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Rapid exclusion of acute myocardial injury and infarction with a single high sensitivity cardiac troponin T in the emergency department: a multicenter United States evaluation

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CONFLICT OF INTEREST DISCLOSURES

Dr. Sandoval has previously served on Advisory Boards for Roche Diagnostics and Abbott Diagnostics without personal financial compensation. He has also been a speaker without personal financial compensation for Abbott Diagnostics.

Dr. Jaffe has consulted or presently consults for most of the major diagnostics companies, including Beckman-Coulter, Abbott, Siemens, Ortho Diagnostics, ET Healthcare, Roche, Radiometer, Sphingotec, RCE Technologies, Astellas, Amgen and Novartis. All other authors have nothing to disclose.

Supplemental Materials

Supplemental Tables 1–13

Supplemental Figures 1–9

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Abstract

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

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

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

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

Keywords

High-sensitivity cardiac troponin; Cardiac troponin; Myocardial infarction; Myocardial injury

There are over 6.5 million emergency department visits for symptoms suspicious for acute myocardial infarction yearly across the United States (US)¹. High-sensitivity cardiac troponin (hs-cTn) assays permit earlier evaluation of these patients²⁻³. Studies indicate that a single hs-cTn measurement with a concentration below the limit of detection (LoD), or for some assays at higher optimized concentrations, is safe to exclude acute myocardial infarction⁴⁻¹³. Since 2015 European Society of Cardiology (ESC) guidelines endorse algorithms that allow single sample rule-out of acute myocardial infarction with class I recommendations when the initial hs-cTn is very low^{14,15}. For hs-cTnT, these guidelines^{14,15} recommend rule-out in those with a baseline hs-cTnT below the LoD of 5 ng/L. There are good data^{4,6,11-13} from outside the US supporting the approach. These

include meta-analyses^{4,6} and 2 randomized trials^{11,12} using hs-cTnT. Most studies in this field have been designed to exclude acute myocardial infarction rather than myocardial injury. In the US, however, the LoD cannot be reported for clinical use per the US Food and Drug Administration (FDA)^{16,17} despite recent guidelines¹ from the American Heart Association (AHA) / American College of Cardiology (ACC) that support this approach to exclude myocardial injury with a class 2a recommendation (level of evidence B – nonrandomized) for patients with suspected acute coronary syndrome with symptom onset at least 3 hours (h) prior to presentation.

In the US, hs-cTn assays were FDA-cleared for clinical use to report down to the limit of quantitation (LoQ) where imprecision is 20% or less^{16,17}, which for high-sensitivity assays is a concentration threshold above the LoD. For hs-cTnT, this means that results can only be reported to hs-cTnT <6 ng/L¹⁷. Whether a single sample rule-out approach using the LoQ is safe for clinical use is unclear.

There are a few small studies evaluating hs-cTnT below the LoQ threshold of 6 ng/L. They often use investigational samples^{18,19} or are secondary analyses from outside the US^{20,21}. Some of these studies have been inconclusive and lack an adequate gold-standard assay^{18,19} for acute myocardial infarction diagnosis, including some data suggesting a single hs-cTnT <6 ng/L may not be safe²². In the US, hs-cTn testing is used more broadly^{23,24} than in Europe, so European data from more selected chest pain populations²¹ may not be as informative for US practice, and validation of the LoQ approach is needed. Further, concerns exist surrounding the analytical performance of hs-cTnT, especially below the LoQ^{25,26}. Despite these uncertainties and a paucity of definitive data, some US centers have implemented this approach^{27–29}. Thus, there is an urgent need for more data to inform whether the single sample rule-out strategy using a hs-cTnT <6 ng/L is an efficient and safe strategy to identify patients at low-risk for acute myocardial infarction.

To address this unmet need, we examined our multicenter US experience with hs-cTnT. Our goals were two-fold. First, we examined the efficacy (proportion of patients identified as low-risk) and safety of a single hs-cTnT <6 ng/L to identify low-risk patients based on its ability to rule-out acute myocardial injury in a large multicenter biomarker cohort. Second, to evaluate the use of this approach to identify patients at low-risk for acute myocardial infarction, we examined the combined use of a nonischemic electrocardiogram with a hs-cTnT <6 ng/L in an adjudicated cohort to assess the diagnostic performance for index acute myocardial infarction and 30-day safety (myocardial infarction or death).

METHODS

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

CV Data Mart Biomarker Cohort: efficacy of a single hs-cTnT below the 6 ng/L LoQ for identifying low-risk patients by excluding acute myocardial injury

The CV Data Mart Biomarker cohort is a multicenter, observational, biomarker study involving consecutive, adult patients who presented to one of the Mayo Clinic emergency

departments (Rochester, Florida, and Arizona campuses or the 19 Mayo Clinic Health System emergency departments across Minnesota and Wisconsin) in whom at least one hs-cTnT measurement was obtained within 12h of presentation from the date of site-specific hs-cTnT implementation until 12/08/20. It does not include electrocardiographic data. Eligible patients including their baseline characteristics and outcomes were identified using the Mayo Clinic CV Data Mart platform. The CV Data Mart is a collection of cardiology databases that facilitates analyses of existing data from the clinical systems. Patients without a required Minnesota Research Authorization form, those that did not present through the emergency department, aged less than 18 years old, with ST-elevation myocardial infarction, cardiac arrest, and/or pregnancy were excluded (Figure S1). In patients with multiple presentations, the earliest was used. The study was approved by the Institutional Review Board (IRB) (ID 20–009951).

In the CV Data Mart Biomarker cohort, the efficacy a single hs-cTnT<6 ng/L to identify low-risk patients was examined. Efficacy was defined as the proportion of patients with a baseline hs-cTnT<6 ng/L that qualified as low-risk among the entire CV Data Biomarker cohort and such proportions were examined across major sites, in patients with chest pain, and according to sex. The safety of a single hs-cTnT<6 ng/L to reliably identify these low-risk patients was evaluated by examining the frequency of acute myocardial injury³⁰ (defined as any subsequent hs-cTnT increase above the sex-specific 99th percentile during the initial 24h) among those with a baseline hs-cTnT<6 ng/L with serial measurements. Analyses were also performed using an overall 99th percentile threshold of 14 ng/L. Given that acute myocardial infarction diagnoses were not adjudicated in the large CV Data Mart biomarker cohort, acute myocardial injury served as an objective measure because it is a central criterion necessary to make any acute myocardial infarction diagnosis³⁰. Previous hs-cTnT and hs-cTnI studies have evaluated single-sample rule-out strategies using this approach^{31,32}. Subgroup evaluations included analyses according to age, sex, chest pain, comorbidities, and site were performed. Given concerns^{25,26} surrounding the analytical performance and imprecision of hs-cTnT at the LoQ, among patients with an initial hs-cTnT<6 ng/L with 0/2h serial measurements, we also examined whether the second sample concentration remained at <6 ng/L.

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

Adjudicated cohort: diagnostic performance and safety for ruling-out acute myocardial infarction

The MAyo Southwest WisConsin 5th Gen Troponin T ImplementatiON (ACTION) study was used to evaluate the diagnostic performance and safety of ruling-out acute myocardial infarction. The study was approved by the IRB (ID 19–002668). The primary results

and methods have been described³⁶. It is a multicenter (n=2), retrospective, observational cohort study across the Southwest Mayo Clinic Health System that evaluated consecutive encounters of adult patients presenting to these emergency departments in whom at least one cTnT measurement was obtained. Data was abstracted and reviewed from the electronic health records by trained study staff following a standardized data collection process and entered in Research Electronic Data Capture (REDCap). For the present study, analyses addressed unique patients based on their 1st presentation during the hs-cTnT study period and excluded patients aged less than 18 years old, those without a 12-lead electrocardiogram, with ischemic ST-elevation on the presenting electrocardiogram, or in whom hs-cTnT was not measured within 12h of emergency department presentation (Figure S1). All cases with at least one hs-cTnT above the sex-specific 99th percentile upper-reference limit (URL) were adjudicated using the Fourth Universal Definition of Myocardial Infarction³⁰ criteria by trained physicians. Details regarding the adjudication are included in the Supplemental Material.

This adjudicated cohort permitted the evaluation of the intended clinical rule-out pathway that combines a nonischemic electrocardiogram with a baseline hs-cTnT<6 ng/L and allowed analyses that examined diagnostic performance and safety for ruling-out acute myocardial infarction, including subgroup analyses according to sex, chest discomfort, early presenters (<3h), electrocardiographic findings, and risk-strata based on HEAR (History, Electrocardiography, Age, Risk Factors) scores³⁷. Given the robust follow-up (median follow-up of 23.3 months available in 1866 patients), it also allowed 30-day safety outcomes analyses based on a composite of myocardial infarction or death, as well as 2-year outcomes. Following guidance from the 2018 American College of Emergency Physicians (ACEP) clinical policy³⁸ and other survey³⁹ analyses on acceptable missed rates, we established that patients identified to be low-risk based on their nonischemic electrocardiogram and baseline hs-cTnT<6 ng/L should have no more than 1–2% adverse event rates during 30-day follow-up to consider the rule-out pathway acceptable.

High-sensitivity cardiac troponin T assay

High sensitivity cardiac troponin T (hs-cTnT) was measured using the Elecsys Troponin T Gen 5 STAT assay (Roche Diagnostics). Per FDA clearance¹⁷, concentrations are reported down to the LoQ of <6 ng/L. For results <6 ng/L, the laboratory inputs a concentration of 5 ng/L for delta calculations. Sex-specific 99th percentile URLs of 10 ng/L for women and 15 ng/L for men are used^{17,40–43}. Results are reported as whole units (no decimals) in ng/L. The 0/2h hs-cTnT protocol for the evaluation of MI has been described^{17,36,43} and is summarized in Figure S2. Except for patients with symptom onset >6h in whom myocardial injury is considered ruled-out if the initial hs-cTnT is below the sex-specific 99th percentile, a single sample rule-out strategy was not recommended by institutional protocols.

Statistical Analysis

Continuous variables are presented as means (standard deviations) or medians (interquartile range, IQR). Between groups comparisons were performed using the Kruskal-Wallis test. Discrete variables are summarized as frequency (percentage) and between groups comparisons analyzed with the chi-square test. Negative predictive values (NPV) and

sensitivities with corresponding 95% confidence intervals (CI) were calculated using exact binomial methods⁴⁴. Diagnostic performance for acute myocardial infarction and 30-safety were determined in the adjudicated cohort. False omission rates defined as false negatives among those with a negative test result (i.e.: baseline hs-cTnT<6 ng/L) are considered “missed” events. Forest plots evaluated NPVs across subgroups. Kaplan-Meier curves compared hs-cTnT groups. The time to event was defined as the arrival date of the index hospitalization to the time of first event. Long term event rates were calculated using Kaplan-Meier methods. Analyses were conducted using SAS version 9.4 (Cary, NC) and R version 4.0.3.

RESULTS

CV Data Mart Biomarker Cohort: efficacy of a single hs-cTnT below the 6 ng/L LoQ for identifying low-risk patients by excluding acute myocardial injury

A total of 85,610 patients were included in the CV Data Mart Biomarker cohort. Baseline characteristics are shown in Table 1 and Tables S2–4. The mean age was 63 (18) years and women represented 50% of the cohort. A total of 24,646 (29%) patients had baseline hs-cTnT<6 ng/L. Similar proportions of patients with baseline hs-cTnT<6 ng/L were observed across major sites (range 28–30%) (Figure 1). Among the 24,646 patients with a baseline hs-cTnT<6 ng/L, 49 (0.2%) acute myocardial infarction diagnoses based on ICD-10 codes and 19 (0.1%) deaths occurred during the index presentation. Among 27,198 patients with chest pain, a total of 11,725 (43%) had baseline hs-cTnT<6 ng/L. Similar proportions were observed across sites (range 41–44%) (Figure 1). In 11,725 patients with chest pain and a baseline hs-cTnT<6 ng/L, 24 (0.2%) acute myocardial infarction diagnoses based on ICD-10 codes and 3 (0.03%) deaths were identified during the index presentation.

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

Baseline hs-cTnT<6 ng/L with serial measurements for acute myocardial injury exclusion

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

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

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

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

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

Adjudicated cohort: diagnostic performance and safety for ruling-out acute myocardial infarction

A total of 1979 emergency department patients who met inclusion criteria were evaluated. Baseline characteristics are presented in Tables S7–9. The incidence of acute myocardial infarction (including both type 1 and 2 myocardial infarctions) was 7.1% (n=141). Overall, 624 (32%) patients had a baseline hs-cTnT <6 ng/L. Using a single baseline hs-cTnT <6 ng/L in isolation (biomarker alone), the NPV and sensitivity for acute myocardial infarction were 99.8% (95% CI 99.1, 100) and 99.3% (95% CI 96.1, 100) respectively (Table 3 and Table S10). At 30-days post-discharge, including index events, 0.3% (2/624) had an event. False

negatives are summarized in Table S11. Sex-specific analyses showed similar diagnostic and safety performance. Subgroup analyses demonstrated no differences in rule-out performance (Figure S7).

Among those with a nonischemic electrocardiogram (n=1849), 610 (33%) patients had a baseline hs-cTnT<6 ng/L. In this group, the NPV and sensitivity for acute myocardial infarction were 100% and there were no missed diagnoses of acute MI during the index hospitalization (Table 3). At 30-days post-discharge, including index events, 0.2% (1/610) had an event. In early presenters (symptom onset <3h) with a baseline hs-cTnT<6 ng/L and a nonischemic electrocardiogram (145/420, 35%), NPV and sensitivity were 100% with no missed diagnoses at index presentation or during 30-day follow-up (Table S12). Sensitivity analyses in those with chest pain showed similar results (Table S13). At 1- and 2-years, myocardial infarction or death occurred in 2.1% and 2.6% of patients with baseline hs-cTnT<6 ng/L (Figure S8), and 2.0% and 2.3% in those with a baseline hs-cTnT<6 ng/L and a non-ischemic electrocardiogram (Figure 2).

Among the 624 patients with a baseline hs-cTnT<6 ng/L, 206 (33%) had serial hs-cTnT measurements. In those with a 2h serial measurement, concentrations remained <6 ng/L in 84% (173/206). Within 24h following the initial baseline hs-cTnT<6 ng/L, 2 patients (0.97%) developed acute myocardial injury. Among patients with baseline hs-cTnT<6 ng/L, there were no differences in myocardial infarction or death between those with 2h hs-cTnT that remained <6 ng/L as compared to those with 2h hs-cTnT \geq 6 ng/L but below the sex-specific 99th percentile (Figure S9).

DISCUSSION

This multicenter study is the largest to evaluate the role of a single hs-cTnT below the LoQ of 6 ng/L to identify patients at very low risk for acute myocardial injury and infarction. While extensive data support single-sample rule-out when hs-cTnT concentrations are below the LoD of 5 ng/L, this concentration threshold is not available for clinical use in the US, and limited data exists for the LoQ, which is the lowest reportable concentration for hs-cTnT per the FDA¹⁷. Our data therefore provides important and timely information to US clinicians as it demonstrates that a single hs-cTnT below the LoQ of 6 ng/L is a safe method to rapidly triage and identify patients at very low risk for acute myocardial injury and infarction.

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

The safety of a single hs-cTnT <6 ng/L to identify low risk patients was comprehensively examined in multiple ways. In the large CV Data Mart Biomarker cohort, we evaluated the ability of a baseline hs-cTnT <6 ng/L to reliably identify low-risk patients. First, based on analyses performed in 11,962 patients with a baseline hs-cTnT <6 ng/L and serial measurements, we demonstrated that acute myocardial injury is unlikely to occur when the initial hs-cTnT <6 ng/L, with only 1.2% of patients identified to have increases in hs-cTnT above the sex-specific 99th percentiles. This is a robust and objective metric as it is central criterion for the diagnosis of acute myocardial infarction³⁰⁻³². Second, in this same subset of patients, we demonstrated the subsequent 2h hs-cTnT measurement remained <6 ng/L in 85% of cases. These findings confirm that these results are reliable for clinical decision-making and attenuate concerns about analytical performance^{25,26}. Third, secondary analyses addressing the entire CV Data Biomarker cohort involving 24,646 patients with a baseline hs-cTnT <6 ng/L further corroborated the safety of this approach, with only 0.2% acute myocardial infarction diagnoses based on ICD-10 codes and only 0.1% deaths occurring in such patients during the index presentation. Although ICD-10 codes have recognized limitations^{34,35}, they provided another complementary layer of safety as they allowed us to evaluate whether any acute myocardial infarction diagnoses were coded among patients with a baseline hs-cTnT <6 ng/L. Last, and most importantly, we validated the safety of this approach in an adjudicated cohort where the combination of nonischemic electrocardiogram with a baseline hs-cTnT <6 ng/L resulted in a NPV of 99.8% and sensitivity of 99.3% for acute myocardial infarction or death at 30-days (including index events). These data support the observations from the CV Data Mart using ICD-10 codes. Patients with a nonischemic electrocardiogram and a baseline hs-cTnT <6 ng/L had favorable short- and long-term outcomes, with only about 2% having myocardial infarction or death at 1- and 2-years, which further corroborates the safety of this approach. These findings underscore how a nonischemic electrocardiogram with a baseline hs-cTnT <6 ng/L allows the reliable identification of very low risk patients in whom in most circumstances hospital admission or observation is often unwarranted for ischemic evaluation purposes, and in whom additional testing during the index presentation can be avoided or if clinically needed, deferred to the outpatient setting.

Our data complements the extensive data on the safety of a single hs-cTnT below the 5 ng/L LoD. There are randomized data^{11,12} using the LoD of hs-cTnT of <5 ng/L that demonstrate that this approach is safe. The RAPID-TNT trial¹² (Rapid Assessment of Possible ACS in the Emergency Department with High-Sensitivity Troponin T) was a prospective, randomized, noninferiority evaluation of the ESC 0/1h protocol that involved rule-out when baseline hs-cTnT was <5 ng/L at >3h after onset of symptoms. The trial demonstrated noninferiority compared to standard care, with a NPV for the 0/1h hs-cTnT protocol for 30-day death or myocardial infarction of 99.6%¹². The LoDED (Limit of Detection and ECG Discharge) trial¹¹ enrolled chest pain patients across 8 UK hospitals with a nonischemic electrocardiogram; no patient with an undetectable hs-cTnT had a major adverse event within 30-days¹¹. There are also large meta-analyses^{4,6} documenting this approach is safe. In a collaborative meta-analysis⁴ of 9241 patients, Pickering et al. demonstrated that low-risk patients defined as those with a nonischemic electrocardiogram and a hs-cTnT <5 ng/L had a pooled sensitivity of 98.7% for acute myocardial infarction

and 98.0% for 30-day major adverse cardiac events and no low-risk patients died. In another recent international collaborative meta-analyses⁶, both the ESC 0/1h and 0/2h hs-cTnT protocols incorporating single sample rule-out using hs-cTnT<5 ng/L were evaluated. The ESC 0/1h protocol was evaluated in 13,899 patients across 12 cohorts and demonstrated a sensitivity of 99.2% and NPV of 99.8%⁶. The ESC 0/2h protocol was evaluated in 2488 patients across 5 cohorts and demonstrated a sensitivity of 99.0% and NPV of 99.5%⁶. Implementation data¹³ from Scotland also confirms safety with cardiovascular death occurring in only 0.1% at both 30-days and 1-year in those with hs-cTnT<5 ng/L in the intervention group. Our data complements the vast experience on the LoD of hs-cTnT<5 ng/L and demonstrates that the LoQ of hs-cTnT<6 ng/L is also safe.

Limited data exists for hs-cTnT below the LoQ of 6 ng/L as used across the US. Small studies often using investigational samples^{18,19} or performed outside the US^{20,21} have probed the performance of hs-cTnT<6 ng/L but no robust data exists. Allen et al. evaluated initial hs-cTnT measurements in 1462 participants in a prospective multicenter observational cohort in which treating clinicians were blinded to the investigational hs-cTnT results and patient care and adjudications were based on local contemporary cTn results¹⁹, which is a less sensitive gold standard biomarker for the detection of myocardial injury and diagnosis of myocardial infarction than the hs-cTnT assay used in our study. This has been a common limitation in US studies probing this approach with hs-cTnT^{18,19}. Many either employ a less sensitive assay for adjudication or higher 99th percentile upper-reference limits than we used. Like our findings, Allen et al demonstrated that 32% of patients had a baseline hs-cTnT<6 ng/L and a nonischemic electrocardiogram, with a NPV of 99.1% and 98.9% respectively for index MI and 30-day cardiac death and MI¹⁹. They demonstrated that the approach associated with the highest NPV required the combination of hs-cTnT<6 ng/L with a low HEART score¹⁹. Our adjudicated cohort analyses showed an excellent performance for acute myocardial infarction rule-out using a baseline hs-cTnT<6 ng/L in combination with a nonischemic electrocardiogram. Further, subgroup analyses demonstrated no heterogeneity among risk-strata using the HEAR score, for which reason our data does not support addition of risk scores for ruling-out acute myocardial infarction.

Several sex-specific findings warrant discussion. First, there is a significant difference between the proportion of men and women with baseline hs-cTnT concentrations below the LoQ, with women almost twice as likely to have hs-cTnT<6 ng/L than men. These differences may be explained in part by the analytical sensitivity of hs-cTnT as several normality studies have shown that women are less likely to have detectable hs-cTnT concentrations than men^{42,45}. Second, sex-specific analyses addressing the exclusion of acute myocardial injury showed no heterogeneity in the rule-out performance among subgroups in men. In women, however, subgroup analyses demonstrated lower NPVs, particularly in the elderly and those with coronary artery disease; similar findings were observed using an overall 99th percentile. Therefore, for the purpose of excluding acute myocardial injury (not acute myocardial infarction), our analyses suggest caution in these patient subsets. When we adjudicated false negative cases with an initial baseline hs-cTnT<6 ng/L that developed myocardial injury, most were due to isolated nonischemic myocardial injury. One possible explanation for the observed differences is that the reduced analytical sensitivity of hs-cTnT in women^{42,45} may diminish the ability of hs-cTnT to screen for

underlying cardiovascular disease as compared to men. Our data suggest this is a plausible explanation as women with hs-cTnT<6 ng/L were older and had more comorbidities than men with hs-cTnT<6 ng/L. Last, while differences were observed between men and women with respect to acute myocardial injury, these differences were not observed for acute myocardial infarction, with NPVs and sensitivities for acute myocardial infarction of 100% in both men and women with a nonischemic electrocardiogram and a hs-cTnT<6 ng/L in the adjudicated cohort.

Our study has multiple strengths. First, it is the largest US study to evaluate the role a single hs-cTnT below the LoQ to identify patients at low-risk for acute myocardial injury and infarction. These findings are of unique importance to clinicians in the US using hs-cTnT because the LoQ is the lowest reportable hs-cTnT concentration for clinical use per the FDA¹⁷ and paucity of data exists. Second, our large multicenter analysis addressing the real-life clinical use of hs-cTnT across 22 US sites allowed us to evaluate the efficacy of this approach in a multi-state, diverse population, including 50% women, and informed that a similar proportion of patients are eligible for this approach across sites. Third, the population evaluated exceeds the combined hs-cTnT data using the LoD from previous meta-analyses^{4,6} and randomized trials^{11,12} evaluating the “single-sample” rule-out. Fourth, we validated the safety of a baseline hs-cTnT in combination with a nonischemic electrocardiogram to exclude acute myocardial infarction in an adjudicated cohort, where we were also able to demonstrate safety among key subgroups, including in early presenters and in those with chest pain.

Limitations exist. First, while electrocardiographic findings and symptom onset were evaluated in the adjudicated cohort, these findings could not be interrogated in the CV Data Mart Biomarker cohort. We did exclude patients with ST-elevation MI diagnoses. Second, our efficacy analyses from the CV Data Mart Biomarker cohort address patients with serial measurements. We cannot exclude a component of selection and workup bias in that these patients were potentially perceived to be higher risk than those that only underwent a single hs-cTnT despite an institutional 0/2h protocol. Our data confirms that patients undergoing serial measurements are likely at higher risk given they are older and have more comorbidities than those undergoing single measurements. This demonstrates that the approach is safe in those potentially at higher risk, for which reason performance would likely be enhanced in all-comers. Third, while only 1.2% of patients with a baseline hs-cTnT<6 ng/L developed acute myocardial injury, 14% had 2h hs-cTnT concentrations within the reference range below the 99th percentile. These patients are older and have more comorbidities (Table S5). Concentration changes at these levels can occur due to analytical and/or biological variation. Additional studies are needed to clarify the prognostic implications, but analyses from the adjudicated cohort suggest these patients have favorable outcomes (Figure S9). However, they are limited by small sample size. Irrespective of the potential for small concentration changes in a modest subset of patients with baseline hs-cTnT<6 ng/L, 5-year outcomes data⁴⁶ from the ADAPT study demonstrate that patients with very low baseline hs-cTnT concentrations have good long-term outcomes. Fourth, larger early presenter studies are needed. Pending such investigations, as recommended by clinical practice guidelines¹, single sample rule-out is favored in those with symptoms that began at least 3h before. Fifth, our analyses are relevant to hs-cTnT, with studies required

using other assays. Sixth, there is no global consensus on acceptable miss rates. Following ACEP³⁸ guidance, we established that an acceptable rule-out strategy should not have more than 1–2% adverse events within 30-days, but we recognize that practice and geographic differences exist. Our data demonstrates excellent sensitivities and NPVs consistent with what the field considers safe and acceptable. Seventh, the potential for verification (workup) bias exists in all such real-life studies, however, the excellent 30-day clinical outcomes should attenuate such concerns. Eighth, our adjudicated cohort has a modest sample size and larger, multicenter, adjudicated cohorts with higher number of events are needed. Last, we recognize ICD-10 codes have limitations^{34,35}, for which reason analyses using ICD-10 codes were restricted to secondary analyses.

CONCLUSIONS

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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NON-STANDARD ABBREVIATIONS AND ACRONYMS

Hs-cTn	high-sensitivity cardiac troponin
LoD	limit of detection
US	United States
FDA	Food and Drug Administration
LoQ	limit of quantitation
AHA	American Heart Association
ACC	American College of Cardiology
ESC	European Society of Cardiology
IRB	Institutional Review Board

ICD	Internal Classification of Disease
ACTION	MAyo Southwest WisConsin 5 th Gen Troponin T ImplementatiON
REDCap	Research Electronic Data Capture
URL	upper-reference limit
HEAR	History, Electrocardiography, Age, Risk Factors
ACEP	American College of Emergency Physicians
NPV	negative predictive values
CI	confidence intervals

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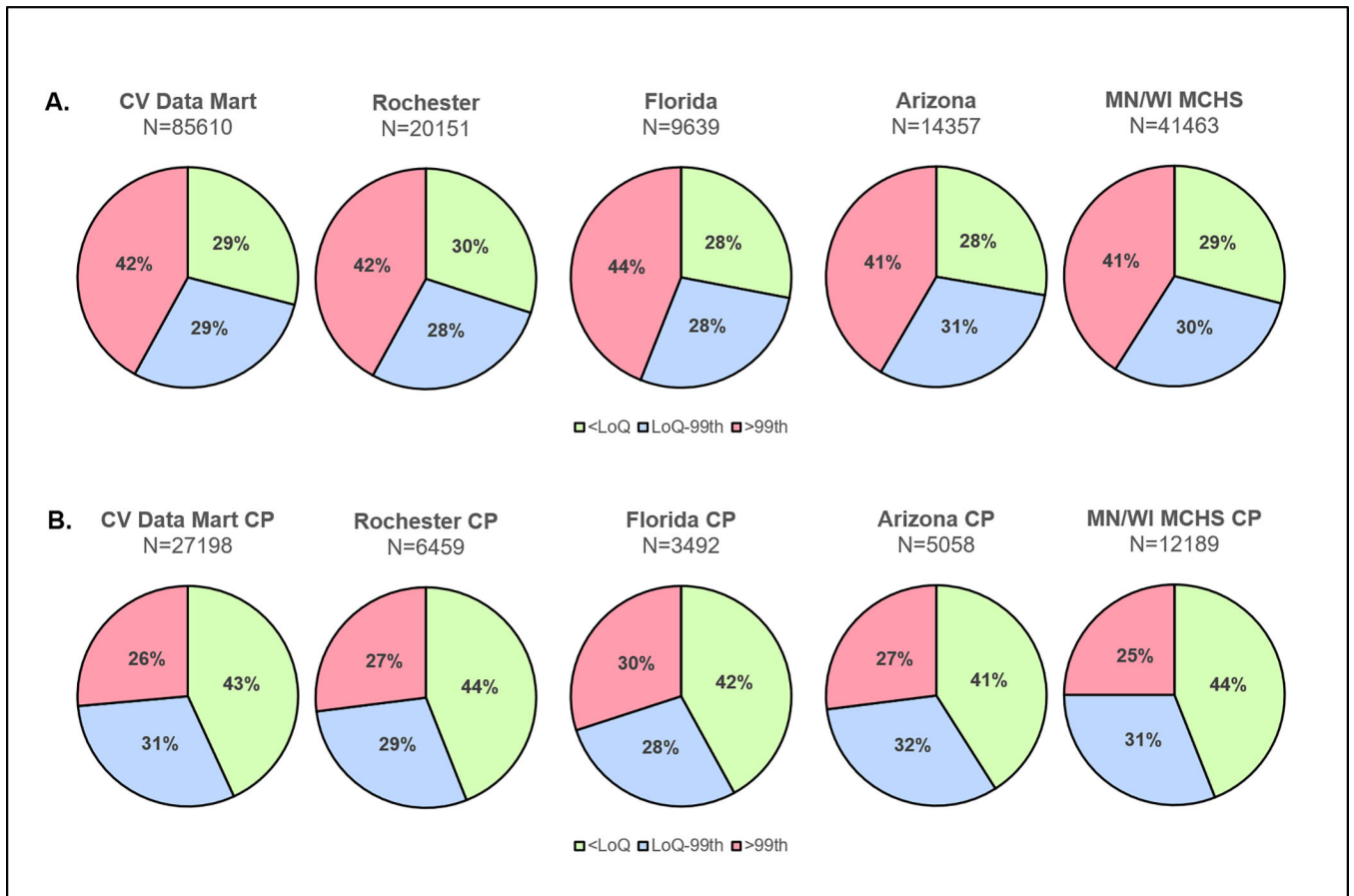
CLINICAL PERSPECTIVE

What is new?

- Data for excluding acute myocardial infarction with a single hs-cTn relies largely on the limit of detection (LoD). This threshold cannot be reported in the United States per the FDA, where the lowest reportable concentration is the limit of quantitation (LoQ).
- This is the largest study evaluating a single hs-cTnT below the LoQ of 6 ng/L to identify patients at low-risk for acute myocardial injury and infarction.
- Among 11,962 patients with hs-cTnT < 6 ng/L and serial measurements, only 1.2% developed acute myocardial injury. In an adjudicated cohort, among those with a nonischemic electrocardiogram, only 0.2% had myocardial infarction or death at 30-days.

What are the clinical implications?

- The latest AHA/ACC clinical practice guidelines recommend the use of a single hs-cTn below the LoD to exclude myocardial injury. This concentration threshold, however, is not available for clinical use in the United States.
- For hs-cTnT, this is a particular issue because there are limited data about exclusion of myocardial injury and infarction based on the LoQ of 6 ng/L.
- The present study demonstrates that a single hs-cTnT below the LoQ of 6 ng/L is a safe and rapid method to identify a substantial number of patients at very low risk for acute myocardial injury and infarction.

**Figure 1.**

Proportion of patients with baseline hs-cTnT < 6 ng/L across the CV Data Mart Biomarker overall cohort (Panel A) and in those with chest pain (Panel B) for the entire population and per-site. CP: chest pain, MCHS: Mayo Clinic Health System.

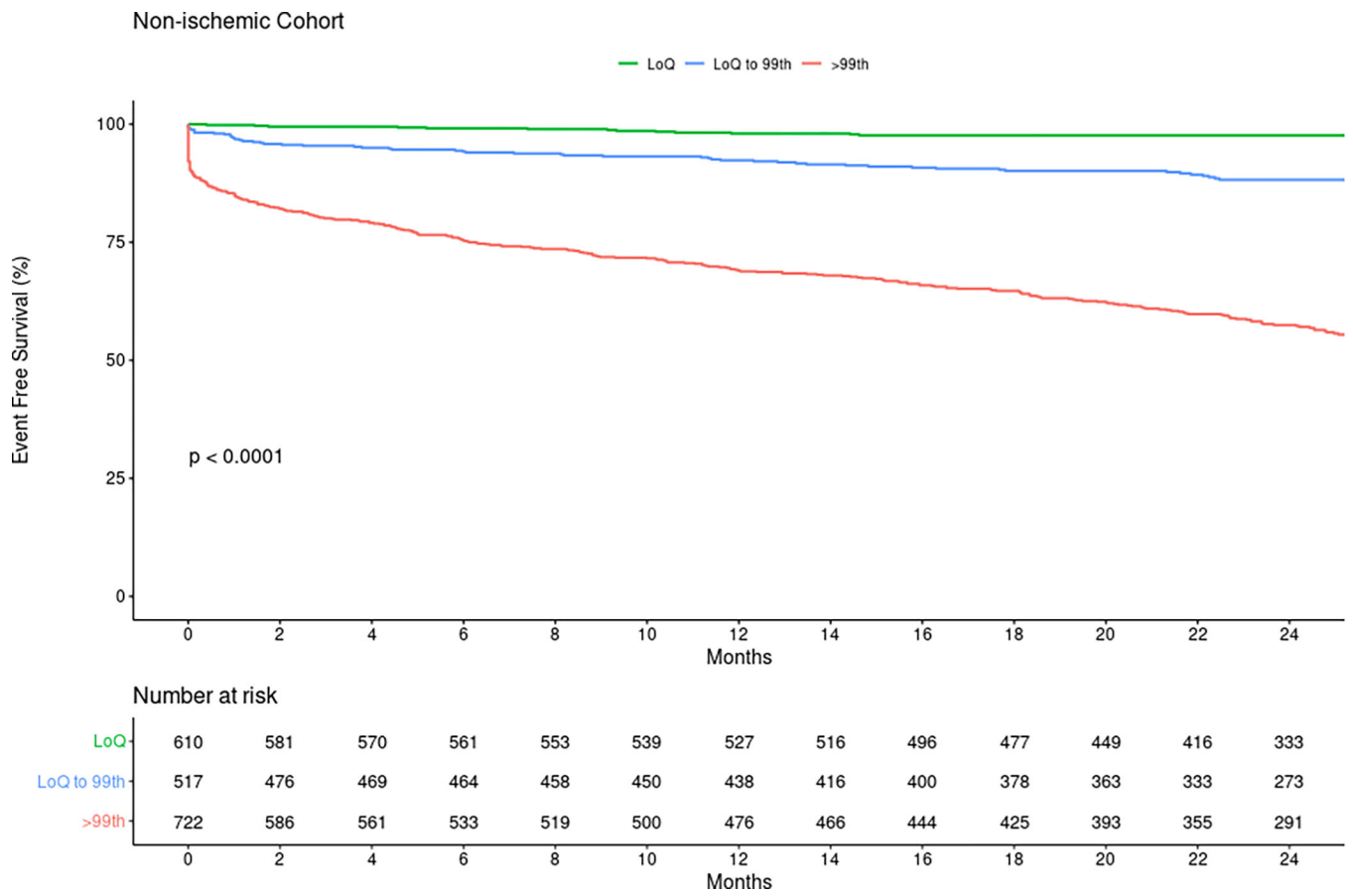


Figure 2. Kaplan-Meier curves for survival free of myocardial infarction or death according to baseline hs-cTnT groups in patients with a nonischemic electrocardiogram from the adjudicated cohort. LoQ: limit of quantitation.

Table 1.

Baseline characteristics for the CV Data Mart Biomarker cohort and according to baseline hs-cTnT concentrations. LoQ: limit of quantitation.

	Total (n=85610)	<LoQ (n=24646)	LoQ-99th percentile (n=25200)	>99th percentile (n=35764)
Age, mean (SD)	63 (18)	47 (15)	63 (15)	74 (14)
Women, n (%)	43043 (50)	16143 (66)	9281 (37)	17619 (49)
Chest pain, n (%)	27198 (32)	11725 (48)	8281 (33)	7192 (20)
Coronary artery disease, n (%)	23636 (28)	1891 (7.7)	6361 (25)	15384 (43)
Prior myocardial infarction, n (%)	9114 (11)	665 (2.7)	2257 (9.0)	6192 (17)
Hypertension, n (%)	48717 (57)	7088 (29)	14230 (57)	27399 (77)
Diabetes mellitus, n (%)	30213 (35)	4604 (19)	8385 (33)	17224 (48)
Chronic kidney disease, n (%)	17070 (20)	693 (2.8)	2939 (12)	13438 (38)
Dialysis, n (%)	1459 (1.7)	26 (0.1)	112 (0.4)	1321 (3.7)
Peripheral vascular disease, n (%)	21394 (25)	1483 (6)	5050 (20)	14861 (42)
Heart failure, n (%)	14986 (18)	625 (2.5)	2589 (10)	11772 (33)
Atrial fibrillation, n (%)	15298 (18)	851 (3.5)	3406 (14)	11041 (31)
Liver cirrhosis, n (%)	10547 (12)	2152 (8.7)	3296 (13)	5099 (14)
Index presentation death, n (%)	775 (0.9)	19 (0.1)	57 (0.2)	699 (2.0)

Table 2.

Diagnostic performance of a single baseline hs-cTnT below the limit of quantitation of 6 ng/L for acute myocardial injury (defined as any hs-cTnT increase above the sex-specific 99th percentiles within 24-hours of presentation) in patients with a baseline hs-cTnT < 6 ng/L with serial measurements in the CV Data Mart Biomarker Cohort. LoQ: limit of quantitation.

CV Data Mart Biomarker Cohort	Baseline hs-cTnT < 6 ng/L (LoQ) with serial hs-cTnT measurements					
	All-comers			Chest Pain Subgroup		
	All	Men	Women	All	Men	Women
Patients with baseline hs-cTnT < 6 ng/L (LoQ) and serial measurements, n (%)	11962	4264	7698	5840	2219	3621
Patients with baseline hs-cTnT < 6 ng/L with 2h hs-cTnT < 6 ng/L (LoQ), n (%)	10184 (85)	3469 (81)	6715 (87)	5085 (87)	1865 (84)	3220 (89)
Negative predictive value of hs-cTnT < 6 ng/L for acute myocardial injury (hs-cTnT > 99 th percentile), % (95% CI)	98.8 (98.6, 99.0)	99.3 (99.0, 99.6)	98.5 (98.2, 98.7)	98.9 (98.6, 99.1)	99.4 (99.0, 99.7)	98.6 (98.1, 98.9)
Sensitivity of hs-cTnT < 6 ng/L for acute myocardial injury (hs-cTnT > 99 th percentile), % (95% CI)	99.6 (99.5, 99.6)	99.8 (99.8, 99.9)	99.3 (99.1, 99.4)	99.0 (98.8, 99.2)	99.6 (99.4, 99.8)	98.4 (97.9, 98.8)
Acute myocardial injury (hs-cTnT > 99 th percentile) among patients with a baseline hs-cTnT < 6 ng/L (LoQ), %	1.2% (146/11962)	0.7% (29/4264)	1.5% (117/7698)	1.1% (65/5840)	0.6% (13/2219)	1.4% (52/3621)
Maximum hs-cTnT concentrations in those with acute myocardial injury (ng/L) (median and Q1, Q3)	20 (14, 43)	40 (21, 71)	16 (13, 33)	25 (14, 48)	40 (24, 70)	21 (14, 47)

Table 3.

Diagnostic performance, efficacy, and safety of a single baseline hs-cTnT below the limit of quantitation of 6 ng/L for index acute MI rule-out in patients in the adjudicated cohort. LoQ: limit of quantitation.

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