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Authors

Montgomery, Connor M

Ashburn, Nicklaus P

Snavely, Anna C

et al.

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ORIGINAL ARTICLE

Sex-specific high-sensitivity troponin T cut-points have similar safety but lower efficacy than overall cut-points in a multisite U.S. cohort

Connor M. Montgomery MD[1] | Nicklaus P. Ashburn MD, MS[1] | Anna C. Snavely PhD[1,2] | Brandon Allen MD[3] | Robert Christenson PhD[4] | Troy Madsen MD[5] | James McCord MD[6] | Bryn Mumma MD, MAS[7] | Tara Hashemian MS[1] | Michael Supples MD, MPH[1] | Jason Stopyra MD, MS[1] | R. Gentry Wilkerson MD[8] | Simon A. Mahler MD, MS[1,9,10]

[1]Department of Emergency Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

[2]Department of Biostatistics and Data Science, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

[3]Department of Emergency Medicine, University of Florida College of Medicine, Gainesville, Florida, USA

[4]Department of Pathology, University of Maryland School of Medicine, Baltimore, Maryland, USA

[5]Department of Emergency Medicine, University of Utah School of Medicine, Salt Lake City, Utah, USA

[6]Department of Cardiology, Henry Ford Health System, Detroit, Michigan, USA

[7]Department of Emergency Medicine, University of California Davis School of Medicine, Sacramento, California, USA

[8]Department of Emergency Medicine, University of Maryland School of Medicine, Baltimore, Maryland, USA

[9]Department of Epidemiology and Prevention, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

[10]Department of Implementation Science, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

Abstract

Background: Data comparing the performance of sex-specific to overall (non–sex-specific) high-sensitivity cardiac troponin (hs-cTn) cut-points for diagnosing acute coronary syndrome (ACS) are limited. This study aims to compare the safety and efficacy of sex-specific versus overall 99th percentile high-sensitivity cardiac troponin T (hs-cTnT) cut-points.

Methods: We conducted a secondary analysis of the STOP-CP cohort, which prospectively enrolled emergency department patients ≥21 years old with symptoms suggestive of ACS without ST-elevation on initial electrocardiogram across eight U.S. sites (January 25, 2017–September 6, 2018). Participants with both 0- and 1-h hs-cTnT measures less than or equal to the 99th percentile (sex-specific 22 ng/L for males, 14 ng/L for females; overall 19 ng/L) were classified into the rule-out group. The safety outcome was adjudicated cardiac death or myocardial infarction (MI) at 30 days. Efficacy was defined as the proportion classified to the rule-out group. McNemar's test and a generalized score statistic were used to compare rule-out and 30-day cardiac death or MI rates between strategies. Net reclassification improvement (NRI) index was used to further compare performance.

Results: This analysis included 1430 patients, of whom 45.8% (655/1430) were female; the mean ± SD age was 57.6 ± 12.8 years. At 30 days, cardiac death or MI occurred in 12.8% (183/1430). The rule-out rate was lower using sex-specific versus overall cut-points (70.6% [1010/1430] vs. 72.5% [1037/1430]; $p = 0.003$). Among rule-out patients, the 30-day cardiac death or MI rates were similar for sex-specific (2.4% [24/1010]) vs. overall (2.3% [24/1037]) strategies ($p = 0.79$). Among patients with cardiac death or MI, sex-specific versus overall cut-points correctly reclassified three females and incorrectly reclassified three males. The sex-specific strategy resulted in

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Correspondence
Nicklaus P. Ashburn, Department of Emergency Medicine, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157, USA.
Email: n.ashburn@wakehealth.edu

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a net of 27 patients being incorrectly reclassified into the rule-in group. This led to an NRI of −2.2% (95% CI −5.1% to 0.8%).

Conclusions: Sex-specific hs-cTnT cut-points resulted in fewer patients being ruled out without an improvement in safety compared to the overall cut-point strategy.

KEYWORDS
99th percentile, chest pain, cut-points, sex-specific, troponin

INTRODUCTION

When evaluating patients presenting to the emergency department (ED) for possible acute coronary syndrome (ACS), clinicians rely on cardiac troponin (cTn) to evaluate for myocardial infarction (MI) or injury.[1,2] Many popular accelerated diagnostic protocols (ADPs), such as the European Society of Cardiology (ESC) 0/1-h algorithm, use overall (non–sex-specific) high-sensitivity cTn (hs-cTn) cut-points rather than sex-specific cut-points to risk stratify patients.[1–3] However, recent guidelines recommend using sex-specific cut-points to improve diagnostic accuracy for MI.[1,2]

Sex is a known biologic variable that is associated with hs-cTn measures. Men have higher 99th percentile upper reference limit (URL) hs-cTn values compared to women due to differences in total cardiac mass,[4,5] variations in the rate of cardiac apoptosis,[6] and differences in body composition.[7] Given these biologic differences and the concern regarding higher rates of missed MI in women (who have lower URLs), the U.S. Food and Drug Administration (FDA) and the American College of Cardiology recommend using sex-specific cut-points when evaluating for ACS.[7,8] Despite these recommendations, limited data exist comparing sex-specific versus overall hs-cTn cut-points and these studies have yet to clearly demonstrate the superiority of sex-specific cut-points for safety and efficacy. Thus, many U.S. EDs continue to use ADPs with overall hs-cTn cut-points.

To address this gap in evidence, we evaluated and compared the diagnostic performance (safety and efficacy) of sex-specific and overall 99th percentile URL high-sensitivity cardiac troponin (hs-cTnT) cut-points in a U.S. cohort. We hypothesized that safety, defined by negative predictive value (NPV) for 30-day cardiac death or MI, would be improved with the sex-specific cut-point strategy. In addition, we anticipated that the efficacy (rule-out rate) would be similar between the two strategies.

METHODS

Study design and setting

We performed a preplanned secondary analysis of the High-Sensitivity Cardiac Troponin T (Gen 5 STAT assay) to Optimize Chest Pain Risk Stratification (STOP-CP; ClinicalTrials.gov: NCT02984436) cohort, which prospectively enrolled ED patients being evaluated for ACS across eight U.S. sites from January 25, 2017, to September 6, 2018. Informed consent was obtained from participants. The study sites were the University of Florida, Wake Forest University, Henry Ford Health System, University of Maryland St. Joseph Medical Center, University of Maryland Medical Center, University of Maryland Baltimore Washington Medical Center, University of California–Davis, and University of Utah. The institutional review board at each relevant institution approved the study. The methods used in STOP-CP have been previously described.[8,9] Guidelines from the Standards for Reporting of Diagnostic Accuracy Studies (STARD) assisted in directing the research and manuscript development operations.[10] Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Study population

A convenience sample of patients ≥ 21 years of age being evaluated for acute chest pain or other symptoms concerning for ACS who had serial troponins ordered were included. Exclusion criteria for participants included ST-elevation MI; systolic blood pressure < 90 mm Hg; a noncardiac illness requiring admission; inability to provide consent or be contacted for follow-up; life expectancy < 90 days; and being non–English-speaking, pregnant, or previously enrolled in the study.

hs-cTn measures

Serial blood samples for hs-cTnT measurement were drawn in lithium heparin tubes at baseline within 1 h from first clinical blood draw and 1 h later (±30 min). Blood samples were centrifuged at 3000 × *g* at 4°C for 15 min. One-milliliter samples of plasma were transferred into cryovials before being frozen and shipped on dry ice to the University of Maryland Medical Center. There they were stored at −70°C for analyses by a central laboratory. All laboratory staff were blinded to participant details and outcome. hs-cTnT was quantified with the Gen 5 STAT assay on the cobas immunoanalyzer (Roche Diagnostics). The assay has a range of 3 to 10,000 ng/L, limit of quantification at 6 ng/L. In this analysis, participants with 0- and 1-h hs-cTnT measures were evaluated using previously established sex-specific and overall URLs for this assay in the United States.[11,12] Serial 0- and 1-h hs-cTnT measures less than or equal to an overall 99th percentile URL of 19 ng/L were considered ruled out by the overall cut-point strategy,

while values less than or equal to the sex-specific 99th percentile URLs of 22 ng/L for men and 14 ng/L for women were considered ruled out based on the sex-specific cut-point strategy.[11] hs-cTnT measures were for investigational use only, not for clinical care. Therefore, treating clinicians were blinded to hs-cTnT results and patient care was guided by contemporary cTn results and local standards of care.

Outcomes

The primary outcome was cardiac death or MI at 30 days. Secondary outcomes included (1) efficacy (defined as the proportion of patients ruled out), (2) major adverse cardiovascular events (MACE: a composite of cardiac death, MI, and coronary revascularization) at 30 days, and (3) the individual MACE subcomponents at index and in the 30-day follow-up period. Thirty-day telephone follow-up calls and medical record reviews were performed to determine outcomes. Individuals who experienced MI or death or had a contemporary cTn > 99th percentile URL were adjudicated by four expert reviewers. MI was identified using 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, a new regional wall motion abnormality on cardiac imaging, or identification of plaque rupture or erosion by coronary angiography.[13] To classify deaths as cardiac or noncardiac, adjudicators used the Action to Control Cardiovascular Risk in Diabetes trial definition with the exception of death due to stroke being classified as noncardiac.[14] The death was considered cardiac if the cause of death was unable to be determined. Coronary revascularization was defined as percutaneous coronary intervention, including stent placement as well as angioplasty without stent placement. Coronary revascularization also included coronary artery bypass grafting. At 30 days, 96.2% of the STOP-CP had complete follow-up information available.[8]

Statistical analysis

Counts, percentages, means with standard deviations (SDs), or medians with interquartile ranges (IQRs) were used to describe the study population overall and by sex. Counts and frequencies were determined for cardiac death, MI, and revascularization, as well as for the composite outcomes of cardiac death or MI and MACE, at the index visit and at 30 days inclusive of the index visit. Sex as assigned at birth was determined by research staff via patient self-report and electronic health record review. Test characteristics were computed for the overall population and within subgroups defined by sex to assess the performance of a 0- and 1-h hs-cTnT rule-out strategy using the sex-specific and overall 99th percentile URL cut-points. This included efficacy, sensitivity, specificity, NPV, and positive predictive value (PPV), all reported along with exact 95% CIs. Negative likelihood ratios (LR−) and positive negative likelihood ratios (LR+) were calculated with 95% CIs using the method of Simel et al.[15] McNemar's test was used to compare efficacy (rule-out proportion) between the sex-specific and overall approaches. The predictive values from the sex-specific and overall cut-point approaches were compared using a generalized score statistic. Performance of the overall and sex-specific strategies was also compared using the net reclassification improvement (NRI) index.

RESULTS

This analysis included 1430 patients with 0- and 1-h hs-cTnT measures, of whom 45.8% (655/1430) were female and 42.2% (604/1430) identified as non-White; the mean ± SD age was 57.6 ± 12.8 years. At 30 days, cardiac death or MI occurred in 12.8% (183/1430) and MACE in 14.2% (203/1430) of participants. Table 1 describes the cohort overall and by sex. Figure 1 shows the study flow diagram.

Using a sex-specific cut-point strategy resulted in fewer patients being ruled out compared to using the overall cut-point strategy (70.6% [1010/1430] vs. 72.5% [1037/1430]; $p = 0.003$). The rate of cardiac death or MI at 30 days was similar among patients ruled out using sex-specific and overall cut-points (2.4% [24/1010] vs. 2.3% [24/1037]), corresponding to NPVs of 97.6% (95% CI 96.5%–98.5%) using sex-specific cut-points and 97.7% (95% CI 96.6%–98.5%) using the overall cut-point ($p = 0.79$). Rates of 30-day MACE were also similar (4.2% [42/1010] vs. 4.1% [42/1037]), with corresponding NPVs of 95.8% (95% CI 94.4%–97.0%) and 95.9% (95% CI 94.6%–97.1%; $p = 0.64$). Among rule-in patients, the PPV was lower for the sex-specific versus overall cut-point approach for 30-day cardiac death or MI (37.9% [95% CI 33.2%–42.7%] vs. 40.5% [95% CI 35.6%–45.5%]; $p = 0.004$) as well as for MACE at 30 days (38.3% [95% CI 33.7%–43.2%] vs. 41.0% [95% CI 36.1%–46.0%]; $p = 0.004$). Outcomes are described in Figures 2 and 3 and Table 2. Table 3 summarizes the test characteristics of each cut-point strategy. Tables S1 and S2 show the test characteristics stratified by sex for 30-day cardiac death or MI as well as 30-day MACE for both the sex-specific and overall cut-point strategies.

Compared to the overall cut-point strategy, use of sex-specific cut-points correctly reclassified three female patients with MIs into the rule-in group and incorrectly reclassified three male patients (false negatives for MI). In addition, use of the sex-specific strategy resulted in 27 patients being incorrectly reclassified into the rule-in group (false positives). This led to an overall NRI of −2.2% (95% CI −5.1% to 0.8%). Table 4 describes the patients with 30-day cardiac death or MI who were reclassified using sex-specific cut-points.

DISCUSSION

This multisite, prospective U.S. study found that using sex-specific hs-cTnT cut-points resulted in lower efficacy (fewer patients being ruled-out) with no improvement in safety compared to using an overall (non–sex-specific) hs-cTnT cut-point strategy. Although a sex-specific cut-point strategy identified three additional women

TABLE 1 Cohort characteristics.

	Men ($n=775$)	Women ($n=655$)	Total ($n=1430$)
Age (years)	56.9 (12.8)	58.4 (12.8)	57.6 (12.8)
Race			
American Indian/ Alaska Native	14 (1.8)	9 (1.4)	23 (1.6)
Asian	6 (0.8)	6 (0.9)	12 (0.8)
Native Hawaiian	2 (0.3)	0 (0)	2 (0.1)
Black or African American	256 (33.0)	268 (40.9)	524 (36.6)
White	470 (60.6)	356 (54.4)	826 (57.8)
Other	22 (2.8)	13 (2.0)	35 (2.4)
Unknown	5 (0.6)	3 (0.5)	8 (0.6)
Ethnicity			
Hispanic or Latino	31 (4.0)	26 (4.0)	57 (4.0)
Not Hispanic or Latino	734 (94.7)	625 (95.4)	1359 (95.0)
Unknown	10 (1.3)	4 (0.6)	14 (1.0)
Risk factors			
Known CAD	297 (38.3)	152 (23.2)	449 (31.4)
Current or history of smoking	473 (59.8)	318 (40.2)	791 (55.3)
Hypertension	524 (67.6)	430 (65.6)	954 (66.7)
Hyperlipidemia	394 (50.8)	289 (44.1)	683 (47.8)
Diabetes	219 (28.3)	201 (30.7)	420 (29.4)
Family history of coronary disease	333 (43.0)	328 (50.1)	661 (46.2)
BMI > 30 kg/m^2	384 (49.6)	364 (55.6)	748 (52.3)
Prior cerebrovascular accident	91 (11.7)	63 (9.6)	154 (10.8)
Prior peripheral vascular disease	52 (6.7)	37 (5.6)	89 (6.2)
Prior end-stage renal disease	41 (5.3)	30 (4.6)	71 (5.0)
Chest pain onset			
≤3 h from arrival	280 (36.3)	225 (34.6)	505 (35.5)
>3 h from arrival	491 (63.7)	426 (65.4)	917 (65.5)
ECG at arrival			
Ischemic	51 (6.6)	37 (5.6)	88 (6.2)
Nonischemic	724 (93.4)	618 (94.4)	1342 (93.9)
Initial study hs-cTnT sample (ng/L)	11 (6–27)	7 (4–15)	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 cardiac troponin T; IQR, interquartile range.

with MIs, this strategy also missed an MI in three men and resulted in 27 false positives (patients being classified into the rule-in group, who were ultimately without MI by expert adjudication). Given the lower efficacy and similar safety of sex-specific versus overall cut-points, recent guideline recommendations supporting the use of sex-specific cut-points may need reconsideration.

Our analysis adds to prior studies, which have been unable to demonstrate improved diagnostic accuracy or improved patient outcomes using sex-specific hs-cTn cut-points.[16–20] While Peacock et al.[20] showed that sex-specific cut-points with the initial 0-h hs-cTn measure improved sensitivity and NPV for MI for women, this came at the expense of lower sensitivity and NPV for MI among men. In addition, incorporating serial hs-cTn testing in this study resulted in similar sensitivities and NPVs for sex-specific and overall cut-point strategies.[20] Thus, serial hs-cTn measures and accounting for delta values may obviate the need for sex-specific cut-points. Furthermore, the overall cut-point had a higher PPV for 30-day cardiac death or MI than the sex-specific cut-point. The prospective, diagnostic, multisite Advantageous Predictors of Acute Coronary Syndrome Evaluation Study found that using sex-specific cut-points resulted in very few patients being re-classified. It also showed that sex-specific cut-points did not improve the ability to predict 1-year mortality compared to using an overall cut-point.[18] Furthermore, sex is just one of many biologic variables such as age, symptom onset, renal disease, congestive heart failure, and other comorbidities known to influence troponin measures.[21,22] Focusing solely on sex-based troponin differences is likely an oversimplified approach. Recent machine learning approaches to personalize troponin measures by weighing multiple variables, including but not limited to sex, have yielded impressive diagnostic performance for MI.[21,22]

In our analysis, use of sex-specific hs-cTnT cut-points resulted in nearly 2% more patients being classified to the rule-in group. This increase is clinically meaningful as patients classified into the rule-in group typically receive lengthy and expensive observation or inpatient ACS evaluations.[23] These evaluations contribute to ED and hospital overcrowding, which is recognized by the National Academy of Medicine as a major threat to public health.[24] Furthermore, these observation and inpatient evaluations contribute to ED boarding, which is known to increase mortality and decrease patient safety, quality, access to care, and patient satisfaction.[25,26] Furthermore, we found that using sex-specific cut-points did not improve patient safety, suggesting that the decreased efficacy of this approach may be difficult to justify. These efficacy and safety data should be considered by multidisciplinary health system leaders when determining optimal hs-cTn pathway implementation for patients with acute chest pain.

Using sex-specific cut-points correctly reclassified three female patients and incorrectly reclassified three male patients with 30-day cardiac death or MI. However, upon further chart review, we found that only two of the correctly reclassified female patients had

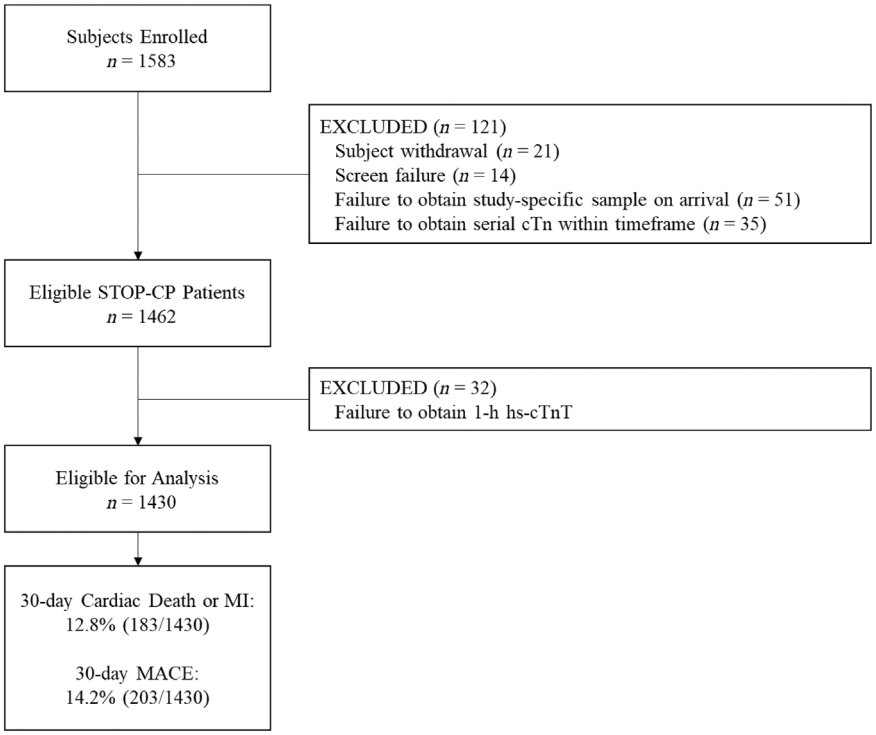

FIGURE 1 Study flow diagram. cTn, cardiac troponin; hs-cTnT, high-sensitivity cardiac troponin T; MI, myocardial infarction; MACE, major adverse cardiovascular event.

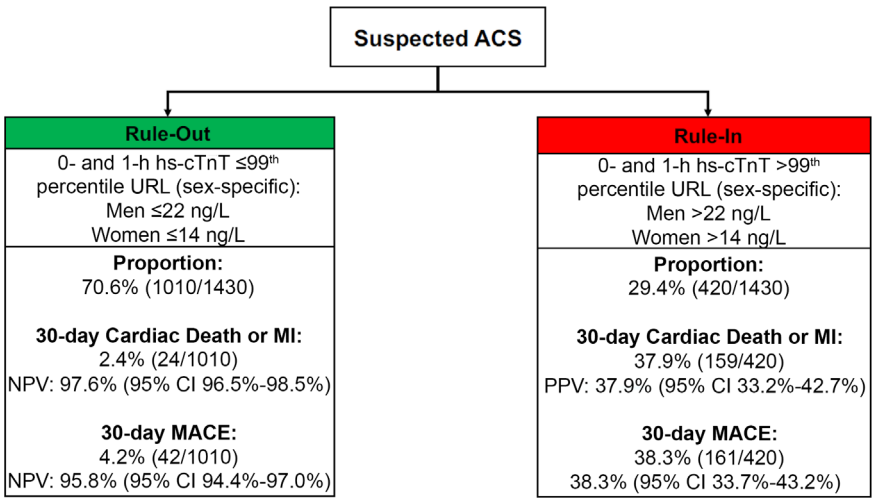

FIGURE 2 Sex-specific hs-cTnT 99th percentile URL cut-point performance. ACS, acute coronary syndrome; hs-cTnT, high-sensitivity cardiac troponin T; MI, myocardial infarction; MACE, major adverse cardiovascular event; NPV, negative predictive value; URL, upper reference limit.

intervenable coronary artery disease while the other female had a Type 2 MI and received no invasive intervention. Meanwhile, the three males who were incorrectly reclassified were false negatives and actually had Type 2 MIs. These findings further suggests that sex-specific cut-points are unlikely to improve patient outcomes.

Several validated ADPs have been designed to assist providers in evaluating patients presenting with symptoms concerning for ACS. In the United States, the History ECG Age Risk factor Troponin Pathway and the ESC 0/1-h algorithm are commonly used ADPs.[1–3,27,28] Neither use sex-specific hs-cTn cut-points, but both achieve similar safety outcomes among men and women.[29,30] Similar safety regardless of sex is likely due to these ADPs leveraging serial hs-cTn measures and delta values. MI is defined, in part, by a temporal rise and fall of troponin; thus in patients experiencing an acute MI, there should be a serial hs-cTn change and significant delta, regardless of sex.[13] Therefore, in an era of ADPs, which utilize serial troponin measures and delta values,[1,2] there is likely little advantage to implementing sex-specific cut-points.

LIMITATIONS

This study has limitations. Our modified 0/1-h algorithm with >99% URL hs-cTnT cut-points did not incorporate delta values. This was a convenient way to study sex-specific versus overall hs-cTnT cut-points, but it does not reflect real-world practice. The STOP-CP cohort was enrolled from eight U.S. sites. However, they were mostly academic medical centers, which limits the generalizability of our

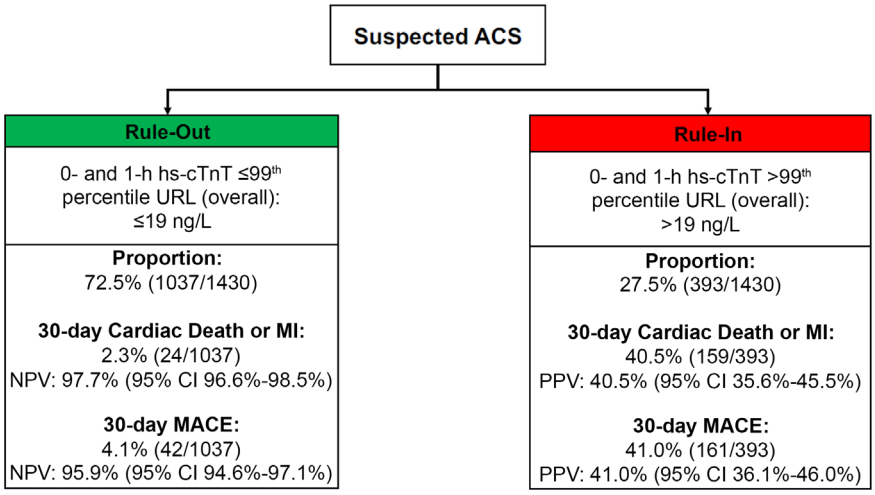

FIGURE 3 Overall (non–sex-specific) hs-cTnT 99th percentile URL cut-point performance. ACS, acute coronary syndrome; hs-cTnT, high-sensitivity cardiac troponin T; MI, myocardial infarction; MACE, major adverse cardiovascular event; NPV, negative predictive value; URL, upper reference limit.

TABLE 2 Safety events by sex-specific and overall hs-cTnT cut-point strategies.

	Sex-specific		Overall		
Safety events	≤ URL ($n=1010$)	> URL ($n=420$)	≤ URL ($n=1037$)	> URL ($n=393$)	Total ($N=1430$)
Index					
Cardiac death	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.3)	2 (0.1)
MI	17 (1.7)	147 (35.0)	18 (1.7)	146 (37.2)	164 (11.5)
Revascularization	15 (1.5)	53 (12.6)	17 (1.6)	51 (13.0)	68 (4.8)
Cardiac death or MI	18 (1.8)	147 (35.0)	19 (1.8)	146 (37.2)	165 (11.5)
MACE (cardiac death + MI + revascularization)	28 (2.8)	148 (35.2)	29 (2.8)	147 (37.4)	176 (12.3)
30-day (index + follow-up)					
Cardiac death	2 (0.2)	7 (1.7)	2 (0.2)	7 (1.8)	9 (0.6)
MI	22 (2.2)	156 (37.1)	22 (2.1)	156 (39.7)	178 (12.4)
Revascularization	23 (2.3)	62 (14.8)	25 (2.4)	60 (15.3)	85 (5.9)
Cardiac death or MI	24 (2.4)	159 (37.9)	24 (2.3)	159 (40.5)	183 (12.8)
MACE (cardiac death + MI + revascularization)	42 (4.2)	161 (38.3)	42 (4.1)	161 (41.0)	203 (14.2)

Abbreviations: hs-cTnT, high-sensitivity cardiac troponin T; MACE, major adverse cardiovascular event; MI, myocardial infarction; URL, 99th percentile upper reference limit.

results to other care settings. Possible selection bias may have resulted from participants being required to give informed consent. Only the Roche hs-cTnT assay was used in this study. Although hs-cTnT and hs-cTnI concentrations are closely correlated, our conclusions cannot be applied to other hs-cTn assays as differences in hs-cTnI versus hs-cTnT assays may influence performance. Additionally, this was an observational study. As such, hs-cTn results were not used to guide patient care. Clinicians were blinded from hs-cTnT results, which helped to minimize verification ("work-up") bias. Furthermore, the primary outcome of cardiac death or MI was chosen in lieu of MACE to help focus on objective cardiovascular outcomes rather than the sometimes subjective and controversial decision to perform revascularization, especially among patients without MI. Although the NRI index is controversial as it gives equal weight to false-positive and false-negative events, we describe the missed events in Table 4 so that readers can make more informed use of the NRI index. Lastly, while the STOP-CP cohort was racially diverse with nearly 40% of the sample being non-White, there were few Hispanic or Latino participants. This was secondary to an exclusion criterion for STOP-CP being non–English-speaking. Future emergency medicine cohorts should strive to be more inclusive.

CONCLUSIONS

Using a sex-specific high-sensitivity cardiac troponin T cut-point strategy resulted in fewer patients being ruled out compared to the overall cut-point strategy. Given ED and hospital crowding, this

TABLE 3 Test characteristics for 30-day cardiac death or MI and MACE using the sex-specific and overall cut-point strategies.

	Sex-specific strategy		Overall strategy	
Test characteristic	30-day cardiac death or MI	30-day MACE	30-day cardiac death or MI	30-day MACE
Efficacy (rule out) (95% CI)	70.6 (68.2–73.0)	70.6 (68.2–73.0)	72.5 (70.1–74.8)	72.5 (70.1–74.8)
Sensitivity (95% CI)	86.9 (81.1–91.4)	79.3 (73.1–84.7)	86.9 (81.1–91.4)	79.3 (73.1–84.7)
Specificity (95% CI)	79.1 (76.7–81.3)	78.9 (76.5–81.1)	81.2 (79.0–83.4)	81.1 (78.8–83.3)
NPV (95% CI)	97.6 (96.5–98.5)	95.8 (94.4–97.0)	97.7 (96.6–98.5)	95.9 (94.6–97.1)
PPV (95% CI)	37.9 (33.2–42.7)	38.3 (33.7–43.2)	40.5 (35.6–45.5)	41.0 (36.1–46.0)
LR– (95% CI)	0.17 (0.11–0.24)	0.26 (0.20–0.34)	0.16 (0.11–0.23)	0.26 (0.19–0.33)
LR+ (95% CI)	4.2 (3.7–4.7)	3.8 (3.3–4.3)	4.6 (4.1–5.3)	4.2 (3.7–4.8)

Note: Data are reported as median (95% CI).

Abbreviations: LR, likelihood ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; NPV, negative predictive value; PPV, positive predictive value.

TABLE 4 Patients reclassified using sex-specific cut-points who had cardiac death or MI at 30 days.

Reclassification type	Event type	Patient description
Incorrect	Type 2 MI	A 33-year-old Black male with a history of congestive heart failure and obesity. Initial hs-cTnT 20 ng/L, 1-h hs-cTnT 22 ng/L. No cardiac catheterization or revascularization procedure was performed.
Incorrect	Type 2 MI	A 62-year-old White male with a history of diabetes, hypertension, hyperlipidemia, obesity, congestive heart failure, stroke, and prior MI with stents. Initial hs-cTnT 22 ng/L, 1-h hs-cTnT 22 ng/L. No cardiac catheterization or revascularization procedure was performed.
Incorrect	Type 2 MI	A 70-year-old White male with obesity, congestive heart failure, and prior MI. Initial hs-cTnT 23 ng/L, 1-h hs-cTnT 22 ng/L. No cardiac catheterization or revascularization procedure was performed.
Correct	Type 2 MI	A 75-year-old White female with hypertension, hyperlipidemia, and a smoking history who had an initial hs-cTnT of 14 ng/L and a 1-h hs-cTnT of 18 ng/L. She was discharged with a diagnosis of nonspecific chest pain. No cardiac catheterization or revascularization procedure was performed.
Correct	Type 1 MI	A 70-year-old White female with diabetes, hypertension, hyperlipidemia, and obesity who had an initial hs-cTnT of 14 ng/L and a repeat hs-cTnT at 1-h of 16 ng/L. She received percutaneous coronary intervention during the index hospitalization.
Correct	Type 1 MI	A 47-year-old Black female with a history of hypertension, hyperlipidemia, and smoking as well as prior MI. Initial hs-cTnT 16 ng/L, 1-h hs-cTnT 19 ng/L. She received percutaneous coronary intervention during the index hospitalization.

Abbreviations: ECG, electrocardiogram; hs-cTnT, high-sensitivity cardiac troponin; MI, myocardial infarction.

decrease in efficacy could have meaningful throughput and operational efficiency implications. Furthermore, there was no significant difference in safety between the two strategies. Therefore, it is likely that using sex-specific high-sensitivity cardiac troponin cut-points adds little clinical value compared to using an overall, non–sex-specific cut-point.

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CONFLICT OF INTEREST STATEMENT

Dr. Ashburn receives funding from NHLBI (K23HL169929), AHRQ (R01HS029017), and the Emergency Medicine Foundation. Dr. Snavely receives funding from Abbott Laboratories, HRSA (1H2ARH399760100), AHRQ (R01HS029017 and R21HS029234), and the Emergency Medicine Foundation. Dr. Stopyra receives research funding from HRSA (H2ARH39976-01-00), AHRQ (R01HS029017 and R21HS029234), The Duke Endowment, Roche Diagnostics, Abbott Laboratories, Pathfast, Genetesis, Cytovale, Forest Devices, Vifor Pharma, and Chiesi Farmaceutici. Dr. Mahler receives funding/support from Roche Diagnostics, Abbott Laboratories, QuidelOrtho, Siemens, Grifols, Pathfast, Beckman Coulter, Genetesis, Cytovale, National Foundation of Emergency Medicine, Duke Endowment, Brainbox, BlueJay Diagnostics, the

Emergency Medicine Foundation, HRSA (1H2ARH399760100), and AHRQ (R01HS029017 and R21HS029234). He is a consultant for Roche, QuidelOrtho, Abbott, Siemens, Inflammatix, and Radiometer and is 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. Mumma has research support from the NIH (5K08HL130546) and Roche Diagnostics. Dr. McCord receives research funding/support from Beckman Coulter, Roche Diagnostics, Abbott Laboratories, and Siemens. He is a consultant for Beckman Coulter, Roche Diagnostics, and Siemens. Dr. Supples receives funding from the NIH (UL1TR001420) and the National Foundation of Emergency Medicine. Dr. Wilkerson received research funding from Regeneron Pharmaceuticals, Inc., Lilly USA, LLC, BioAge Labs, Inc., Roche Diagnostics, Global Blood Therapeutics, Inc., Novartis Pharmaceuticals, Egetis Therapeutics AB, EndPoint Health, Inc., Blade Therapeutics, Janssen R&D LLC, ProvePharma, Beckton, Dickinson and Company, and Pfizer Inc. He has received research funding from CoapTech, LLC through an NIH/NIDDK grant (R44DK115325). He has received research support in the form of equipment and supplies from Cepheid and Eldon Biologicals A/S. He was an uncompensated advisor to CSL Behring. Dr. Christenson is a consultant for and receives funding/support from Roche Diagnostics, Siemens Healthineers, Beckman Coulter Diagnostics, Beckton Dickinson and Company, Quidel Corp., and Sphingotec GMBH. The other authors report no conflicts of interest.

ORCID

Nicklaus P. Ashburn https://orcid.org/0000-0002-3466-8813
Michael Supples https://orcid.org/0000-0001-5999-4554
Jason Stopyra https://orcid.org/0000-0001-7457-3969
Simon A. Mahler https://orcid.org/0000-0003-2199-4078

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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