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Prognostic Performance of a High-Sensitivity Cardiac Troponin I Assay in Patients with Non–ST-Elevation Acute Coronary Syndrome

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BACKGROUND: High-sensitivity assays for cardiac troponin enable more precise measurement of very low concentrations and improved diagnostic accuracy. However, the prognostic value of these measurements, particularly at low concentrations, is less well defined.

METHODS: We evaluated the prognostic performance of a new high-sensitivity cardiac troponin I (hs-cTnI) assay (Abbott ARCHITECT) compared with the commercial fourth generation cTnT assay in 4695 patients with non–ST-segment elevation acute coronary syndromes (NSTE-ACS) from the EARLY-ACS (Early Glycoprotein IIb/IIIa Inhibition in NSTE-ACS) and SEPIA-ACS1-TIMI 42 (Otamixaban for the Treatment of Patients with NSTE-ACS) trials. The primary endpoint was cardiovascular death or new myocardial infarction (MI) at 30 days. Baseline cardiac troponin was categorized at the 99th percentile reference limit (26 ng/L for hs-cTnI; 10 ng/L for cTnT) and at sex-specific 99th percentiles for hs-cTnI.

RESULTS: All patients at baseline had detectable hs-cTnI compared with 94.5% with detectable cTnT. With adjustment for all other elements of the TIMI risk score, patients with hs-cTnI ≥99th percentile had a 3.7-fold higher adjusted risk of cardiovascular death or MI at 30 days relative to patients with hs-cTnI <99th percentile (9.7% vs 3.0%; odds ratio, 3.7; 95% CI, 2.3–5.7; $P < 0.001$). Similarly, when stratified by categories of hs-cTnI, very low concentrations demonstrated a graded association with cardiovascular death or MI (P-trend < 0.001). Use of sex-specific cutpoints did not improve prognostic performance. Patients with negative fourth generation cTnT (<10 ng/L) but hs-cTnI ≥26 ng/L were at increased risk of cardiovascular death/MI compared to those with hs-cTnI <26 ng/L (9.2% vs 2.9%, $P = 0.002$).

CONCLUSIONS: Application of this hs-cTnI assay identified a clinically relevant higher risk of recurrent events among patients with NSTE-ACS, even at very low troponin concentrations.

Cardiac troponin is the preferred biomarker for diagnosis of acute myocardial infarction (MI)[4] and is useful for risk stratification of patients with acute coronary syndrome (ACS) and stable ischemic heart disease *(1–8)*. The European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force, which prepared the third universal definition of MI, recommended a diagnostic cutoff for MI set at a cardiac troponin concentration above the 99th percentile of a healthy reference population, with optimal precision of the assay defined as a CV of ≤10% at the 99th percentile *(1)*. Experts have also proposed defining high-sensitivity assays as those assays that can detect troponin in >50% of apparently healthy individuals *(9)*. Newer high-sensitivity assays for cardiac troponin that meet these specifications have been approved for clinical use and are available in Europe and under regulatory consideration in the US. Although several high-sensitivity cardiac troponin assays have been shown to improve diagnostic accuracy for ACS, the prognostic implications of testing using these assays are less well defined and will require clinical evaluation for each as-

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[4] Nonstandard abbreviations: MI, myocardial infarction; ACS, acute coronary syndrome; hs-cTnI, high-sensitivity cardiac troponin I; NSTE-ACS, non–ST-segment elevation ACS; EARLY-ACS, Early Glycoprotein IIb/IIIa Inhibition in NSTE-ACS; SEPIA-ACS1-TIMI 42, Otamixaban for the Treatment of Patients with NSTE-ACS; PCI, percutaneous coronary intervention; LoD, limit of detection; OR, odds ratio.

say *(10, 11)*. Additionally, the lower detection limits of high-sensitivity cardiac troponin assays allow for better characterization of the normal distribution of troponin concentrations in a healthy reference population. As a result, several high-sensitivity cardiac troponin assays have identified sex-based differences at the 99th percentile *(12, 13)*. However, the clinical and prognostic significance of this finding is unclear. To address these questions, we investigated the prognostic performance of a new high-sensitivity cardiac troponin I (hs-cTnI) assay (Abbott ARCHITECT STAT) in a well-characterized cohort of patients with non–ST-segment elevation ACS (NSTE-ACS).

Materials and Methods

STUDY POPULATION AND ENDPOINTS

For this study, we pooled individual patient-level clinical and biomarker data from 2 trials of patients with NSTE-ACS *(14, 15)*. Entry criteria for the Early Glycoprotein IIb/IIIa Inhibition in NSTE-ACS (EARLY-ACS) (n = 9492) and Otamixaban for the Treatment of Patients with NSTE-ACS (SEPIA-ACS1-TIMI 42) (n = 3241) trials were similar, with both trials enrolling patients with resting chest pain lasting more than 10 min within 24 h of randomization with ischemic electrocardiographic changes or biomarker increases (creatine kinase MB fraction or troponin above the local laboratory upper limit of the reference interval). In EARLY-ACS, patients were randomized to early routine glycoprotein IIb/IIIa inhibitor therapy (eptifibatide) before invasive angiography or delayed, provisional use at the time of percutaneous coronary intervention (PCI) *(14)*. SEPIA-ACS1-TIMI 42 was a dose-ranging randomized study of otamixaban (an intravenous factor Xa inhibitor) vs heparin plus eptifibatide *(15)*. For the purposes of this analysis, we examined the 30-day rates of cardiovascular death or new or recurrent MI (distinct from the qualifying ACS). One of 2 independent clinical event committees, blinded to treatment allocation as well as the investigational biomarker results used in this analysis, adjudicated each endpoint according to definitions that we have published previously *(14, 15)*.

CARDIAC TROPONIN TESTING

Baseline blood samples were obtained on enrollment in EARLY-ACS and SEPIA-ACS1-TIMI 42 for all patients participating in the biomarker substudies. In EARLY-ACS, participation in the biomarker study was limited to sites in North America (n = 2888). All sites in SEPIA were eligible to participate. Serum samples were frozen to temperatures of −20 °C or colder and stored at the TIMI Clinical Trials Laboratory (Boston, MA). Cardiac troponin was measured in all available baseline samples (n = 4695) using an hs-cTnI assay (Abbott ARCHITECT STAT High Sensitive Troponin-I). This hs-cTnI assay is a 2-step, sandwich chemiluminescent magnetic microparticle immunoassay that uses 2 mouse monoclonal antibodies recognizing amino acids 41–49 (capture) and 24–40 (detection) on human cTnI *(16)*. The assay has a limit of detection (LoD) of 1.5 ng/L and a CV of 10% at 3.0 ng/L *(16, 17)*. Recent analytic characterization in 1531 apparently healthy individuals identified an overall 99th percentile reference limit of 26 ng/L, with sex-specific 99th percentile reference limits of 16 ng/L for females and 34 ng/L for males *(17)*. Troponin T was also measured, using the troponin T assay that is currently available commercially in the US (cTnT, fourth generation, Roche Diagnostics), in 4221 of the 4695 study participants with hs-cTnI data. This assay has an LoD of 10 ng/L, a 99th percentile limit of 10 ng/L and a 10% CV at 30 ng/L.

STATISTICAL METHODS

Baseline characteristics were compared using χ^2 or Wilcoxon rank–sum testing for categorical and continuous variables, respectively. Event rates were stratified by using guideline-based hs-cTnI cutpoints, including the overall 99th percentile (26 ng/L) and sex-specific 99th percentile (34 ng/L for males, 16 ng/L for females), as well as capturing a range of concentrations below the 99th percentile. Event rates are presented as proportions at 30 days. Logistic regression analysis was used to evaluate the relationship between hs-cTnI and 30-day clinical outcomes. Adjusted analyses incorporated clinical elements of the TIMI risk score for unstable angina/NSTEMI, including age, recent aspirin use, multiple coronary risk factors, known coronary disease, and ST-segment deviation *(18)*. Testing for heterogeneity by treatment group for each trial was performed using logistic regression with a term for interaction of hs-cTnI status with treatment allocation. All statistical analyses were performed using SAS version 9.2 and STATA version 12.

Results

BASELINE CHARACTERISTICS

Baseline characteristics are shown in Table 1 for the 4695 patients with baseline samples available for determination of hs-cTnI. The baseline hs-cTnI concentration was detectable (>LoD) in 100% of patients and was ≥99th percentile in 85% of the patients in this population with NSTE-ACS; 82% were >50 ng/L, 78% >100 ng/L, and 50% >1500 ng/L. The mean (SD) time from symptom onset to randomization and cardiac troponin measurement [13 (8) h] was not found to be significantly different in those with hs-cTnI above or below the 99th percentile ($P = 0.21$). In general, pa-

Table 1. Baseline characteristics.

	hs-TnI <26 ng/L (n = 703)	hsTnI ≥26 ng/L (n = 3992)	*P*
General characteristics			
Age, years, mean (SD)	63 (11)	64 (11)	0.039
Male, %	58.2	70.8	<0.001
CrCl <50 mL/min, %	9.6	13.3	0.0069
Medical history, %			
Hypertension	76.1	71.3	0.0092
Hyperlipidemia	63.4	56.4	<0.001
Current smoker	23.7	32.1	<0.001
Diabetes mellitus	28.9	31.1	0.25
Previous MI	24.1	26.4	0.20
Previous congestive heart failure	7.4	8.1	0.56
Previous PCI or coronary artery bypass graft	35.0	30.8	0.026
Index presentation			
ST-segment deviation ≥0.1 mV, %	76.3	44.0	<0.001
Increased local troponin or creatine kinase MB, %	28.4	91.6	<0.001
Time from symptom onset, hours, mean, (SD)	13 (8)	13 (8)	0.21
TIMI risk score on presentation, %			
High (5–7)	21.6	34.7	<0.001
Intermediate (3–4)	59.3	55.7	
Low (0–2)	19.1	9.5	
Therapy during index hospitalization, %			
Aspirin	98.2	98.1	0.95
Clopidogrel	87.5	86.3	0.43
β blocker	77.8	87.5	<0.001
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	63.1	71.1	<0.001
Statin	81.1	86.1	<0.001
Revascularization during index hospitalization, %			
PCI	44.0	60.6	<0.001
Coronary artery bypass graft	4.7	10.9	<0.001

tients with an hs-cTnI ≥26 ng/L were older with a higher TIMI risk score on presentation. They were also more likely to receive evidence-based therapies. Among patients with available fourth generation cTnT results, cTnT was ≥99th percentile (10 ng/L) in 94.5%.

OUTCOMES BY hs-cTnI CONCENTRATION

Overall 99th percentile reference limit. At 30 days, patients with a baseline hs-cTnI ≥26 ng/L had a significantly higher rate of cardiovascular death or MI compared with those with a baseline measurement below the reference limit [9.7% vs 3.0%; adjusted odds ratio (OR) 3.7; 95%, CI 2.3–5.7; $P < 0.001$] (Fig. 1), translating to a 3.7-fold increased risk after adjustment for elements of the TIMI risk score. This relationship was consistent for individual endpoints of cardiovascular death ($P = 0.002$), MI ($P < 0.001$), and all-cause death ($P < 0.001$) at 30 days (Table 2).

Importantly, patients with concentrations of hs-cTnI in the range immediately above the 99th percentile (26–50 ng/L, n = 149) were at similarly increased risk of cardiovascular death or MI (8.7%, $P = 0.003$ vs hs-cTnI <26 ng/L) to those with hs-cTnI >1500 ng/L (10.4%, n = 2332, $P < 0.0001$). Moreover, when hs-cTnI and fourth generation cTnT were compared, hs-cTnI identified patients with negative cTnT who were at high risk and offered an improved negative predictive value (Fig. 2). Patients with positive hs-cTnI and negative cTnT had significantly higher rates of cardiovascular death/MI (9.2% vs 2.9%, $P = 0.003$) and MI

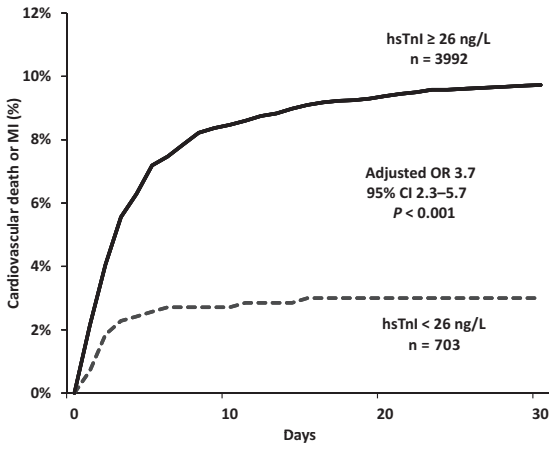

Fig. 1. Kaplan–Meier estimated rates of cardiovascular death or MI through 30 days stratified by baseline hs-cTnI at the 99th percentile reference limit (26 ng/L).
Adjusted analyses incorporated clinical elements of the TIMI risk score for unstable angina/NSTEMI, including age, recent aspirin use, multiple coronary risk factors, known coronary disease, and ST-segment deviation.

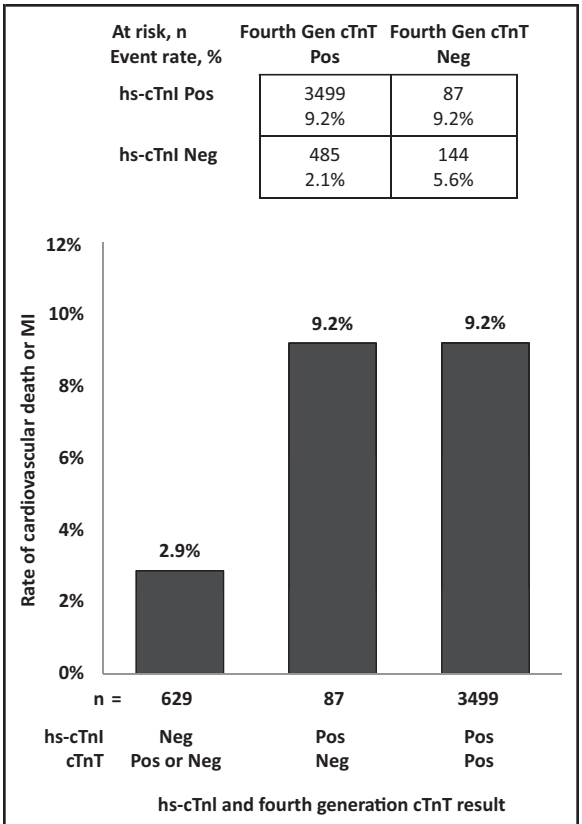

Fig. 2. Cardiovascular death or MI at 30 days stratified by both baseline hs-cTnI and fourth generation cTnT results. Pos, positive; Neg, negative.

(9.2% vs 2.5%, $P = 0.001$) at 30 days compared with patients who had negative results for hs-cTnI (Fig. 2). For all analyses, there was no detectable treatment interaction between baseline hs-cTnI and outcomes with otamixaban (P-interaction = 0.98) or early eptifibatide (P-interaction = 0.45).

Detectable hs-cTnI below the 99th percentile. Among the 15% (n = 703) of the total population with a baseline hs-cTnI concentration below the overall 99th percentile reference limit (26 ng/L), all of whom had detectable troponin (>1.5 ng/L), stratification into tertiles identified an apparent gradient of risk that was significant (P-trend <0.001) when considered across the entire range of troponin values (Fig. 3).

Sex-specific 99th percentile reference limit. Using the sex-specific 99th percentile reference limits, men and women with increased hs-cTnI were at higher risk of cardiovascular death/MI (Fig. 4; 9.7% vs 3.4%, $P \leq 0.0001$). Compared with using the overall 99th percentile cutpoint, application of the sex-specific reference range resulted in a net reclassification of 6 patients to a low-risk category by virtue of a negative baseline hs-cTnI. Three of these reclassified patients experienced cardiovascular death or MI in the subsequent 30 days, resulting in a slight decrease in the overall negative predictive performance of the assay from 97.0% to 96.6%, P = not significant. When stratified by sex, all 3 reclassified events occurred in the male cohort between the

Table 2. hs-cTnI and 30-day cardiovascular outcomes.

Outcome	hs-cTnI <26 ng/L, n (%) (n = 703)	hs-cTnI ≥26 ng/L, n (%) (n = 3992)	Adjusted OR (95% CI)	*P*
Cardiovascular death or MI	21 (3.0%)	388 (9.7%)	3.7 (2.3, 5.7)	<0.001
Cardiovascular death	3 (0.4%)	91 (2.3%)	6.2 (2.0, 19.7)	0.002
MI	19 (2.7%)	322 (8.1%)	3.2 (2.0, 5.2)	<0.001
All-cause death	3 (0.4%)	110 (2.8%)	7.2 (2.3, 22.9)	<0.001

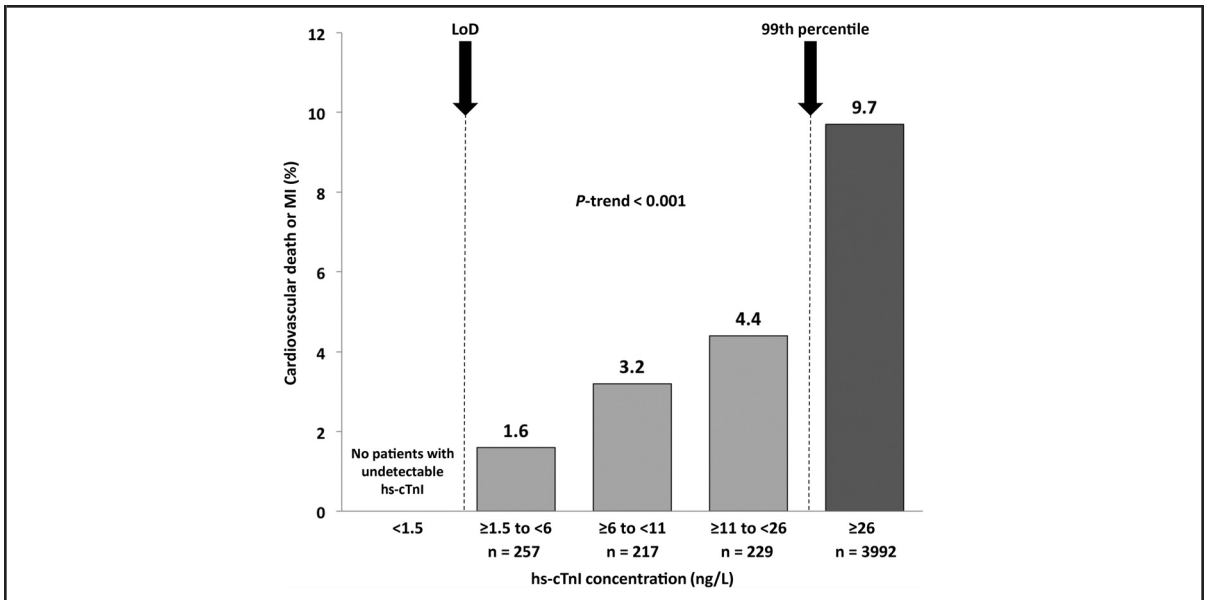

Fig. 3. Graded relationship between hs-cTnI and cardiovascular death or MI at 30 days.
Testing for a trend across all categories of hs-cTnI was significant (*P*-trend $<$ 0.001).

overall and sex-specific 99th percentile range (26–34 ng/L) (Fig. 4B).

Discussion

With the development of high-sensitivity cardiac troponin assays, it is possible to measure low concentrations of troponin and to characterize troponin distribution in healthy populations with greater precision. In this context, the recommended clinical decision limits have moved toward lower concentrations *(1)*. While this improved analytic performance has resulted in better diagnostic accuracy, the clinical relevance of low or very low levels of troponin increase requires evaluation with each new assay. Moreover, the high-sensitivity assays have more clearly indi-

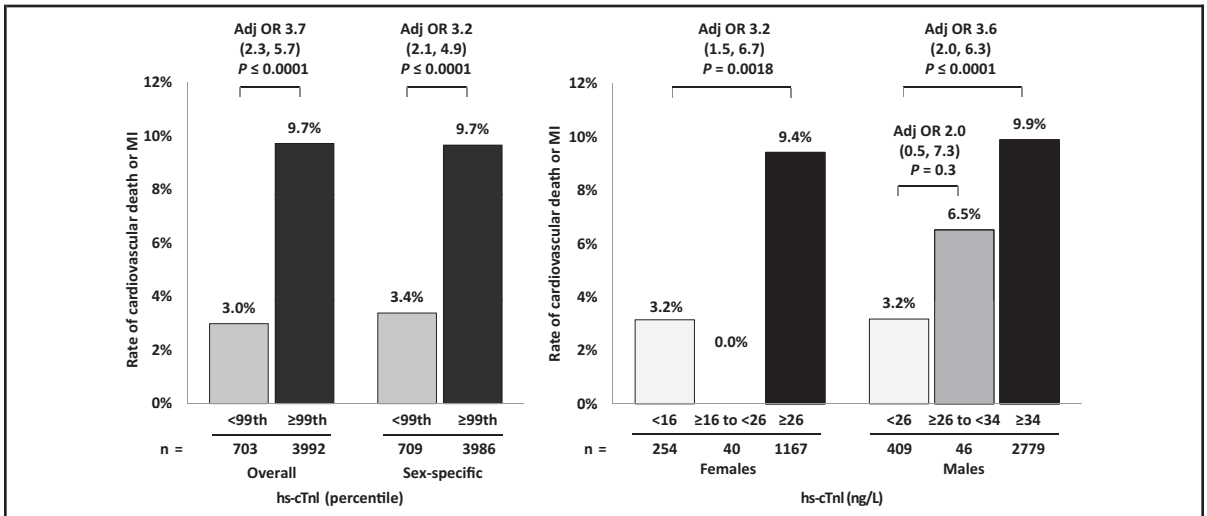

Fig. 4. Cardiovascular death or MI at 30 days stratified by sex-specific 99th percentile cutpoints for hs-cTnI. Adj, adjusted.

cated a difference between the 99th percentile for men compared with women. However, the implications for the application of sex-specific prognostic decision limits remain unclear *(12, 13)*.

In this study of a new hs-cTnI assay in more than 4600 patients, we found that the assay performed well prognostically, identifying patients at significantly higher 30-day risk of cardiovascular death or new MI using the guideline-based 99th percentile decision limit. Moreover, our findings revealed a gradient of risk at the very low end of concentrations not reliably measured with previous generations of the same assay, supporting the prognostic relevance of cardiac troponin values detected with this hs-cTnI assay. Furthermore, when compared to the current generation cTnT assay that is presently used in the US, the hs-cTnI assay demonstrated improved prognostic performance. Notably, a cardiac troponin concentration less than the 99th percentile cutpoint identified a cohort of patients with a clinical diagnosis of NSTE-ACS who were at low risk for death or recurrent ischemic events over 30 days; identification of this low-risk group was improved with hs-cTnI compared with the current commercial assay for cTnT. Notably, we found that the hs-cTnI assay not only identified high-risk patients who had a negative result with the fourth generation cTnT assay but also correctly stratified lower-risk patients who had positive results with fourth generation cTnT at the 99th percentile. Therefore, the enhanced prognostic performance of the hs-cTnI assay derives not solely from increased clinical sensitivity but rather is likely related to overall improved analytical performance and the relatively poor precision of the fourth generation cTnT assay at the low end of concentration (<30 ng/L). The concept that improved analytical performance can confer improved clinical risk assessment has been suggested previously *(9)* and is supported by our findings.

In addition, our finding of a graded pattern of risk among patients with very low increases in hs-cTnI concentration, between the LoD and 99th percentile, is consistent with and adds to observations from other studies revealing an association between troponin values below the 99th percentile and adverse cardiovascular events in patients without known heart disease, those with stable coronary artery disease, and patients who were 6 months post-ACS *(5, 7, 19, 20)*. Whereas our previous work with a sensitive assay for cTnI showed an apparent threshold of risk at the 99th percentile decision limit *(21)*, this work with a high-sensitivity assay further revealed a probable graded pattern of risk below the 99th percentile.

We also were able to evaluate the application of sex-specific cutpoints and found that use of a higher sex-specific decision limit for male patients led to misclassification of study participants at intermediate to high- risk of recurrent cardiovascular events into a lower risk group. Despite the substantial sample size in our study, the number of patients who fell into the range between the overall and sex-specific cutpoints was small. Nevertheless, our findings in this data set would not support the need for sex-specific cutpoints for prognosis when weighed against the potential to confuse clinicians with multiple decision limits for the same assay.

A limitation of the study relates to the patient population. The population studied was enrolled in a clinical trial on the basis of typical ischemic symptoms along with other evidence of ischemia (either ST-segment changes or increases in biomarkers). As such, these patients are more selected than the average patient presenting to the emergency room with chest pain. Specifically, our study does not address the prognostic significance of increased cardiac troponin in patients with symptoms atypical for MI or with other acute illnesses. Therefore, it is possible that our findings cannot be generalized to patients with a low suspicion for ACS who are found to have increased troponin concentrations in the emergency setting. However, this aspect renders the observation of the very high negative predictive value (in the presence of typical symptoms) for those without detectable hs-cTnI even more compelling.

In conclusion, testing using a high-sensitivity assay for cTnI at presentation gives robust prognostic performance at the 99th percentile cutpoint, demonstrates a gradient of risk at very low ranges of concentrations, and performs better with respect to prognosis than a current commercial assay in the US. Sex-specific decision limits did not improve prognostic performance in this dataset.

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