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ORIGINAL INVESTIGATIONS

Myocardial Infarction Risk Stratification With a Single Measurement of High-Sensitivity Troponin I

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ABSTRACT

BACKGROUND Limited data exist on rapid risk-stratification strategies using the U.S. Food and Drug Administration–cleared high-sensitivity cardiac troponin I (hs-cTnI) assays.

OBJECTIVES This study sought to examine single measurement hs-cTnI to identify patients at low and high risk for acute myocardial infarction (MI).

METHODS This was a prospective, multicenter, observational study of patients with suspected acute MI enrolled across 29 U.S. sites with hs-cTnI measured using the Atellica IM TnIH and ADVIA Centaur TNIH (Siemens Healthineers) assays. To identify low-risk patients, sensitivities and negative predictive values (NPVs) for acute MI and MI or death at 30 days were examined across baseline hs-cTnI concentrations. To identify high-risk patients, positive predictive values and specificities for acute MI were evaluated.

RESULTS Among 2,212 patients, acute MI occurred in 12%. The limits of detection or quantitation resulted in excellent sensitivities (range 98.6% to 99.6%) and NPVs (range 99.5% to 99.8%) for acute MI or death at 30 days across both assays. An optimized threshold of <5 ng/l identified almost one-half of all patients as low risk, with sensitivities of 98.6% (95% confidence interval: 97.2% to 100%) and NPVs of 99.6% (95% confidence interval: 99.2% to 99.9%) for acute MI or death at 30 days across both assays. For high-risk patients, hs-cTnI ≥120 ng/l resulted in positive predictive values for acute MI of ≥70%.

CONCLUSIONS Recognizing the continuous relationship between baseline hs-cTnI and risk for adverse events, using 2 Food and Drug Administration–cleared hs-cTnI assays, an optimized threshold of <5 ng/l safely identified almost one-half of all patients as low risk at presentation, with hs-cTnI ≥120 ng/l identifying high-risk patients.
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ABBREVIATIONS AND ACRONYMS

CI = confidence interval
cTn = cardiac troponin
CV = coefficient of variation
ECG = electrocardiogram
ED = emergency department
FDA = Food and Drug Administration
hs = high-sensitivity
LoD = limit of detection
LoQ = limit of quantitation
MI = myocardial infarction
NPV = negative predictive value
PPV = positive predictive value
RCT = randomized clinical trial
URL = upper reference limit

Cardiac troponin (cTn) measurements are used to detect myocardial injury and support the diagnosis of acute myocardial infarction (MI) (1). High-sensitivity (hs) cTnI and hs-cTnT assays have been used clinically outside the United States for several years (2–4), with limited data and experience in the United States. The improved analytical performance offered by hs assays has allowed for the quantification of cTn at lower concentrations and enabled the development and validation of several novel, rapid risk-stratification strategies that were not possible using contemporary cTn assays (2–6). The implementation of hs-cTn assays permits the use of evidence-based triaging algorithms that facilitate the more rapid evaluation and risk stratification of patients with suspected MI; enabling early emergency department (ED) discharge in selected patients, reducing overcrowding and costs. European guidelines have provided Class I recommendations for protocols that rule out acute MI within 3 h since 2011, and within 1 h since 2015 (7,8).

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Single-measurement strategies promise a simple, practical approach offering an immediate estimation of risk upon presentation. Several studies, including 2 large meta-analyses, suggest that a single hs-cTnI (Abbott Diagnostics, Chicago, Illinois) or hs-cTnT (Roche Diagnostics, Rotkreuz, Switzerland) measurement can be used to safely exclude acute MI and identify patients at very low risk for adverse cardiac events on 30-day follow-up (9–11). These approaches remain limited in the United States because data are based on either the Abbott hs-cTnI assay, which has not been cleared by the U.S. Food and Drug Administration (FDA) for clinical use, and the Roche hs-cTnT assay that was FDA cleared as the Gen 5 cTnT assay (January 2017) but only reports down to 6 ng/l, the limit of quantitation (LoQ) (defined as the 20% coefficient of variation [CV] concentration). Prior hs-cTnT studies used 3 ng/l or 5 ng/l, the limit of detection (LoD) concentration used outside the United States, based on the Roche instrument and assay used. For single-sample MI rule-out in the United States, more data are needed using the 6 ng/l threshold (12–14).

In early 2018, several hs-cTnI assays (Siemens Healthineers [Erlangen, Germany] and Beckman) received FDA clearance for clinical use. However, no studies to date have examined rapid, single-measurement, risk-stratification strategies using these hs-cTnI assays in a U.S.-based population. Our goals were to examine the diagnostic performance, safety, and efficiency of single hs-cTnI measurement strategies using the Atellica IM TnIH and ADVIA Centaur TNIH assays (Siemens Healthineers) to identify patients at low and high risk for acute MI in a multicenter U.S.-based study.

METHODS

STUDY DESIGN AND POPULATION. Following institutional review board approval at each participating site, 29 U.S. centers (Online Table 1) prospectively enrolled ED patients 22 years of age or older with suspected acute MI. Paired serum and lithium heparin samples were collected at presentation and 4 additional time points, when possible, from April 2015 to April 2016. Written informed consent was obtained from all participants as part of enrollment. This analysis is a substudy of the HIGH-US (High-Sensitivity Cardiac Troponin I Assays in the United States) study, for which a detailed description of the study design and methods has been reported (15). The

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present study required patients to have at least 1 hs-cTnI concentration available at presentation using both the Atellica IM TnIH and ADVIA Centaur TNIH assays. Patients in whom results were not available for either 1 or both assays, did not have a valid baseline hs-cTnI result, did not have a 12-lead electrocardiogram (ECG), in whom post-discharge follow-up was missing, or presented with ST-segment elevation MI were excluded from analyses.

cTnI ASSAYS. The Atellica IM and ADVIA Centaur hs-cTnI assays (Siemens Healthineers) are 3-site sandwich immunoassays sharing the same assay design, antibodies (capture amino acids: 41 to 50, 171 to 190; detection amino acids: 29 to 34), and direct chemiluminescent technology (15). Both assays meet hs designation as defined by the International Federation of Clinical Chemistry Committee on Clinical Applications of Cardiac Bio-Markers and the American Association of Clinical Chemistry Academy (6), with the Atellica IM assay measuring cTn ≥LoD in 75% of healthy individuals and having a total imprecision (%CV) of <4.0% at the 99th percentile upper reference limit (URL), and the ADVIA Centaur measuring 63% ≥LoD with a %CV of 4.9% at the 99th percentile URL (16). For both assays, the manufacturer reports the same LoD (lowest analyte concentration that can be reliably detected being different than zero) and LoQ (lowest concentration that has a total imprecision of ≤20% [20% CV]) values of 1.6 ng/l and 2.5 ng/l, respectively (17). For the Atellica IM assay, the mean value at the 10% CV is 4.85 (95% confidence interval [CI]: 4.56 to 5.43) ng/l and for the ADVIA Centaur assay is 4.46 (95% CI: 3.28 to 5.85) ng/l. For the Atellica IM assay (lithium heparin samples), the overall 99th percentile URL is 45 ng/l, with sex-specific 99th percentile URLs of 34 ng/l for women and 53 ng/l for men. For the ADVIA Centaur assay (lithium heparin samples), the overall 99th percentile is 47 ng/l, with sex-specific 99th percentile URLs of 37 ng/l for women and 57 ng/l for men (Online Table 2) (17). Following International Federation of Clinical Chemistry Committee on Clinical Applications of Cardiac Bio-Markers recommendations to use whole numbers (ng/l) (no decimals) for laboratory reporting of hs assays in clinical practice (5,6), values were rounded up or down to the nearest whole number (e.g., LoQ 2.5 ng/l was analyzed as 3.0 ng/l). These assays were measured for investigational purposes, with the local contemporary cTn assays (Online Table 3) used for clinical decision-making.

MI ADJUDICATION. Following review of relevant clinical information and the local hospital standard cTn results, including both the manufacturers' package and locally established cTn cutoffs (where applicable) (15), cases were adjudicated for MI (including type 1 and 2 MI) following the Third Universal Definition of MI consensus recommendations (18). Each case was adjudicated by a unique combination of 5 adjudicators, with a majority rule applied to determine the final MI classification. The adjudicators were blinded to the investigational Atellica IM and ADVIA Centaur hs-cTnI results and patient diagnosis established by the treating hospital. Each adjudicator independently used their expert opinion to assess whether the requirements of an MI diagnosis were met.

OUTCOMES. For the evaluation of single-measurement rule-out strategies, a diagnostic outcome of acute MI at the index hospitalization, and a composite safety outcome of MI or death at 30 days including events occurring during the index hospitalization, were examined. To evaluate efficiency, the proportion of patients eligible for safe rule-out was examined.

For the evaluation of single measurement strategies to identify patients at high risk for MI at presentation, positive predictive values (PPVs) and diagnostic specificities for index hospitalization MI were examined across baseline hs-cTnI concentrations using both the Atellica IM and ADVIA Centaur assays.

STATISTICAL ANALYSES. Categorical variables were compared using the chi-square test. Continuous variables were compared using the F-test. Negative predictive values (NPV) and diagnostic sensitivities with corresponding 95% CIs were calculated to examine the diagnostic performance and safety of rule-out strategies across baseline hs-cTnI concentrations for both the Atellica IM and ADVIA Centaur assays. They were examined for established analytical thresholds such as the LoD and LoQ, and across the continuum of baseline concentrations at presentation to identify thresholds, if possible, tailored to maximize efficiency (proportion of patients eligible for safe rule-out) that provided an acceptable miss rate (19). Single-measurement rule-out strategies were also examined in combination with a non-ischemic 12-lead ECG.

Following recommendations from the 2018 American College of Emergency Physicians clinical policy on the evaluation of patients with suspected non-ST-segment elevation acute coronary syndromes, missed diagnostic rates of 1% to 2% for 30-day major adverse cardiac events were considered acceptable (19). To evaluate the safety of single-measurement rule-out strategies, subgroup analyses were performed according to age, sex, chest pain, ECG findings (normal ECG defined as a sinus rhythm with

TABLE 1 Baseline Characteristics (N = 2,212)

Demographics	
Age, yrs	57 ± 13
Female	969 (44.0)
Race	
White	1,235 (56.0)
Black	886 (40.0)
Asian	22 (1.0)
Hawaiian	3 (0.1)
American Indian	15 (0.7)
Multiple	18 (0.8)
Other	33 (1.5)
Comorbidities	
Hypertension	1,539 (70.0)
Diabetes mellitus	658 (30.0)
Coronary artery disease	834 (38.0)
Congestive heart failure	443 (20.0)
Smoking	597 (27.0)
Presenting symptoms	
Chest pain	1,799 (81.0)
Shortness of breath	230 (10.0)
Other	183 (8.3)
Symptom onset <3 h, early presenters	795 (36.0)
Laboratory measurements	
Atellica IM hs-cTnI assay	
Baseline <LoD 1.6 ng/l	505 (23.0)
Baseline <LoQ	732 (33.0)
Baseline concentration	170 ± 1,109
ADVIA Centaur hs-cTnI assay	
Baseline <LoD 1.6 ng/l	455 (21.0)
Baseline <LoQ	690 (31.0)
Baseline concentration, ng/l	178 ± 1,131

Values are mean ± SD or n (%).
hs-cTnI = high-sensitivity cardiac troponin I; LoD = limit of detection; LoQ = limit of quantitation.

normal ST-T wave segments), coronary artery disease, suspicion risk for acute coronary syndrome, and early presenters (<3 h after symptom onset). PPVs and diagnostic specificities with corresponding 95% CIs were calculated across the continuum of baseline hs-cTnI concentrations to identify concentration thresholds at presentation associated with a high-risk of acute MI.

RESULTS

Following study exclusions (Online Figure 1), 2,212 patients met criteria for the present analysis. Baseline characteristics are shown in **Table 1**. Patients with baseline hs-cTnI concentrations <LoQ using either the Atellica IM or ADVIA Centaur assays were younger and less likely to have comorbidities as compared with those with quantifiable cTn (Online Tables 4 and 5). The diagnostic outcome of adjudicated acute MI during the index hospitalization occurred in 12% (n = 259) of patients, of which 37% were type 2 MIs. The safety outcome of acute MI or death, including index MIs, occurred in 13% (n = 277 events) of patients, including 22 deaths.

SINGLE-MEASUREMENT RISK-STRATIFICATION STRATEGIES USING THE ATELLICA IM hs-cTnI ASSAY. Use of analytical threshold to identify patients at low risk. Using the Atellica IM hs-cTnI assay, 23% (n = 505) and 33% (n = 732) had baseline hs-cTnI concentrations below the LoD (<2 ng/l) and LoQ (<3 ng/l), respectively. For ruling-out MI, using hs-cTnI concentrations below the LoD or LoQ resulted in excellent diagnostic performance for index hospitalization MI with sensitivities of 99.6% (95% CI: 98.9% to 100%) and 98.8% (95% CI: 97.5% to 100%) and NPVs of 99.8% (95% CI: 99.4% to 100%) and 99.6% (95% CI: 99.1% to 100%), respectively (**Table 2**). Single-measurement strategies using these analytical thresholds was shown to be safe, with sensitivities of 99.3% (95% CI: 98.3% to 100%) and 98.6% (95% CI: 97.2% to 100%) for death or MI at 30 days using concentrations <LoD and <LoQ, respectively. The use of baseline hs-cTnI <LoQ resulted in a higher efficiency than the LoD (33% vs. 23%) based on the proportion of patients safely identified as low risk. There were no statistical differences observed in the safety of hs-cTnI <LoQ across selected subgroups (including early presenters) as shown in Online Figure 2.

Use of optimized thresholds to identify patients at low and high risk. Diagnostic metrics for acute MI across baseline hs-cTnI concentrations are shown in **Figures 1A and 1B**. A continuous relationship was observed between baseline hs-cTnI concentrations and the risk for acute MI, with very low hs-cTnI concentrations associated with high diagnostic sensitivities and NPVs (i.e., enable the identification of patients at low risk), and higher hs-cTnI concentrations associated with higher specificities and PPVs (i.e., enable the identification of patients at high risk).

For the identification of patients at low risk, a baseline hs-cTnI concentration <5 ng/l was identified as the optimal concentration threshold that maximized efficiency (i.e., proportion of patients eligible for rule-out) while maintaining safety. Baseline hs-cTnI <5 ng/l identified 47% of patients as low risk and resulted in a diagnostic sensitivity and NPV of 98.8% (95% CI: 97.5% to 100%) and 99.7% (95% CI: 99.4% to 100%) for acute MI, respectively, with a sensitivity and NPV of 98.6% (95% CI: 97.2% to 100%) and 99.6% (95% CI: 99.2% to 100%), respectively, for acute MI or death at 30 days (Online Table 6). This

TABLE 2 Diagnostic Performance, Safety, and Efficacy of the Atellica IM and ADVIA Centaur Hs-cTnI Assay for Selected Single-Measurement Rule-Out Strategies

	Analytical Thresholds				Optimized Rule-Out Thresholds	
	Baseline Hs-cTnI <LoD <2 ng/l		Baseline Hs-cTnI <LoQ <3 ng/l		Baseline Hs-cTnI <5 ng/l	
	Atellica IM	ADVIA Centaur	Atellica IM	ADVIA Centaur	Atellica IM	ADVIA Centaur
Diagnostic performance of rule-out strategies for ruling out index hospitalization acute MI						
Sensitivity, %	99.6 (98.9-100)	100 (98.6-100)	98.8 (97.5-100)	99.2 (98.2-100)	98.8 (97.5-100)	99.2 (98.2-100)
NPV, %	99.8 (99.4-100)	100 (99.2-100)	99.6 (99.1-100)	99.7 (99.3-100)	99.7 (99.4-100)	99.8 (99.5-100)
Missed MIs	1	0	3	2	3	2
Missed MI rate among those with a negative test	0.2 (1/505)	0 (0/455)	0.4 (3/732)	0.3 (2/690)	0.3 (3/1040)	0.2 (2/1015)
Safety of rule-out strategies based on 30-day acute MI or death						
Sensitivity, %	99.3 (98.3-100)	99.6 (98.9-100)	98.6 (97.2-100)	98.9 (97.7-100)	98.6 (97.2-100)	98.6 (97.2-100)
NPV, %	99.6 (99.1-100)	99.8 (99.3-100)	99.5 (98.9-100)	99.6 (99.1-100)	99.6 (99.2-100)	99.6 (99.2-100)
Missed events	2	1	4	3	4	4
Missed event rate among those with a negative test	0.4 (2/505)	0.2 (1/455)	0.5 (4/732)	0.4 (3/690)	0.4 (4/1,040)	0.4 (4/1,015)
Proportion of patients qualifying as low risk (efficacy)						
Proportion qualifying, %	23	21	33	31	47	46

Values are mean (95% confidence interval), n, or % (n/N), unless otherwise indicated.
MI = myocardial infarction; NPV = negative predictive value; PPV = positive predictive value; other abbreviations as in Table 1.

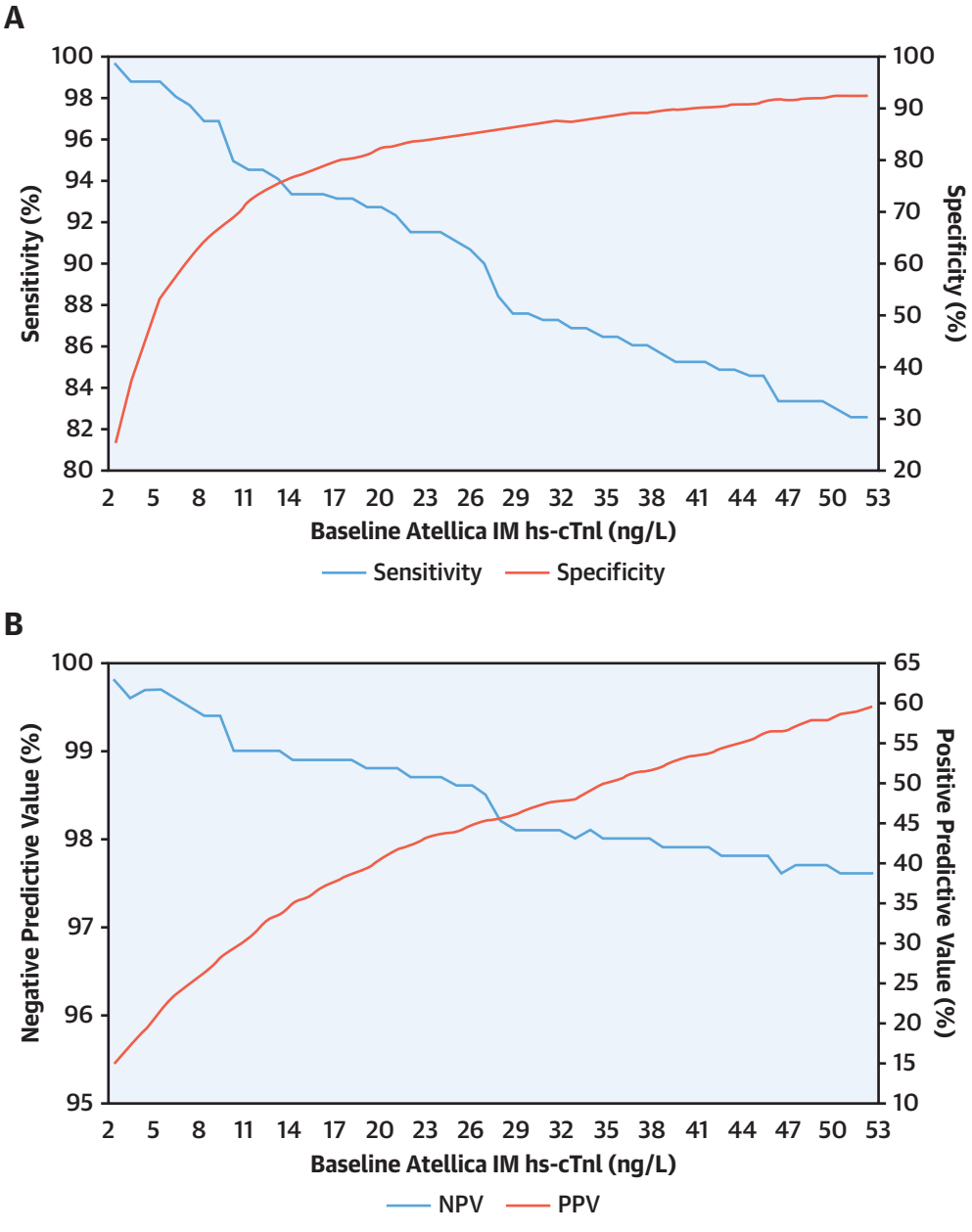
optimized rule-out threshold identified a higher proportion of patients as low risk as compared with the LoQ (47% vs. 33%), with no statistical differences observed in safety across subgroups (including early presenters) as shown in Online Figure 2. In combination with a nonischemic 12-lead ECG (Online Table 7), single-measurement rule-out strategies using either the analytical or optimized concentration thresholds resulted in sensitivities and NPVs >99% for both the diagnostic and safety outcomes.

For the identification of patients at high risk at presentation, PPVs for index acute MI across baseline Atellica IM hs-cTnI concentrations are shown in **Figure 2** and Online Table 8. Hs-cTnI concentrations ≥120 ng/l resulted in PPVs ≥70%. The use of higher hs-cTnI concentrations resulted in higher PPVs but reduced substantially the percentage of patients above such thresholds, with the higher the threshold, the fewer the MIs captured, as shown in **Figure 2** and Online Table 8.

SINGLE-MEASUREMENT RISK-STRATIFICATION STRATEGIES USING THE ADVIA CENTAUR hs-cTnI ASSAY. Use of analytical threshold to identify patients at low risk. Using the ADVIA Centaur hs-cTnI assay, 21% (n = 455) and 31% (n = 690) had baseline hs-cTnI concentrations below the LoD (<2 ng/l) and LoQ (<3 ng/l), respectively. For ruling out MI, using either hs-cTnI concentrations below the LoD or LoQ resulted in excellent diagnostic performance for index hospitalization MI with sensitivities and NPVs ≥99% (**Table 2**). Single measurement strategies using these analytical thresholds was shown to be safe, with sensitivities of 99.6% (95% CI: 98.9% to 100%) and 98.9% (95% CI: 97.7% to 100%) for death or MI at 30 day follow-up using concentrations <LoD and <LoQ, respectively. The use of baseline hs-cTnI <LoQ resulted in a higher efficiency than the <LoD (31% vs. 21%) based on the proportion of patients safely identified as low-risk. There were no statistical differences observed in the safety of hs-cTnI <LoQ across selected subgroups (including early presenters) as shown in Online Figure 2.

Use of optimized thresholds to identify patients at low and high risk. Diagnostic metrics for acute MI across baseline hs-cTnI concentrations are shown in **Figures 3A and 3B**, with a continuous relationship observed between baseline hs-cTnI concentrations and the risk for acute MI. For the identification of patients at low-risk, similar to the Atellica IM assay, a baseline hs-cTnI concentration <5 ng/l was also identified as the optimal concentration threshold that maximized efficiency (i.e., proportion of patients eligible for rule-out) while maintaining safety. Baseline hs-cTnI <5 ng/l identified 46% of patients as low risk and resulted in a diagnostic sensitivity and NPV of 99.2% (95% CI: 98.2% to 100%) and 99.8% (95% CI: 99.5% to 100%) for acute MI, respectively, with a sensitivity and NPV of 98.6% (95% CI: 97.2% to 100%) and 99.6% (95% CI: 99.2% to 100%), respectively, for acute MI or death at 30 days (Online Table 6). This optimized rule-out threshold identified a higher proportion of patients as low risk as compared with the

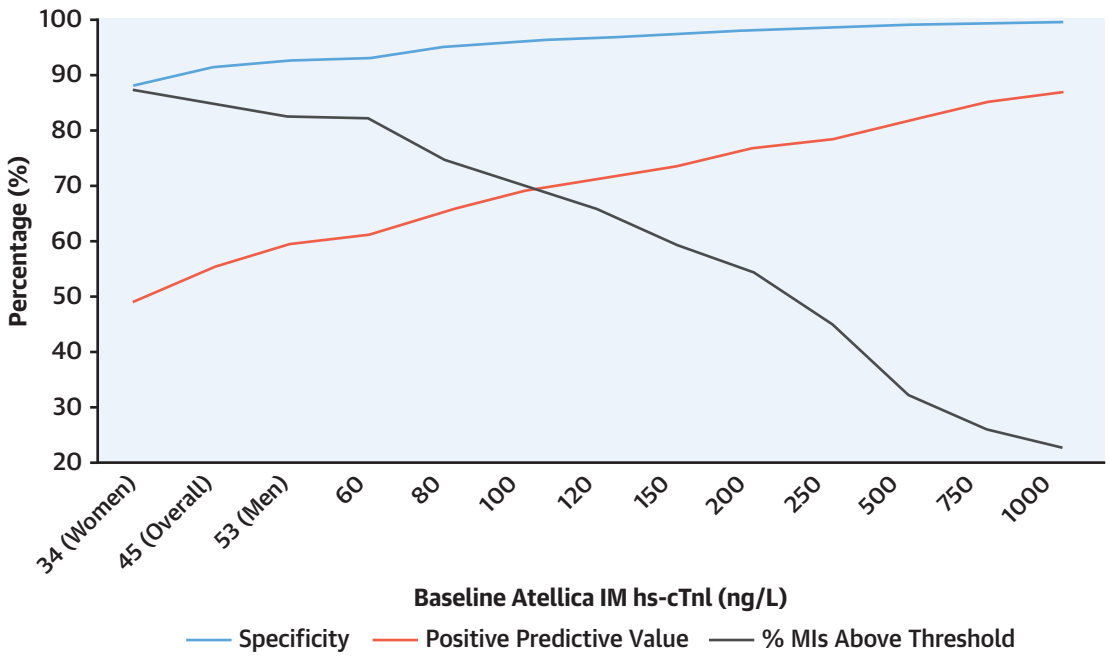
FIGURE 1 Sensitivities, Specificities, NPV, and PPV Across Baseline Atellica IM Hs-cTnI Concentrations



(A) Sensitivities and specificities across baseline Atellica IM hs-cTnI concentrations. Diagnostic sensitivities **(blue line)** and specificities **(red line)** (both y-axis) for acute MI according to baseline Atellica IM hs-cTnI (ng/l) (x-axis). **(B)** Negative and positive predictive values across baseline Atellica IM hs-cTnI concentrations. Negative **(blue line)** and positive **(red line)** predictive values (both y-axis) for acute MI according to baseline Atellica IM hs-cTnI (ng/l) (x-axis). hs-cTnI = high-sensitivity cardiac troponin I; MI = myocardial infarction; NPV = negative predictive value; PPV = positive predictive value.

LoQ (46% vs. 31%) with no statistical differences observed in safety across subgroups (including early presenters) as shown in Online Figure 2. In combination with a nonischemic 12-lead ECG (Online Table 7), single-measurement rule-out strategies using either the analytical or optimized threshold resulted in sensitivities and NPVs >99% for both the diagnostic and safety outcomes.

FIGURE 2 Diagnostic Specificities and PPVs for Acute MI Across Baseline Atellica IM Hs-cTnI Concentrations



Diagnostic specificities **(blue line)** and positive predictive values **(red line)** (both y-axis) for acute MI across baseline Atellica hs-cTnI (ng/l) (x-axis), as well as percentage of patients with acute MI above each threshold **(gray line)** (y-axis). Abbreviations as in Figure 1.

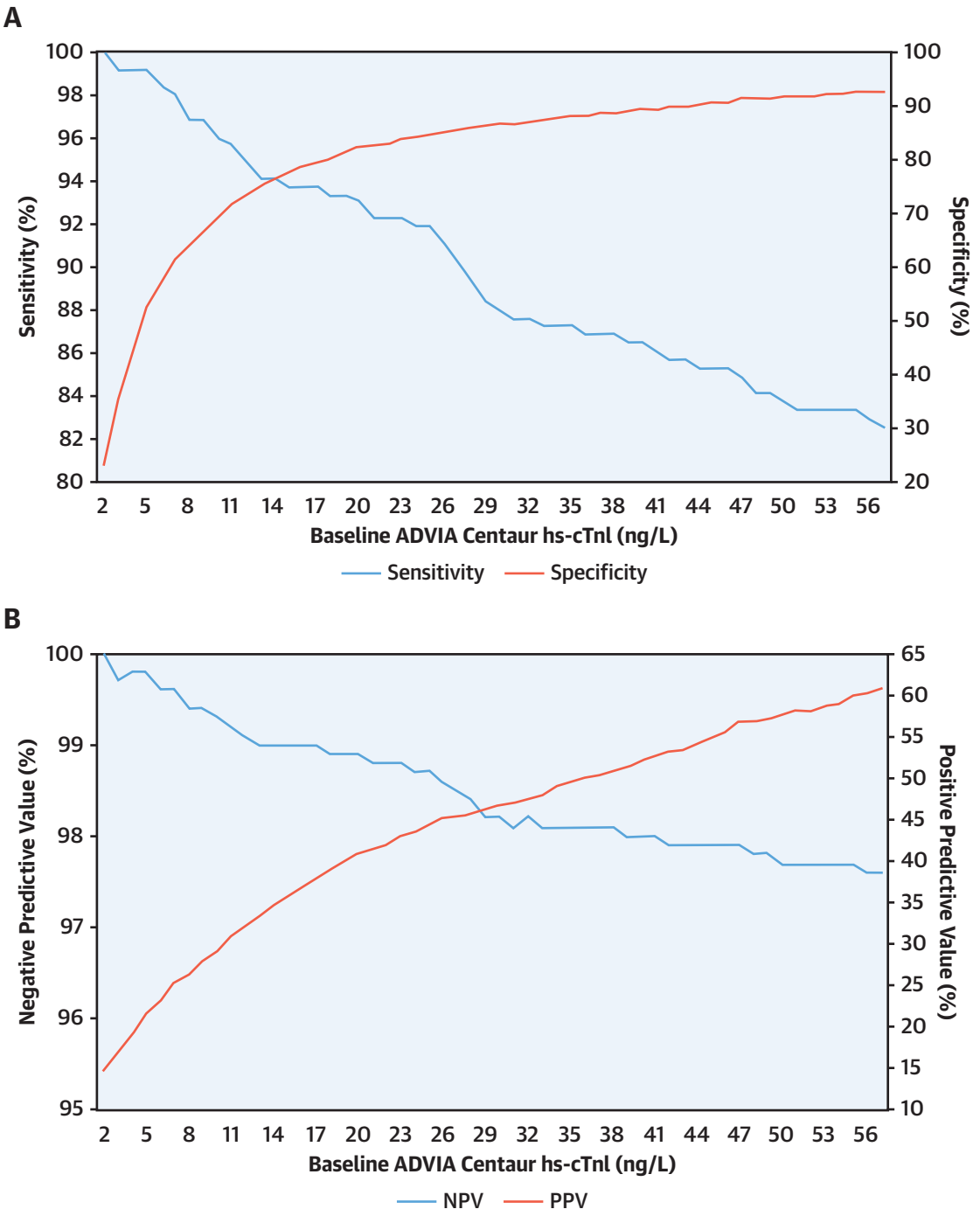
For the identification of high-risk patients at presentation, PPVs for index acute MI across baseline ADVIA Centaur hs-cTnI concentrations are shown in Figure 4 and Online Table 9, with concentrations ≥120 ng/l resulting in PPVs ≥70%, similar findings as observed for the Atellica IM assay.

DISCUSSION

The present investigation represents the first and largest analysis evaluating the diagnostic performance and safety of single-measurement risk-stratification strategies among patients with suspected MI using 2 recently FDA-cleared hs-cTnI assays in a multicenter U.S.-based study (the HIGH-US study) enrolling a diverse, inclusive patient population. The principal findings of our study were as follows. First, we identified a uniform, optimized hs-cTnI concentration of <5 ng/l across both assays as the preferred concentration that balanced safety, as demonstrated by the excellent sensitivities for acute MI or death at 30 days, and efficiency, identifying almost 50% of patients as low risk. Second, the use of analytical thresholds such as the LoD or LoQ offers excellent diagnostic performance and safety. Third, optimized thresholds identify a higher proportion of low-risk patients without missing additional MIs. Fourth, recognizing the continuous relationship between hs-cTnI concentrations and cardiovascular risk, a single measurement at presentation can also facilitate the triage of patients at high risk, with concentrations ≥120 ng/l identifying a subset of patients at high risk for acute MI at presentation in whom prompt evaluation and/or management is needed in the appropriate clinical context.

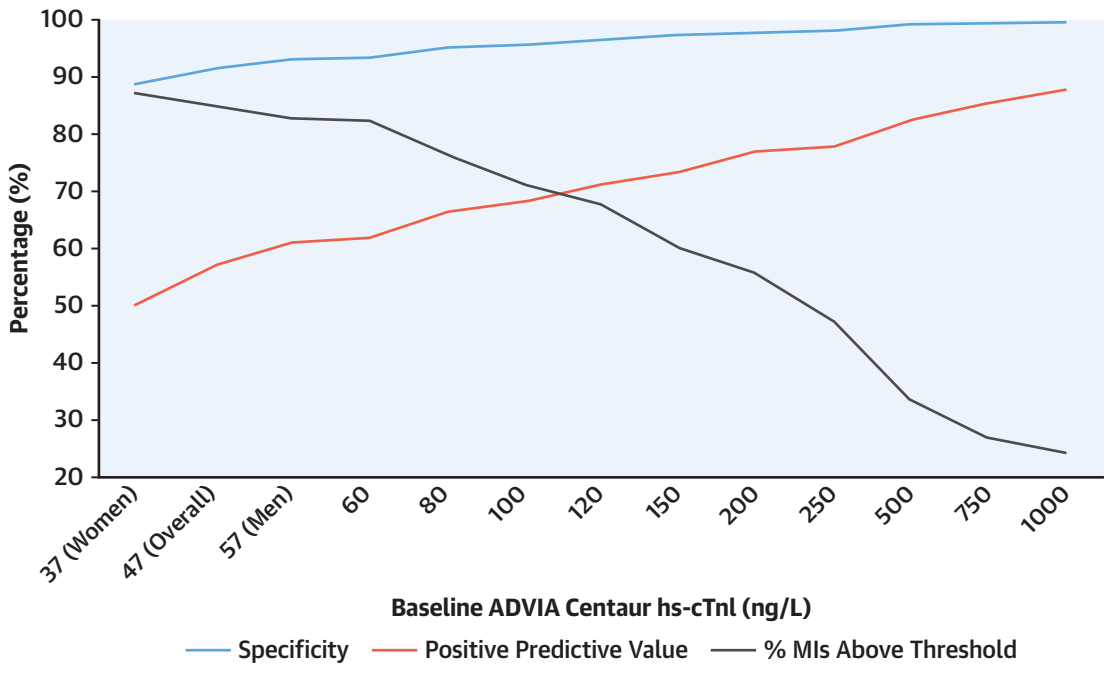
Our study has several important, unique strengths. First, we emphasize that although single-measurement strategies using other hs-cTn assays have been used clinically and/or investigated extensively outside the United States for several years (9,10), such assays have either yet to be cleared for clinical use in the United States (Abbott Diagnostics, hs-cTnI) or require further study and validation using the FDA-cleared thresholds (Roche Diagnostics, 5th Gen cTnT). The present study informs on how to best use the initial hs-cTnI sample to rapidly triage nearly 60% of patients as either low or high risk at presentation (Central Illustration). Second, compared with most study designs evaluating hs-cTn outside the United States that evaluate the performance of cTn in more select patient cohorts (9,10), the HIGH-US study evaluated these novel hs-cTnI assays in a diverse

FIGURE 3 Sensitivities, Specificities, NPV, and PPV Across Baseline ADVIA Centaur Hs-cTnI Concentrations



(A) Sensitivities and specificities across baseline ADVIA Centaur hs-cTnI concentrations. Diagnostic sensitivities **(blue line)** and specificities **(red line)** (both y-axis) for acute MI according to baseline ADVIA Centaur hs-cTnI (ng/l) (x-axis). **(B)** Negative and positive predictive values across baseline ADVIA Centaur hs-cTnI concentrations. Negative **(blue line)** and positive **(red line)** predictive values (both y-axis) for acute MI according to baseline ADVIA Centaur hs-cTnI (ng/l) (x-axis).

FIGURE 4 Diagnostic Specificities and PPVs for Acute MI Across Baseline ADVIA Centaur Hs-cTnI Concentrations



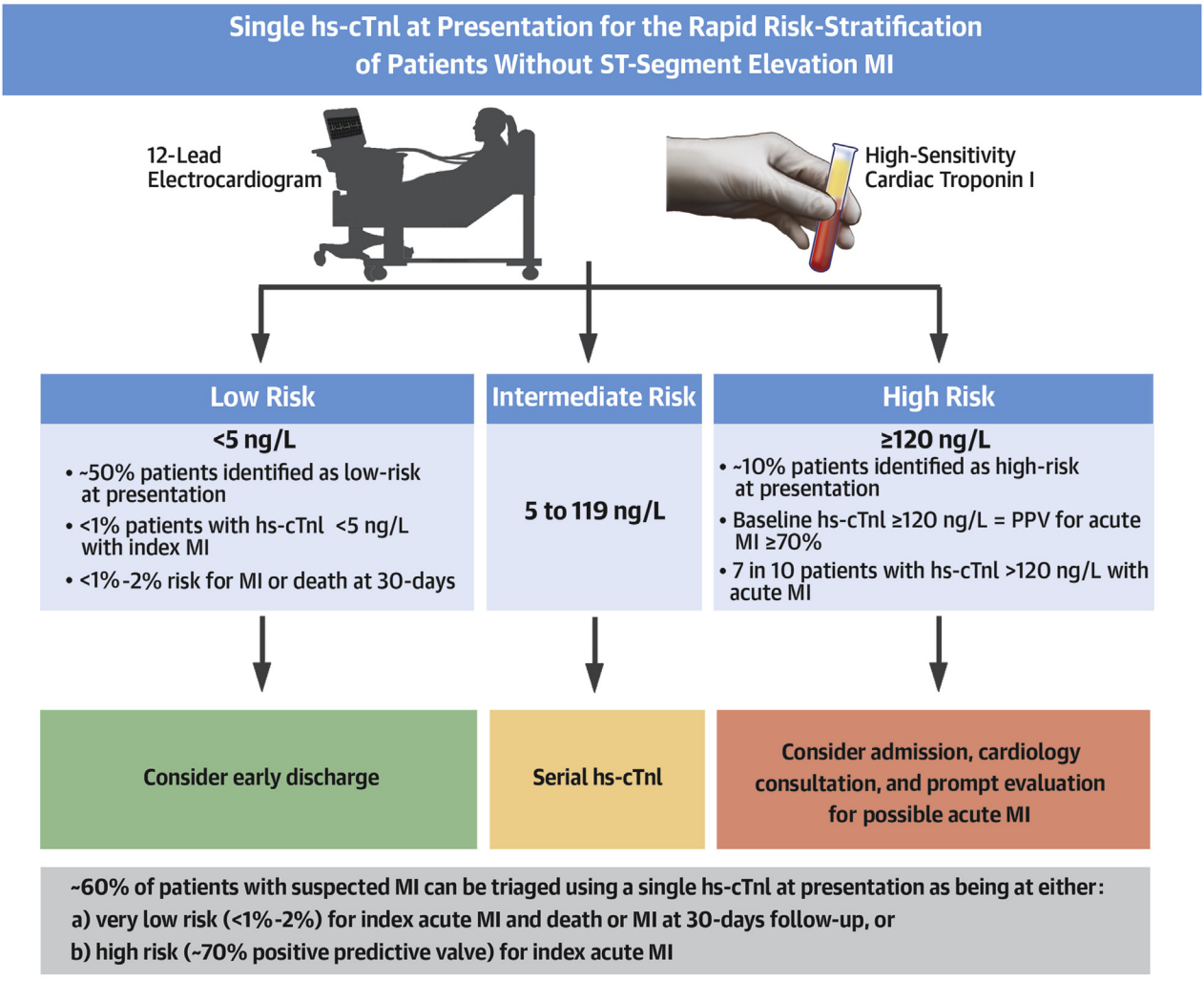
Diagnostic specificities **(blue line)** and positive predictive values **(red line)** (both y-axis) for acute MI across baseline ADVIA Centaur hs-cTnI (ng/l) (x-axis), as well as percentage of patients with acute MI above each threshold **(gray line)** (y-axis).

population across 29 U.S. clinical sites. Third, the present analysis is the first to evaluate multiple FDA-cleared hs-cTnI assays (Atellica IM TnIH and ADVIA Centaur TNIH, Siemens Healthineers) in the same population, with 2 smaller European-based studies having examined each separately (20,21).

The superior analytical performance offered by hs-cTn assays enables the potential of using a single cTn measurement at presentation to safely rule out acute MI if the initial results are below analytical thresholds such as the LoD or LoQ or concentrations thresholds tailored to maximize efficiency while maintaining safety (9–11,22). In the present study, we identified a concentration threshold of <5 ng/l as the optimized concentration that maximized efficiency while maintaining safety across both assays. Incidentally, this concentration threshold is consistent with what other studies have identified to categorize patients as low risk (23). In the High-STEACS (High-Sensitivity Troponin in the Evaluation of Patients with Acute Coronary Syndrome) cohort study (22), using the Abbott hs-cTnI assay, a concentration threshold of <5 ng/l had a very high NPV for MI and was associated with a very low risk for adverse cardiac events on follow-up. Using hs-cTnT (Roche Diagnostics), studies evaluated the use of the 5 ng/l LoD for the rapid rule-out of acute MI, with a meta-analysis of 9,241 patients showing that such approach identified almost a third of patients as low risk (0.5% had acute MI) with pooled sensitivities of 98.7% for acute MI and 98.0% for 30-day major adverse cardiac events (10). Using the Atellica IM hs-cTnI assay, following the approach derived for the Abbott hs-cTnI assay (21), the same 5 ng/l concentration threshold was used pragmatically without recalibration as part of a clinical pathway in a substudy the of High-STEACS trial (20). The potential of using a uniform threshold to identify patients at low risk would likely provide a simple, safe, and attractive approach to clinicians globally.

Most studies evaluating single-measurement rule-out strategies using hs-cTnT or hs-cTnI assays have examined the LoD and shown such an approach to be safe (9,10). In the United States, however, the first of these assays to receive FDA clearance (5th Gen cTnT in January 2017; Roche Diagnostics) was approved to report down to the LoQ, not the LoD, that had a %CV >20% (12). Likewise, the Siemens Healthineers and Beckman hs-cTnI assays were FDA-cleared to report down to the LoQ concentration. Although the LoD is used clinically outside the United States and endorsed with Class I

CENTRAL ILLUSTRATION **Algorithm to Triage Patients With Suspected Acute Myocardial Infarction as Either Low or High Risk Using a Single High-Sensitivity Cardiac Troponin I Measurement at Presentation**



Sandoval, Y. et al. J Am Coll Cardiol. 2019;74(3):271-82.

Patients with symptoms suspicious for acute myocardial infarction (MI) should first undergo immediate 12-lead electrocardiography (ECG) to exclude ST-segment elevation MI. Subsequently, high-sensitivity cardiac troponin I (hs-cTnI) can help categorize patients as either low or high risk at presentation, with those with hs-cTnI <5 ng/l at very low risk (<1% to 2%) for MI or death at 30 days and early discharge possible. Patients with hs-cTnI ≥120 ng/l are at high risk for acute MI, and prompt evaluation and/or management is needed. For those with intermediate hs-cTnI (5 to 119 ng/l), serial testing is needed to rule in/out acute MI.

recommendations in the 2015 European Society of Cardiology guidelines (8), the U.S. data on the diagnostic performance and safety will be required for the LoQ. Our study shows that single-measurement rule-out strategies using either the LoD or LoQ for both the Atellica IM and ADVIA Centaur hs-cTnI assays are safe as demonstrated by the excellent sensitivities for 30-day acute MI or death. Further, our data also illustrate the contemporary role of cTn as an objective measure of cardiovascular health, with hs-cTnI concentrations <LoQ identifying healthier patients unlikely to experience adverse events, as compared with those with higher hs-cTnI concentrations who have more comorbidities and an increasing likelihood for adverse events.

We also evaluated whether baseline hs-cTnI concentrations at presentation could facilitate the identification of patients at high risk for acute MI. Compared with rule-out strategies for which clearer consensus exists on acceptable miss rates and risk tolerance (19), no clear standard exists on what constitutes high risk. Our study demonstrates that the higher the hs-cTnI at presentation, the higher the PPV for acute MI. For both the Atellica IM and ADVIA Centaur hs-cTnI assays, concentrations ≥120 ng/l resulted in PPVs ≥70% for acute MI, a threshold at which 7 in 10 patients will have an acute MI. In the appropriate clinical context, the identification of such marked hs-cTnI increases at presentation should facilitate patient triage in the ED and prompt the evaluation and management for suspected MI. Other studies evaluating the 0/1-h European Society of Cardiology pathway have used classification and regression tree analysis targeting a minimal PPV of 70%, and also identified 120 ng/l as the concentration threshold to determine high risk and examined such for both the Centaur and Atellica IM assays (20,21). In our study, concentrations ≥120 ng/l provided such PPVs, and importantly, although the use of higher hs-cTnI concentrations results in higher PPVs, the higher the threshold, the smaller the percentage of patients above such thresholds, and the fewer the MIs identified.

STUDY LIMITATIONS. First, like most observational cTn diagnostic performance studies, hs-cTnI was measured for investigational purposes, with contemporary cTn assays used for clinical decision-making. Randomized clinical trials (RCT) evaluating the use of single-measurement rule-out strategies are ongoing. The LoDED (Limit of Detection of Troponin and ECG Discharge) trial (ISRCTN86184521) is a RCT evaluating whether the LoD results in a successful earlier discharge without adverse events at 30 days as compared with routine care (24). The HiSTORIC (High-Sensitivity Cardiac Troponin on Presentation to Rule Out Myocardial Infarction) trial (NCT03005158) is a RCT evaluating hs-cTnI (Abbott) <5 ng/l among patients with suspected acute coronary syndrome with symptom onset ≥2 h within the High-STEACS pathway (25). Second, the reference standard used to guide the adjudication of acute MI was based on various local contemporary cTn results used at each U.S. clinical site; more studies are needed using hs-cTnI as the reference standard. Third, patient enrollment was not consecutive 7 days a week, 24 h a day, and for patients that were enrolled, the need for appropriate informed consent delayed the collection of the first study sample (15).

CONCLUSIONS

Recognizing the continuous relationship between baseline hs-cTnI concentrations and the risk for adverse cardiovascular events, using 2 different FDA-cleared hs-cTnI assays, we have identified a uniform, optimized, concentration threshold of <5 ng/l that safely identifies almost one-half of all patients as low risk at presentation, with concentrations thresholds ≥120 ng/l at presentation identifying a subset of patients at high risk for acute MI.

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PERSPECTIVES

COMPETENCY IN SYSTEMS-BASED PRACTICE: hs-cTnI can identify and expedite triage of patients at low or high risk of myocardial infarction.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients without ST-segment elevation MI, a single hs-cTnI level <5 ng/l at presentation can identify nearly 50% of patients at low risk of adverse events for whom early discharge may be considered, whereas hs-cTnI ≥120 ng/l identifies patients at high risk of acute MI.

TRANSLATIONAL OUTLOOK: Randomized studies are needed to confirm the efficiency and safety of risk stratification strategies based on single hs-cTn measurements.

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KEY WORDS acute myocardial infarction, high-sensitivity cardiac troponin, risk stratification, troponin

APPENDIX For supplemental figures and tables, please see the online version of this paper.