses demonstrated no heterogeneity among risk strata using the HEAR score, for which reason our data do not support the addition of risk scores for ruling out acute myocardial infarction.

Several sex-specific findings warrant discussion. First, there is a significant difference between the proportion of men and women with baseline hs-cTnT concentrations below the LoQ, with women almost twice as likely to have hs-cTnT<6 ng/L as men. These differences may be explained in part by the analytic sensitivity of hs-cTnT, because several normality studies have shown that women are less likely to have detectable hs-cTnT concentrations than men.[42,45] Second, sex-specific analyses addressing the exclusion of acute myocardial injury showed no heterogeneity in the rule-out performance among subgroups in men. In women, however, subgroup analyses demonstrated lower NPVs, in particular, in older adults and those with coronary artery disease; similar findings were observed using an overall 99th percentile. Therefore, for the purpose of excluding acute myocardial injury (not acute myocardial infarction), our analyses suggest caution in these patient subsets. When we adjudicated false-negative cases with an initial baseline hs-cTnT<6 ng/L that developed myocardial injury, most were attributable to isolated nonischemic myocardial injury. One possible explanation for the observed differences is that the reduced analytic sensitivity of hs-cTnT in women[42,45] may diminish the ability of hs-cTnT to screen for underlying cardiovascular disease compared with men. Our data suggest this is a plausible explanation because women with hs-cTnT<6 ng/L were older and had more comorbidities than men with hs-cTnT<6 ng/L. Last, although differences were observed between men and women with respect to acute myocardial injury, these differences were not observed for acute myocardial infarction, with NPVs and sensitivities for acute myocardial infarction of 100% in both men and women with a nonischemic ECG and a hs-cTnT<6 ng/L in the adjudicated cohort.

Our study has multiple strengths. First, it is the largest US study to evaluate the role a single hs-cTnT below the LoQ to identify patients at low risk for acute myocardial injury and infarction. These findings are of unique importance to clinicians in the United States using hs-cTnT, because the LoQ is the lowest reportable hs-cTnT concentration for clinical use per the FDA,[17] and paucity of data exists. Second, our large multicenter analysis addressing the real-life clinical use of hs-cTnT across 22 US sites allowed us to evaluate the efficacy of this approach in a multistate, diverse population, including 50% women, and informed that a similar proportion of patients are eligible for this approach across sites. Third, the population evaluated exceeds the combined hs-cTnT data using the LoD from previous meta-analyses[4,6] and randomized trials[11,12] evaluating the single-sample rule-out. Fourth, we validated the safety of a baseline hs-cTnT in combination with a nonischemic ECG to exclude acute myocardial infarction in an adjudicated cohort, where we were also able to demonstrate safety among key subgroups, including in early presenters and in those with chest pain.

Limitations exist. First, although electrocardiographic findings and symptom onset were evaluated in the adjudicated cohort, these findings could not be interrogated in the CV Data Mart Biomarker cohort. We did exclude patients with ST-segment–elevation myocardial infarction diagnoses. Second, our efficacy analyses from the CV Data Mart Biomarker cohort address patients with serial measurements. We cannot exclude a component of selection and workup bias in that these patients were potentially perceived to be at higher risk than those that only underwent a single hs-cTnT despite an institutional 0/2-hour protocol. Our data confirm that patients undergoing serial measurements are likely at higher risk given they are older and have

more comorbidities than those undergoing single measurements. This demonstrates that the approach is safe in those potentially at higher risk, so that performance would likely be enhanced in all-comers. Third, although only 1.2% of patients with a baseline hs-cTnT<6 ng/L developed acute myocardial injury, 14% had 2-hour hs-cTnT concentrations within the reference range below the 99th percentile. These patients are older and have more comorbidities (Table S5). Concentration changes at these levels can occur because of analytic and biological variation. Additional studies are needed to clarify the prognostic implications, but analyses from the adjudicated cohort suggest that these patients have favorable outcomes (Figure S9). However, they are limited by small sample size. Irrespective of the potential for small concentration changes in a modest subset of patients with baseline hs-cTnT<6 ng/L, 5-year outcomes data[46] from the ADAPT study (Accelerated Diagnostic Protocol to Assess Patients with Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker Trial) demonstrate that patients with very low baseline hs-cTnT concentrations have good long-term outcomes. Fourth, larger early presenter studies are needed. Pending such investigations, as recommended by clinical practice guidelines,[1] single-sample rule-out is favored in those with symptoms that began at least 3 hours before. Fifth, our analyses are relevant to hs-cTnT, with studies required using other assays. Sixth, there is no global consensus on acceptable miss rates. Following American College of Emergency Physicians[38] guidance, we established that an acceptable rule-out strategy should not have >1% to 2% adverse events within 30 days, but we recognize that practice and geographic differences exist. Our data demonstrate excellent sensitivities and NPVs consistent with what the field considers safe and acceptable. Seventh, the potential for verification (workup) bias exists in all such real-life studies; however, the excellent 30-day clinical outcomes should attenuate such concerns. Eight, our adjudicated cohort has a modest sample size, and larger, multicenter, adjudicated cohorts with higher number of events are needed. Last, we recognize that ICD-10 codes have limitations,[34,35] for which reason analyses using ICD-10 codes were restricted to secondary analyses.

Conclusions

A single hs-cTnT measurement <6 ng/L is a safe method to rapidly triage and identify patients at very low risk for acute myocardial infarction, in particular, among those with a nonischemic ECGs. This approach can facilitate the identification of a substantial number of low-risk patients that are potentially eligible for early discharge and likely will be associated with important reductions in length of stay and cost.

ARTICLE INFORMATION

Received January 23, 2022; accepted April 4, 2022.

Affiliations

Department of Cardiovascular Diseases (Y.L., L.D.M., R.L., R.G., A.S.J.), Division of Biomedical Statistics and Informatics (B.R.L.), Department of Internal Medicine (J.D.K.), Department of Laboratory Medicine and Pathology (A.S.J.), Mayo Clinic, Rochester, MN. Department of Health Sciences Research (R.A.M.), Mayo College of Medicine, Rochester, MN. Division of Hospital Internal Medicine (O.O., A.A., S.K.), Department of Cardiovascular Diseases (M.D., N.R., T.T., C.C.), Department of Family Medicine (E.C.), Department of Emergency Medicine (E.G.), Department of Laboratory Medicine and Pathology (S.W.), Mayo Clinic Health System, La Crosse, WI. Center for Clinical and Translational Science, Mayo Clinic Graduate School of Biomedical Sciences, Rochester MN (O.O., A.A.). Department of Cardiac, Thoracic and Vascular Sciences and Public Health, University of Padova, Italy (L.D.M.). Department of Cardiovascular Diseases, Mayo Clinic, Phoenix, AZ (E.H.Y.). Department of Cardiovascular Diseases, Mayo Clinic, Jacksonville, FL (S.M.G.). Department of Health Sciences Research, Mayo College of Medicine, Jacksonville, FL (D.O.H.).

Acknowledgments

The authors acknowledge the multidisciplinary hs-cTnT implementation team across the Mayo Clinic enterprise that facilitated the introduction of 5th Gen cTnT into clinical practice.

Sources of Funding

This work was supported in part by the Mayo Clinic CTSA through grant UL-1TR002377 from the National Center for Advancing Translational Sciences, a component of the National Institutes of Health.

Disclosures

Dr Sandoval has previously served on Advisory Boards for Roche Diagnostics and Abbott Diagnostics without personal financial compensation. He has also been a speaker without personal financial compensation for Abbott Diagnostics. Dr Jaffe has consulted or presently consults for most of the major diagnostics companies, including Beckman-Coulter, Abbott, Siemens, Ortho Diagnostics, ET Healthcare, Roche, Radiometer, Sphingotec, RCE Technologies, Astellas, Amgen, and Novartis. All other authors have nothing to disclose.

Supplemental Material

Tables S1–S13

Figures S1–S9

REFERENCES

1. Gulati M, Levy PD, Mukherjee D, Amsterdam E, Bhatt DL, Birtcher KK, Blankstein R, Boyd J, Bullock-Palmer RP, Conejo T, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2021;144:e368–e454. doi: 10.1161/CIR.0000000000001030
2. Apple FS, Sandoval Y, Jaffe AS, Ordonez-Llanos J; IFCC Task Force on Clinical Applications of Cardiac Bio-Markers. Cardiac troponin assays: guide to understanding analytical characteristics and their impact on clinical care. *Clin Chem.* 2017;63:73–81. doi: 10.1373/clinchem.2016.255109
3. Sandoval Y, Smith SW, Apple FS. Present and future of cardiac troponin in clinical practice: a paradigm shift to high-sensitivity assays. *Am J Med.* 2016;129:354–365. doi: 10.1016/j.amjmed.2015.12.005
4. Pickering JW, Than MP, Cullen L, Aldous S, Ter Avest E, Body R, Carlton EW, Collinson P, Dupuy AM, Ekelund U, et al. Rapid rule-out of acute myocardial infarction with a single high-sensitivity cardiac troponin t measurement below the limit of detection: a collaborative meta-analysis. *Ann Intern Med.* 2017;166:715–724. doi: 10.7326/M16-2562
5. Chapman AR, Lee KK, McAllister DA, Cullen L, Greenslade JH, Parsonage W, Worster A, Kavsak PA, Blankenberg S, Neumann J, et al. Association of high-sensitivity cardiac troponin I concentration with cardiac outcomes in patients with suspected acute coronary syndrome. *JAMA.* 2017;318:1913–1924. doi: 10.1001/jama.2017.17488
6. Chiang CH, Chiang CH, Pickering JW, Stoyanov KM, Chew DP, Neumann JT, Ojeda F, Sörensen NA, Su KY, Kavsak P, et al. Performance of the European Society of Cardiology 0/1-hour, 0/2-hour, and 0/3-hour algorithms for rapid triage of acute myocardial infarction: an international collaborative meta-analysis. *Ann Intern Med.* 2022;175:101–113. doi: 10.7326/M21-1499
7. Shah AS, Anand A, Sandoval Y, Lee KK, Smith SW, Adamson PD, Chapman AR, Langdon T, Sandeman D, Vaswani A, et al; High-STEACS investigators.

High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. *Lancet.* 2015;386:2481–2488. doi: 10.1016/S0140-6736(15)00391-8
8. Sandoval Y, Nowak R, deFilippi CR, Christenson RH, Peacock WF, McCord J, Limkakeng AT, Sexter A, Apple FS. Myocardial infarction risk stratification with a single measurement of high-sensitivity troponin I. *J Am Coll Cardiol.* 2019;74:271–282. doi: 10.1016/j.jacc.2019.05.058
9. Sandoval Y, Smith SW, Love SA, Sexter A, Schulz K, Apple FS. Single high-sensitivity cardiac troponin I to rule out acute myocardial infarction. *Am J Med.* 2017;130:1076–1083.e1. doi: 10.1016/j.amjmed.2017.02.032
10. Anand A, Lee KK, Chapman AR, Ferry AV, Adamson PD, Strachan FE, Berry C, Findlay I, Cruikshank A, Reid A, et al; HiSTORIC Investigators†. High-sensitivity cardiac troponin on presentation to rule out myocardial infarction: a stepped-wedge cluster randomized controlled trial. *Circulation.* 2021;143:2214–2224. doi: 10.1161/CIRCULATIONAHA.120.052380
11. Carlton EW, Ingram J, Taylor H, Glynn J, Kandiyali R, Campbell S, Beasant L, Aziz S, Beresford P, Kendall J, et al. Limit of detection of troponin discharge strategy versus usual care: randomised controlled trial. *Heart.* 2020;106:1586–1594. doi: 10.1136/heartjnl-2020-316692
12. Chew DP, Lambrakis K, Blyth A, Seshadri A, Edmonds MJR, Briffa T, Cullen LA, Quinn S, Karnon J, Chuang A, et al. A Randomized trial of a 1-hour troponin t protocol in suspected acute coronary syndromes: the Rapid Assessment of Possible Acute Coronary Syndrome in the Emergency Department With High-Sensitivity Troponin T Study (RAPID-TnT). *Circulation.* 2019;140:1543–1556. doi: 10.1161/CIRCULATIONAHA.119.042891
13. Sandeman D, Syed MBJ, Kimenai DM, Lee KK, Anand A, Joshi SS, Dinnel L, Wenham PR, Campbell K, Jarvie M, et al. Implementation of an early rule-out pathway for myocardial infarction using a high-sensitivity cardiac troponin T assay. *Open Heart.* 2021;8:e001769. doi: 10.1136/openhrt-2021-001769
14. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, et al; ESC Scientific Document Group. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2016;37:267–315. doi: 10.1093/eurheartj/ehv320
15. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, et al; ESC Scientific Document Group. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* 2021;42:1289–1367. doi: 10.1093/eurheartj/ehaa575
16. Apple FS, Fantz CR, Collinson PO; IFCC Committee on Clinical Application of Cardiac Bio-Markers. Implementation of high-sensitivity and point-of-care cardiac troponin assays into practice: some different thoughts. *Clin Chem.* 2021;67:70–78. doi: 10.1093/clinchem/hvaa264
17. Sandoval Y, Jaffe AS. Using high-sensitivity cardiac troponin T for acute cardiac care. *Am J Med.* 2017;130:1358–1365.e1. doi: 10.1016/j.amjmed.2017.07.033
18. Peacock WF, Baumann BM, Bruton D, Davis TE, Handy B, Jones CW, Hollander JE, Limkakeng AT, Mehrotra A, Than M, et al. Efficacy of high-sensitivity troponin T in identifying very-low-risk patients with possible acute coronary syndrome. *JAMA Cardiol.* 2018;3:104–111. doi: 10.1001/jamacardio.2017.4625
19. Allen BR, Christenson RH, Cohen SA, Nowak R, Wilkerson RG, Mumma B, Madsen T, McCord J, Huis In't Veld M, Massoomi M, et al. Diagnostic performance of high-sensitivity cardiac troponin T strategies and clinical variables in a multisite US cohort. *Circulation.* 2021;143:1659–1672. doi: 10.1161/CIRCULATIONAHA.120.049298
20. Chapman AR, Sandeman D, Ferry AV, Stewart S, Strachan FE, Wereski R, Bularga A, Anand A, Shah ASV, Mills NL. Risk stratification using high-sensitivity cardiac troponin T in patients with suspected acute coronary syndrome. *J Am Coll Cardiol.* 2020;75:985–987. doi: 10.1016/j.jacc.2019.12.036
21. Twerenbold R, Badertscher P, Boeddinghaus J, Nestelberger T, Wildi K, Rubini Gimenez M, Miró Ò, Martín-Sánchez FJ, Reichlin T, Mueller C. Effect of the FDA regulatory approach on the 0/1-h algorithm for rapid diagnosis of MI. *J Am Coll Cardiol.* 2017;70:1532–1534. doi: 10.1016/j.jacc.2017.07.746
22. McRae AD, Innes G, Graham M, Lang E, Andruchow JE, Ji Y, Vatanpour S, Abedin T, Yang H, Southern DA, et al. Undetectable concentrations of a Food and Drug Administration-approved high-sensitivity cardiac troponin T Assay to rule out acute myocardial infarction at emergency department arrival. *Acad Emerg Med.* 2017;24:1267–1277. doi: 10.1111/acem.13229
23. Shah ASV, Sandoval Y, Noaman A, Sexter A, Vaswani A, Smith SW, Gibbins M, Griffiths M, Chapman AR, Strachan FE, et al. Patient selection for high sensitivity cardiac troponin testing and diagnosis of myocardial infarction: prospective cohort study. *BMJ.* 2017;359:j4788. doi: 10.1136/bmj.j4788
24. Makam AN, Nguyen OK. Use of cardiac biomarker testing in the emergency department. *JAMA Intern Med.* 2015;175:67–75. doi: 10.1001/jamainternmed.2014.5830
25. Donato LJ, Wockenfus AM, Katzman BM, Baumann NA, Jaffe AS, Karon BS. Analytical and clinical considerations in implementing the Roche Elecsys Troponin T Gen 5 STAT assay. *Am J Clin Pathol.* 2021;156:1121–1129. doi: 10.1093/ajcp/aqab082
26. Saenger AK, Beyrau R, Braun S, Cooray R, Dolci A, Freidank H, Giannitsis E, Gustafson S, Handy B, Katus H, et al. Multicenter analytical evaluation of a high-sensitivity troponin T assay. *Clin Chim Acta.* 2011;412:748–754. doi: 10.1016/j.cca.2010.12.034
27. Vigen R, Kutscher P, Fernandez F, Yu A, Bertulfo B, Hashim IA, Molberg K, Diercks DB, Metzger JC, Soto J, et al. Evaluation of a novel rule-out myocardial infarction protocol incorporating high-sensitivity troponin T in a US hospital. *Circulation.* 2018;138:2061–2063. doi: 10.1161/CIRCULATIONAHA.118.033861
28. Ford JS, Chaco E, Tancredi DJ, Mumma BE. Impact of high-sensitivity cardiac troponin implementation on emergency department length of stay, testing, admissions, and diagnoses. *Am J Emerg Med.* 2021;45:54–60. doi: 10.1016/j.ajem.2021.02.021
29. Baugh CW, Scirica BM, Januzzi JL, Morrow DA, Lewandrowski KB, Jarolim P, White BA, Weinfeld MS, Hoffmann U, Nagurney JT. Implementation of an emergency department high-sensitivity troponin chest pain pathway in the United States. *Crit Pathw Cardiol.* 2019;18:1–4. doi: 10.1097/HPC.0000000000000164
30. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth universal definition of myocardial infarction (2018). *Circulation.* 2018;138:e618–e651. doi: 10.1161/CIR.0000000000000617
31. Body R, Carley S, McDowell G, Jaffe AS, France M, Cruickshank K, Wibberley C, Nuttall M, Mackway-Jones K. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. *J Am Coll Cardiol.* 2011;58:1332–1339. doi: 10.1016/j.jacc.2011.06.026
32. Sandoval Y, Smith SW, Shah AS, Anand A, Chapman AR, Love SA, Schulz K, Cao J, Mills NL, Apple FS. Rapid rule-out of acute myocardial injury using a single high-sensitivity cardiac troponin I measurement. *Clin Chem.* 2017; 63: 369: 376. doi: 10.1373/clinchem.2016.264523
33. Wassie M, Lee MS, Sun BC, Wu YL, Baecker AS, Redberg RF, Ferencik M, Shen E, Musigdilok V, Sharp AL. Single vs serial measurements of cardiac troponin level in the evaluation of patients in the emergency department with suspected acute myocardial infarction. *JAMA Netw Open.* 2021;4:e2037930. doi: 10.1001/jamanetworkopen.2020.37930
34. McCarthy C, Murphy S, Cohen JA, Rehman S, Jones-O'Connor M, Olshan DS, Singh A, Vaduganathan M, Januzzi JL Jr, Wasfy JH. Misclassification of myocardial injury as myocardial infarction: implications for assessing outcomes in value-based programs. *JAMA Cardiol.* 2019;4:460–464. doi: 10.1001/jamacardio.2019.0716
35. Díaz-Garzón J, Sandoval Y, Smith SW, Love S, Schulz K, Thordsen SE, Johnson BK, Driver B, Jacoby K, Carlson MD, et al. Discordance between ICD-coded myocardial infarction and diagnosis according to the universal definition of myocardial infarction. *Clin Chem.* 2017;63:415–419. doi: 10.1373/clinchem.2016.263764
36. Ola O, Akula A, De Michieli L, Dworak M, Crockford E, Lobo R, Rastas N, Knott JD, Mehta RA, Hodge DO, et al. Clinical impact of high-sensitivity cardiac troponin T implementation in the community. *J Am Coll Cardiol.* 2021; 77: 3160–3170. doi: 10.1016/j.jacc.2021.04.050
37. Mahler SA, Lenoir KM, Wells BJ, Burke GL, Duncan PW, Case LD, Herrington DM, Diaz-Garelli JF, Futrell WM, Hiestand BC, et al. Safely identifying emergency department patients with acute chest pain for early discharge. *Circulation.* 2018;138:2456–2468. doi: 10.1161/CIRCULATIONAHA.118.036528
38. American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Suspected Non-ST-Elevation Acute Coronary Syndromes; TomaszewskiCA, Nestler D, Shah KH, Sudhir A, Brown MD. Clinical policy: critical issues in the evaluation and management of emergency department patients with suspected non-ST-elevation acute coronary syndromes. *Ann Emerg Med.* 2018;72:e65–e106. doi: 10.1016/j.annemergmed.2018.07.045
39. Than M, Herbert M, Flaws D, Cullen L, Hess E, Hollander JE, Diercks D, Ardagh MW, Kline JA, Munro Z, et al. What is an acceptable risk of major

adverse cardiac event in chest pain patients soon after discharge from the emergency department?: a clinical survey. *Int J Cardiol.* 2013;166:752–754. doi: 10.1016/j.ijcard.2012.09.171

40. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. *Clin Chem.* 2010;56:254–261. doi: 10.1373/clinchem.2009.132654
41. Saenger AK, Beyrau R, Braun S, Cooray R, Dolci A, Freidank H, Giannitsis E, Gustafson S, Handy B, Katus H, et al. Multicenter analytical evaluation of a high-sensitivity troponin T assay. *Clin Chim Acta.* 2011;412:748–754. doi: 10.1016/j.cca.2010.12.034
42. Apple FS, Wu AHB, Sandoval Y, Sexter A, Love SA, Myers G, Schulz K, Duh SH, Christenson RH. Sex-specific 99th percentile upper reference limits for high sensitivity cardiac troponin assays derived using a universal sample bank. *Clin Chem.* 2020;66:434–444. doi: 10.1093/clinchem/hvz029
43. Sandoval Y, Askew JW 3rd, Newman JS, Clements CM, Grube ED, Ola O, Akula A, Dworak M, Wohlrab S, Karon BS, et al. Implementing high-sensitivity cardiac troponin T in a US regional healthcare system. *Circulation.* 2020;141:1937–1939. doi: 10.1161/CIRCULATIONAHA.119.045480
44. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika.* 1943; 26: 404–413.
45. Kimenai DM, Henry RM, van der Kallen CJ, Dagnelie PC, Schram MT, Stehouwer CD, van Suijlen JD, Niens M, Bekers O, Sep SJ, et al. Direct comparison of clinical decision limits for cardiac troponin T and I. *Heart.* 2016;102:610–616. doi: 10.1136/heartjnl-2015-308917
46. Than MP, Aldous SJ, Troughton RW, Pemberton CJ, Richards AM, Frampton CMA, Florkowski CM, George PM, Bailey S, Young JM, et al. Detectable high-sensitivity cardiac troponin within the population reference interval conveys high 5-year cardiovascular risk: an observational study. *Clin Chem.* 2018;64:1044–1053. doi: 10.1373/clinchem.2017.285700