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Diagnostic Reclassification by a High-Sensitivity Cardiac Troponin Assay

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Abstract

Objective: Our objective was to describe the rates of diagnostic reclassification between conventional cardiac troponin I (cTnI) and high-sensitivity cardiac troponin T (hs-cTnT) and between combined and sex-specific hs-cTnT thresholds in adult emergency department (ED) patients in the United States.

Methods: We conducted a prospective, single-center, before-and-after, observational study of ED patients 18 years undergoing single or serial cTn testing in the ED for any reason before and after hs-cTnT implementation. Conventional cTnI and hs-cTnT results were obtained from a laboratory quality assurance database. Combined and sex-specific thresholds were the published 99th percentile upper reference limits for each assay. Cases underwent physician adjudication using the Fourth Universal Definition of Myocardial Infarction (MI). Diagnostic reclassification occurred when a patient received a diagnosis of MI or myocardial injury using one assay but not the other assay. Our primary outcome was diagnostic reclassification between the conventional cTnI and hs-cTnT assays. Diagnostic reclassification probabilities were assessed using sample proportions and 95% confidence intervals for binomial data.

Results: We studied 1,016 patients [506 (50%) male; median age 60 years (25th, 75th percentiles: 49, 71)]. Between the conventional cTnI and hs-cTnT assays, six patients (0.6%, 95% CI 0.2–

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1.3%) underwent diagnostic reclassification with regard to MI (5/6 reclassified as no MI) and 166 patients (16%, 95% CI 14–19%) underwent diagnostic reclassification with regard to myocardial injury (154/166 reclassified as having myocardial injury) by hs-cTnT.

Conclusions: Compared to conventional cTnI, the hs-cTnT assay resulted in no clinically relevant change in MI diagnoses but substantially more myocardial injury diagnoses.

INTRODUCTION

Background:

Cardiac troponin (cTn) testing is performed in nearly one in five emergency department (ED) visits in the United States (US).¹ cTn is a protein integral to cardiac muscle contraction and is the preferred biomarker for the diagnosis of myocardial infarction (MI).² Commercial assays detect two cTn subtypes, cTnI and cTnT. The latest generation of cTn assays, known as high-sensitivity (hs) cTn assays, detect rises in cTn earlier than conventional cTn assays and may expedite the diagnosis and exclusion of MI.^{3–6} By definition, hs-cTn assays measure cTn levels within the normal range in at least 50% of healthy individuals with high precision, defined as a coefficient of variance (CV) \leq 10% at the 99th percentile. These characteristics allow hs-cTn assays to reliably detect clinically significant changes at lower cTn levels in shorter time intervals than conventional cTn assays.^{7,8} Hs-cTn assays are also the first cTn assays approved for use with both combined and sex-specific thresholds.⁸ Although widely used internationally for nearly a decade, the first hs-cTn assay was approved for use in the US in January 2017 and was introduced clinically later that year.

Importance:

As US hospitals introduce hs-cTn assays, concerns have been raised that MI will be over-diagnosed and elevated troponin results will lead to unnecessary admissions for cardiac testing.^{9,10} Available data suggest that hs-cTn assays will result in 4% to 28% more elevated cTn results than conventional cTn assays.^{11–13} However, the conclusions drawn from these studies are limited by small sample sizes, restricted patient populations, non-US populations and use of biomarkers other than hs-cTnT.^{11–13}

Compared to men, women with MI and myocardial injury experience longer delays to diagnosis, receive less aggressive care, and have worse outcomes.^{14–20} Hs-cTnT assays employing sex-specific diagnostic thresholds may improve diagnostic sensitivity for MI and myocardial injury in female patients. However, the clinical benefit of sex-specific diagnostic thresholds remains unproven with recent reports finding no long-term survival benefit despite increased MI and injury diagnoses in women.^{18,19,21–24}

Goals of This Investigation:

Little is known about how hs-cTnT compares to conventional assays in an intended-use US population, particularly with regard to changes in the rates of MI diagnoses and elevated cTn results. Our objective in this study was to describe the rates of diagnostic and specimen reclassification between conventional cTnI and hs-cTnT and between combined and sex-specific hs-cTnT thresholds in adult ED patients. We also sought to describe admission rates

and 30-day cardiac stress testing and catheterization rates when conventional cTnI and hs-cTnT were used clinically.

METHODS

Study Design and Setting:

We conducted a prospective, observational, before-and-after cohort study in a single, urban, academic, tertiary medical center with approximately 65,000 adult ED visits annually. Trained research coordinators screened and enrolled ED patients during two periods: the “before” period from 3/12/18 to 6/15/18 while conventional cTnI (TnI-Ultra, Siemens, Malvern, PA) was used clinically and the “after” period from 8/20/18 to 1/3/19 while hs-cTnT (Gen 5 TnT, Roche Diagnostics, Indianapolis, IN) was used clinically. Hs-cTnT was implemented on 6/18/18 with a suggested algorithm for hs-cTnT testing and interpretation in patients with suspected non-ST segment elevation MI (NSTEMI) that was developed by a multidisciplinary work group and closely based on European Society of Cardiology guidelines²⁵ (Appendix). Physicians were educated on hs-cTnT and the associated algorithm prior to implementation. Our institution did not have a similar algorithm for conventional cTnI. Orders available in the electronic medical record (EMR) for conventional cTnI testing included a single cTn and serial cTn testing at 0 and 3 hour time points; for hs-cTnT, available orders included a single hs-cTnT and serial hs-cTnT testing at 0, 1, and 3 hour time points. This study, including the use of the laboratory’s quality assurance database described below, was approved by our Institutional Review Board.

The Department of Pathology and Laboratory Medicine maintains a biorepository that archives remnant plasma samples from cTn tests ordered for routine care. During the study period, the laboratory was conducting cTn testing using both conventional cTnI and hs-cTnT assays on these samples as part of their method verification and ongoing quality assurance initiatives. The 99th percentile upper reference limit threshold where imprecision was <10% CV for the conventional cTnI assay was 40 ng/L.²⁶ The combined 99th percentile upper reference limit threshold exhibiting imprecision of <10% CV for the hs-TnT assay was 19 ng/L; the sex-specific thresholds were 14 ng/L for females and 22 ng/L for males.²⁷ These are the thresholds approved by the US Food and Drug Administration for clinical use of this assay in the US.^{27,28} Our laboratory reports values in ng/L in accordance with Fourth Universal Definition of MI recommendations.²

Selection of Participants:

We enrolled a convenience sample of adults (age ≥ 18 years) who underwent single or serial cTn testing in the ED for any reason during the before and after study periods. The decision to perform single versus serial troponin testing as well as the frequency of serial testing was at the discretion of the treating physician. We did not restrict our sample to patients with chest pain to reflect the population in whom cTn testing is used in clinical practice.¹ Similarly, we did not restrict our sample to patients undergoing serial cTn measurements to reflect real-world clinical practice regarding cTn testing. Patients were excluded if they were not included in the laboratory quality assurance database due to having no remnant specimen. We also excluded children, prisoners, adults unable to consent, and patients with

ST segment elevation on initial electrocardiogram (ECG) undergoing emergent cardiac catheterization. We used historical day-and-time data on when patients who undergo cTn testing arrive in the ED to establish quotas for 24/7 enrollment. Research assistants enrolled patients to meet each quota, yielding a quota sample of patients whose ED arrival time distribution was representative of ED patients undergoing standard of care cTn testing at our institution.

Measurements:

Trained research assistants blinded to the study's objectives screened and enrolled patients during their ED visit and prospectively recorded treating physician rationale for cTn testing. Troponin results and collection times were exported from the EMR and laboratory biorepository. For patients undergoing serial cTn testing, all available cTn results were exported. Trained research assistants blinded to the study's objectives abstracted the following data from the EMR: clinical presentation, past medical history, ECG findings, laboratory results including baseline cTn values, diagnostic testing, and cardiac interventions. They used a uniform data dictionary and standardized electronic data collection forms. In-person and online meetings were held to ensure uniform handling of missing and ambiguous data. Follow-up was obtained at 30 days. Trained research assistants attempted to contact all patients directly via phone, email, and/or text message. Additionally, EMR review was performed for all patients. The study site and other regional health systems participate in an integrated electronic exchange that allows clinical documentation from other regional hospitals to be integrated into the EMR. This exchange includes ED visits and hospitalizations at most of the hospitals in the surrounding area and allows for follow up data on patients who are unable to be contacted directly. Data collected included cardiac testing, cardiac revascularization, MI, return ED visits, re-hospitalizations, and death. Study data were collected and managed using the Research Electronic Data Capture (REDCap) tool hosted at our institution.^{29,30}

All cases with any cTn result above the 99th percentile threshold were reviewed by an attending ED physician and an attending internist who directs the ED Chest Pain Evaluation Unit. The reviewers integrated clinical, diagnostic, and 30-day follow up information to assign a diagnosis of MI, myocardial injury, or neither (Figure 1). When a patient's baseline cTn values were available, these were provided to reviewers. Thus, reviewers were able to use both absolute and delta cTn values to assess for MI and injury in patients with baseline or serial cTn measurements. Thirty-day follow up information available to reviewers included cardiac tests and procedures; return visits to the ED or clinic; hospitalizations; and death. MI diagnoses were further classified as type 1 vs type 2 NSTEMI.² Disagreement between the two reviewers was adjudicated by an attending cardiologist. Cases were reviewed and adjudicated in three phases separated by at least two weeks: conventional cTnI values, hs-cTnT values with combined thresholds, and hs-cTnT values with sex-specific thresholds. Reviewers were provided with the published 99th percentile upper reference limit thresholds for each assay. MI and myocardial injury were defined according to the Fourth Universal Definition of MI.² Briefly, a diagnosis of MI requires a rise and/or fall in cTn with at least one cTn value above the 99th percentile threshold and clinical signs or symptoms of ischemia. Myocardial injury is diagnosed when the cTn value is above the 99th percentile

threshold but the patient lacks clinical signs or symptoms of ischemia (Figure 1). A 20% change was suggested but not mandated as the threshold for defining a rise or fall in cTn.³¹ The institutional algorithm for cTn testing and interpretation in patients with suspected NSTEMI (Appendix) was also available to reviewers, and they were experienced with its use in the clinical setting. Patients with a clinically significant rise and/or fall in serial troponin results from one assay with insufficient remnant specimen to obtain serial troponin results from the other assay were excluded from the analysis. These patients could not be diagnosed with respect to the assay type lacking serial results. Patients with a single elevated troponin and insufficient clinical data to be diagnosed were also excluded.

The same review and adjudication process and definitions were used to determine 30-day outcomes of (1) STEMI or type 1 NSTEMI and (2) cardiac death. Cardiac death included those from acute MI, sudden cardiac death, heart failure, and cardiovascular procedures.³² Death from stroke was not considered a cardiac death. Deaths were adjudicated to be cardiac, non-cardiac, or undetermined.³²

Diagnostic reclassification was defined as a change in diagnosis (MI, myocardial injury or neither) between the assays (conventional cTnI vs. hs-cTnT) or thresholds utilized (combined vs. sex-specific) during adjudication. Specimen reclassification was defined as a specimen being above the 99th percentile threshold using one assay or threshold and below the 99th percentile threshold using the alternate assay or threshold.

Outcomes:

Our primary outcome was diagnostic reclassification between the conventional cTnI and hs-cTnT assays using combined thresholds. Secondary outcomes were diagnostic reclassification between combined and sex-specific hs-cTnT thresholds; specimen reclassification between conventional cTnI and hs-cTnT assays; specimen reclassification between combined and sex-specific hs-cTnT thresholds; admission rates between the before and after periods; and cardiac stress testing or cardiac catheterization within 30 days between the before and after periods. Specimen reclassification was analyzed at the patient level, such that a patient who had 1 reclassified specimen(s) was considered to have undergone specimen reclassification. Admission was defined as admission from the ED to full inpatient or observation status.

Analysis:

Diagnostic and specimen reclassification probabilities as well as admission and cardiac stress testing or catheterization were assessed using sample proportions and 95% confidence intervals (CIs) for binomial data. Sub-group analyses restricted to patients with serial troponin testing and patients with chronic kidney disease (CKD) on dialysis were also conducted. For the subset of patients classified as having no MI or myocardial injury according to conventional cTnI, a binary dependent variable based on the hs-cTnT assay (coded 0 for 'no MI or myocardial injury' and 1 for 'either MI or myocardial injury') was analyzed via multiple logistic regression to assess adjusted associations of predictor variables with reclassification to MI or myocardial injury based on hs-cTnT. Similar multiple logistic regression models were fitted to assess the adjusted association of period

(before vs. after) with the secondary outcomes of admission and cardiac stress testing or catheterization. Predictor variables for these models were selected *a priori* and included age, sex, history of coronary artery disease, history of diabetes, history of CKD on dialysis, and history of heart failure. Model outputs were expressed as odds ratios (ORs) with 95% confidence intervals (CI). Analyses were conducted using Stata 14 (StataCorp LP, College Station, TX).

RESULTS

Characteristics of Study Subjects:

We studied 1,016 patients after excluding 60 patients who were not in the in the laboratory quality assurance database; three patients with a clinically significant rise and/or fall in serial troponin results from one assay who had insufficient remnant specimen to obtain serial troponin results from the other assay; and one patient who left “against medical advice” after a single elevated troponin (Figure 2). Half of the study participants were male (50%, 506/1,016) and median age was 60 years (25th, 75th percentiles 49, 71). Just over half (545/1,016; 54%) of patients underwent serial cTn testing as part of their clinical care, and half of patients (50%, 508/1,016) received clinical care with hs-cTnT. The most common reason for cTn testing was suspected acute coronary syndrome (ACS; 75%, 758/1,016). (Table 1) In comparison, the population of all adult ED patients (n=10,103; Figure 2) undergoing cTn testing during the overall study period was 50% male (5,069/10,103) with median age 60 years (25th, 75th percentiles 48, 72). The distributions of conventional cTnI and hs-cTnT values on the initial and serial measurements are shown in Figure 3.

30 Day Follow Up:

At 30-day follow up, 877/1,016 (86%) of patients were reached directly via phone, text message, or email. The remaining 139 (14%) patients underwent EMR review only; 27 (2.7%) had no information in EMR to determine vital status at 30 days. No (0/1,016; 0%) patients had a STEMI or type 1 NSTEMI between their index encounter and 30-day follow up. Sixteen (16/1,016; 1.6%) patients died between their index encounter and 30-day follow up; 15 (15/1,016; 1.5%) had non-cardiac death, and one (1/1,016; 0.1%) had cardiac death. The latter patient was admitted during the index encounter for type 1 NSTEMI in the setting of heart failure and CKD on hemodialysis. The patient was found to have multivessel coronary artery disease on angiography, declined coronary artery bypass graft surgery, and was placed on hospice care. Stress testing, cardiac catheterization, and revascularization within 30 days are shown in Table 1.

Main Results:

Diagnostic Reclassification Between Conventional cTnI and hs-cTnT—Between the conventional cTnI and hs-cTnT assays with combined thresholds, the diagnostic reclassification rate was 0.6% (6/1,016; 95% CI 0.2–1.3%) with regard to MI and 16% (166/1,016; 95% CI 14–19%) with regard to myocardial injury (Tables 2–3, Figure 4). Using hs-cTnT results, five patients (0.5%, 95% CI 0.2–1.1%) diagnosed with MI – one with type 1 NSTEMI and four with type 2 NSTEMI - using the cTnI assay were reclassified as not having had an MI by the hs-cTnT assay. Overall, these patients had modestly elevated

conventional cTnI values with a rise and/or fall pattern; and normal to slightly elevated but flat hs-cTnT values. The single patient with a type 1 NSTEMI was referred from his primary care physician for an episode of chest pressure that occurred two days prior. His conventional cTnI was modestly elevated, and his hs-cTnT was normal. He underwent cardiac catheterization with percutaneous coronary intervention. One patient (0.1%, 95% CI 0.0–0.5%) who did not receive the diagnosis of MI using the cTnI assay was reclassified as having MI (type 1 NSTEMI) using the hs-cTnT assay. In this patient, serial cTnI results were normal and flat, whereas hs-cTnT values were modestly elevated and fell approximately 20% over nearly 6 hours.

Using hs-cTnT results, 154 (15%, 95% CI 13–18%) patients were reclassified as having myocardial injury; two (0.2%, 95% CI 0.02–0.7%) had an MI diagnosis using conventional cTnI, and 152 (15%, 95% CI 13–17%) had no MI or myocardial injury using conventional cTnI. Twelve (1.2%, 95% CI 0.6–2.1%) patients with myocardial injury using conventional cTnI were reclassified by hs-cTnT as having no MI or injury (Table 2).

Diagnostic Reclassification Between Combined and Sex-Specific Thresholds

—Between combined and sex-specific hs-cTnT thresholds, the diagnostic reclassification rate was 0.0% (0/1,016; 95% CI 0–0.4%) with regard to MI and 3.7% (38/1,016; 95% CI 2.7–5.1%) with regard to myocardial injury. Sex-specific 99th percentile thresholds reclassified 13 men (13/506; 2.6%, 95% CI 1.4–4.4%) as having no myocardial injury and reclassified 25 women (25/510; 4.9%, 95% CI 3.1–7.2%) as having myocardial injury (Table 2).

Specimen Reclassification—Between the conventional cTnI and hs-cTnT assays with combined thresholds, 226 (22%, 95% CI 20–25%) patients had at least one specimen that was reclassified. In most patients, specimen reclassification (206/226; 91%, 95% CI 87–95%) occurred with a hs-cTnT value above the 99th percentile threshold and a cTnI value below the 99th percentile threshold. Of the six patients who experienced diagnostic reclassification with regard to MI, half (3/6; 50%) also had specimen reclassification (Table 3). Between combined and sex-specific hs-cTnT thresholds, 44 men (44/506; 8.7%, 95% CI 6.4–11%) and 53 (53/510; 10%, 95% CI 7.9–13%) women had at least one specimen that was reclassified.

Subgroup Analyses—In the subgroup of 545 patients with serial cTn testing, the reclassification rate with regard to MI diagnosis was 0.9% (5/545; 95% CI 0.3–2.1%) and with regard to myocardial injury was 21% (117/545; 95% CI 18–25%). The one patient (1/471; 0.2%, 95% CI 0.01–1.2%) with a single troponin who was reclassified with regard to MI between the assays was referred by his primary care physician to the ED for typical chest pain with a modified HEART score of six. He had a single cTn that was modestly elevated on the conventional cTnI assay and normal on the hs-cTnT assay prior to undergoing cardiac catheterization and percutaneous coronary intervention. In the subgroup of 85 patients with CKD on dialysis, 34 patients (40%, 95% CI 26–51%) were reclassified by hs-cTnT as having myocardial injury. Using hs-cTnT, 95% (81/85, 95% CI 88–99%) of patients with CKD on dialysis were diagnosed with MI or myocardial injury.

Multiple Regression Model for Reclassification—For the multiple logistic regression analysis concerned with reclassification to MI or myocardial injury based on hs-cTnT among those patients with no MI or myocardial injury based on conventional cTnI, older age (OR 1.4 per 10 years, 95% CI 1.2–1.7), male sex (OR 2.7, 95% CI 1.8–4.2), history of CKD on dialysis (OR 72, 95% CI 23–225), history of heart failure (OR 3.4, 95% CI 2.1–5.5), and history of diabetes (OR 2.8, 95% CI 1.8–4.4) were predictors of reclassification. Personal history of coronary artery disease was not associated with reclassification.

Temporal Patterns in Troponin—Among the 27 patients diagnosed with acute MI using both the conventional cTnI and hs-cTnT assays (Figure 4), both assays followed similar temporal patterns. In the majority of patients (20/27; 74%), the initial cTn result was elevated on both assays; in five patients (5/27; 19%), it was below the 99th percentile threshold on both assays; in one patient (1/27; 4%), only the initial conventional cTnI result was elevated; and in one patient (1/27, 4%), only the initial hs-cTnT result was elevated. All serial conventional cTnI results were elevated; one patient had a 2nd hs-cTnT result that was below the 99th percentile threshold but increased by 10 ng/L from the initial draw and would have been classified as “likely NSTEMI” using our institutional algorithm (Appendix) and European Society of Cardiology guidelines.²⁵ Of the nine (9/27; 33%) patients with chest pain or equivalent symptoms for ≥ 3 hours prior to presentation, two (2/9; 22%) had initial results below the 99th percentile threshold using both the conventional cTnI and hs-cTnT assays.

Admission—During the before period, 51% (259/508; 95% CI 47–55%) of patients were admitted; during the after period, 57% (288/508; 95% CI 52–61%) were admitted. In multiple regression models, period was not independently associated with admission (OR 1.1, 95% CI 0.9–1.5). Among patients with an adjudicated diagnosis of myocardial injury using conventional cTnI in the before period, 83% (57/68; 95% CI 73–92%) were admitted. Among patients with an adjudicated diagnosis of myocardial injury using hs-cTnT in the after period, 81% (121/149; 95% CI 74–87%) were admitted.

Cardiac Stress Testing and Catheterization—During the before and after periods, 60 patients (60/508; 12%, 95% CI 9–15%) and 65 patients (65/508; 13%, 95% CI 10–16%), respectively, underwent cardiac stress testing or catheterization within 30 days. In multiple regression models, period was not associated with cardiac stress testing or catheterization within 30 days (OR 1.1, 95% CI 0.7–1.5). Among patients in whom cTn was ordered due to suspicion for ACS, 55 (55/379; 15%, 95% CI 11–18%) in the before and 56 (56/379; 15%, 95% CI 11–19%) in the after period underwent cardiac stress testing or catheterization within 30 days. Among patients in whom cTn was not ordered to evaluate for ACS, five (5/129; 4%, 95% CI 1–9%) in the before and nine (9/129; 7%, 95% CI 3–13%) in the after periods, respectively, underwent cardiac stress testing or catheterization within 30 days. Among patients with myocardial injury using cTnI in the before period, 10% (7/68; 95% CI 4–20%) underwent cardiac stress testing or catheterization within 30 days. Among patients with myocardial injury using hs-cTnT in the after period, 9% (14/149; 95% CI 5–15%) underwent cardiac stress testing or catheterization within 30 days.

LIMITATIONS

We enrolled patients undergoing single or serial cTn testing for any reason with any comorbidities arriving 24/7 to the ED to represent the overall patient population undergoing cTn testing in the ED. However, this was a single-center study, and our results may not be generalizable to other patient populations or physician practice patterns. Our study depended on patients having remnant samples in the laboratory biobank. Three patients with a clinically significant rise and/or fall in serial troponin results from one assay who had insufficient remnant specimen to obtain serial troponin results from the other assay were excluded from the analysis. While we evaluated predictors of myocardial injury reclassification, we were unable to evaluate predictors of MI reclassification due to the rarity of this outcome. However, this study is among the earliest to assess the particular issue of comparative diagnostic utility of conventional cTn and hs-cTn in the US and provides an important perspective on the value and limitations of the latter marker.

DISCUSSION

Our results suggest that hospitals transitioning to a hs-cTnT assay should expect more elevated cTn results and myocardial injury diagnoses without a substantial change in MI diagnoses, admissions, cardiac stress testing, or cardiac catheterization. Hs-cTn assays have been used outside of the US for nearly a decade.²⁵ Despite concerns about MI overdiagnosis,^{9,10} our results align with several European studies that fail to demonstrate overdiagnosis of MI using hs-cTn.^{5,33,34} Our trained reviewers followed the Fourth Universal Definition of MI, and the increase in the number of patients with elevated cTn results using hs-cTnT creates the potential for an increase in MI diagnoses if clinicians do not strictly adhere to this definition. Clinicians must consider not only whether hs-cTnT is elevated, but also whether the elevation has a rise and/or fall pattern and whether the patient has signs or symptoms of ischemia, before making a diagnosis of MI.² Future studies should evaluate rates of clinically diagnosed MI when hs-cTnT is used in practice. Importantly, our results suggest that conventional cTn assays are not “missing” MIs when used appropriately.

Sex-specific thresholds for hs-cTnT affected only myocardial injury diagnoses, not MI diagnoses. Given that sex-specific thresholds are only a few ng/L higher (men) or lower (women) than the combined threshold, it is not surprising that changes within the discriminatory zone between the combined and sex-specific thresholds had a small effect on the overall hs-cTnT rise and/or fall pattern and thus did not change MI diagnoses. The primary effect of sex-specific thresholds is an increase in myocardial injury diagnoses in women, the clinical significance of which is unclear.^{3,22,35,36} Hospitals implementing hs-cTn must weigh these potential clinical benefits against the complexity created by sex-specific thresholds and protocols in their specific population.

The High-Sensitivity Troponin in the Evaluation of patients with suspected Acute Coronary Syndrome (High-STEACS) trial recently demonstrated an hs-cTnI assay to be associated with increased diagnosis of both myocardial injury and MI.¹² Overall, our study had higher rates of specimen reclassification and myocardial injury reclassification; and a lower rate of MI reclassification.

Our results may differ from those of High-STEACS because we enrolled all patients undergoing cTn testing, including those with CKD on dialysis and those whose cTn test was ordered for a reason other than suspected ACS, and we used the Fourth Universal Definition of MI for adjudication of diagnoses. Baseline ACS risk between the US and European ED populations and differences between the hs-cTnI and hs-cTnT assays may also contribute to the increased MI diagnosis in the HI-STEACS study.

The proportion of patients with specimen reclassification in our study is consistent with previous reports of specimen reclassification using hs-cTnT.¹¹⁻¹³ Nearly one in five patients had at least one reclassified specimen with most specimen reclassification due to an elevated hs-cTnT and normal conventional cTnI. Several factors likely contribute to the observed specimen reclassification rates. First, patients presenting early to the ED with chest pain (or equivalent symptoms) for less than three hours may have elevated hs-cTnT assay results but normal conventional cTn levels.^{37,38} Second, our study population included patients with various stages of CKD. CKD is associated with persistently elevated cTn levels, with cTnT elevations occurring more frequently than cTnI elevations.³⁹ Thus, some of our observed reclassification may have been due to a difference in cTn subtype measured (cTnI vs. cTnT) rather than a difference in assay (conventional vs. high-sensitivity assay). The reasons for cTn elevation in CKD are likely multifactorial, and choice of hemodialysis membrane having been shown to affect post-dialysis concentrations of cTn.^{40,41} Importantly, elevated hs-cTnT in patients with CKD on hemodialysis is associated with increased mortality and cardiovascular events.^{42,43} Third, inter-assay differences in the coefficient of variance around the 99th percentile may contribute.⁴⁴ Fourth, false negative hs-cTnT values due to hemolysis and biotin supplement use have been reported.⁴⁵ Finally, our comparison of cTnI to cTnT may have affected reclassification in both directions. Cardiac TnI and cTnT exist in multiple fragments, form distinct protein-protein complexes and undergo different post-translational modifications within the cardiac myocyte that may complicate inter-assay reproducibility.⁴⁵

Hospitals transitioning to hs-cTn assays should prepare for more elevated cTn results above the 99th percentile threshold, regardless of whether combined or sex-specific thresholds are selected. Laboratory personnel and clinicians should agree on the degree of hs-cTn elevation that will trigger clinician notification in order to optimize clinical and laboratory workflows. Clinicians should be educated on the interpretation of elevated hs-cTn results, and guidelines for the interpretation of elevated hs-cTn results^{25,46} should be agreed upon by the clinical departments involved in the care of these patients. The higher rates of myocardial injury seen with hs-cTn may create challenges for clinicians, as myocardial injury was only recently differentiated from MI in the Fourth Universal Definition of MI and no evidence-based guidelines exist for the management of patients with myocardial injury.² Any evaluation of myocardial injury will likely be based on the patient's history, risk factors, and presentation. In our study, similar proportions of patients with myocardial injury were admitted during the before (conventional cTnI) and after (hs-cTnT) periods, suggesting that ED physicians are comfortable discharging selected patients with myocardial injury for outpatient follow up. Given the strong association between elevated hs-cTn and both future cardiovascular events and all-cause mortality,^{12,47} elevated hs-cTn results have prognostic implications for patients even if they do not change immediate ED management.

Notably, nearly half of patients in our study received a single cTn measurement during their clinical care. While this practice strays from the intended use for both conventional cTnI and hs-cTnT assays,^{26,27} it occurs frequently in clinical practice. Some of patients in the after period may have received a single cTn test because their initial hs-cTnT result <6 ng/L and symptom duration of at least three hours placed them in the “ruled out” for acute MI category in our institutional algorithm (Appendix). However, no algorithm for ruling out acute MI with a single conventional cTnI existed at our institution or in professional society guidelines, suggesting that other factors influenced the decision to perform single versus serial cTn testing. Physicians likely performed serial cTn measurements in patients they assessed to be at higher risk for NSTEMI, as suggested by baseline differences in the two groups in Table 1. Patients with a single cTn may have had an alternate etiology for their symptoms identified prior to the second cTn, such that the physician felt a second cTn was not indicated. Another possibility is that the patient had a long duration of symptoms and a single cTn measurement at their baseline. As the precision of hs-cTn assays allows them to detect changes at lower cTn levels than conventional cTn assays,^{7,8} the possibility of rapidly excluding acute MI by comparing a single hs-cTn measurement to baseline values in selected patients warrants further study.

In our study, transition to hs-cTnT was not associated with changes in admission during index visit or cardiac stress testing or catheterization within 30 days. While concerns have been raised that hs-cTn implementation in the US will lead to increased admissions and cardiac evaluations,^{48–51} our data align with international and early US data showing no change in admissions or cardiac evaluations in the period shortly after hs-cTnT implementation.^{5,34,52–54} The overall low rate of cardiac stress testing and catheterization in our study suggests that physicians are not reflexively performing these tests and procedures for all patients with suspected ACS or all patients with myocardial injury. The prognostic ability of a hs-cTnT result below the limit of quantification (<6 ng/L in the US) combined with a non-ischemic electrocardiogram to indicate low probability of 30-day MI or death may reduce cardiac stress testing for further risk stratification in patients meeting these criteria.⁵⁵ A decline in testing in this group may offset any increase in testing driven by an increase myocardial injury diagnoses. Future studies should evaluate these metrics over a longer time frame post-implementation to determine whether the declines in admissions and cardiac stress testing seen in European populations are realized in the US.^{5,34,54}

In summary, compared to conventional cTnI, hs-cTnT resulted in few cases of MI reclassification but substantially more patients with elevated cTn results and myocardial injury diagnoses. Introducing hs-cTnT has potentially important implications on patient care and clinical workflows that warrant investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Makam AN, Nguyen OK. Use of Cardiac Biomarker Testing in the Emergency Department. *JAMA Intern Med* 2015;175:67–75. [PubMed: 25401720]
2. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). *Eur Heart J* 2019;40:237–69.
3. Mueller C, Giannitsis E, Christ M, et al. Multicenter Evaluation of a 0-Hour/1-Hour Algorithm in the Diagnosis of Myocardial Infarction with High-Sensitivity Cardiac Troponin T. *Ann Emerg Med* 2016;68:76–87 e4. [PubMed: 26794254]
4. Kurz K, Giannitsis E, Becker M, et al. Comparison of the New High Sensitive Cardiac Troponin T with Myoglobin, H-Fabp and CtnT for Early Identification of Myocardial Necrosis in the Acute Coronary Syndrome. *Clin Res Cardiol* 2011;100:209–15. [PubMed: 20852870]
5. Twerenbold R, Jaeger C, Rubini Gimenez M, et al. Impact of High-Sensitivity Cardiac Troponin on Use of Coronary Angiography, Cardiac Stress Testing, and Time to Discharge in Suspected Acute Myocardial Infarction. *Eur Heart J* 2016;37:3324–32. [PubMed: 27357358]
6. Reichlin T, Schindler C, Drexler B, et al. One-Hour Rule-out and Rule-in of Acute Myocardial Infarction Using High-Sensitivity Cardiac Troponin T. *Arch Intern Med* 2012;172:1211–8. [PubMed: 22892889]
7. Apple FS, Jaffe AS, Collinson P, et al. IFCC Educational Materials on Selected Analytical and Clinical Applications of High Sensitivity Cardiac Troponin Assays. *Clin Biochem* 2015;48:201–3. [PubMed: 25204966]
8. Apple FS, Collinson PO, Biomarkers ITFoCAoC. Analytical Characteristics of High-Sensitivity Cardiac Troponin Assays. *Clin Chem* 2012;58:54–61. [PubMed: 21965555]
9. Odqvist M, Andersson PO, Tygesen H, et al. High-Sensitivity Troponins and Outcomes after Myocardial Infarction. *J Am Coll Cardiol* 2018;71:2616–24. [PubMed: 29880121]
10. de Lemos JA, Morrow DA, deFilippi CR. Highly Sensitive Troponin Assays and the Cardiology Community: A Love/Hate Relationship? *Clin Chem* 2011;57:826–9. [PubMed: 21471249]
11. Jairam S, Jones P, Samaraie L, et al. Clinical Diagnosis and Outcomes for Troponin T ‘Positive’ Patients Assessed by a High Sensitivity Compared with a 4th Generation Assay. *Emerg Med Australas* 2011;23:490–501. [PubMed: 21824317]
12. Shah ASV, Anand A, Strachan FE, et al. High-Sensitivity Troponin in the Evaluation of Patients with Suspected Acute Coronary Syndrome: A Stepped-Wedge, Cluster-Randomised Controlled Trial. *Lancet* 2018;392:919–28. [PubMed: 30170853]
13. Christenson RH, Jacobs E, Uettwiller-Geiger D, et al. Comparison of 13 Commercially Available Cardiac Troponin Assays in a Multicenter North American Study. *J Appl Lab Med* 2017;1:544–61.
14. Gulati M, Shaw LJ, Bairey Merz CN. Myocardial Ischemia in Women: Lessons from the NHLBI WISE Study. *Clin Cardiol* 2012;35:141–8. [PubMed: 22389117]
15. Shaw LJ, Bairey Merz CN, Pepine CJ, et al. Insights from the Nhlbi-Sponsored Women’s Ischemia Syndrome Evaluation (WISE) Study: Part I: Gender Differences in Traditional and Novel Risk Factors, Symptom Evaluation, and Gender-Optimized Diagnostic Strategies. *J Amer Coll Cardiol* 2006;47:S4–S20. [PubMed: 16458170]
16. Chandra NC, Ziegelstein RC, Rogers WJ, et al. Observations of the Treatment of Women in the United States with Myocardial Infarction: A Report from the National Registry of Myocardial Infarction-I. *Arch Intern Med* 1998;158:981–8. [PubMed: 9588431]
17. Bugiardini R, Yan AT, Yan RT, et al. Factors Influencing Underutilization of Evidence-Based Therapies in Women. *Eur Heart J* 2011;32:1337–44. [PubMed: 21383003]

18. Lee KK, Ferry AV, Anand A, et al. Sex-Specific Thresholds of High-Sensitivity Troponin in Patients with Suspected Acute Coronary Syndrome. *J Amer Coll Cardiol* 2019;74:2032–43. [PubMed: 31623760]
19. Shah AS, Griffiths M, Lee KK, et al. High Sensitivity Cardiac Troponin and the under-Diagnosis of Myocardial Infarction in Women: Prospective Cohort Study. *Brit Med J* 2015;350:g7873. [PubMed: 25609052]
20. Kaul P, Chang WC, Westerhout CM, et al. Differences in Admission Rates and Outcomes between Men and Women Presenting to Emergency Departments with Coronary Syndromes. *Can Med Assoc J* 2007;177:1193–9. [PubMed: 17984470]
21. Rubini Gimenez M, Twerenbold R, Boeddinghaus J, et al. Clinical Effect of Sex-Specific Cutoff Values of High-Sensitivity Cardiac Troponin T in Suspected Myocardial Infarction. *JAMA Cardiol* 2016;1:912–20. [PubMed: 27653005]
22. Howell SJ, Amsterdam EA, Mumma BE, et al. Implementation of High-Sensitivity Cardiac Troponin: Challenges from the International Experience. *Crit Pathw Cardiol* 2018;17(4):173–178. [PubMed: 30418246]
23. Yang S, Huai W, Qiao R, et al. Age and Gender Tailored Cutoff Value of hs-cTnT Contributes to Rapidly Diagnose Acute Myocardial Infarction in Chest Pain Patients. *Clin Lab* 2016;62:1451–9. [PubMed: 28164616]
24. Mueller-Hennessen M, Lindahl B, Giannitsis E, et al. Diagnostic and Prognostic Implications Using Age- and Gender-Specific Cut-Offs for High-Sensitivity Cardiac Troponin T - Sub-analysis from the TRAPID-AMI Study. *Int J Cardiol* 2016;209:26–33. [PubMed: 26878470]
25. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation. *Eur Heart J* 2016;37:267–315. [PubMed: 26320110]
26. United States Food and Drug Administration. 510(k) Substantial Equivalence Determination Decision Summary Assay Only Template. https://www.accessdata.fda.gov/cdrh_docs/reviews/K053020.pdf. Accessed 21 May 2020.
27. Roche Diagnostics. Elecsys Troponin T Gen 5 STAT. Indianapolis, IN: Roche Diagnostics; 2017.
28. United States Food and Drug Administration. 510(k) Substantial Equivalence Determination Decision Summary Assay Only Template. https://www.accessdata.fda.gov/cdrh_docs/reviews/K162895.pdf. Accessed 20 May 2020.
29. Harris PA, Taylor R, Minor BL, et al. The Redcap Consortium: Building an International Community of Software Platform Partners. *J Biomed Inform* 2019;95:103208. [PubMed: 31078660]
30. Harris PA, Taylor R, Thielke R, et al. Research Electronic Data Capture (Redcap)--a Metadata-Driven Methodology and Workflow Process for Providing Translational Research Informatics Support. *J Biomed Inform* 2009;42:377–81. [PubMed: 18929686]
31. Thygesen K, Mair J, Giannitsis E, et al. How to Use High-Sensitivity Cardiac Troponins in Acute Cardiac Care. *Eur Heart J* 2012;33:2252–7. [PubMed: 22723599]
32. Hicks KA, Mahaffey KW, Mehran R, et al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. *Circulation* 2018;137:961–72. [PubMed: 29483172]
33. Ambavane A, Lindahl B, Giannitsis E, et al. Economic Evaluation of the One-Hour Rule-out and Rule-in Algorithm for Acute Myocardial Infarction Using the High-Sensitivity Cardiac Troponin T Assay in the Emergency Department. *PLoS One* 2017;12:e0187662. [PubMed: 29121105]
34. Corsini A, Vagnarelli F, Bugani G, et al. Impact of High-Sensitivity Troponin T on Hospital Admission, Resources Utilization, and Outcomes. *Eur Heart J Acute Card Care* 2015;4:148–57.
35. Pickering JW, Greenslade JH, Cullen L, et al. Assessment of the European Society of Cardiology 0-Hour/1-Hour Algorithm to Rule-out and Rule-in Acute Myocardial Infarction. *Circulation* 2016;134:1532–41. [PubMed: 27754881]
36. Pickering JW, Than MP, Cullen L, et al. Rapid Rule-out of Acute Myocardial Infarction with a Single High-Sensitivity Cardiac Troponin T Measurement Below the Limit of Detection: A Collaborative Meta-Analysis. *Ann Intern Med* 2017;166:715–24. [PubMed: 28418520]
37. Mueller C. Biomarkers and Acute Coronary Syndromes: An Update. *Eur Heart J* 2014;35:552–6. [PubMed: 24357507]

38. Twerenbold R, Neumann JT, Sorensen NA, et al. Prospective Validation of the 0/1-H Algorithm for Early Diagnosis of Myocardial Infarction. *J Amer Coll Cardiol* 2018;72:620–32. [PubMed: 30071991]
39. Wang AY, Lai KN. Use of Cardiac Biomarkers in End-Stage Renal Disease. *J Am Soc Nephrol* 2008;19:1643–52. [PubMed: 18322158]
40. Gaze DC, Collinson PO. Cardiac Troponin I but Not Cardiac Troponin T Adheres to Polysulfone Dialyser Membranes in an in Vitro Haemodialysis Model: Explanation for Lower Serum cTnI Concentrations Following Dialysis. *Open Heart* 2014;1:e000108. [PubMed: 25332816]
41. Szczykowska J, Hryszko T, Naumnik B. Cardiac Troponins in Chronic Kidney Disease Patients with Special Emphasis on Their Importance in Acute Coronary Syndrome. *Adv Med Sci* 2019;64:131–6. [PubMed: 30641274]
42. Keller T, Wanner C, Krane V, et al. Prognostic Value of High-Sensitivity Versus Conventional Cardiac Troponin T Assays Among Patients With Type 2 Diabetes Mellitus Undergoing Maintenance Hemodialysis. *Am J Kidney Dis* 2018;71:822–30. [PubMed: 29310884]
43. Ahmed KA, Al-Attab WM. Prognostic Performance of Combined Use of High-Sensitivity Troponin T and Creatine Kinase MB Isoenzyme in High Cardiovascular Risk Patients with End-Stage Renal Disease. *Kidney Res Clin Pract* 2017;36:358–67. [PubMed: 29285428]
44. Reiter M, Twerenbold R, Reichlin T, et al. Early Diagnosis of Acute Myocardial Infarction in the Elderly Using More Sensitive Cardiac Troponin Assays. *Eur Heart J* 2011;32:1379–89. [PubMed: 21362702]
45. Mair J, Lindahl B, Muller C, et al. What to Do When You Question Cardiac Troponin Values. *Eur Heart J Acute Card Care* 2018;7:577–86.
46. Vigen R, Kutscher P, Fernandez F, et al. Evaluation of a Novel Rule-out Myocardial Infarction Protocol Incorporating High-Sensitivity Troponin T in a Us Hospital. *Circulation* 2018;138:2061–3. [PubMed: 30372140]
47. Roos A, Bandstein N, Lundback M, et al. Stable High-Sensitivity Cardiac Troponin T Levels and Outcomes in Patients with Chest Pain. *J Amer Coll Cardiol* 2017;70:2226–36. [PubMed: 29073949]
48. Spiegel R Myths in Emergency Medicine: Is hs-cTnTWorth th Downstream Testing? *Emerg Med News* 2019;41:1,32.
49. Spiegel R Myths in Emergency Medicine: Hoopla Aside, hs-cTnI is Not Catching Missed MIs. *Emerg Med News* 2019:1,32.
50. Peck D, Knott J, Lefkovits J. Clinical Impact of a High-Sensitivity Troponin Assay Introduction on Patients Presenting to the Emergency Department. *Emerg Med Australas* 2016;28:273–8. [PubMed: 26989877]
51. Fitzgerald G, Kerley RN, Kiernan TJ. High-Sensitivity Troponin Assays: Development and Utility in a Modern Health-care System. *Expert Rev Cardiovasc Ther* 2019;17:763–70. [PubMed: 31574239]
52. Crowder KR, Jones TD, Lang ES, et al. The iImpact of High-Sensitivity Troponin Implementation on Hospital Operations and Patient Outcomes in 3 Tertiary Care centers. *Am J Emerg Med* 2015;33:1790–4. [PubMed: 26387473]
53. Furmaga J, McDonald SA, Hall HM, et al. Impact of High-sensitivity Troponin Testing on Operational Characteristics of an Urban Emergency Department. *Acad Emerg Med* 2020.
54. Bandstein N, Ljung R, Lundback M, et al. Trends in Admissions for Chest Pain After the Introduction of High-Sensitivity Cardiac Troponin T. *Int J Cardiol* 2017;240:1–7. [PubMed: 28431769]
55. Neumann JT, Twerenbold R, Ojeda F, et al. Application of High-Sensitivity Troponin in Suspected Myocardial Infarction. *N Engl J Med* 2019;380:2529–40. [PubMed: 31242362]

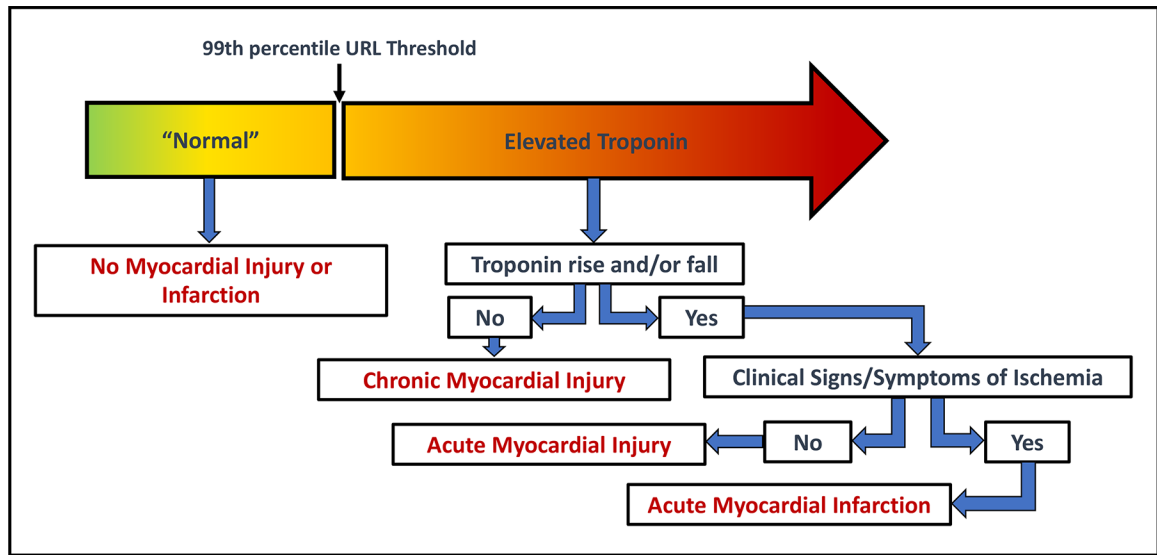


Figure 1.
Classification of patients with regard to myocardial infarction and injury.
URL = Upper reference limit

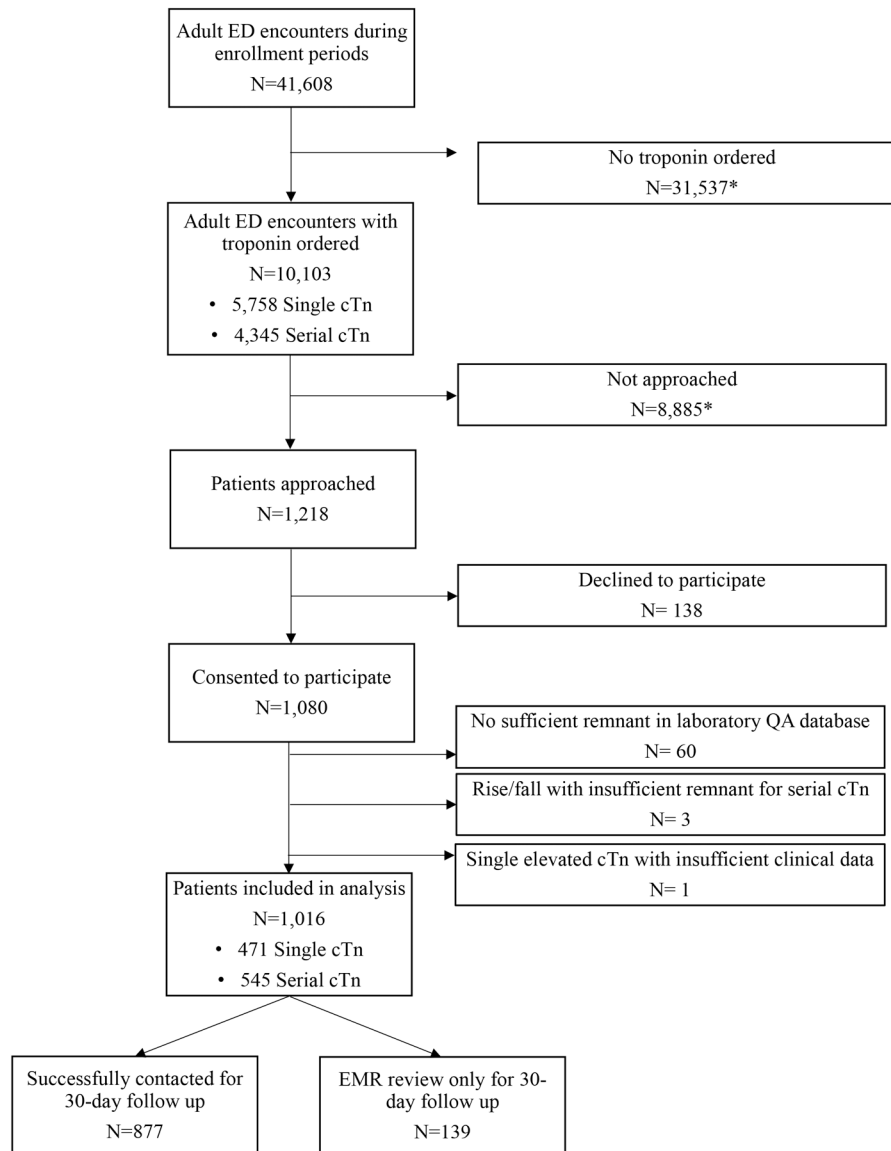


Figure 2.
Derivation of study population.
ED = Emergency department; QA = Quality assurance; cTn = Cardiac troponin *Value calculated from known data.

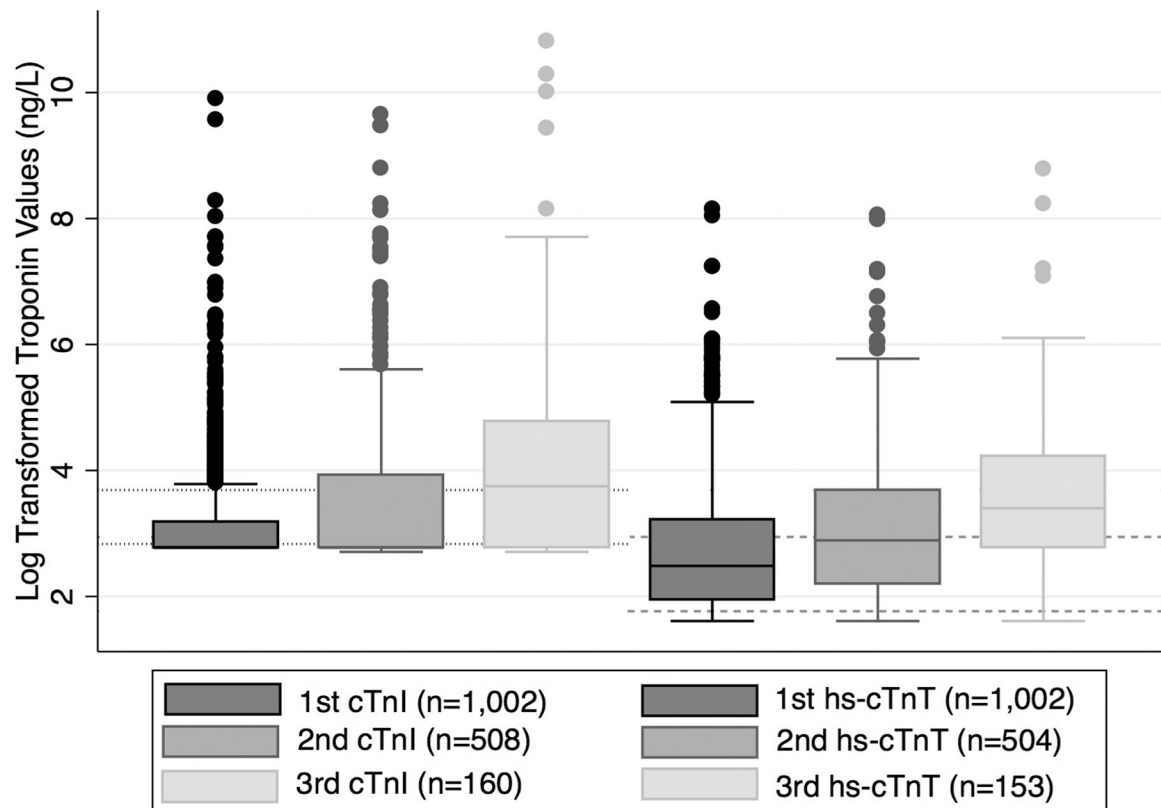


Figure 3.

Distribution of conventional cTnI and hs-cTnT values.

Legend. Dotted lines represent the limit of quantification (17 ng/L) and 99th percentile upper reference limit (40 ng/L) for the conventional cTnI assay. Dashed lines represent the limit of quantification (6 ng/L) and 99th percentile combined upper reference limit (19 ng/L) for the hs-cTnT assay. All values are log transformed.

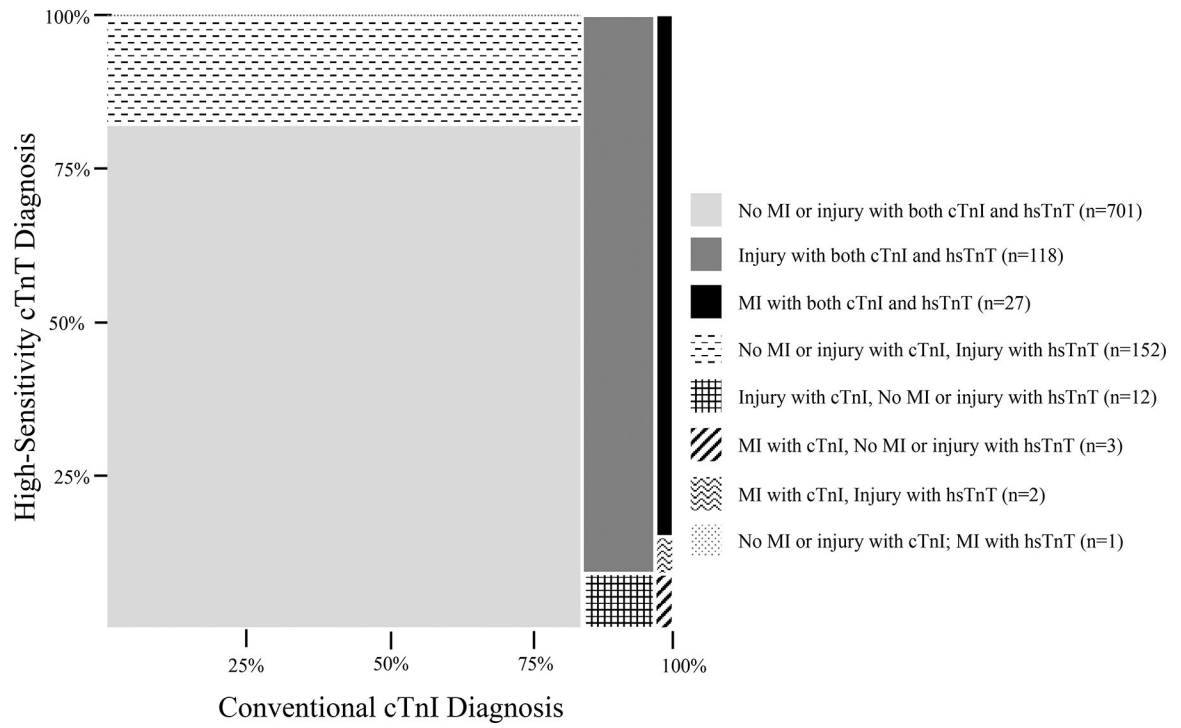


Figure 4. Diagnoses of acute myocardial infarction (AMI) and myocardial injury using conventional cTnI and high-sensitivity cTnT
 cTnI = Cardiac troponin I; cTnT = Cardiac troponin T; MI = Myocardial infarction

Table 1.

Patient demographics and clinical characteristics.

Characteristic	Overall N=1,016	Single cTn N=471	Serial cTn N=545	cTnI N=508	hs-cTnT N=508
Age [†]	60 (49, 71)	58 (45, 69)	63 (53, 72)	60 (48, 70)	61 (51, 72)
Male sex	506 (50%)	204 (43%)	302 (55%)	242 (48%)	264 (52%)
Race					
White	506 (50%)	229 (49%)	277 (51%)	265 (52%)	241 (47%)
Black	225 (22%)	104 (22%)	121 (22%)	104 (20%)	121 (24%)
Asian	44 (4%)	17 (4%)	27 (5%)	22 (4%)	22 (4%)
Other	165 (16%)	80 (17%)	85 (15%)	80 (16%)	85 (17%)
Decline to state/Unknown	76 (7%)	41 (9%)	35 (6%)	37 (7%)	39 (8%)
Ethnicity					
Hispanic or Latino	128 (13%)	71 (15%)	57 (10%)	61 (12%)	67 (13%)
Not Hispanic or Latino	873 (86%)	392 (83%)	481 (88%)	440 (87%)	433 (85%)
Decline to state/Unknown	15 (1.5%)	8 (1.7%)	7 (1.3%)	7 (1.4%)	8 (1.6%)
Past medical history					
CKD on dialysis	85 (8%)	22 (5%)	63 (12%)	45 (9%)	40 (8%)
Heart failure	242 (24%)	74 (16%)	168 (31%)	107 (21%)	135 (27%)
Coronary artery disease	230 (23%)	50 (11%)	180 (33%)	98 (19%)	132 (26%)
Diabetes mellitus	297 (29%)	105 (22%)	192 (35%)	136 (27%)	161 (32%)
Chest pain present [†]	600 (59%)	255 (54%)	345 (63%)	325 (64%)	275 (54%)
Duration of symptoms >3 hours at presentation	637 (63%)	280 (60%)	357 (66%)	295 (58%)	342 (67%)
Reason for troponin testing					
Suspected ACS	758 (75%)	309 (66%)	449 (82%)	379 (75%)	379 (75%)
Syncope/altered mental status	98 (10%)	59 (13%)	39 (7%)	52 (10%)	46 (9%)
Suspected non-ACS myocardial injury	83 (8%)	48 (10%)	35 (6%)	43 (8%)	40 (8%)
Suspected cardiac contusion	20 (2%)	10 (2%)	10 (2%)	14 (3%)	6 (1%)
Stroke protocol	16 (2%)	13 (3%)	3 (1%)	5 (1%)	11 (2%)
Other	41 (4%)	32 (7%)	9 (2%)	15 (3%)	26 (5%)
Median interval from ED arrival to first troponin (minutes) [†]	46 (28, 88)	49 (30, 92)	43 (27, 85)	45 (28, 82)	49 (29, 92)

Characteristic	Overall N=1,016	Single cTn N=471	Serial cTn N=545	cTnI N=508	hs-cTnT N=508
Median interval from 1st to 2nd troponin (minutes) ^{1,4}	n/a	n/a	160 (99, 230)	191 (153, 256)	120 (77, 191)
Admission ³	547 (54%)	196 (42%)	351 (64%)	259 (51%)	288 (57%)
Cardiac stress test within 30 days ⁵	78 (8%)	17 (4%)	61 (11%)	39 (8%)	39 (8%)
Cardiac catheterization within 30 days ⁵	56 (6%)	16 (3%)	40 (7%)	26 (5%)	30 (6%)
Coronary revascularization within 30 days ^{5,6}	19 (1.9%)	5 (1.1%)	14 (2.6%)	10 (2.0%)	9 (1.8%)

CKD = Chronic kidney disease; ACS = Acute coronary syndrome

¹ Presented as median (25th, 75th percentile)

² Chest pain documented as present in Emergency Department physician note

³ Includes admission to observation and full inpatient status

⁴ Data reflect 237 patients in the cTnI (before) cohort and 308 patients in the hs-cTnT (after) cohort with serial troponin measurements.

⁵ Includes tests and procedures performed during the index visit and those performed after discharge within 30 days

⁶ Includes percutaneous coronary intervention and coronary artery bypass graft surgery

Table 2.

Patients with reclassification between cardiac troponin (cTn) assays and thresholds.

	Diagnostic Reclassification			Specimen Reclassification
	Myocardial Infarction	Myocardial Injury		
All patients (n=1,016)				
Conventional cTnI vs. hs-cTnT combined threshold	0.6% (0.2–1.3%) 6/1,016 (5–, 1+)	16% (14–19%) 164/1,016 (12–, 152+)		22% (20–25%) 226/1,016 (21–, 206+)*
Hs-cTnT combined threshold vs. hs-cTnT sex-specific threshold	0.0% (0–0.0.4%) 0/1,016	3.7% (2.7–5.1%) 38/1,016 (13–, 25+)		9.5% (7.8–12%) 97/1,016 (44–, 53+)
Serial cTn measurements (n=545)				
Conventional cTnI vs. hs-cTnT combined threshold	0.9% (0.3–2.1%) 5/545 (4–, 1+)	21% (18–25%) 117/545 (11–, 106+)		30% (26–34%) 162/545 (19–, 144+)*
Hs-cTnT combined threshold vs. hs-cTnT sex-specific threshold	0.0% (0.0–0.7%) 0/545	5.3% (3.6–7.6%) 29/545 (10–, 19+)		12% (9.7–15%) 67/545 (32–, 35+)
Single cTn measurements (n=471)				
Conventional cTnI s. hs-cTnT combined threshold	0.2% (0.01–1.2%) 1/471 (1–)	10% (7.4–13%) 47/471 (1–, 46+)		14% (11–17%) 64/471 (2– 62+)
Hs-cTnT combined threshold vs. hs-cTnT sex-specific threshold	0.0% (0.0–0.8%) 0/471	1.9% (0.9–3.6%) 9/471 (3–, 6+)		6.4% (4.3–9.0%) 30/470 (12–, 18+)

cTnI = cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T

Data are presented as proportions with 95% confidence intervals.

The first assay and threshold in each row serves as the reference; (–) indicates the patient was reclassified as negative for the outcome by the second assay and threshold; (+) indicates the patient was reclassified as positive for the outcome by the second assay and threshold.

* One patient had specimen reclassification in both directions. The first specimen was below the 99th percentile using cTnI and above the 99th percentile using hs-cTnT; the second specimen was above the 99th percentile using cTnI and below the 99th percentile using hs-cTnT.

Table 3.

Myocardial infarction (MI) diagnosis and specimen reclassification for all patients (3a), patients with a single cTn measurement (3b) and patients with serial cTn measurements (3c).

Table 3a. Reclassification in all patients.

		Specimen reclassification?		
		No	Yes	Total
MI diagnosis reclassification?	No	787	223	1,010
	Yes	3	3	6
Total		790	226	1,016

Table 3b. Reclassification in patients with a single cTn measurement.

		Specimen reclassification?		
		No	Yes	Total
MI diagnosis reclassification?	No	407	63	470
	Yes	0	1	1
Total		407	64	471

Table 3c. Reclassification in patients with serial cTn measurements.

		Specimen reclassification?		
		No	Yes	Total
MI diagnosis reclassification?	No	380	160	540
	Yes	3	2	5
Total		383	162	545