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Discordance of High-Sensitivity Troponin Assays in Patients with Suspected Acute Coronary Syndromes

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Abstract

Background: High-sensitivity cardiac troponin (hs-cTn) assays have different analytic characteristics.

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Clinical Trial Registration: NCT00990262; NCT01084239.

Objectives: The goal of this study was to quantify differences between assays for common analytical benchmarks and to determine whether they may result in differences in the management of patients with suspected acute coronary syndrome (ACS).

Methods: We included patients with suspected ACS enrolled in the Rule Out Myocardial Infarction/ Ischemia Using Computer-Assisted Tomography (ROMICAT) I and II trials, with blood samples taken at ED presentation (ROMICAT-I and II) or at two and four hours thereafter (ROMICAT-II). Hs-cTn concentrations were measured using three assays (Roche Diagnostics, Elecsys 2010 platform; Abbott Diagnostics, ARCHITECT i2000SR; Siemens Diagnostics, HsVista). Per blood sample, we determined concordance across analytic benchmarks (<limit of detection [<LOD]/LOD-99th percentile/>99th percentile). Per-patient, we determined concordance of management recommendations (rule-out/observe/rule-in) per the 0/2 hour algorithm, and their association with diagnostic test findings (coronary artery stenosis >50% on coronary CT angiography or inducible ischemia on perfusion imaging) and ACS.

Results: Among 1,027 samples from 624 patients (52.8 ± 10.0 years, 39.4% female), samples classified as <LOD (56.3% vs 10.4% vs 41.2%; p<0.001), LOD-99th percentile (36.5% vs 83.5% vs 52.6; p<0.001) >99th percentile (7.2% vs 6.0% vs 6.2%) by Roche, Abbott, and Siemens, respectively. 37.4% (n=384/1,027) of blood samples were classified into the same analytical benchmark category, with low concordance across benchmarks (<LOD 11.1%; LOD-99th percentile 29.3%; >99th percentile 43.6%). Serial samples were available in 242 patients (40.1% female; mean age: 52.8±8.0 years). The concordance of management recommendations across assays was 74.8% (n=181/242) considering serial hs-cTn measurements. 19.6–21.1% of patients who were recommended to discharge had positive diagnostic test findings and 2.8–4.3% had ACS at presentation.

Conclusion: Caregivers should be aware that there are significant differences between hs-cTn assays in stratifying individual samples and patients with intermediate likelihood of ACS according to analytical benchmarks that may result in different management recommendations.

CONDENSED ABSTRACT

High-sensitivity cardiac troponin (hs-cTn) assays have known differences in analytic performance. We evaluated the concordance between three hs-cTn assays in patients with intermediate likelihood of ACS enrolled in the ROMICAT I and II trials for analytical benchmarks (<LOD, LOD-99th percentile, and >99th percentile) and management recommendations per the 0/2 hour algorithm. Overall, 37.4% (n=384/1,027) of blood samples were classified into the same analytical benchmark and 74.8% (n=181/242) into the same management recommendations category. Caregivers should be aware that there are significant differences between hs-cTn assays in stratifying individual samples and patients according to analytical benchmarks that may result in different management recommendations.

Keywords

High-sensitivity cardiac troponin; High-sensitivity cardiac troponin assays; Acute coronary syndrome; Concordance

INTRODUCTION

Cardiac troponin measurement and clinical assessment are the cornerstones of early risk stratification for patients presenting to the emergency department (ED) with suspicion of acute coronary syndrome (ACS). Analytical advancements have led to the development of high-sensitivity cardiac troponin (hs-cTn) assays, which allow the detection of very low levels and small changes in troponin concentration, already within one hour.(1–4) Because even in the absence of ACS most patients have a measurable troponin concentrations, the binary nature of information derived by conventional assays (positive or negative) has evolved more into a continuous measure, requiring more nuanced interpretation.(5)

Several diagnostic algorithms for various hs-cTn assays have been developed for the diagnosis of ACS. These diagnostic protocols may 1) set the threshold for early rule-out after a single blood testing to the limit of detection (LOD), 2) use the 99th percentile cut point to define abnormal troponin values (as defined by the Fourth Universal Definition of Myocardial Infarction [MI](6)) and 3) recommend serial testing at one, two or three hours in patients with measurable troponin below the 99th percentile and recommend management based on the change in troponin concentration.(7,8)

Three assays referred clinically as high sensitivity assays (Roche Diagnostics, Elecsys 2010; Abbott Diagnostics, ARCHITECT i2000SR; Siemens Diagnostics, HsVista) cleared by the Food and Drug Administration (FDA) are now clinically available.(9–11) Diagnostic algorithms, such as the 0/2 hour algorithms (12–15), developed for these three assays acknowledge differences in performance characteristics and recommend assay-specific cut points instead of generally applicable thresholds for clinical decisions.

Factors that contribute to the need for assay specific thresholds are the known differences in the assays' analytic characteristics e.g. their analytic sensitivities (as per the LOD) and the use of different reference populations to derive each assay's 99th percentile.(16) This ultimately leads to difficulties in establishing general patient management rules across assays.

While many published studies, including those based on analytical benchmarks or assay specific diagnostic algorithms have reported excellent negative predictive values (99.5 to 99.8%) to rule out and high specificities (95.0 to 99.0%) to rule in MI for the individual assays(12–14,17); it remains unknown whether differences in assay sensitivity and derivation of the 99th percentile affect classification of blood samples into analytic categories, or render different management recommendations. To address these uncertainties, we measured troponin using three hs-cTn assays in patients with suspected ACS in the Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography (ROMICAT) I and II trials.

METHODS

Patient population and study design

We included patients with suspected ACS enrolled in the ROMICAT-I and II trials (18,19) (NCT00990262 and NCT01084239) who were referred to further non-invasive diagnostic testing after inconclusive initial ED triage, defined as negative conventional troponin measurement (<99th upper reference limit) and non-ischemic electrocardiogram (ECG), detailed in the Supplemental Appendix.

All included patients provided written informed consent, and the studies were approved by the local institutional review board. In both studies, ACS was defined as either MI or UAP and adjudicated by an independent events committee. In this sub-study of the ROMICAT trials, we included patients who consented to blood draw and whose blood samples were analyzed with three hs-cTn assays (Central Illustration).

High-sensitivity cardiac troponin measurements

Blood samples—In the ROMICAT-I trial (23) a single blood draw was performed at the time of CT angiography, at a median of 4.2 hours from initial presentation, while in ROMICAT-II (24) sequential blood testing was performed at the time of ED presentation and at two- and four hours thereafter.(20–22) Blood was collected into tubes containing EDTA and immediately centrifuged and stored in microcentrifuge tubes at −80°C until sample assessment. For the analysis serum was used. All blood samples were tested with three assays: Roche Elecsys Cobas Gen 5 assays (ROMICAT-I: e2010, ROMICAT-II: e411; Roche Diagnostics, Penzberg, Germany), Abbott ARCHITECT (Abbott Laboratories, Irving, TX), and a pre-commercial Siemens Vista (Siemens Diagnostics, Newark, DE) (Central Illustration).(9–11) The analytic properties of assays are summarized in Table 1. All blood samples were analyzed in a blinded fashion for clinical information.

Analytic benchmarks—We defined analytic benchmarks along assay specific analytic characteristics (*table 1*): <LOD, LOD to 99th percentile and >99th percentile. Non-sex-specific 99th percentile were used for primary analysis while sex-specific 99th percentiles as recommended by both laboratory guidelines and Fourth Universal Definition of MI were used for secondary analyses.(6,23) In a per-sample analysis, we determined the agreement across assays to classify blood samples obtained in the ROMICAT-I and ROMICAT-II trials, independent of the timing of blood drawn (treated as independent blood samples), according to analytic benchmarks (Central Illustration).

Patient management recommendations—As a primary analysis, we applied 0/2 hour algorithms developed for the evaluated assays (12–14) to determine management recommendation of rule-out or rule-in for MI or observation: 1) *rule-out*: patients with low likelihood for non-ST segment MI (NSTEMI) with low baseline levels and lack of a relevant increase in serial hs-cTn, 2) *rule-in*: patients with a high likelihood for NSTEMI with a moderately elevated hs-cTn concentration at presentation or clearly rising hs-cTn concentrations, and 3) *observe*: any patient who cannot be ruled-out or ruled-in. We determined the agreement across assays to stratify patients with serial blood samples

available from the ROMICAT-II trial for management recommendations according to 0/2 hour algorithms defined assay specific thresholds (Central Illustration).

As a secondary analysis, we applied the 99th percentile threshold based on the Fourth Universal Definition of MI(6) to determine the agreement across assays to stratify patients with serial blood samples from the ROMICAT-II trial according to clinical management recommendations.

Non-invasive diagnostic testing

In ROMICAT-II patients with serial blood samples and who underwent coronary CTA or nuclear myocardial stress perfusion imaging (SPECT), we assessed the association of management recommendations with test findings. Coronary CTA was defined as positive if obstructive coronary artery disease (luminal narrowing >50%) was detected; SPECT was defined as positive if stress induced ischemia (reversible myocardial perfusion defect) was detected.

Acute coronary syndrome

Diagnosis of ACS was adjudicated by an external, independent clinical events committee, blinded to the hs-cTn results, based on prospectively collected data on patients' demographics, cardiovascular risk factors, symptoms and clinical presentation, serial ECG and conventional troponin measurements as well as diagnostic testing results during the index hospital admission.(18,19) ACS was defined as either MI or unstable angina pectoris (UAP) (Supplemental Appendix).

Statistical analysis—Continuous variables are presented as means and standard deviations, while categorical variables as numbers and percentages. Baseline characteristics of subjects from the ROMICAT-I and II trials were compared by using the Fisher exact test, Student T test, or Wilcoxon rank sum test as appropriate.

hs-cTn measurements were classified as <LOD, from LOD to 99th percentile, and >99th percentile for each assay (Central Illustration). We determined the concordance of classification between assays using McNemar's test (pairwise comparison), Cochran's Q test (overall comparison between all three assays) and provided Kappa values to indicate the statistical strength of concordance/discordance.

We determined the concordance of patient stratification along patient management recommendations (rule-out/observe/rule-in) based on the 0/2 hour algorithms with assay specific thresholds (Central Illustration). We used McNemar's test for pairwise comparison and Cochran's Q test for overall comparison of management recommendations between assays.

Statistical analyses were performed using Stata 14.2 (StataCorp LP). For all analyses, a 2-tailed p value <0.05 was required to reject the null hypothesis.

Results

Study Population

We included 322/368 patients enrolled to the ROMICAT-I trial and 302/1,000 ROMICAT-II patients who contributed altogether 1,027 individual blood samples (608 obtained at arrival, 251 at two hours and 168 at four hours) (Figure 1). Patients were 52.8±10.0 years old, 39.4% were female, most had a low Thrombolysis in MI (TIMI) risk score (TIMI score 0 or 1: 84.8%; n=529/624), and 7.9% (n=49/624) had an adjudicated diagnosis of ACS. Among patients referred to non-invasive testing, 20.5% (n=98/479) had obstructive CAD on coronary CTA and 24.3% (n=46/189) had inducible myocardial ischemia on SPECT (Table 2). The time since chest pain onset was 3.1 hours (IQR:1.5–9.2) in the ROMICAT I population. Characteristics of ROMICAT-I and ROMICAT-II patients did not show clinically meaningful differences in demographics, cardiovascular risk factors, TIMI score, or rate of ACS during index hospitalization. Patients included in this sub-study were not significantly different from those not included (Supplemental Table 1).

Agreement between hs-cTn assays in classifying blood samples according to analytic benchmarks

The proportion of samples <LOD and between LOD to 99th percentile was significantly different between all assays (<LOD: 56.3% [n=578/1,027] vs 10.4% [n=107/1,027] vs 41.2% [n=423/1,027]; LOD to 99th percentile: 36.5% [n=375/1,027] vs 83.5% [n=858/1,027] vs 52.6% [n=540/1,027] for Roche Elecsys, Abbott Architect and Siemens Vista, respectively, p<0.001). The proportion of samples classified >99th percentile on the other hand did not differ significantly (7.2% [n=74/1,027] vs 6.0% [n=62/1,027] vs 6.2% [n=64/1,027], p=0.114) (Table 3).

The proportion of samples concordantly classified into the same analytic benchmarks was low with 37.4% (n=384/1,027; Kappa: 0.22). The highest concordance occurred for classification of samples >99th percentile (43.6%, n=44/101; Kappa: 0.70); however, among the 57 discordant blood samples, 9 were classified simultaneously as <LOD by at least one assay. Concordance was lower for LOD to 99th percentile (29.3%, n=266/908; Kappa: 0.15), where 56 discordant cases classified >99th percentile in parallel, while the rest was overlapping with the benchmark of <LOD resulting in a very low concordance for <LOD (11.1%, n=74/669; Kappa: 0.16) (Figure 2). In pairwise comparison, Roche vs Abbott agreed in 47.8% (overall: n=491/1027; Kappa=0.17; <LOD: 15.9%, n=94/591; Kappa=0.12; LOD to 99th percentile: 39.6%, n=350/883; Kappa=0.12; >99th percentile: 52.8%, n=47/89; Kappa=0.67), Roche vs Siemens in 64.0% (overall: n=657/1027; Kappa=0.37; <LOD: 50.8%, n=337/664; Kappa=0.38; LOD to 99th percentile: 43.2%, n=276/639; Kappa=0.30; >99th percentile: 46.8%, n=44/94; Kappa=0.61) and Abbott vs Siemens in 62.2% (overall: n=639/1027; Kappa=0.27; <LOD: 18.3%, n=82/448; Kappa=0.17; LOD to 99th percentile: 56.6%, n=505/893; Kappa=0.22; >99th percentile: 70.3%, n=52/74; Kappa=0.81), respectively (Supplemental Figures 1A–C).

When using sex-specific thresholds, significant disagreement was observed between the assays. As stratified by sex, the overall rate of measurable samples was 50.3%, 92.7%, and

65.0% in males and 33.7%, 84.8%, and 49.4% in females for Roche, Abbott and Siemens, respectively. There were significant differences between the proportion of samples <LOD and LOD to 99th percentile; however, for the >99th percentile no differences were identified for males, and significant difference were seen for females (Supplemental Table 2A–C).

When using the 99th percentile as a binary threshold, the proportion of blood samples above the 99th percentile was similar for all assays when non-sex specific 99th percentiles were applied (7.2%, 6.0% and 6.2% per Roche, Abbott and Siemens, respectively) but differed between the Roche vs Siemens (7.4%vs 4.9%, p<0.001) and Abbott vs Siemens (7.0% vs 4.9%, p<0.001) for sex-specific 99th percentiles. Stratified by sex, no differences were identified for males, and significant difference were seen for females (Supplemental Table 3A–D).

Agreement between hs-cTn assays to risk stratify patients according to 0/2 hour algorithms

The proportion of patients with similar management recommendation was significantly different between the assays for both rule-out (87.2%, 73.1%, and 78.5%) and observe (9.5%, 24.0%, 17.8%, respectively; p<0.001 for both) recommendations; there was no significant difference for rule-in strata (3.3%, 2.9%, and 3.7%; all p=0.687) (Table 4). All three assays were concordant for management recommendations in 74.8% (n=181/242). When stratified by sex, we observed similar results as in the overall group (Supplemental Table 4A–B). Within the management strata, concordance was 74.7% for rule-out, 15.7% for observe, and 38.5% for admission (Figure 3).

As a secondary analysis, we assessed the agreement between the assays based on the Fourth Universal Definition of MI (99th percentile).(6) Patient risk stratification based on serial testing was similar across the three assays: rate of patients above the 99th percentile was 6.6% (n=16/242) vs 5.4% (n=13/242) vs 5.4% (n=13/242) per Roche, Abbott and Siemens, respectively, p=0.50; using sex-specific 99th percentiles similarly resulted in no differences between the assays (Supplemental Tables 5A–B).

Hs-cTn, non-invasive diagnostic testing, and acute coronary syndrome

Overall, n=148/242 patients received non-invasive testing (n=104/148 CTA, n=29/148 SPECT, n=15/148 CTA and SPECT) (Supplemental Table 6A). Among patients in whom serial hs-cTn suggested rule-out, 21.1% (n=28/133), 19.6% (n=22/112) and 21.0% (n=25/119) for Roche, Abbott and Siemens, respectively, had positive non-invasive testing finding. Among those patients, who were ruled out by at least one assay, 4.3% (n=9/211), 2.8% (n=5/177) and 3.7% (n=7/190) were diagnosed with ACS (MI: 0.5% [1/211], 0.0% [0/177], 0.0% [0/190]; UAP: 3.8% [8/211], 2.8% [5/177)], 3.7% [7/190]). Additionally, in those with a troponin measurement <LOD, 17.7% (n=15/85), 33.3% (n=5/15) and 22.2% (n=12/54) had a positive test finding as tested with Roche, Abbott and Siemens, respectively (Supplemental Table 6B). Among 221 patients in whom at least one assay met the clinical decision of rule-out, 9 patients (4.1%) had ACS (1 NSTEMI, 8 UAP).

Discussion

We provide a head-to-head comparison of three hs-cTn assays cleared by the FDA in patients with intermediate likelihood of ACS who were referred to non-invasive diagnostic testing after inconclusive initial triage. Our data suggest substantial differences between the assays both in terms of stratification into common analytical benchmarks with the potential for differences in management. We report four major findings: 1) on a blood sample basis, the agreement between the three assays based on analytic benchmarks was low at 37.4%; 2) on a per-patient basis, the agreement based on 0/2 hour algorithm was 74.7% for rule-out, 15.7% for observe, and 38.5% for admission for rule-in ACS; 3) assays were concordant to classify samples >99th percentile when the general 99th percentile was applied, but significantly disagreed when sex-specific 99th percentiles were used and 4) obstructive CAD/myocardial ischemia was found in around 20% of patients with serial hs-cTn who had troponin measurements <LOD.

Analytic benchmarks as threshold: Limit of detection

Differences in assay analytic performance, predominantly on the level of sensitivity, have been recognized previously.(24) Our data extend these observations by quantifying the differences for analytic benchmarks, suggesting a two-fold difference between assays in the proportion of samples with measurable values (43.7%, 89.6% and 58.8% samples with measurable troponin for Roche, Abbott and Siemens, respectively, p<0.001). This may highlight e.g. the reduced sensitivity of Roche assay at lower concentrations of analyte with an inability to resolve differences between 3 and 6ng/L and may justify restrictions placed on reporting of this assay by the FDA to only reporting concentrations above the limit of quantification.(25) Notably however, throughout the pairwise comparison we discovered poor agreement between Abbott vs Siemens (<LOD: 18.3%), suggesting that Roche was not the only driver of the observed discordances below the LOD.

99th percentile and Fourth Universal Definition of MI to define ACS

The 99th percentile of hs-cTn is defined as the threshold for myocardial injury by the Fourth Universal Definition of MI(6), with an emphasis on sex-specific differences. However, there are identified concerns regarding the use of the 99th percentile as a general threshold.

One issue is that there is a substantial degree of discordance between assays when their respective 99th percentiles are used to define MI. Ungerer et al. assessing all-comer ED patients, described rates of misclassification ranging between 3–17% across four hs-cTn platforms (Abbott Archiect i2000SR, Beckman Coulter Access2, Roche Cobas e601, and Siemens ADVIA Centaur XP) when their respective 99th percentile was used to diagnose MI.(26) In fact, it has been shown that re-derivation of the 99th percentile permits more concordant diagnosis of AMI between two assays (Abbott Architect i2000R and Roche Cobas 601).(27) In our per-sample analysis, the studied FDA cleared hs-cTn assays were concordant when non-sex specific 99th percentile thresholds were used, as recommended by the FDA, but were discordant when the sex-specific 99th percentiles were applied. This does not exclude the possibility that using sex-specific percentiles improves accuracy for detection of MI for each assay; for example, clinical data suggests that sex-specific

thresholds help to overcome the under-diagnosis of MI in women.(28) Nevertheless, according to our results, if the recommended sex-specific thresholds are applied, then different assays might stratify patients substantially differently potentially translating into clinically meaningful discordances between triaging centers, depending on which assay is used. Interestingly, our sex-stratified analysis indicated the discordance stems from differences between the assays among females (supplemental tables 3A–D). One of the possible reasons for this finding could be differences in the representation of men and women in the various reference populations used for each assay, strengthening the argument for a common reference biobank to derive the 99th percentile for assays.(24) A further important consideration is that a >50% analytical sensitivity is recommended for both men and women. A critical difference between the evaluated assays, is that while the Abbott and Siemens assays fulfil this criterion, Roche has a lower sensitivity for men (50%) and fails to detect troponin in over 50% in women.(23) However, this difference in the evaluated platforms' analytical properties rendered no differences in clinical performance: e.g. altogether 4 men and 1 woman had clinically adjudicated diagnosis of an AMI; of the 4 men all three assays classified 1 individual below the 99th percentile and 3 above the 99th percentile, while the 1 female was classified above the 99th percentile by all three assays – when using both non-sex specific and sex-specific 99th percentiles. Important to note, that because of the relatively low number of events, concluding that these differences in analytical sensitivity do not have an impact on clinical performance is unsubstantiated.

Another concern in using the 99th percentile as a threshold for MI is that for the same assay, different 99th percentile thresholds have been published based on different reference cohorts. According to the vendor's recommendations and FDA approval document for the Roche Elecsys assay, a cut-off of 19ng/L is provided as 99th percentile, based on data from 1,301 healthy individuals in the US (50.4% female; median 48 years [IQR: 21–89 years]).(29) Using the same assay, in 616 healthy volunteers from Germany (49.8% female; 44±14 years), a 99th percentile of 13.5ng/L was reported.(30) While deriving 99th percentiles from the Dallas Heart Study suggested 18ng/L, the Atherosclerosis Risk in Communities Studies reported 22ng/L, and the Cardiovascular Health Study found 36ng/L. One potential reason for the variation in 99th percentiles is the different representation of genders in the reference populations, which is suggested to be resolved with the use of sex specific thresholds. However, the use of sex-specific cut-off values were shown to reclassify only a small percentage of patients compared to a common cut-off.(31)

To overcome concerns regarding the 99th percentile, a universal sample bank has been created to provide a common reference to define the 99th percentile across all hs-cTn assays.(4,32,33) Whether a single reference cohort is sufficient to ensure generalizability across age, sex, and race, or whether unique 99th percentile definitions are required with multiple reference cohorts, it is still unanswered. Moreover, recommendations specify various details for the derivation of the 99th percentile (e.g. use of non-parametric method, sample size of at least 300 male and 300 female healthy subjects etc.) – although these recommendations exist, the lack of adherence to follow such designs may introduce variation.(23)

0/2 hour algorithm: Rule-out, Rule-in and Observe

Assay-specific cut-off values provided by the 0/2 hour algorithm to rule out an MI have been shown to have excellent sensitivity.(12–14,17) Our study provides a direct comparison of hs-cTn assays in a cohort with suspected ACS referred to further non-invasive testing, suggesting a 74.8% (n=181/242) overall agreement between the three assays. We observed, that across three commercially available hs-cTn assays the rate of patients ruled-out (87.2% vs 73.1%, vs 78.5%) differ significantly.

Applying thresholds proposed by the 0/2 hour algorithm, we found good agreement for rule-in decision across assays (3.3% vs 2.9% vs 3.7%). Throughout the per-patient analysis, two patients who were classified as rule-out by either Siemens or Abbott were classified as rule-in by Roche indicating a still considerable degree of disagreement.

This may translate into substantial differences in patient care between hospitals: e.g. by using a troponin-I assay (Abbott or Siemens) the rate of those who cannot be discharged nor can be admitted is around double compared to Roche (24.0% and 17.8% vs 9.5%), leading to an almost two-fold difference between these assays. It is not surprising thus, that we observed the poorest agreement within observe management strata with 15.7% concordance between all three assays (Figure 3).

Hs-cTn, CAD, myocardial ischemia and ACS

Our results highlight prior findings, that about 20% of patients (70% in agreement by all three assays) stratified to rule-out for ACS had a positive test finding. In our study the majority of patients with ACS in whom ACS was ruled out by at least one assay were diagnosed with UAP (Roche: 1 AMI, 8 UAP; Abbott: 0 AMI, 5 UAP; Siemens: 0 AMI, 7 UAP). Importantly, the 0/2 hour algorithm and 99th percentile were validated to identify MIs. However, because the known short-term (30-day) and long-term prognostic significance of obstructive CAD and inducible myocardial ischemia, it is important to take into account the degree of underlying disease potentially unrecognized via hs-cTn testing. Overall, around 4% (2.8–4.3%) of patients who were ruled-out (<LOD) by the three assays were diagnosed with ACS. This is in contrast to previous publications reporting almost perfect negative predictive value for ACS for these assays (Roche: 99.0%; Abbott: 100.0%; Siemens: 98.9%(34–36)). Notably, these studies differ from our analysis in that we defined ACS as both NSTEMI and UAP, while most of the other studies defined ACS synonymous with MI. The clinical significance of UAP is debated, however it is recognized that patients with UAP have increased risk for future cardiovascular events compared to those without, thus patients with unidentified UAPs could constitute an important subgroup.(37)

Comparison of hs-cTn assays measuring troponin-I vs T

Finally, it could be argued whether comparing troponin-I with T assays is feasible, because of the known differences in the behavior of the two isotypes of troponin molecules.(12) For example troponin-I concentration increases earlier when cardiomyocyte injury occurs (38), while troponin-T concentrations follow diurnal changes but troponin-I does not (39), and in renal failure troponin-T clearance is affected in a greater extent.(40) However, as both the analytic benchmarks and the 0/2 hour thresholds are assay specific, these differences are

assumed to be incorporated and reflected by the recommended thresholds. A pairwise comparison between assays on a per-sample level showed that the concordance between troponin-I assays was not higher compared to troponin-I vs troponin-T assays (Abbott vs Siemens: 62.2%; Abbott vs Roche: 47.8%; Siemens vs Roche: 64.0%). These results are in line with previously reported findings demonstrating a discordance rate of 18.2% between the Roche and the Abbott assays to diagnose patients with AMI as assessed among all-comer ED patients.(41) In our per-patient analysis, the all three assays differed significantly for rule-out (Roche: 87.2% vs Abbott: 73.1% vs Siemens: 78.5%, $p<0.001$), suggesting that the observed discordances are not likely the result of differences in release dynamics between isotypes, but perhaps reflect a threshold-related disagreement.

Patient population

We report variability between hs-cTn assays in a highly selected population eligible for further non-invasive testing with coronary CTA, representing about 10–20% of all comers, and excluding high-risk groups e.g. those with a prior history of CAD, kidney disease, or those with objective signs of ACS.(18) Thus, the ACS rate in this population (between 2–7%; (18,42–44)) is lower than reported in all-comers (ranging from 10–30% (12,31,45,46)) and troponin values tend to be lower as well. Nevertheless, we report substantial discordance of three high-sensitivity troponin assays to risk-stratify patients with suspected ACS, in a particularly challenging subgroup of the ED chest pain population.

Implications and future directions

Our data suggest that in patients with suspected ACS, clinical management based hs-cTn assay-specific thresholds such as the 99th percentile might deviate significantly when using three hs-cTn assays. This might lead to differences in referral to further non-invasive diagnostic testing and detection of underlying CAD. Because the reported discrepancies are not likely to be attributable to differences in diagnostic performance of the studied assays, as these were all reported to have excellent diagnostic properties, it is more probable that differences in reference populations used for derivation of thresholds factored in. It is known, that age and gender distribution of reference populations could impact substantially the upper limit of detection of normal healthy population.(16,33) Therefore, potential solutions include endorsement of thresholds (99th percentile) derived with the use of a standardized reference population for all hs-cTn platforms (24,33) or methods to express likelihood for ACS in a probabilistic fashion.(47,48)

Limitations

This study has limitations. First, our patient cohort does not reflect the entire spectrum of patients presenting with suspicion for ACS to ED’s in the US. However, we included patients at intermediate likelihood of ACS, who were referred to further noninvasive diagnostic testing after inconclusive initial triage (normal conventional troponin-T and non-ischemic ECG). This group represents about 20% of all comers with suspicion of ACS presenting to US ED’s and moreover, poses the highest diagnostic challenge for safe and efficient triage. Second, only patients in ROMICAT-II, but not ROMICAT-I, underwent serial troponin measurements limiting the assessments of guideline-based management recommendation. Third, the 0/2 hour algorithm was developed for the Siemens Centaur

platform, but not for the Siemens Dimension Vista. Moreover, the assay we used was a pre-commercial assay and is likely different from the platform that has been commercially implemented. Given that the differences between the two assays are relatively small with the Centaur being a slightly more sensitive assay(49), a small proportion of samples and patients may be reclassified; however, it is unlikely that this would have altered our results substantially in terms of agreement between the three assays. Our data on the Siemens assay, however, warrant replication with the commercially available platform. Fourth, both the 0/2 hour algorithms and the 99th percentile analytic benchmarks were derived and validated to identify MIs, while the majority of ACS in the ROMICAT trials was UAP. It is important to note that this adjudication was based on conventional non-highly sensitive assays and further analyses have shown that about 40% of UAP would have been adjudicated as MI using hs-cTn. (29). Nevertheless, this constitutes a limitation of the data.

Conclusion

Caregivers should be aware of the substantial discordance between commercially available hs-cTn assays in stratifying patients with intermediate likelihood of ACS according to standard analytical benchmarks that may result in different management recommendations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

DISCLOSURE

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ABBREVIATIONS

ACS	Acute Coronary Syndrome
AMI	Acute Myocardial Infarction
CTA	Computed Tomographic Angiography
ED	Emergency Department
ECG	Electrocardiogram
FDA	Food and Drug Administration
Hs-cTn	High-Sensitivity Cardiac Troponin
LOD	Limit of Detection
ROMICAT	Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography
SPECT	Single Photon Emission Computed Tomography
TIMI	Thrombolysis in Myocardial Infarction
UAP	Unstable Angina Pectoris

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CLINICAL PERSPECTIVES

Competency in Patient Care:

Comparison of three commercially available high-sensitivity blood troponin (hs-cTn) assays in patients with suspected acute coronary syndromes (ACS) found up to 2-fold differences in results that could influence the proportion of patients referred for further observation or investigation.

Translational Outlook:

Additional work is necessary to create a universal sample bank encompassing all hs-cTn assays and standardize thresholds to guide triage of patients with suspected ACS.

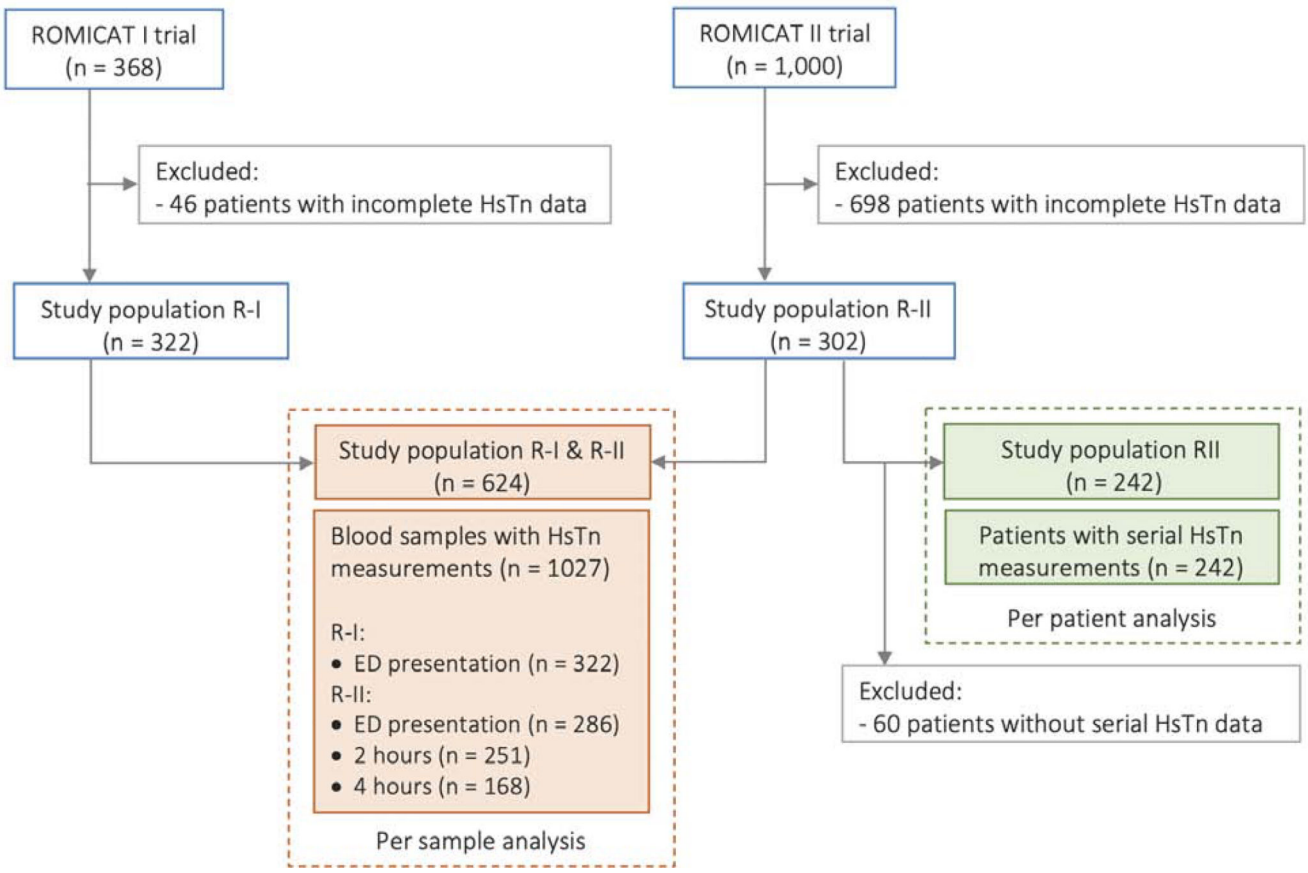


Figure 1. Study Population enrollment, exclusion, and inclusion.

The flow chart summarizes the selection of the patient population included in the per-sample and per-patient analyses. ED=emergency department; Hs-cTn=High-sensitivity cardiac troponin; R-I=ROMICAT-I; R-II=ROMICAT-II; ROMICAT=Rule Out Myocardial Infarction/Ischemia Using Computer-Assisted Tomography II.

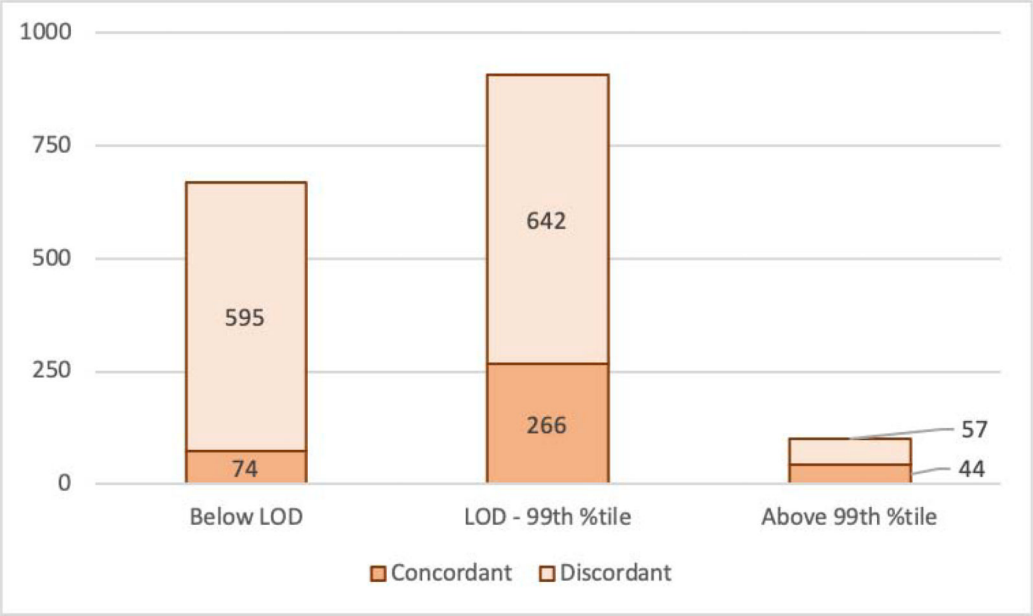


Figure 2.

Agreement between assays in classifying blood samples along analytic benchmarks using non-sex specific 99th percentile. Concordant is defined as agreement between all three assays, anything else is considered as discordant*. LOD=Limit of detection; 99th%tile=99th percentile.*Discordant cases are classified to more than one analytic benchmark, therefore the overall sum of the columns is not equal to the overall sum of studied blood samples (n=1,027), but it is higher because of the redundancy.

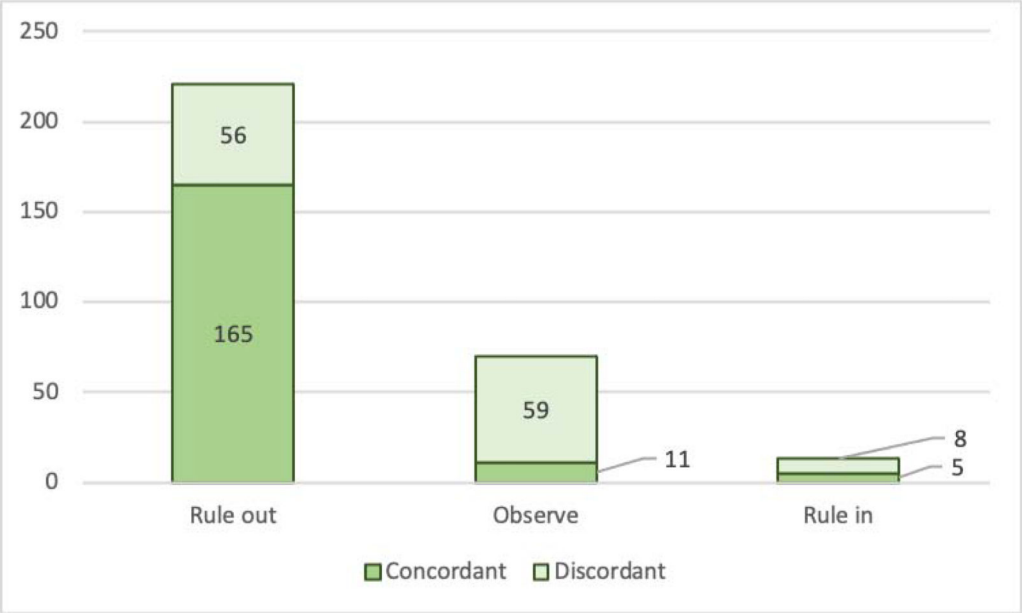
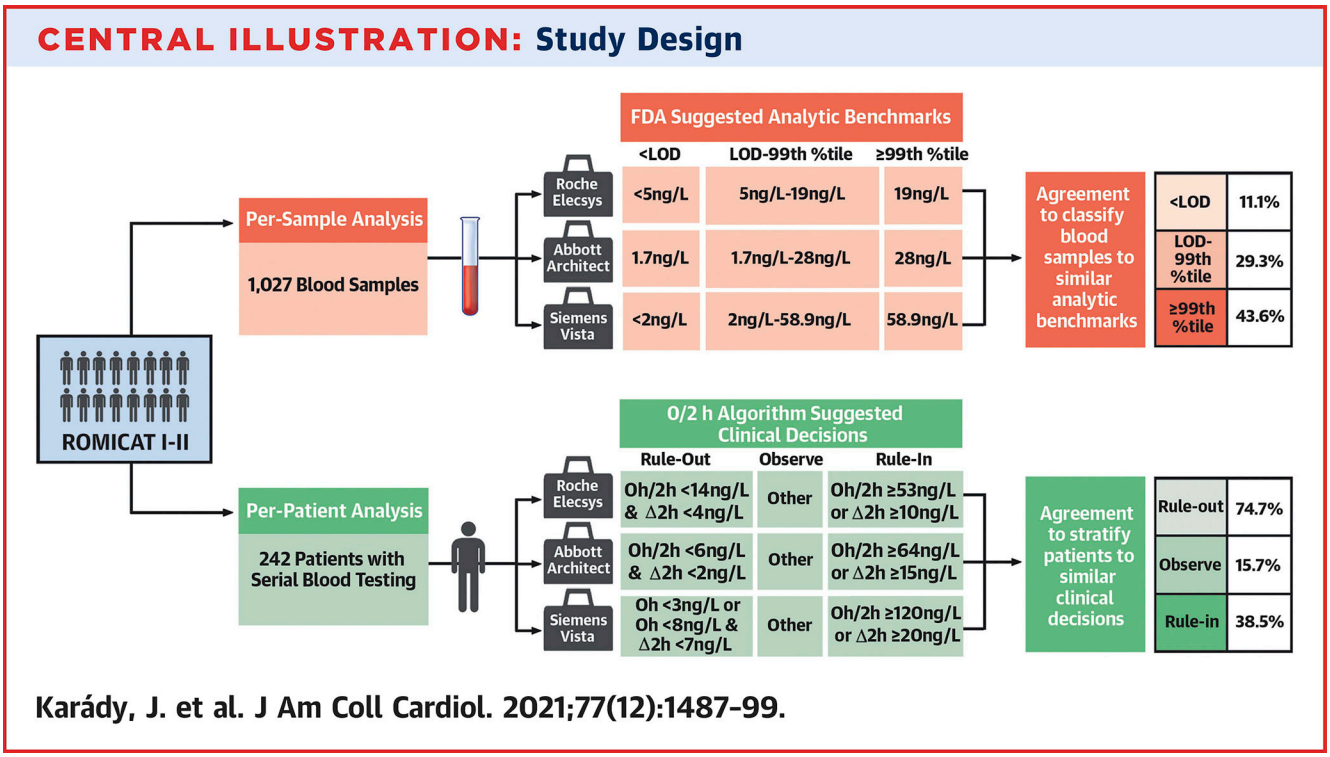


Figure 3.

Agreement between assays in patient management recommendations based on the 0/2 hour algorithm. Concordant is defined as agreement between all three assays, anything else is considered as discordant*. *Discordant cases are stratified to more than one analytic benchmark, therefore the overall sum of the columns is not equal to the overall sum of studied patients (n=242), but it is higher because of the redundancy.



Central illustration: Study design.

Outline of the per-sample and per-patient analysis to assess the concordance between the three assays. Hs-cTn=High-Sensitivity Cardiac Troponin; LOD=Limit of Detection; %tile=Percentile.

Table 1.

Analytic benchmarks of high-sensitivity troponin assays.

	FDA recommended analytic benchmarks (9–11)					%CV at the 99th %tile (49)	Epitopes recognized by antibodies (49)	
	LOD	LOQ	99th %tile	Sex-specific 99th %tiles				
				99th %tile of males	99th %tile of females		Detection	Capture
Roche Elecsys, TnT, ng/L	5	6	19	22	14	<10.0%	23–29	87–91
Abbott ARCHITECT, TnI, ng/L	1.7	3.5	28	35	17	4.0%	41–49	24–40
Siemens Vista, TnI, ng/L	2.0	3	58.9	78.5	53.7	<5.0%	41–56	27–32

References used for FDA recommended analytic benchmarks: (6–8); Reference for the %CV at the 99th percentile and Epitopes recognized by antibodies: (9).

AMI=Acute Myocardial Infarction; TnI=Troponon I; TnT=Troponin T. LOD=Limit of detection; LOQ=Limit of quantification; CV=Coefficient of variance; %tile=Percentile.

Table 2.

Demographic data.

	Total (n=624)	ROMICAT-I (n=322)	ROMICAT-II (n=302)	P value
Age, years	52.8 ± 10.0	52.6 ± 11.7	52.9 ± 7.8	0.70
Female sex, n (%)	246 (39.4)	121 (37.6)	125 (41.4)	0.37
BMI, kg/m^2	28.9 ± 5.4	28.9 ± 5.9	28.9 ± 4.7	0.91
Cardiovascular risk factors				
Hypertension, n (%)	286 (45.8)	128 (39.8)	158 (52.3)	**0.002**
Diabetes mellitus, n (%)	82 (13.1)	37 (11.5)	45 (14.9)	0.24
Dyslipidemia, n (%)	249 (39.9)	121 (37.6)	128 (42.4)	0.25
Former/current smoker, n (%)	303 (48.6)	155 (48.1)	148 (49.0)	0.87
Family history of premature CAD, n (%)	193 (30.9)	80 (24.8)	113 (37.4)	**0.001**
Number of cardiovascular risk factors, n (%)				**0.003**
0–1	268 (43.0)	159 (49.4)	109 (36.1)	
2–3	307 (49.2)	142 (44.1)	165 (54.6)	
≥4	49 (7.9)	21 (6.5)	28 (9.3)	
TIMI score, n (%)				**<0.001**
0	342 (54.8)	154 (47.8)	188 (62.3)	
1	187 (30.0)	101 (31.4)	86 (28.5)	
2	75 (12.0)	50 (15.5)	25 (8.3)	
≥3	20 (3.2)	17 (5.3)	3 (1.0)	
Prior medication				
Aspirin, n (%)	171 (27.4)	103 (32.0)	68 (22.5)	**0.009**
Beta-blocker, n (%)	127 (20.4)	75 (23.3)	52 (17.2)	0.07
Statin, n (%)	174 (27.9)	91 (28.3)	83 (27.5)	0.86
Non-invasive diagnostic testing				
Positive test, n (%)	125/517 (24.2)	80/322 (24.8)	45/195 (23.1)	0.67
Positive coronary CTA*, n (%)	98/479 (20.5)	58/322 (18.0)	40/157 (25.5)	0.07
Positive SPECT†, n (%)	46/189 (24.3)	38/132 (28.8)	8/57 (14.0)	**0.041**
Clinical events				
ACS, n (%)	49 (7.9)	24 (7.5)	25 (8.3)	0.77
AMI, n (%)	11 (1.8)	5 (1.6)	6 (2.0)	0.77
UAP, n (%)	38 (6.1)	19 (5.9)	19 (6.3)	0.87

*Positive coronary CTA: >50% luminal narrowing

†Positive SPECT: evidence of stress induced ischemia defined as reversible myocardial perfusion defect.

ACS=Acute coronary syndrome; BMI=Body mass index; CAD=Coronary artery disease; MI=Myocardial infarction; UAP=Unstable angina pectoris.

Table 3.

Agreement between assays in classifying blood samples according to analytic benchmarks.

Analytic benchmarks:	Roche Elecsys n (%)	Abbott Architect n (%)	Siemens Vista n (%)	P values*			
				Roche vs. Abbott	Roche vs. Siemens	Abbott vs. Siemens	Overall Comparison
< LOD	578 (56.3)	107 (10.4)	423 (41.2)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
LOD - 99th %tile	375 (36.5)	858 (83.5)	540 (52.6)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
> 99th %tile	74 (7.2)	62 (6.0)	64 (6.2)	0.064	0.157	0.670	0.114
Total	1,027 (100.0)	1,027 (100.0)	1,027 (100.0)	N/A	N/A	N/A	N/A

*Indicating the differences between the assays. LOD=Limit of detection; %tile=Percentile.

Table 4.

Agreement between assays in stratifying patients based on the 0/2 h algorithm using serial hs-cTn measurements.

Clinical decision	Roche Elecsys n (%)	Abbott Architect n (%)	Siemens Vista n (%)	P values*			
				Roche vs. Abbott	Roche vs. Siemens	Abbott vs. Siemens	Overall comparison
Rule-out	211 (87.2)	177 (73.1)	190 (78.5)	**<0.001**	**<0.001**	**0.007**	**<0.001**
Observe	23 (9.5)	58 (24.0)	43 (17.8)	**<0.001**	**0.002**	**0.004**	**<0.001**
Rule-in	8 (3.3)	7 (2.9)	9 (3.7)	0.655	0.706	0.317	0.687
Total	242 (100.0)	242 (100.0)	242 (100.0)	N/A	N/A	N/A	N/A

* Indicating the differences between the assays.