Received: 8 August 2023 | Revised: 4 October 2023 | Accepted: 13 October 2023

DOI: 10.1111/acem.14827

Academic Emergency Medicine

ORIGINAL ARTICLE

Performance of the 0/2-hour high-sensitivity cardiac troponin T diagnostic protocol in a multisite United States cohort

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Funding information
This investigator-initiated study was funded by Roche Diagnostics.

Abstract

Background: The diagnostic performance of the high-sensitivity troponin T (hs-cTnT) 0/2-h algorithm is unclear among U.S. emergency department (ED) patients with acute chest pain.

Methods: A preplanned subgroup analysis of the STOP-CP cohort study was conducted. Participants with 0- and 2-h hs-cTnT measures prospectively enrolled at eight U.S. EDs from January 2017 to September 2018 were stratified into rule-out, observation, and rule-in zones using the hs-cTnT 0/2-h algorithm alone and combined with the history, electrocardiogram, age, and risk factor (HEAR) score. The primary outcome was adjudicated 30-day cardiac death or myocardial infarction (CDMI). The sensitivity and negative predictive value (NPV) of the 0/2-h rule-out zone and specificity and positive predictive value (PPV) of the rule-in zone for 30-day CDMI were calculated.

Results: Of the 1307 patients accrued, 53.6% (700/1307) were male and 58.6% (762/1307) were White, with a mean ± SD age of 57.5 ± 12.7 years. At 30 days, CDMI

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Trial registration High-Sensitivity Cardiac Troponin T to Optimize Chest Pain Risk Stratification (STOP-CP; ClinicalTrials.gov: NCT02984436; https://clinicaltrials.gov/ct2/show/NCT02984436).

Supervising Editor: Paul I Musey

occurred in 12.9% (168/1307) of participants. The 0/2-h algorithm ruled out 61.4% (802/1307) of patients. Among rule-out patients, 1.9% (15/802) experienced 30-day CDMI, resulting in a sensitivity of 91.1% (95% confidence interval [CI] 85.7%–94.9%) and NPV of 98.1% (95% CI 96.9%–98.9%). The 0/2-h algorithm ruled in 12.4% (162/1307) patients of whom 61.7% (100/162) experienced 30-day CDMI. The rule-in zone specificity was 94.6% (95% CI 93.1%–95.8%) and PPV was 61.7% (95% CI 53.8%–69.2%) for 30-day CDMI. The 0/2-h algorithm combined with HEAR score ruled out 30.7% (401/1307) of patients with a sensitivity and NPV for 30-day CDMI of 98.2% (95% CI 94.9%–99.6%) and 99.3% (95% CI 97.8%–99.8%), respectively.

Conclusions: The hs-cTnT 0/2-h algorithm ruled out most patients. With NPV of <99% for 30-day CDMI, the hs-cTnT 0/2-h algorithm, many emergency physicians may not consider it safe to use for U.S. ED patients. When combined with a low-risk HEAR score, NPV was >99% for 30-day CDMI at the cost of reduced efficacy.

INTRODUCTION

Approximately 6.5 million emergency department (ED) visits in the United States each year are for patients experiencing chest pain.[1,2] Accelerated diagnostic protocols (ADPs) have been developed to evaluate these patients' risk for acute coronary syndrome (ACS) and guide their ED disposition. While some ADPs use a risk score, incorporating a patient's history, electrocardiogram (ECG), age, risk factors, and high-sensitivity cardiac troponin (hs-cTn) level to determine risk,[3–6] others rely solely on hs-cTn measurements.[7–10]

Originally developed and validated in Europe and Australia, the hs-cTnT 0/2-h algorithm is an ADP that relies solely on hs-cTnT measures. In prior studies, it has demonstrated nearly 100% negative predictive value (NPV) for 30-day cardiac death or myocardial infarction (CDMI).[11–14] A Canadian validation study found an NPV of 99.5% and 97.0% for 30-day CDMI and 30-day major adverse cardiovascular events (MACE). However, the hs-cTnT 0/2-hour algorithm developed by Reichlin et al. has not been validated in a U.S. cohort.

The primary objective of this study was to evaluate the diagnostic performance of the hs-cTnT 0/2-h algorithm for 30-day CDMI within the hs-cTnT to Optimize Chest Pain Risk Stratification (STOP-CP) cohort. A secondary objective was to evaluate the diagnostic performance for index-visit CDMI, CDMI at 90 days, and MACE (defined as cardiac death, MI, or coronary revascularization) at index and 30 and 90 days. Finally, we evaluated whether the combination of the hs-cTnT 0/2-h with the history, ECG, age, and risk factor (HEAR) score improves diagnostic performance.[15]

METHODS

Study design and setting

This is a preplanned secondary analysis of the STOP-CP (Gen 5 STAT assay; ClinicalTrials.gov NCT02984436) prospective, multicenter cohort study. STOP-CP enrolled patients with symptoms concerning for ACS at eight U.S. EDs from January 25, 2017, to September 6, 2018. Study sites are detailed in the primary STOP-CP article.[16] Institutional review board approval was obtained at all sites. Written informed consent was obtained for enrollment. STOP-CP methods are previously described.[16–18] The Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines helped direct the research and manuscript development processes.[19]

Study population

We prospectively enrolled ED patients ≥21 years of age with serial troponins ordered for the evaluation of possible ACS. Exclusion criteria included ST-elevation myocardial infarction, systolic blood pressure <90 mm Hg, life expectancy <90 days, a noncardiac illness requiring admission, inability to provide consent or be contacted for follow-up, non-English speaking, pregnancy, being a prisoner, or previous enrollment in the study.

Data collection

Serial blood samples were collected for hs-cTnT measurement at baseline (<1 h from first clinical blood draw) and 2 h later in lithium heparin tubes. hs-cTnT was quantified with the Gen 5 STAT assay on the cobas immunoanalyzer (Roche Diagnostics). The assay has a range of 3000–10,000 ng/L, limit of quantification at 6 ng/L, and a 99th percentile upper reference limit (URL) of 19 ng/L in the United States with a coefficient of variation of <10%.[20] Treating providers were blinded to hs-cTnT results. Therefore, patient care was dictated by local standards of care and guided by contemporary cTn results. Each patient had a HEAR score calculated by their treating ED provider.

Demographic data were collected by research staff from the patient by self-report and were supplemented by the patient's electronic medical record. These included age on the day of ED visit,

sex, race and ethnicity, and risk factors (current or prior tobacco use, hypertension, hyperlipidemia, diabetes, family history of coronary artery disease [CAD], obesity, prior cerebrovascular accident, peripheral vascular disease, and end-stage renal disease). ECG findings of acute ischemia were indicated by the treating physician.

0/2-Hour algorithm

The 0/2-h algorithm used was originally described by Reichlin et al.[21] In each patient, hs-cTnT measures were used to stratify patients into rule-out, observation, and rule-in zones using established assay-specific cut-points shown in Figure 1.[9,16,22] However, the hs-cTnT 0/2-h algorithm's 0-h rule-out cut-point of 5 ng/L (the limit of detection) was modified to 6 ng/L (the limit of quantification), because the U.S. Food and Drug Administration does not allow reporting below the limit of quantification. Based on prior derivation and validation studies, patients stratified to the rule-out zone were expected to have ≥99% NPV for 30-day CDMI.[8,23–25]

Outcomes

The primary outcome was 30-day CDMI, inclusive of index visit events. Secondary outcomes included: (1) index and 90-day CDMI; (2) index, 30-day, and 90-day MACE (cardiac death, MI, and coronary revascularization); (3) the individual MACE components at index, 30 days, and 90 days; and (4) efficacy, defined as the proportion of patients classified into the rule-out zone during the index visit.[5,26] Medical record review and telephone follow-up through 90 days were completed to determine outcomes. Expert reviewers adjudicated any patient who experienced death or a clinical diagnosis of MI or had an elevated contemporary cTn. Expert adjudicators (Mate Huis in't Veld, MD; Michael Massoomi, MD; Jason P. Stopyra, MD, MS; and James McCord, MD) classified deaths as cardiac or noncardiac based on the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial definition, with the exception of death due to stroke, which was classified as a noncardiac death.[27] If the cause of death could not be determined, it was considered cardiac. MI was determined by the Fourth Universal Definition of MI: rise and fall of troponin (with at least one value >99th percentile URL) with symptoms of ischemia, ECG evidence of ischemia, imaging evidence of new nonviable myocardium, a new regional wall motion abnormality, or evidence of thrombus on angiography.[28] Event rates at 30 days are inclusive of index events, and rates at 90 days are inclusive of both 30 day and index events.

Statistical analysis

Counts, percentages, means and standard deviations, or medians and interquartile ranges (IQRs) were used to describe the study population. To evaluate the performance of the hs-cTnT 0/2-h algorithm, sensitivity, specificity, NPV and positive predictive value (PPV), and negative and positive likelihood ratios (−LR and +LR) for index, 30-day, and 90-day outcomes were calculated. For efficacy, sensitivity, specificity, NPV, PPV, −LR, and + LR, exact 95% confidence intervals (95% CIs) were computed. Consistent with prior studies, sensitivity, NPV, and −LR were calculated for the rule-out zone (i.e., rule-out vs. rule-in or observation) and specificity, PPV, and +LR were calculated for the rule-in zone (i.e., rule-in vs. observation or rule-out).[8,15,16,24,29] In addition, we evaluated the diagnostic performance of the combination of the hs-cTnT 0/2-h algorithm with a HEAR score. For this combination, patients were classified to the rule-out zone only if they met both the hs-cTnT 0/2-h algorithm rule-out cut-points and had a low-risk HEAR score of 0–3. Patients with a HEAR score of ≥7 were classified to the rule-in zone regardless of hs-cTnT measures. Patients meeting the hs-cTnT 0/2-hour algorithm's rule-out criteria, who had a HEAR score of 4–6, were reclassified to the observation zone.

RESULTS

This preplanned secondary analysis included 1307 patients. The patient flow diagram is shown in Figure 2. The cohort was 53.6% (700/1307) male and 58.6% (762/1307) white, with a mean ± SD age of 57.5 ± 12.7 years. Patient demographics are presented in Table 1. Using the hs-cTnT 0/2-h algorithm, most patients were stratified to the rule-out zone, yielding an efficacy of 61.4% (802/1307), with 26.2% (343/1307) stratified to the observation zone and 12.4% (162/1307) to the rule-in zone.

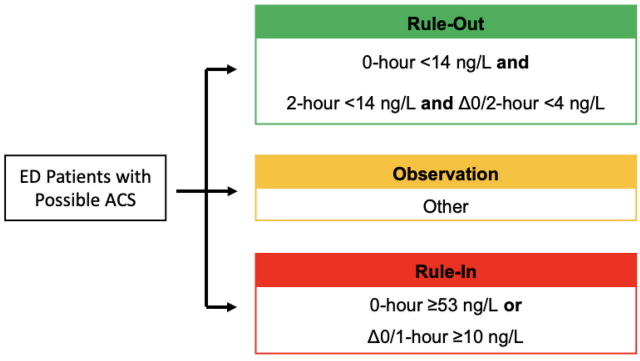

FIGURE 1 hs-cTnT 0/2-h algorithm. ACS, acute coronary syndrome; hs-cTnT, high sensitivity troponin T.

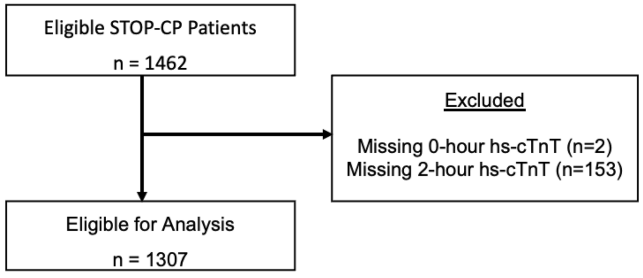

FIGURE 2 Patient flow diagram. hs-cTnT, high-sensitivity troponin T.

TABLE 1 Cohort characteristics.

	Total ($N = 1307$)
Age (years)	57.5 (±12.7)
Male sex	700 (53.6)
Race	
American Indian/Alaska Native	19 (1.5)
Asian	12 (0.9)
Native Hawaiian	2 (0.1)
Black or African American	476 (36.6)
White	762 (58.6)
Other	30 (2.3)
Ethnicity	
Hispanic or Latino	14 (1.1)
Not Hispanic or Latino	1244 (98.0)
Unknown	11 (0.9)
Risk factors	
Current or history of smoking	282 (21.6)
Hypertension	882 (67.5)
Hyperlipidemia	640 (49.0)
Diabetes	390 (29.8)
Family history of CAD	607 (46.4)
BMI ≥ 30 kg/m^2	688 (52.6)
History	
CAD	433 (33.2)
Prior MI	290 (22.2)
Prior stroke	144 (11.0)
Peripheral artery disease	86 (6.6)
End-stage renal disease	70 (5.4)
Chest pain onset	
≤3 h from arrival	458 (35.3)
>3 h from arrival	841 (64.7)
ECG at arrival	
Ischemic	81 (6.2)
Nonischemic	1226 (93.8)
Initial study hs-cTnT sample (ng/L)	9 (5–21)

Note: Data are reported as mean (±SD), *n* (%), or median (IQR).

Abbreviations: BMI, body mass index; CAD, coronary artery disease; ECG, electrocardiogram; hs-cTnT, high-sensitivity troponin T; MI, myocardial infarction.

Index-visit outcomes

During the index visit, MI occurred in 11.6% (151/1307) and cardiac death occurred in 0.2% (2/1307) of the cohort. Among rule-out patients, cardiac death occurred in 0.1% (1/802), MI in 1.0% (8/802), and composite CDMI among 1.1% (9/802). This yielded a sensitivity, NPV, and −LR for index CDMI of 94.1% (95% CI 89.1%–97.3%), 98.9% (95% CI 97.9%–99.5%), and 0.09 (95% CI 0.05–0.16), respectively.

TABLE 2 Outcomes for hs-cTnT 0/2-h algorithm zones.

	Rule out ($n = 802$)	Observation ($n = 343$)	Rule in ($n = 162$)
Index			
Cardiac death	1 (0.1)	0 (0)	1 (0.6)
MI	8 (1)	47 (13.7)	96 (59.3)
Revascularization	9 (1.1)	14 (4.1)	40 (24.7)
CDMI	9 (1.1)	47 (13.7)	96 (59.3)
MACE	15 (1.9)	50 (14.6)	96 (59.3)
30-day (index + follow-up)			
Cardiac death	1 (0.1)	0 (0)	3 (1.9)
MI	14 (1.7)	53 (15.5)	100 (61.7)
Revascularization	13 (1.6)	22 (6.4)	44 (27.2)
CDMI	15 (1.9)	53 (15.5)	100 (61.7)
MACE	19 (2.4)	62 (18.1)	102 (63)
90-day (index + follow-up)			
Cardiac death	1 (0.1)	1 (0.3)	5 (3.1)
MI	15 (1.9)	62 (18.1)	103 (63.6)
Revascularization	17 (2.1)	22 (6.4)	47 (29)
CDMI	16 (2)	62 (18.1)	103 (63.6)
MACE	30 (3.7)	70 (20.4)	104 (64.2)

Abbreviations: CAD, coronary artery disease; CDMI, cardiac death or myocardial infarction; ECG, electrocardiogram; hs-cTnT, high sensitivity troponin T; MACE, major adverse cardiovascular events; MI, myocardial infarction.

Index-visit MACE occurred in 1.9% (15/802) of rule-out patients, resulting in a sensitivity of 90.8% (95% CI 85.1%–94.7%), NPV of 98.1% (95% CI 96.9%–98.9%), and −LR of 0.14 (95% CI 0.08–0.22). Among rule-in patients, index CDMI or MACE occurred among 59.3% (96/162) with a specificity of 94.3% (95% CI 92.8%–95.6%) and PPV of 59.3% (95% CI 51.3%–66.9%). Index-visit outcomes are detailed in Tables 2 and 3, and Figure 3.

30-day outcomes

At 30 days, 17 additional MIs and two additional cardiac deaths occurred, resulting in a total of 12.9% (168/1307) of patients experiencing CDMI. Among patients in the rule-out zone, at 30 days there were six additional MIs and no additional cardiac deaths. The total 30-day CDMI rate was 1.7% (14/802), resulting in a sensitivity of 91.1% (95% CI 85.7%–94.9%), NPV of 98.1% (95% CI 96.9%–98.9%), and −LR of 0.13 (95% CI 0.08–0.21). MACE at 30 days occurred among 2.4% (19/802), which resulted in a sensitivity of 89.6% (95% CI 84.3–93.6%), NPV of 97.6% (95% CI 96.3–98.6%), and −LR of 0.15 (95% CI 0.10–0.23). For the 12.4% (162/1307) of patients in the rule-in zone, 30-day CDMI occurred in 61.7% (100/162) yielding a specificity of 94.6% (95% CI 93.1%–95.8%) and PPV of 61.7% (95% CI 53.8%–69.2%). MACE at 30 days occurred among 63.0% (102/162) of rule-in patients, resulting in a specificity of 94.8% (95% CI

TABLE 3 Test characteristics at index and 30 and 90 days and efficacy for hs-cTnT 0/2-h ADP with and without the HEAR score.

	Sensitivity (95% CI), %	NPV (95% CI), %	−LR (95% CI)	Specificity (95% CI), %	PPV (95% CI), %	+LR (95% CI)	Efficacy %
Index CDMI							
hs-cTnT 0/2-h ADP	94.1 (89.1–97.3)	98.9 (97.9–99.5)	0.09 (0.05–0.16)	94.3 (92.8–95.6)	59.3 (51.3–66.9)	11.1 (8.5–14.4)	63.40
hs-cTnT 0/2-h ADP + HEAR	99.3 (96.4–100)	99.8 (98.6–100)	0.02 (0.00–0.13)	91.9 (90.1–93.4)	51.3 (44.0–58.5)	8.0 (6.4–10.0)	30.70
Index MACE							
hs-cTnT 0/2-h ADP	90.8 (85.1–94.7)	98.1 (96.9–98.9)	0.14 (0.08–0.22)	94.3 (92.8–95.6)	59.3 (51.3–66.9)	10.4 (7.9–13.5)	63.40
hs-cTnT 0/2-h ADP + HEAR	97.5 (93.8–99.3)	99.0 (97.5–99.7)	0.08 (0.03–0.19)	92.0 (90.2–93.5)	52.3 (45.0–59.6)	7.8 (6.2–9.8)	30.70
30-day CDMI							
hs-cTnT 0/2-h ADP	91.1 (85.7–94.9)	98.1 (96.9–98.9)	0.13 (0.08–0.21)	94.6 (93.1–95.8)	61.7 (53.8–69.2)	10.9 (8.3–14.4)	63.40
hs-cTnT 0/2-h ADP + HEAR	98.2 (94.9–99.6)	99.3 (97.8–99.8)	0.05 (0.02–0.16)	92.1 (90.4–93.6)	53.4 (46.1–60.6)	7.8 (6.2–9.8)	30.70
30-day MACE							
hs-cTnT 0/2-h ADP	89.6 (84.3–93.6)	97.6 (96.3–98.6)	0.15 (0.10–0.23)	94.8 (93.2–95.9)	63.0 (55.0–70.4)	10.4 (7.9–13.8)	63.40
hs-cTnT 0/2-h ADP + HEAR	97.8 (94.5–99.4)	99.0 (97.5–99.7)	0.06 (0.02–0.16)	92.4 (90.7–93.9)	56.0 (48.7–63.1)	7.9 (7.2–9.9)	30.70
90-day CDMI							
hs-cTnT 0/2-h ADP	91.2 (86.0–94.9)	98.0 (96.8–98.9)	0.13 (0.08–0.20)	94.8 (93.3–96.0)	63.6 (55.7–71.0)	10.9 (8.2–14.4)	63.40
hs-cTnT 0/2-h ADP + HEAR	98.3 (95.2–99.7)	99.3 (97.8–99.8)	0.05 (0.02–0.14)	92.4 (90.7–93.8)	55.4 (48.1–62.6)	7.7 (6.1–9.8)	30.70
90-day MACE							
hs-cTnT 0/2-h ADP	85.3 (79.7–89.9)	96.3 (94.7–97.5)	0.21 (0.15–0.29)	94.7 (93.3–96.0)	64.2 (56.3–71.6)	9.7 (7.3–12.9)	63.40
hs-cTnT 0/2-h ADP + HEAR	96.1 (92.4–98.3)	98.0 (96.1–99.1)	0.11 (0.06–0.22)	92.5 (90.8–94.0)	57.0 (49.7–64.1)	7.2 (5.6–9.1)	30.70

Abbreviations: ADP, accelerated diagnostic protocol; HEAR, history, electrocardiogram, age, and risk factor score; hs-cTnT, high sensitivity troponin T; MACE, major adverse cardiovascular events; MI, myocardial infarction; NPV, negative predictive value; PPV, positive predictive value.

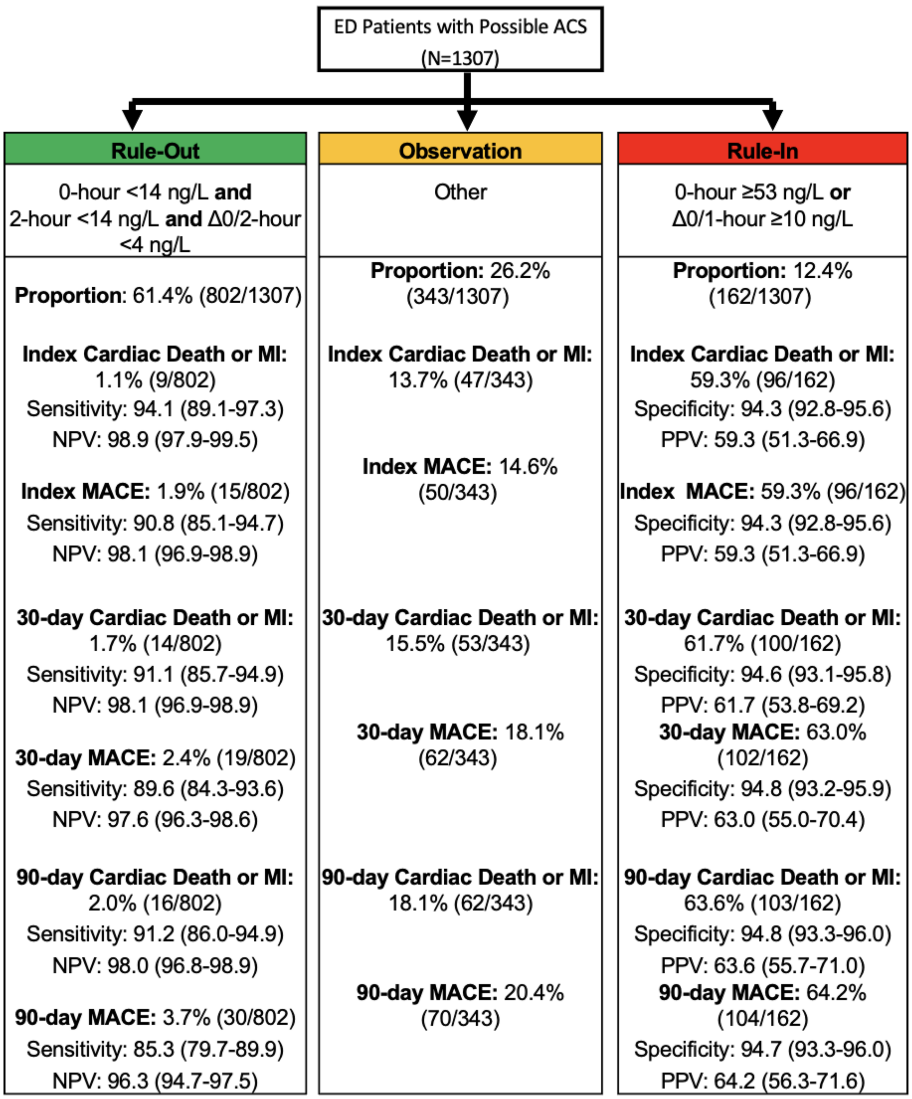

FIGURE 3 hs-cTnT 0/2-h ADP outcomes at index and 30 and 90 days. ACS, acute coronary syndrome; ADP, accelerated diagnostic protocol; hs-cTnT, high-sensitivity troponin T; MACE, major adverse cardiovascular event; MI, myocardial infarction; NPV, negative predictive value; PPV, positive predictive value.

93.2%–95.9%) and PPV of 63.0% (95% CI 55.0%–70.4%). Outcomes at 30 days are detailed in Tables 2 and 3, and Figure 3.

90-day outcomes

CDMI occurred in 13.8% (181/1307) of patients at 90 days, including 13 additional MIs and three additional cardiac deaths. For those stratified to the rule-out zone, one additional MI and no additional cardiac deaths were recorded, resulting in a 90-day CDMI rate of 2.0% (16/802) and yielding a sensitivity of 91.2% (95% CI 86.0%–94.9%), NPV of 98.0% (95% CI 96.8%–98.9%), and –LR of 0.13 (95% CI 0.08–0.20). MACE occurred among 3.7% (30/802) of patients at 90 days, producing a sensitivity of 85.3% (95% CI 79.7%–89.9%), NPV of 96.3% (95% CI 94.7%–97.5%), and –LR of 0.21 (0.15–0.29). For patients stratified to the rule-in zone, 90-day CDMI occurred in 63.6% (103/162) with a specificity of 94.8% (95% CI 93.3%–96.0%) and PPV of 63.6% (95% CI 55.7%–71.0%). MACE at 90 days occurred among 64.2% (104/162) of rule-in patients, resulting in a specificity of 94.7% (95% CI 93.3%–96.0%) and PPV of 64.2% (95% CI 56.3–71.6). Outcomes at 90 days are detailed in Tables 2 and 3, and Figure 3.

Combination of hs-cTnT 0/2 ADP with the HEAR score

Incorporation of the HEAR score into the algorithm, as detailed in Figure 4 and Table 4, reduced efficacy to 30.7% (401/1307). Among rule-out patients, 0.1% (1/401) had index-visit CDMI and 0.4% (3/401) had CDMI at 30 and 90 days. The sensitivities for CDMI at index and 30- and 90-day follow-up were 99.3% (95% CI 96.4%–100%), 98.2% (95% CI 94.9%–99.6%), and 98.3% (95.2%–99.7%), respectively. NPVs for CDMI were 99.8% (95% CI 98.6%–100%), 99.3%

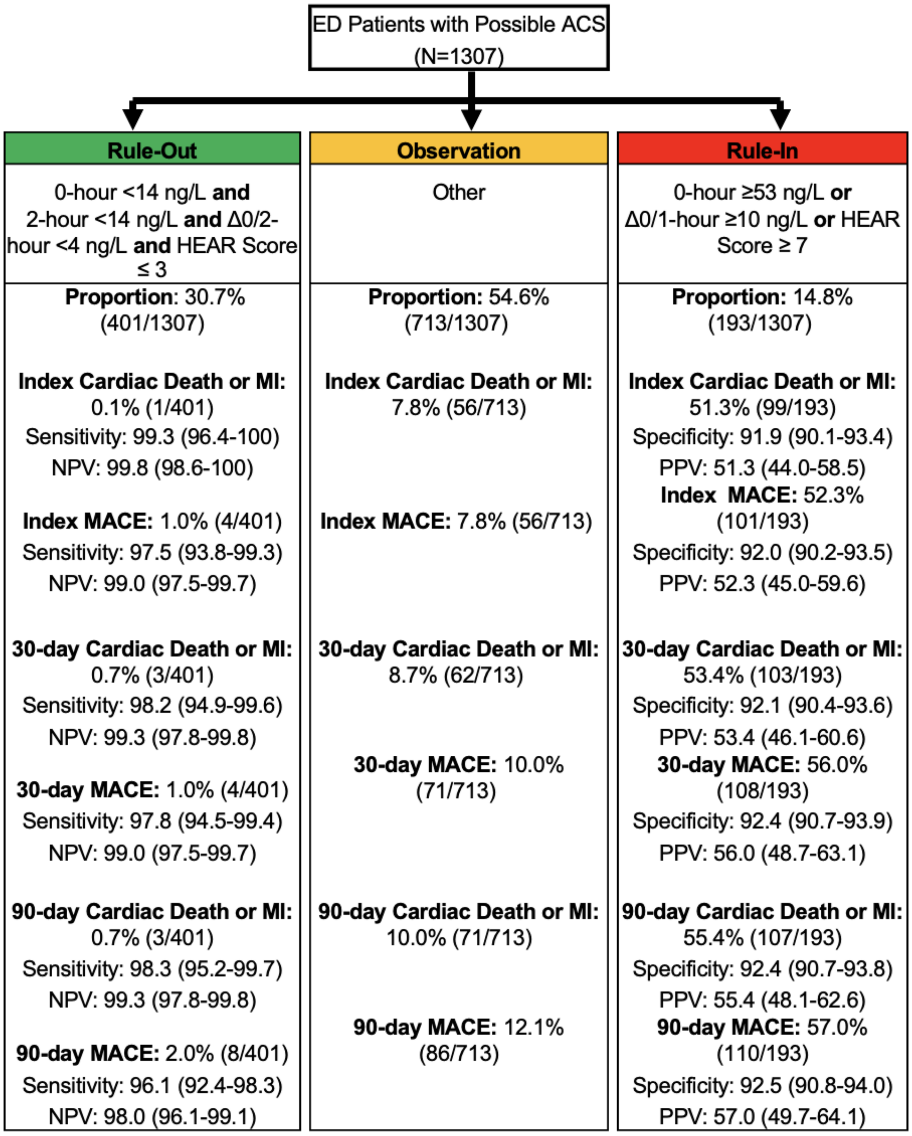

FIGURE 4 hs-cTnT 0/2-h ADP + HEAR score outcomes at index and 30 and 90 days. ACS, acute coronary syndrome; HEAR, history, electrocardiogram, age, and risk factor; hs-cTnT, high sensitivity troponin T; MACE, major adverse cardiovascular event; MI, myocardial infarction; NPV, negative predictive value; PPV, positive predictive value.

(95% CI 97.8%–99.8%), and 99.3% (95% CI 97.8%–99.8%) for index and 30- and 90-day follow-up, respectively.

Among the 14.8% (193/1307) of patients ruled in, 61.1% (99/193), 63.6% (103/193), and 66.0% (107/193) had CDMI at index and 30 and 90 days, respectively. The specificities for CDMI were 91.9% (95% CI 90.1–93.4), 92.1% (95% CI 90.4%–93.6%), and 92.4% (95% CI 90.7%–93.9%) at index and 30 and 90 days. PPVs for CDMI at index and 30 and 90 days were 51.3% (95% CI 44.0%–58.5%), 53.5% (95% CI 46.1%–60.6%), and 55.4% (95% CI 48.1%–62.6%), respectively.

DISCUSSION

In this secondary analysis of a multicenter prospective U.S.-based study of ED patients with suspected ACS, the hs-cTnT 0/2-h algorithm did not achieve an NPV of ≥99% to rule out index or 30- or 90-day CDMI or MACE. A previous investigation of physicians' comfort with chest pain risk stratification demonstrated most physicians desire an NPV of ≥99% for 30-day MACE.[30] This acceptable miss rate is echoed in 2021 guidelines on reasonable and appropriate care of ED patients with chest pain and is commonly used in other algorithms aimed at evaluating ED patients with chest pain.[29,31] Thus, our findings suggest that many physicians may not be comfortable with the diagnostic performance of the hs-cTnT 0/2-h algorithm when used alone. However, the combination of the hs-cTnT 0/2-h algorithm with a HEAR score was able to improve safety and yield an NPV of ≥99% for index and 30- and 90-day CDMI and for index and 30-day MACE at the cost of substantively reduced efficacy.

Our finding of a low NPV for 30-day outcomes differs from prior studies of the hs-cTnT 0/2-h algorithm. Among European, Australian, and Canadian populations, the hs-cTnT 0/2-h algorithm achieved nearly 100% NPV for 30-day MI and composite of CDMI.[11,21]

TABLE 4 Outcomes for hs-cTnT 0/2-h algorithm + HEAR score zones.

	Rule out ($n=401$)	Observation ($n=713$)	Rule in ($n=193$)
Index			
Cardiac death	0 (0)	1 (0.1)	1 (0.5)
MI	1 (0.2)	51 (7.2)	99 (51.3)
Revascularization	3 (0.7)	18 (2.5)	42 (21.8)
CDMI	1 (0.2)	56 (7.9)	99 (51.3)
MACE	4 (1)	56 (7.9)	101 (52.3)
30-day (index + follow-up)			
Cardiac death	0 (0)	1 (0.1)	3 (1.6)
MI	3 (0.7)	61 (8.6)	103 (53.4)
Revascularization	4 (1)	29 (4.1)	46 (23.8)
CDMI	3 (0.7)	62 (8.7)	103 (53.4)
MACE	4 (1)	71 (10)	108 (56)
90-day (index + follow-up)			
Cardiac death	0 (0)	2 (0.3)	5 (2.6)
MI	3 (0.7)	70 (9.8)	107 (55.4)
Revascularization	4 (1)	29 (4.1)	46 (23.8)
CDMI	3 (0.7)	71 (10)	107 (55.4)
MACE	8 (2)	86 (12.1)	110 (57)

Abbreviations: CDMI, cardiac death or myocardial infarction; hs-cTnT, high sensitivity troponin T; MACE, major adverse cardiovascular events; MI, myocardial infarction.

These NPVs are significantly higher than those found in our study. However, the validation in Canada, by McRae et al.[11] had an NPV for 30-day MACE of 97.0%, which is similar to our results. The difference in our findings to prior studies may be due to differences in the baseline characteristics of our population compared to previous international studies. For example, the rate of hypertension and diabetes in our study was much higher than in Reichlin's validation cohort (68% vs. 52% and 30% vs. 15%, respectively).[21] Similarly, the rates of known CAD, prior MI, and peripheral artery disease were higher in our cohort compared to Reichlin's (33% vs. 26%, 22% vs. 20%, and 7% vs. 2%, receptively).[21]

Data addressing the combination of troponin-only ADPs, like the 0/2-h algorithm and risk scores among U.S. patients are limited. In a study in Europe by Wildi et al.,[12] the addition of a nonischemic ECG and a Thrombolysis in Myocardial Infarction (TIMI) score of ≤1 to the hs-cTnT 0/2-h algorithm improved NPV for 30-day MACE from 99.4% to 100% and 98.8% to 99.4% in two cohorts. Chapman et al.[32] found no significant improvement in NPV of 30-day CDMI when the HEAR score was combined with the High-STEACs pathway; however, the NPV of the High-STEACs pathway alone was 99.7%. By incorporating ECG findings and historical features to a 0/1-h hs-cTnT algorithm, Mokhtari et al.[33] found an improvement in NPV for 30-day MACE from 97.8% to 99.5%. Our results of incorporating a HEAR score into the hs-cTnT 0/2-h pathway demonstrate improvement of potentially clinical significance in safety with NPV improvement to 99.8%, 99.3%, and 99.3% for index and 30- and 90-day CDMI, respectively.

Efficacy of the hs-cTnT 0/2-h algorithm in this cohort was high and similar to results found in prior studies.[11,21] This was also similar to the efficacies reported for the hs-cTnI 0/2-h algorithm.[12,13] In our study, the efficacy of the hs-cTnT 0/2-h protocol was dramatically reduced when the HEAR score was incorporated. This is consistent with prior studies that have shown that the addition of clinical and historical features, such as risk scores, improve safety, but at the cost of efficacy.[6,12] Wildi et al.[12] found that efficacy was reduced from 63.6% to 36.2% and 67.6% to 40.7% in two separate cohorts when the hs-cTnT 0/2-h algorithm was combined with additional clinical features.

Overall, our findings suggest the hs-cTnT 0/2-h algorithm used by itself among U.S. ED patients with chest pain does not achieve a sufficiently high NPV to be considered safe by most clinicians. However, the combination of this pathway with a HEAR score increases NPVs above 99%, though substantively reducing efficacy. Thus, clinicians and hospitals must weigh enhanced safety versus a large reduction in efficacy when considering whether to add a risk score to the 0/2-h algorithm. Further study is necessary to determine methods to improve efficacy of chest pain risk stratification pathways while maintaining safety. In this study, the hs-cTnT 0/2-h algorithm combined with the HEAR score reclassified about half of the hs-cTnT 0/2-h algorithm rule-out zone patients to the observation zone. Identifying which observation zone patients can be safety discharged and receive outpatient care may be one future strategy to improve efficacy while maintaining safety.

LIMITATIONS

Although this study was conducted at eight U.S. EDs, these were mostly academic sites, which limits generalizability to other care settings. Informed consent was required to participate in STOP-CP, resulting in possible selection bias. We describe a safety threshold of NPV ≥99% for 30-day MACE, but acknowledge that some clinicians are willing to accept lower NPV thresholds.[35] The 30-day CDMI and MACE rates in STOP-CP are higher than in previous U.S. cohorts, and this increased prevalence may impact NPV.[29,36] Event rates among hs-cTnT 0/2-hour algorithm zones were low. This study used only the Roche hs-cTnT assay. Therefore, these conclusions cannot be applied to 0/2-hour hs-cTnI algorithm derivations. Time from chest pain onset is included in chest pain pathways, however, in the primary STOP-CP analysis we found no difference in performance as a function of time of chest pain onset and was not included in this analysis.[9,16,34] This study was observational and as such, the hs-cTnT 0/2-h algorithm was not used to guide patient care; thus the clinical impact of the algorithm is unknown. We include index events in test characteristics to provide the most accurate estimation of the effects of the hs-cTnT 0/2-h algorithm application to STOP-CP cohort patients but recognize the study design may cause these index event rates in the rule-out group to be overestimated compared to

a clinical implementation. As such, further prospective evaluation of the hs-cTnT 0/2-h algorithm is necessary.

CONCLUSIONS

In this multisite, prospective U.S. cohort study, the high-sensitivity cardiac troponin T 0/2-h algorithm did not achieve a negative predictive value of ≥99% for 30-day cardiac death or myocardial infarction or major adverse cardiovascular events, suggesting many emergency physicians may not find it sufficient to rule out acute coronary syndrome among U.S. ED patients. Adding a HEAR score to the high-sensitivity cardiac troponin T 0/2-h algorithm improved safety at 30 and 90 days with an negative predictive value of >99% at the expense of efficacy. Further study of algorithms incorporating clinical features with the high-sensitivity cardiac troponin T 0/2-h algortihm is warranted to achieve a better balance between safety and efficacy.

ACKNOWLEDGMENTS

The authors appreciate Mate Huis in't Veld, MD; Michael Massoomi, MD; and James McCord, MD, for adjudicating outcomes in the STOP-CP study. We appreciate Brennan E. Paradee, MS, for her contribution to the analysis.

CONFLICT OF INTEREST STATEMENT

Dr. Supples receives funding from the NIH (UL1TR001420), the National Foundation of Emergency Medicine. Dr. Ashburn receives funding from NHLBI (T32HL076132). Dr. Snavely receives funding from Abbott, HRSA (1H2ARH399760100), and AHRQ (R01HS029017). Dr. Stopyra receives research funding from NCATS/NIH (KL2TR001421), HRSA (H2ARH39976-01-00), Roche Diagnostics, Abbott Laboratories, Pathfast, Genetesis, Cytovale, Forest Devices, Vifor Pharma, and Chiesi Farmaceutici. Dr. Mahler receives funding/support from Roche Diagnostics, Abbott Laboratories, Ortho Clinical Diagnostics, Siemens, Grifols, Pathfast, Quidel, Genetesis, Cytovale, HRSA (1H2ARH399760100), and AHRQ (R01HS029017). He is a consultant for Roche, Quidel, Abbott, Genetesis, Inflammatix, Radiometer, and Amgen and the chief medical officer for Impathiq Inc. Dr. Allen receives research funding/support from Roche Diagnostics, Siemens, and Beckman Coulter. He is a consultant for Roche Diagnostics and Beckman Coulter. Dr. Nowak receives research funding/support from Roche Diagnostics, Beckmann Coulter, Siemens, Abbott Diagnostics, and Ortho Clinical Diagnostics. He is a consultant for Roche Diagnostics, Beckman Coulter, Siemens, Abbott Diagnostics, and Ortho Clinical Diagnostics. Dr Mumma has research support from the NIH (5K08HL130546) and Roche Diagnostics. Dr. Christenson is a consultant for and receives funding/support from Roche Diagnostics, Siemens Healthineers, Beckman Coulter Diagnostics, Becton Dickinson and Co., Quidel Corp, and Sphingotec GMBH. The other authors declare no conflicts of interest.

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How to cite this article: Supples MW, Snavely AC, Ashburn NP, et al. Performance of the 0/2-hour high-sensitivity cardiac troponin T diagnostic protocol in a multisite United States cohort. *Acad Emerg Med*. 2024;31:239-248. doi:10.1111/acem.14827