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Diagnostic Performance of High Sensitivity Cardiac Troponin T Strategies and Clinical Variables in a Multisite United States Cohort

Running Title: *Allen et al.; High Sensitivity Troponin T in United States*

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Abstract

Background: European data support the use of low high-sensitivity troponin (hs-cTn) measurements or a 0/1-hour (0/1-h) algorithm for myocardial infarction (MI) or to exclude major adverse cardiac events (MACE) among Emergency Department (ED) patients with possible acute coronary syndrome (ACS). However, modest US data exist to validate these strategies. This study evaluated the diagnostic performance of an initial hs-cTnT measure below the limit of quantification (LOQ: 6 ng/L), a 0/1-h algorithm, and their combination with HEART scores for excluding MACE in a multisite US cohort.

Methods: A prospective cohort study was conducted at 8 US sites, enrolling adult ED patients with symptoms suggestive of ACS and without ST-elevation on electrocardiogram. Baseline and 1-hour blood samples were collected and hs-cTnT (Roche, Basel Switzerland) measured. Treating providers blinded to hs-cTnT results prospectively calculated HEART scores. MACE (cardiac death, MI, and coronary revascularization) at 30-days was adjudicated. The proportion of patients with initial hs-cTnT measures <LOQ and risk based on a 0/1-h algorithm was determined. The negative predictive value (NPV) was calculated for both strategies when used alone or with a HEART score.

Results: Among 1,462 participants with initial hs-cTnT measures, 46.4% (678/1,462) were women and 37.1% (542/1,462) were African American with a mean age of 57.6 (SD±12.9) years. MACE at 30-days occurred in 14.4% (210/1,462). Initial hs-cTnT measures <LOQ occurred in 32.8% (479/1,462), yielding a NPV of 98.3% (95%CI: 96.7-99.3%) for 30-day MACE. A low risk HEART score with an initial hs-cTnT < LOQ occurred in 20.1% (294/1,462) yielding a NPV of 99.0% (95%CI: 97.0-99.8%) for 30-day MACE. A 0/1-h algorithm was complete in 1,430 patients, ruling-out 57.8% (826/1,430) with a NPV of 97.2% (95%CI: 95.9-98.2%) for 30-day MACE. Adding a low HEART score to the 0/1-h algorithm ruled-out 30.8% (441/1430) with a NPV of 98.4% (95%CI: 96.8-99.4%) for 30-day MACE.

Conclusions: In a prospective multisite US cohort, an initial hs-cTnT <LOQ combined with a low risk HEART score has 99% NPV for 30-day MACE. The 0/1-h hs-cTnT algorithm did not achieve a NPV > 99% for 30-day MACE when used alone or with a HEART score.

Clinical Trial Registration: URL: https://clinicaltrials.gov Unique Identifier: NCT02984436

Key Words: acute coronary syndrome; high-sensitivity cardiac troponin; chest pain; myocardial infarction

Non-Standard Abbreviations and Acronyms:
0/1-h = 0/1-hour
ACS = acute coronary syndrome
CABG = coronary artery bypass grafting
ECG = electrocardiogram
ED = emergency department
hs-cTn = high-sensitivity cardiac troponin
LOB = limit of blank
LOD = limit of detection
LOQ = limit of quantification
MACE = major adverse cardiac events

MI = myocardial infarction
NPV = negative predicitive value
PPV = positive predictive value
SD = standard deviation
URL = upper reference limit
US = United States

Clinical Perspective

What is new?

- In the largest prospective multisite US study of hs-cTnT strategies to date, an initial hs-cTnT below the level of quantification (LOQ, <6 ng/L) was associated with a negative predictive value (NPV) of 98.3% (95%CI: 96.7-99.3%) for 30-day major adverse cardiac events (MACE).
- A 0/1-h algorithm ruled-out 57.8% of patients with a NPV of 97.2% (95%CI: 95.9-98.2%) for 30-day MACE.
- The addition of a low-risk HEART Score to an initial hs-cTnT <LOQ and the 0/1-h algorithm improved NPV for 30-day MACE to 99.0% (95%CI: 97.0-99.8%) and 98.4% (95%CI: 96.8-99.4%) respectively.

What are the clinical implications?

- When used without a risk score, an initial hs-cTnT measure <LOQ or a 0/1-h algorithm, may have insufficient sensitivity and NPV to exclude 30-day MACE in US Emergency Department patients.
- The addition of a low-risk HEART Score to an initial hs-cTnT measure <LOQ and a 0/1-h algorithm, improves sensitivity and NPV for cardiac events, but rules-out fewer patients.
- In total our results suggest that adding a risk score to hs-cTnT strategies increases their safety.

Introduction

Among patients presenting to the emergency department (ED) with symptoms concerning for acute coronary syndrome (ACS), clinicians rely on cardiac troponin measures to diagnose and exclude myocardial infarction (MI) and injury.[1–3] High-sensitivity cardiac troponin (hs-cTn) T and I assays, which have recently been approved for use in the United States (US), can quantify lower cTn concentrations with greater precision than prior cTnT or cTnI assays.[4] Although hs-cTn assays have been used in Europe, Canada, and in the Asia-Pacific Region for many years and are well studied there, prospective data on their performance in US populations remains limited.[5,6]

Two important hs-cTn risk stratification strategies have emerged from international data: 1) use of an initial very low hs-cTnT measure (below the limit of quantification [LOQ]) and 2) the use of an algorithm with an initial and 1-hour hs-cTnT measure (0/1-h algorithm), which is currently recommended by the European Society of Cardiology.[7–11]Some US hospitals that transitioned to hs-cTn have integrated these strategies into their risk stratification algorithms for patients with possible ACS.[12] In addition, most of these algorithms also incorporate electrocardiogram (ECG) data and risk scores, such as the history, ECG, age, risk factors, and troponin (HEART) score, into their clinical decision making. Recent analyses of the HIGH US cohort suggested that single low hs-cTn measures and a 0/1-h algorithm using a Siemens hs-cTnI assay are safe strategies for excluding MI in a US population of patients with possible ACS.[6,13,14] However, multisite US data for these strategies using hs-cTnT assay are lacking. [15–18] In addition, there are few studies evaluating the utility of adding clinical variables, such as ECG ischemia and HEART score to hs-cTn strategies.[19] Furthermore, while the ability of hs-cTnT assays to detect MI during patients' index ED encounters has been established, their ability to

detect downstream major adverse cardiac events (MACE), such as cardiac death, MI, and revascularization, is less clear.

This study was designed to address these evidence gaps and determine whether there are aspects of hs-cTnT use which are uniquely American. Thus, the goal of this study was to prospectively evaluate the diagnostic performance (safety and efficacy) of the Roche hs-cTnT assay for the detection of 30-day MACE and the composite of cardiac death or MI at 30 days using an initial hs-cTnT <LOQ and a 0/1-h algorithm with or without the inclusion of important clinical variables: ECG interpretation and HEART score.

Methods

Study Design and Oversight

This is a prospective observational cohort study of ED patients with acute chest pain, or other symptoms suggestive of ACS enrolled at eight US EDs from 1/25/2017 to 09/06/2018 (University of Florida, Gainesville, Florida; Wake Forest University, Winston Salem, North Carolina; Henry Ford Health System, Detroit, Michigan; University of Maryland St. Joseph Medical Center, Towson, Maryland, University of Maryland Medical Center, Baltimore, Maryland; University of Maryland Baltimore Washington Medical Center, Glen Burnie, Maryland; University of California-Davis, Sacramento, California; and University of Utah, Salt Lake City, Utah;). Prior to the study start, ethics approval was obtained from all relevant institutional review boards, and the study was registered at clinicaltrials.gov (NCT02984436). The study was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonization guidelines for Good Clinical Practice, and the Code of Federal Regulations 21, Part 50. The data, analytic methods, and study materials will not be

made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Setting and Population

Patients aged 21 years and older presenting to the ED with chest discomfort or other symptoms consistent with possible ACS were prospectively enrolled. Possible ACS was defined by the ED provider ordering serial troponins. Exclusion criteria included ST-segment elevation MI at ED presentation, systolic blood pressure less than 90, a life expectancy less than 90 days, a non-cardiac illness requiring admission, lack of capacity to provide consent, inability to be contacted for follow-up, non-English speaking, pregnancy, and prior enrollment in the current study. To be included in this analysis, patients meeting the above criteria were required to be enrolled within one hour of the site's first clinical blood draw and have a second standard of care cTn measurement within the next 2-12 hours.

Study Procedures

After written informed consent, serial blood samples were collected from study participants for hs-cTnT analysis at baseline (<1h from first clinical sample) and 1, 2, and 3 hours later plus or minus 30 minutes. Treating providers were blinded to hs-cTnT results. Thus, the care of participants was determined by the local standard of care, based in part on their local contemporary cTn results. Each patient had an ECG performed as part of routine clinical care and interpreted prospectively by the treating ED provider and recorded on the STOP-CP treating provider case report form. ECGs were defined as ischemic if they had new T-wave inversions or ST segment depressions greater than 1mm in at least 2 contiguous leads. In addition, HEART score data were collected prospectively from the treating ED provider. For this analysis, the history, ECG, age, and risk factor (HEAR) components of the HEART score from the treating

provider were used in combination with the hs-cTnT value. Consistent with prior studies, a score of 0-3 was considered low-risk, while scores ≥4 were non-low-risk.[20–22]

Blood samples for hs-cTnT measurement were collected in lithium heparin and Ethylenediaminetetraacetic acid (EDTA) tubes. Following collection, samples were centrifuged for 10-15 minutes and maintained in storage at –70°C. Hs-cTnT concentrations were measured by a central laboratory (University of Maryland School of Medicine, Baltimore, MD) with personnel blinded to the time of collection and other patient information, using the Troponin T hs assay on the cobas e 601 analyzer. The assay is an electrochemiluminescence sandwich immunoassay, which uses both ruthenium-labeled and biotin-labeled antibodies to form a sandwich complex with cTnT. It has a measuring range of 3 ng/L to 10000 ng/L and a LOQ of 6 ng/L. Although the limit of blank (LOB) for the hs-cTnT used in this analysis has been reported to be 3 ng/L, results less than the LOQ are not reported in the US, per FDA specification. The assay has an overall 99th percentile upper reference limit (URL) of 19 ng/L in the US with a coefficient of variation of <10%.[23] No changes occurred in the manufacturing or specifications of this assay during the duration of this study.

Outcomes

The primary outcome for this study was major adverse cardiac events (cardiac death, MI, and coronary revascularization) at 30-days inclusive of index-visit events. Secondary outcomes include the composite of cardiac death or MI, and individual components of the MACE outcomes at index-visit and 30-days. Thirty-day phone follow-up calls and medical record reviews were completed on all participants to identify MACE outcomes. Patients with a clinical diagnosis of MI, an elevated local contemporary cTn, or death during the follow-up period were adjudicated by expert reviewers (MHV, MRM, JPS, JKM). Adjudicators classified deaths as

cardiac or non-cardiac. Cardiac death was defined based on the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.[24] Death from stroke was not considered a cardiac death. In cases where the cause of death could not be determined, the death was considered cardiovascular. To determine MI, adjudicators used the 4th Universal Definition of MI: rise and/or fall of troponin with at least one value above the 99th percentile of the upper reference limit with at least one of the following: a) symptoms of ischemia, b) ECG changes indicative of new ischemia, c) development of pathological Q waves on the ECG, d) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.[3] Coronary revascularization was defined as coronary artery bypass grafting (CABG) or angioplasty with or without stent placement. Adjudicators had access to all clinical data including the local clinical contemporary troponin assay results but were blinded to hs-cTnT results. Any discrepancies between adjudicators were resolved through review by the third adjudicator.

Statistical Analysis

All study data were collected by individual sites and managed in Research Electronic Data Capture (REDCap) version 9.1.1.[25] Statistical analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics, including means, standard deviations, frequencies, and percent, appropriate for measurement level were used to examine distribution of values and identify missing and extreme values for verification. Hs-cTnT strategies evaluated included an initial hs-cTnT <LOQ and a 0/1-h algorithm with or without the inclusion of ECG interpretation and HEART score. To evaluate test performance of these strategies and cut points, measures of efficacy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated by the construction of two by two contingency tables.[26] Consistent with prior studies, a NPV ≥99% was considered sufficient for

the clinical use of a rule-out strategy.[27,28] Efficacy was defined as the proportion of the cohort that would be ruled-out by a cut point or algorithm, which is consistent with prior hs-cTn studies.[29–31] Their 95% confidence intervals were calculated by the Clopper Pearson exact method using the GenBinomApps package.[32]

Next, the cohort was stratified into early presenters (patients presenting with < 3 hours of symptoms) and late presenters (≥3 hours of symptoms), and test performance of hs-cTnT strategy including or excluding clinical variables of ischemic or non-ischemic ECG and treating provider HEART score calculation. The Bayesian logistic regression was performed to impute the missing values and study the impact of loss to follow-up by using the mice.impute.logreg function in R package mice**.** Missing follow-up data were imputed using demographic variables and troponin results. The imputation procedure was repeated 25 times, and results were averaged among the 25 imputed datasets.

Four sensitivity analyses were conducted. First, to assess whether test performance differed when patients were adjudicated based on hs-cTnT measures, patients were re-adjudicated for MACE outcomes using hs-cTnT results with the adjudicators blinded to the local contemporary troponin assay measures. Second, test performance was evaluated after outcomes for patients lost to follow-up were imputed (n=25 datasets) using multiple imputation based on patients' demographics, cardiovascular risk factors, and hs-cTnT results. Third, test performance was evaluated after including only Type 1 MI, rather than both Type 1 and Type 2 MI, in the MACE and cardiac death and MI composite outcomes. Finally, we tested whether performance differed if patients with an uncertain cause of death were classified as having non-cardiovascular deaths.

Results

A total of 1,583 patients with symptoms suggestive of ACS were enrolled, of which 1,462 were eligible for analysis (Figure 1). Of these, 46.4% (678/1,462) were women, and 37.1% (542/1,462) were African American. The average age was 57.6 years (standard deviation ±12.9 years). Additional characteristics of the STOP CP cohort are summarized in Table 1. Samples for hs-cTnT measurement were collected at 0 hours in 99.9% (1460/1462) and at 1 hour in 97.9% (1432/1462) of participants. The median time from ED arrival to baseline study blood draw was 82 minutes (Interquartile range: 63 – 106 minutes). Follow-up at 30-days was complete in 96.2% (1406/1462) of patients, with 3.8% (56/1462) lost to follow-up. MACE at 30 days occurred in 14.4% (210/1462). This included 0.6% (9/1462) with cardiac death, 12.7% (185/1462) with MI, and 1.6% (24/1462) with coronary revascularization without MI. MACE at index visit occurred in 12.4% (181/1462), with index cardiac deaths in 0.1% (2/1462), MI in 11.6% (169/1462), and revascularization without MI in 0.8% (11/1462). After the index visit (during the 30-day follow-up period) MACE occurred in 3.1% (46/1462), with 0.5% (7/1462) having cardiac death, 1.8% (26/1462) with MI, and revascularization without MI in 1.0% (14/1462).

Diagnostic Performance of LOQ

Diagnostic performance of the initial hs-cTnT measures below the LOQ (<6 ng/L) is presented in Table 2. Initial hs-cTnT measures below the LOQ occurred in 32.8% (95%CI: 30.4-35.3%) of the cohort. Among these patients, zero had cardiac death, five had MI, and three had revascularization without MI during the 30-day follow-up. Thus, the NPV of an initial hs-cTnT measure <LOQ was 98.3% (95%CI: 96.7-99.3%) for MACE at 30-days with a sensitivity of 96.2% (95%CI: 92.6-98.3%). For cardiac death and MI at 30-days the NPV was 99.0% (95%CI: 97.6-99.7%) and sensitivity was 97.4% (95%CI: 94.0-99.1%). For index-visit MI the NPV was

99.2% (95%CI: 97.9-99.8%) and sensitivity was 97.6% (95%CI: 94.1-99.4%). The characteristics of the eight patients with an initial hs-cTnT below the LOQ who experienced MACE are summarized in Table I in the Supplement.

Additional diagnostic test characteristics of an initial hs-cTnT measure <LOQ with and without clinical variables are summarized in Table 2. The addition of a non-ischemic ECG to an initial hs-TnT <LOQ had an efficacy of 31.9% (95%CI: 29.5-34.4%) with a NPV of 98.3% (95%CI: 96.6-99.3%) and 98.9% (95%CI: 97.5-99.7%) for 30-day MACE and 30-day cardiac death or MI respectively. For index-visit MI the NPV was 99.1% (95%CI: 97.8-99.8%) and sensitivity was 97.6% (95%CI: 94.1-99.4%). A HEART score of 0-3 with an initial hs-TnT <LOQ had an efficacy of 20.1% (95%CI: 18.1-22.3%) with a NPV of 99.0% (95%CI: 97.0-99.8%) for 30-day MACE and 99.7% (95%CI: 98.1-100.0%) for 30-day cardiac death or MI. For index-visit MI the NPV was 99.7% (95%CI: 98.1-100.0%) and sensitivity was 99.4% (95%CI: 96.7-100.0%). An initial hs-TnT below the LOQ combined with both a non-ischemic ECG and HEART score of 0-3 had an efficacy of 20.1% (95%CI: 18.0-22.2%) with a NPV of 99.0% (95%CI: 97.0-99.8%) and 99.7% (95%CI: 98.1-100.0%) for 30-day MACE and 30-day cardiac death or MI respectively. For index-visit MI the NPV was 99.7% (95%CI: 98.1-100.0%) and sensitivity was 99.4% (95%CI: 96.7-100.0%).

Diagnostic Performance of the 0/1-h Algorithm

Diagnostic performance of the the hs-cTnT 0/1-h algorithm is presented in Table 3 and Figure 2. Among 1430 patients with 0 and 1-hour hs-cTnT measurements, 57.8% (826/1430) had values in the rule-out range, 29.0% (414/1430) in the observation zone, and 13.3% (190/1430) in the rule-in range. The rule-out range had a NPV of 97.2% (95%CI: 95.9-98.2%) and sensitivity of 88.7% (95%CI: 83.5-92.7%) for 30-day MACE. For 30-day cardiac death or MI the rule-out range had

a NPV of 98.4% (95%CI: 97.3-99.2%) and a sensitivity of 92.9% (95%CI: 88.2-96.2%). Index visit MI occurred in 1.0% (8/826) of patients in the rule-out range with a NPV of 99.0% (95%CI: 98.1-99.6%) and a sensitivity of 95.1% (95%CI: 90.6-97.9%).

The rule-in range yielded a PPV of 58.4% (95%CI: 51.1-65.5%) and a specificity of 93.6% (95%CI: 92.0-94.9%) for 30-day MACE, while the PPV and specificity for 30-day cardiac death or MI were 58.4% (95%CI: 51.1-65.5%) and 93.7% (95%CI: 92.2-95.0%), respectively. Index visit MI occurred in 55.3% (105/190) with the PPV and specificity of 55.3% (95%CI: 47.9-62.5%) and 93.3% (95%CI: 91.8-94.6%), respectively. However, for non-rule-out patients (the combination of the observation and rule-in zones) the PPV and specificity for 30-day MACE were 29.8% (95%CI: 26.2-33.6%) and 65.4% (95%CI: 62.7-68.1%)respectively, while PPV and specificity for 30-day cardiac death or MI were 28.2% (95%CI: 24.6-31.9%) and 65.2% (95%CI: 62.5-67.8%). Among the patients in the observation zone, 16.7% (69/414) had 30-day MACE, 14.2% (59/414) had 30-day cardiac death or MI, and 12.3% (51/414) had index-visit MI. The 0/1-h Algorithm results are summarized in Figure 2. True negatives and positives and false negatives and positives of the 0/1-h algorithm for 30-day MACE are summarized in Table II in the Supplement.

The rule-out range of the 0/1-h algorithm combined with a non-ischemic ECG occurred in 55.7% (797/1430) of patients. This combination yielded a NPV of 97.1% (95%CI: 95.7-98.2%) and sensitivity of 88.7% (95%CI: 83.5-92.7%) for 30-day MACE. For 30-day cardiac death or MI the rule-out range had a NPV of 98.4% (95%CI: 97.2-99.1%) and sensitivity of 92.9% (95%CI: 88.2-96.2%). For index visit MI the NPV was 99.0% (95%CI: 98.0-99.6%) and sensitivity was 95.1% (95%CI: 90.6-97.9%).

The addition of a low-risk HEART score to the rule-out range of the 0/1-h algorithm had an efficacy of 30.8% (441/1430). This combination yielded a NPV of 98.4% (95%CI: 96.8-99.4%) and sensitivity of 96.6% (95%CI: 93.0-98.6%) for 30-day MACE. For 30-day cardiac death or MI, the rule-out range with a low-risk HEART score had a NPV of 99.3% (95%CI: 98.0-99.9%) and sensitivity of 98.4% (95%CI: 95.3-99.7%). For index visit MI the NPV was 99.5% (95%CI: 98.4-99.9%) and sensitivity was 98.8% (95%CI: 95.7-99.9%). Additional test characteristics for the 0/1-h algorithm with and without clinical variables are summarized in Table 3 and Figure 3.

Among the 1.6% (23/1430) of patients with 30-day MACE who had hs-cTnT measures in the rule-out range of the 0/1-h algorithm, one patient had a cardiac-related death, nine patients had an index visit MI, four had 30-day MI, six had index revascularization without MI, three had revascularization during the 30-day follow-up, and one patient revascularization events at index and within 30-days. Ten of the patients with missed MIs had a type 2 MIs, while three had a type 1 MIs (one of which developed into a ST-elevation myocardial infarction). All 23 patients had a non-ischemic ECG and seven had a low-risk HEART score. The maximum absolute delta in the missed event group was 2 ng/L. The age range of these patients was 38-75 years, 26.1% (6/23) were African American, 4.3% (1/23) were Hispanic, 34.8% (8/23) were female, 52.2% (12/23) had a BMI greater than 30, and 39.1% (9/23) were early presenters. Characteristics of patients with MACE who had hs-cTnT measures in the rule-out range, are summarized in Table III in the Supplement.

Early and Late Presenters

Among 516 patients with chest pain onset less than 3 hours in the early presenter group, 15.3% (79/516) had MACE. In this group an initial hs-cTnT measure < LOQ had an efficacy of 28.9%

(95%CI: 25.0-33.0%), a NPV of 98.6% (95%CI: 95.2-99.8%) and sensitivity of 97.5% (95%CI: 91.2-99.7%) for 30-day MACE. For 30-day cardiac death or MI an initial hs-cTnT measures < LOQ had a NPV of 98.6% (95%CI: 95.1-99.8%) and a sensitivity of 97.3% (95%CI: 90.6-99.7%). The initial hs-cTnT measure < LOQ had a NPV of 99.3% (95%CI: 96.3-100.0%) and a sensitivity of 98.4% (95%CI: 91.3-100.0%)for index visit MI. A HEART score of 0-3 with an initial hs-cTnT <LOQ in early presenters had an efficacy of 20.5% (95%CI: 17.1-24.3%) with a NPV of 100.0% (95%CI: 97.2-100.0%) for 30-day MACE and 100.0% (95%CI: 97.2-100.0%) for 30-day cardiac death or MI. The combination of a low-risk HEART score and initial hs-cTnT <LOQ in early presenters resulted in a NPV of 100.0% (95%CI: 97.2-100.0%) and sensitivity was 100.0% (95%CI: 95.3-100.0%) for index visit MI.

In early presenters, the 0/1-h algorithm rule-out range had a NPV of 96.8% (95%CI: 93.9-98.5%) and sensitivity of 87.8% (95%CI: 78.2-94.3%) for 30-day MACE. For 30-day cardiac death or MI the rule-out range had a NPV of 97.8% (95%CI: 95.3-99.2%) and a sensitivity of 91.3% (95%CI: 82.0-96.7%). For index visit MI, the rule-out range had a NPV of 98.6% (95%CI: 96.3-99.6%) and a sensitivity of 93.2% (95%CI: 83.5-98.1%). The addition of a low-risk HEART score to the rule-out range of the 0/1-h algorithm in early presenters yielded a NPV of 98.2% (95%CI: 94.9-99.6%) and sensitivity of 95.9% (95%CI: 88.6-99.2%) for 30-day MACE. For 30-day cardiac death or MI the rule-out range combined with a low-risk HEART score had a NPV of 98.8% (95%CI: 95.8-99.9%) and sensitivity of 97.1% (95%CI: 89.9-99.6%). For index visit MI the NPV of the rule-out range combined with a low-risk HEART score was 99.4% (95%CI: 96.7-100.0%), and sensitivity was 98.3% (95%CI: 90.9-100.0%). Additional diagnostic performance data among early and late presenters are presented in Tables 4-5 and Tables IV and V in the Supplement.

Sensitivity Analyses

A sensitivity analysis using outcomes from re-adjudication of MACE and cardiac death or MI using hs-cTnT values did not substantively change results (Tables VI and VII in the Supplement). Test performance for 30-day MACE and cardiac death or MI, including only Type 1 MI, is presented in Tables VIII and IX in the Supplement. In addition, a sensitivity analysis imputing events for patients lost to follow-up produced no substantive differences in results (Tables X and XI in the Supplement). Finally, a sensitivity analysis for uncertain causes of death classified as non-cardiovascular deaths produced no substantive differences in results (Tables XII and XIII in the Supplement).

Discussion

This multisite, prospective study of hs-cTnT strategies in US ED patients suggests that adding a HEART score to these strategies improves safety. When used alone, a single hs-cTnT measure <LOQ had insufficient NPV and sensitivity to rule-out 30-day MACE. However for 30-day cardiac death or MI, the NPV was 99.0%, but with a lower bound of the 95% confidence interval extending to 97.6%, many clinicians may find this unacceptable. Further, the addition of a low-risk HEART score to an initial hs-cTnT value <LOQ, increases the NPV for 30-day cardiovascular death and MI to 99.7%. The trade-off with adding the HEART score to an initial hs-cTnT value <LOQ is that efficacy is decreased from 32.8% to 20.1%.[20,22]

Prior studies demonstrated that very low initial hs-cTnT measures in patients with chest pain onset greater than 3 hours were associated with a >99% NPV for MI.[8,9,33] These studies used the LOB (3 ng/L) and limit of detection (LOD, 5 ng/L) as cut points, which are concentrations less than the LOQ (Figure 1 in the Supplement). Unfortunately, due to concerns

about measurement imprecision, the FDA does not allow reporting of values below the LOQ,[34] which makes extrapolating these data to the US difficult. Among late presenters (those with chest pain onset > 3 hours), use of the LOQ at arrival for the cutoff yielded a 98.2% NPV for 30-day MACE. These results are consistent with the findings of a sub-analysis of the TRAPID-AMI cohort and a Canadian study, which reported NPVs <99% for MACE at the LOD and LOQ, respectively.[9,35] Our sensitivity analysis of Type 1 and 2 MIs (Tables VIII and IX in the Supplement) suggests that Type 2 MIs, are more frequently missed by low initial hs-cTnT measures. Given that the clinical significance of Type 2 MIs varies and their treatment is based on the underlying cause, the importance of missing Type 2 MI events is unclear. However, many studies suggest that Type 2 MI events are prognostically important.[36]

The hs-cTnT 0/1-h algorithm, which is recommended by the ESC guidelines, has been well validated in Europe for the detection of index MI.[8, 12, 38-41]In the original derivation and validation study by Reichlin et al., the 0/1-h algorithm ruled-out 60% of patients with 100% sensitivity and NPV for MI.[37] This was validated in separate rest-of-world cohorts, demonstrating a 99.1-100% NPV.[15,38–40] On the basis of these data, several US EDs, which were early adopters of hs-cTnT, are currently using protocols based on a 0/1-h algorithm.[12,41] While a small number of patients in the TRAPID-AMI cohort were enrolled in the US, our study represents the first large prospective multisite US examination of a hs-cTnT 0/1-h algorithm. Our results, which demonstrate that the hs-cTnT 0/1-h algorithm had a NPV of 99.0% for index visit MI, are similar to prior studies. This includes a recent analysis of the 0/1-h algorithm using a hs-cTnI assay in the HIGH US cohort.[6]

While prior studies of the 0/1-h algorithm have largely focused on index MI as an outcome, studies of risk stratification algorithms designed to identify ED patients for early discharge (e.g., the HEART Pathway or the Emergency Department Assessment of Chest pain Score [EDACS] accelerated diagnostic protocol) have focused on 30-day MACE or the composite of 30-day cardiac death and MI as outcomes.[42–46] While there is some debate about the acceptable missed 30-day MACE rate, and the importance of coronary revascularization outcomes, Than et al, demonstrated that most ED providers find a NPV of <99% for 30 day MACE to be unacceptable.[47] In our study, the diagnostic performance of the 0/1-h algorithm for 30-day MACE or 30-day cardiac death or MI, NPV was below 99%. Thus, for many ED providers, the hs-cTnT 0/1-h algorithm, when used alone, may not have a sufficient NPV to support early ED discharge. However, the addition of a low-risk HEART score to the rule-out range of the 0/1-h algorithm achieved improved NPV, with a 99.3% NPV for 30-day cardiac death or MI. Our results are similar to a study by Mokhtari et al. which reported a NPV of 97.8% for the hs-cTnT 0/1-h algorithm for 30-day MACE when used alone versus 99.5% when combined with clinical variables (i.e. clinical history and a non-ischemic ECG).[19]

In this cohort the 0/1-h algorithm had a PPV <60% for all outcomes, including a PPV of 55.3% for index MI. These results differ from prior studies in which the PPV for index MI ranged from 63.4-84.0%.[39,40,48–50] Our lower than expected PPV occurred despite inclusion of adjudicated type 2 MIs as part of the index MI outcome definition, which improved PPV. The PPV for index visit type 1 MI was only 26.8%. Furthermore, using the HEART score with the 0/1-h algorithm lowered PPV to <50% for each outcome. The low PPV of the 0/1-h algorithm with or without the HEART score suggest that its use may be associated with over-triage and

over-testing. Higher hs-cTnT cut points and delta values for the 0/1-h algorithm's rule-in range may need to be explored and validated in the US chest pain population to improve PPV.

While an ischemic ECG is well recognized as a predictor of adverse cardiac events, in this analysis, the addition of ischemic ECG changes to hs-cTnT strategies (the 0/1-h algorithm and initial hs-cTnT <LOQ) did not improve diagnostic performance.[11] None of the patients with 30-day MACE who had initial hs-cTnT measures < LOQ or were in the rule-out range of the 0/1-h algorithm had an ischemic ECG as determined by their treating provider. These findings are consistent with a sub-analysis of TRAPID-MI, which found that adding an ischemic ECG to an initial hs-cTnT < 5 ng/L only correctly reclassified two patients with 30-day MACE events as non-low-risk.[9] By contrast, the HEART score, which includes ECG findings in its scoring along with other historical features, was able to improve the diagnostic performance of hs-cTnT strategies in this analysis. Thus, these data suggest that ECGs should be used as part of the assessment of patients with possible ACS within the broader context of the historical and hs-cTn data.

Although it is well described that time of chest pain onset influences the diagnostic performance of hs-cTn cut points,[15–17,51–53] in our cohort these differences were small and non-significant. The combination of a low-risk HEART score and an initial hs-cTnT measure < LOQ yielded high sensitivity and NPV for MACE even among early presenters. Finally, sensitivity analyses testing a variety of assumptions yielded similar diagnostic performance of the LOQ and the 0/1-h algorithm when used with or without clinical variables.

Our study has limitations. Although our study was conducted across eight US EDs, our sites were mostly urban academic medical centers. Thus, our results may not be generalizable to all US ED settings. Furthermore, our cohort had a higher MACE rate than has been reported in

many prior US studies.[42,54] While our lost to follow-up rate was small,[55,56] we were unable to contact <4% (56/1442) of the cohort, which may have caused misclassification and underestimation of MACE. However, a sensitivity analysis imputing events based on patient variables (demographics, risk factors, and hs-cTnT measures) did not substantively change our results (Tables X and XI in the Supplement). This study utilized only the Roche hs-cTnT assay, and results cannot be extrapolated to other hs-cTn assays. Our classification of patients as early or late presenters was susceptible to patient recall bias.[57] In addition, subgroup analysis of early presenters was limited to 516, i.e. 35% of the total population. Thus the confidence intervals for this group are somewhat broader than the overall population. Finally, no patient was managed according to the use of the hs-cTnT assay or the strategies evaluated. Thus, the efficacy and safety of hs-cTnT strategies need to be prospectively evaluated in the setting of implementation into clinical practice in a US population.

Conclusions

In this first multisite prospective US cohort study to evaluate hs-cTnT strategies, our results suggest that use of a single hs-cTnT measure <LOQ alone had insufficient sensitivity and NPV to rule-out 30-day MACE. For 30-day cardiac death and MI, using a single hs-cTnT <LOQ was associated with a NPV of 99%, which is widely acceptable.[28] Substantial improvement was contributed to the addition of a low-risk HEART score to an initial hs-cTnT <LOQ the NPV for 30-day cardiac death or MI rises to 99.7%. In addition, this first, large prospective multisite validation of the hs-cTnT 0/1-h algorithm in the US yielded a NPV below 99% for MACE and cardiac death or MI at 30-days and 99% for index MI. However, when the HEART score is combined with a 0/1 hs-cTnT algorithm, NPV and sensitivity for cardiac events improved to the acceptable range. These data indicate that in a US population of patients with symptoms

concerning for ACS, combining hs-cTnT strategies with a HEART score achieves acceptable performance for the diagnosis of adverse cardiac events.

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Supplemental Materials

Supplemental Tables I - XIII

Supplemental Figure I

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Table 1. STOP CP cohort patient characteristics.

Patient Characteristics	With MACE (n=210)	Without MACE (n=1252)	Total (n=1462)
Age (yrs), mean ± SD	61.4 ± 12.1	57.0 ± 12.9	57.6 ± 12.9
Gender, n (%)			
Female	66 (31.4)	612 (48.9)	678 (46.4)
Race, n (%)			
American Indian/Alaska Native	4 (2.0)	20 (1.6)	24 (1.6)
Asian	2 (1.0)	10 (0.8)	12 (0.8)
Native Hawaiian	0 (0.0)	2 (0.2)	2 (0.1)
Black or African American	64 (30.5)	478 (38.2)	542 (37.1)
White	135 (64.3)	704 (56.2)	839 (57.4)
Other	5 (2.4)	38 (3.0)	43 (2.9)
Ethnicity, n (%)			
Hispanic or Latino	6 (2.9)	55 (4.4)	61 (4.2)
Not Hispanic or Latino	199 (94.8)	1187 (94.8)	1386 (94.8)
Unknown	5 (2.4)	10 (0.8)	15 (1.0)
Risk Factors, n (%)			
Current or History of smoking	117 (55.7)	689 (55)	806 (55.1)
Current or History of Cocaine	30 (14.3)	141 (11.3)	171 (11.7)
Hypertension	161 (76.7)	809 (64.6)	970 (66.3)
Hyperlipidemia	125 (59.5)	567 (45.3)	692 (47.3)
Diabetes	84 (40.0)	347 (27.7)	431 (29.5)
Family history of coronary disease	102 (48.6)	572 (45.7)	674 (46.1)
BMI >30 (kg/m^2)	96 (45.7)	658 (52.6)	754 (51.6)
Prior Coronary Disease	114 (54.3)	359 (28.7)	473 (32.4)
Prior MI	82 (39.0)	236 (18.8)	318 (21.8)
Prior PCI	65 (31.0)	181 (14.5)	246 (16.8)
Prior CABG*	39 (18.6)	66 (5.3)	105 (7.2)
Prior Cerebral Vascular Accident	25 (11.9)	133 (10.6)	158 (10.8)
Prior Peripheral Vascular Disease	21 (10.0)	69 (5.5)	90 (6.2)
Prior End Stage Renal Disease	19 (9.0)	54 (4.3)	73 (5.0)
Prior Congestive Heart Failure	68 (32.4)	238 (19.0)	306 (20.9)
Chest Pain at ED Arrival, n (%)*	124 (59.3)	889 (71.0)	1013 (69.6)
Chest Pain Onset, n (%)*			
≤ 3 Hours from Arrival (Early)	79 (37.8)	437 (35.1)	516 (35.5)
> 3 Hours from Arrival (Late)	130 (62.2)	808 (64.9)	938 (64.5)
Electrocardiogram at Arrival, n (%)			
Ischemic ECG	26 (12.4)	65 (5.2)	91 (6.2)
Non-Ischemic ECG	184 (87.6)	1187 (94.8)	1371 (93.8)
HEART Score, median (IQR)	6 (5 - 7)	4 (3 - 5)	4 (3 - 5)
Time from Arrival to Initial Sample (min), median (IQR)	78 (62 - 97)	82 (63 - 107)	82 (63 - 105)

Initial Study hs-cTnT Sample (ng/L), median (IQR)	44.6 (22.4 - 104.7)	7.88 (4.61 - 15.4)	9.22 (4.91 - 21.2)
Creatinine at Index Visit (mg/dL), median (IQR)	1.01 (0.84 - 1.42)	0.90 (0.76 - 1.11)	0.92 (0.77 - 1.13)

BMI= body mass index, CABG= coronary artery bypass graft, ED = emergency department, ECG = electrocardiogram, hs-cTn = high-sensitivty cardiac troponin, IQR = interquartile range, MACE= major adverse cardiac event, MI= myocardial infarction, PCI = percutaneous coronary intervention, SD= standard deviation

* Missing responses for Prior CABG (n=1), Chest Pain at ED Arrival (n=6), and Chest Pain Onset (n=8).

Table 2. Test characteristics for 30-day MACE, 30-day cardiac death and MI and index-visit MI for risk stratification strategies using the initial hs-cTnT below the LOQ alone or in combination with ECG interpretation or HEART score.

Risk Stratification Strategy	**Sensitivity** (95% CI)	**Specificity** (95% CI)	**PPV** (95% CI)	**NPV** (95% CI)	**Efficacy** (95% CI)
30-Day MACE					
hs-cTnT <6 ng/L	96.2% (92.6, 98.3)	37.7% (35.0, 40.4)	20.6% (18.1, 23.3)	98.3% (96.7, 99.3)	32.8% (30.4, 35.3)
hs-cTnT <6 ng/L & non-ischemic ECG	96.2% (92.6, 98.3)	36.6% (34.0, 39.4)	20.3% (17.9, 23.0)	98.3% (96.6, 99.3)	31.9% (29.5, 34.4)
hs-cTnT <6 ng/L & HEART score 0-3	98.6% (95.9, 99.7)	37.4% (34.7, 40.2)	20.5% (18.0, 23.2)	99.0% (97.0, 99.8)	20.1% (18.1, 22.3)
hs-cTnT <6 ng/L & HEART score 0-3 & non-ischemic ECG	98.6% (95.9, 99.7)	36.5% (33.8, 39.2)	20.3% (17.8, 22.9)	99.0% (97.0, 99.8)	20.1% (18.0, 22.2)
30-Day Cardiac Death and MI					
hs-cTnT <6 ng/L	97.4% (94.0, 99.1)	37.3% (34.7, 40.0)	18.9% (16.5, 21.4)	99.0% (97.6, 99.7)	32.8% (30.4, 35.3)
hs-cTnT <6 ng/L & non-ischemic ECG	97.4% (94.0, 99.1)	36.3% (33.6, 39.0)	18.6% (16.2, 21.2)	98.9% (97.5, 99.7)	31.9% (29.5, 34.4)
hs-cTnT <6 ng/L & HEART score 0-3	99.5% (97.1, 100.0)	37.1% (34.4, 39.8)	18.8% (16.4, 21.4)	99.7% (98.1, 100.0)	20.1% (18.1, 22.3)
hs-cTnT <6 ng/L & HEART score 0-3 & non-ischemic ECG	99.5% (97.1, 100.0)	36.1% (33.5, 38.9)	18.6% (16.2, 21.1)	99.7% (98.1, 100.0)	20.1% (18.0, 22.2)
Index-visit MI					
hs-cTnT <6 ng/L	97.6% (94.1, 99.4)	36.8% (34.2, 39.5)	16.8% (14.5, 19.3)	99.2% (97.9, 99.8)	32.8% (30.4, 35.3)
hs-cTnT <6 ng/L & non-ischemic ECG	97.6% (94.1, 99.4)	35.8% (33.2, 38.5)	16.6% (14.3, 19.1)	99.1% (97.8, 99.8)	31.9% (29.5, 34.4)
hs-cTnT <6 ng/L & HEART score 0-3	99.4% (96.7, 100.0)	36.6% (33.9, 39.3)	16.8% (14.5, 19.3)	99.7% (98.1, 100.0)	20.1% (18.1, 22.3)
hs-cTnT <6 ng/L & HEART score 0-3 & non-ischemic ECG	99.4% (96.7, 100.0)	35.6% (33.0, 38.3)	16.6% (14.3, 19.0)	99.7% (98.1, 100.0)	20.1% (18.0, 22.2)

ECG = electrocardiogram, hs-cTn = high-sensitivty cardiac troponin, LOQ = limit of quantification, MACE= major adverse cardiac event, MI= myocardial infarction, NPV = negative predictive value, PPV = positive predictive value

Table 3. Test characteristics for 30-day MACE, 30-day cardiac death and MI, and index visit MI for the 0/1-h algorithm alone or in combination with ECG interpretation or HEART score.

Risk Stratification Strategy	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Efficacy (95% CI)
30-Day MACE					
0/1-h	88.7% (83.5, 92.7)	93.6% (92.0, 94.9)	58.4% (51.1, 65.5)	97.2% (95.9, 98.2)	57.8% (55.2, 60.3)
0/1-h & non-ischemic ECG	88.7% (83.5, 92.7)	89.0% (87.1, 90.7)	47.3% (41.0, 53.6)	97.1% (95.7, 98.2)	55.7% (53.1, 58.3)
0/1-h & HEART score 0-3	96.6% (93.0, 98.6)	88.9% (87.0, 90.6)	48.7% (42.5, 54.9)	98.4% (96.8, 99.4)	30.8% (28.5, 33.3)
0/1-h & HEART score 0-3 & non-ischemic ECG	96.6% (93.0, 98.6)	85.5% (83.4, 87.4)	42.6% (37.0, 48.3)	98.4% (96.7, 99.4)	30.7% (28.3, 33.2)
30-Day Cardiac Death and MI					
0/1-h	92.9% (88.2, 96.2)	93.7% (92.2, 95.0)	58.4% (51.1, 65.5)	98.4% (97.3, 99.2)	57.8% (55.2, 60.3)
0/1-h & non-ischemic ECG	92.9% (88.2, 96.2)	89.0% (87.1, 90.7)	46.5% (40.3, 52.8)	98.4% (97.2, 99.1)	55.7% (53.1, 58.3)
0/1-h & HEART score 0-3	98.4 (95.3, 99.7)	88.9% (87.1, 90.6)	47.9% (41.8, 54.1)	99.3% (98.0, 99.9)	30.8% (28.5, 33.3)
0/1-h & HEART score 0-3 & non-ischemic ECG	98.4 (95.3, 99.7)	85.5% (83.4, 87.4)	41.6% (36.1, 47.3)	99.3% (98.0, 99.9)	30.7% (28.3, 33.2)
Index Visit MI					
0/1-h	95.1% (90.6, 97.9)	93.3% (91.8, 94.6)	55.3% (47.9, 62.5)	99.0% (98.1, 99.6)	57.8% (55.2, 60.3)
0/1-h & non-ischemic ECG	95.1% (90.6, 97.9)	88.6% (86.7, 90.3)	43.8% (37.6, 50.1)	99.0% (98.0, 99.6)	55.7% (53.1, 58.3)
0/1-h & HEART score 0-3	98.8% (95.7, 99.9)	88.5% (86.7, 90.2)	45.3% (39.2, 51.5)	99.5% (98.4, 99.9)	30.8% (28.5, 33.3)
0/1-h & HEART score 0-3 & non-ischemic ECG	98.8% (95.7, 99.9)	85.2% (83.1, 87.1)	39.4% (33.9, 5.0)	99.5% (98.4, 99.9)	30.7% (28.3, 33.2)

ECG = electrocardiogram, hs-cTn = high-sensitivty cardiac troponin, LOQ = limit of quantification, MACE= major adverse cardiac event, MI= myocardial infarction, NPV = negative predictive value, PPV = positive predictive value

Table 4. Test characteristics for 30-day MACE, 30-day cardiac death and MI and index-visit MI among early presenters for risk stratification strategies using the initial hs-cTnT below the LOQ alone or in combination with ECG interpretation or HEART score.

Risk Stratification Strategy	**Sensitivity** (95% CI)	**Specificity** (95% CI)	**PPV** (95% CI)	**NPV** (95% CI)	**Efficacy** (95% CI)
30-Day MACE					
hs-cTnT <6 ng/L	97.5% (91.2, 99.7)	33.7% (29.3, 38.4)	21.2% (17.1, 25.7)	98.6% (95.2, 99.8)	28.9% (25.0, 33.0)
hs-cTnT <6 ng/L & non-ischemic ECG	97.5% (91.2, 99.7)	33.0% (28.6, 37.7)	21.0% (16.9, 25.5)	98.6% (95.1, 99.8)	28.3% (24.5, 32.4)
hs-cTnT <6 ng/L & HEART score 0-3	100.0% (96.3, 100.0)	33.5% (29.1, 38.1)	21.1% (17.0, 25.6)	100.0% (97.2, 100.0)	20.5% (17.1, 24.3)
hs-cTnT <6 ng/L & HEART score 0-3 & non-ischemic ECG	100.0% (96.3, 100.0)	32.8% (28.4, 37.4)	20.9% (16.9, 25.4)	100.0% (97.2, 100.0)	20.3% (16.9, 24.1)
30-Day Cardiac Death and MI					
hs-cTnT <6 ng/L	97.3% (90.6, 99.7)	33.3% (28.9, 38.0)	19.8% (15.8, 24.2)	98.6% (95.1, 99.8)	28.9% (25.0, 33.0)
hs-cTnT <6 ng/L & non-ischemic ECG	97.3% (90.6, 99.7)	32.6% (28.3, 37.3)	19.6% (15.7, 24.1)	98.6% (95.1, 99.8)	28.3% (24.5, 32.4)
hs-cTnT <6 ng/L & HEART score 0-3	100.0% (96.0, 100.0)	33.1% (28.7, 37.7)	19.7% (15.8, 24.2)	100.0% (97.2, 100.0)	20.5% (17.1, 24.3)
hs-cTnT <6 ng/L & HEART score 0-3 & non-ischemic ECG	100.0% (96.0, 100.0)	32.4% (28.1, 37.0)	19.6% (15.6, 24.0)	100.0% (97.2, 100.0)	20.3% (16.9, 24.1)
Index-visit MI					
hs-cTnT <6 ng/L	98.4% (91.3, 100.0)	32.7% (28.3, 37.2)	16.8% (13.1, 21.0)	99.3% (96.3, 100.0)	28.9% (25.0, 33.0)
hs-cTnT <6 ng/L & non-ischemic ECG	98.4% (91.3, 100.0)	32.0% (27.7, 36.5)	16.6% (13.0, 20.8)	99.3% (96.3, 100.0)	28.3% (24.5, 32.4)
hs-cTnT <6 ng/L & HEART score 0-3	100.0% (95.3, 100.0)	32.4% (28.1, 37.0)	16.7% (13.0, 20.9)	100.0% (97.2, 100.0)	20.5% (17.1, 24.3)
hs-cTnT <6 ng/L & HEART score 0-3 & non-ischemic ECG	100.0% (95.3, 100.0)	31.8% (27.5, 36.3)	16.6% (12.9, 20.8)	100.0% (97.2, 100.0)	20.3% (16.9, 24.1)

ECG = electrocardiogram, hs-cTn = high-sensitivty cardiac troponin, LOQ = limit of quantification, MACE= major adverse cardiac event, MI= myocardial infarction, NPV = negative predictive value, PPV = positive predictive value

Table 5. Test characteristics for 30-day MACE, 30-day cardiac death and MI, and index visit MI among early presenters for the 0/1-h algorithm alone or in combination with ECG interpretation or HEART score.

Risk Stratification Strategy	**Sensitivity** (95% CI)	**Specificity** (95% CI)	**PPV** (95% CI)	**NPV** (95% CI)	**Efficacy** (95% CI)
30-Day MACE					
0/1-h	87.8% (78.2, 94.3)	93.0% (90.1, 95.2)	58.9% (46.8, 70.3)	96.8% (93.9, 98.5)	55.3% (50.8, 59.7)
0/1-h & non-ischemic ECG	87.8% (78.2, 94.3)	88.8% (85.4, 91.6)	48.4% (37.9, 59.0)	96.6% (93.7, 98.4)	53.3% (48.8, 57.7)
0/1-h & HEART score 0-3	95.9% (88.6, 99.2)	88.8% (85.4, 91.6)	50.0% (39.6, 60.4)	98.2% (94.9, 99.6)	33.7% (29.6, 38.1)
0/1-h & HEART score 0-3 & non-ischemic ECG	95.9% (88.6, 99.2)	85.7% (82.0, 88.9)	44.5% (35.1, 54.3)	98.2% (94.9, 99.6)	33.5% (29.4, 37.9)
30-Day Cardiac Death and MI					
0/1-h	91.3% (82.0, 96.7)	93.1% (90.2, 95.3)	58.9% (47.8, 70.3)	97.8% (95.3, 99.2)	55.3% (50.8,59.7)
0/1-h & non-ischemic ECG	91.3% (82.0, 96.7)	88.9% (85.5, 91.7)	48.4% (37.9, 59.0)	97.8% (95.2, 99.2)	53.3% (48.8, 57.7)
0/1-h & HEART score 0-3	97.1% (89.9, 99.6)	88.9% (85.5, 91.7)	50.0% (39.6, 60.4)	98.8% (95.8, 99.9)	33.7% (29.6, 38.1)
0/1-h & HEART score 0-3 & non-ischemic ECG	97.1% (89.9, 99.6)	85.9% (82.2, 89.0)	44.5% (35.1, 54.3)	98.8% (95.8, 99.9)	33.5% (29.4, 37.9)
Index Visit MI					
0/1-h	93.2% (83.5, 98.1)	92.3% (89.4, 94.6)	53.4% (41.4, 65.2)	98.6% (96.3, 99.6)	55.3% (50.8, 59.7)
0/1-h & non-ischemic ECG	93.2% (83.5, 98.1)	88.2% (84.9, 91.1)	44.1% (33.8, 54.8)	98.5% (96.2, 99.6)	53.3% (48.8, 57.7)
0/1-h & HEART score 0-3	98.3% (90.9, 100.0)	88.2% (84.9, 91.1)	45.8% (35.6, 56.3)	99.4% (96.7, 100.0)	33.7% (29.6, 38.1)
0/1-h & HEART score 0-3 & non-ischemic ECG	98.3% (90.9, 100.0)	85.3% (81.6, 88.5)	40.9% (31.6, 50.7)	99.4% (96.7, 100.0)	33.5% (29.4, 37.9)

ECG = electrocardiogram, hs-cTn = high-sensitivty cardiac troponin, LOQ = limit of quantification, MACE= major adverse cardiac event, MI= myocardial infarction, NPV = negative predictive value, PPV = positive predictive value

Figure Legends

Figure 1. Flow diagram of study inclusion and adjudication

*Cardiac-related or uncertain death is not mutually exclusive from other adjudicated outcomes

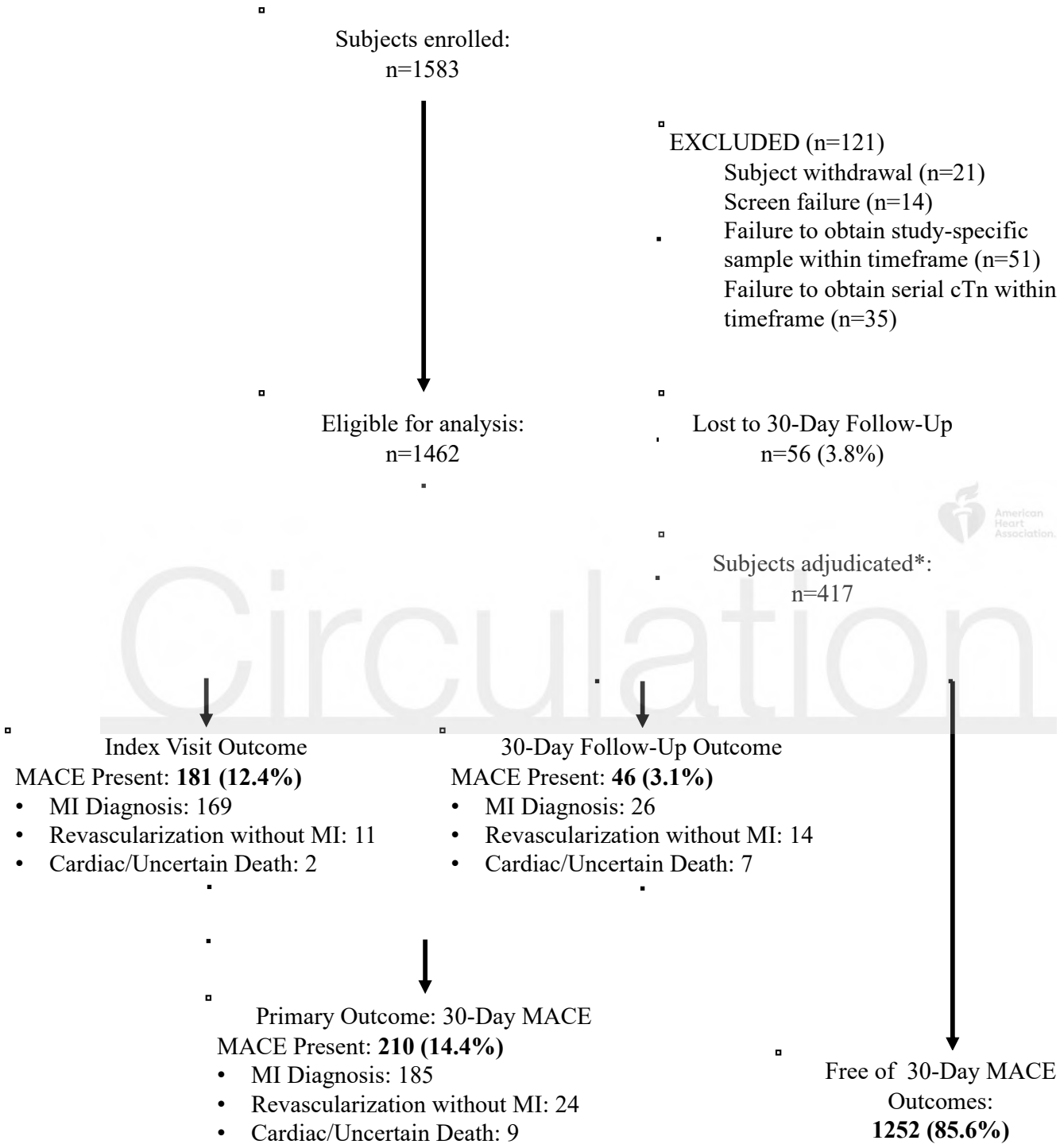
cTn = cardiac troponin, MACE= major adverse cardiac event, MI= myocardial infarction

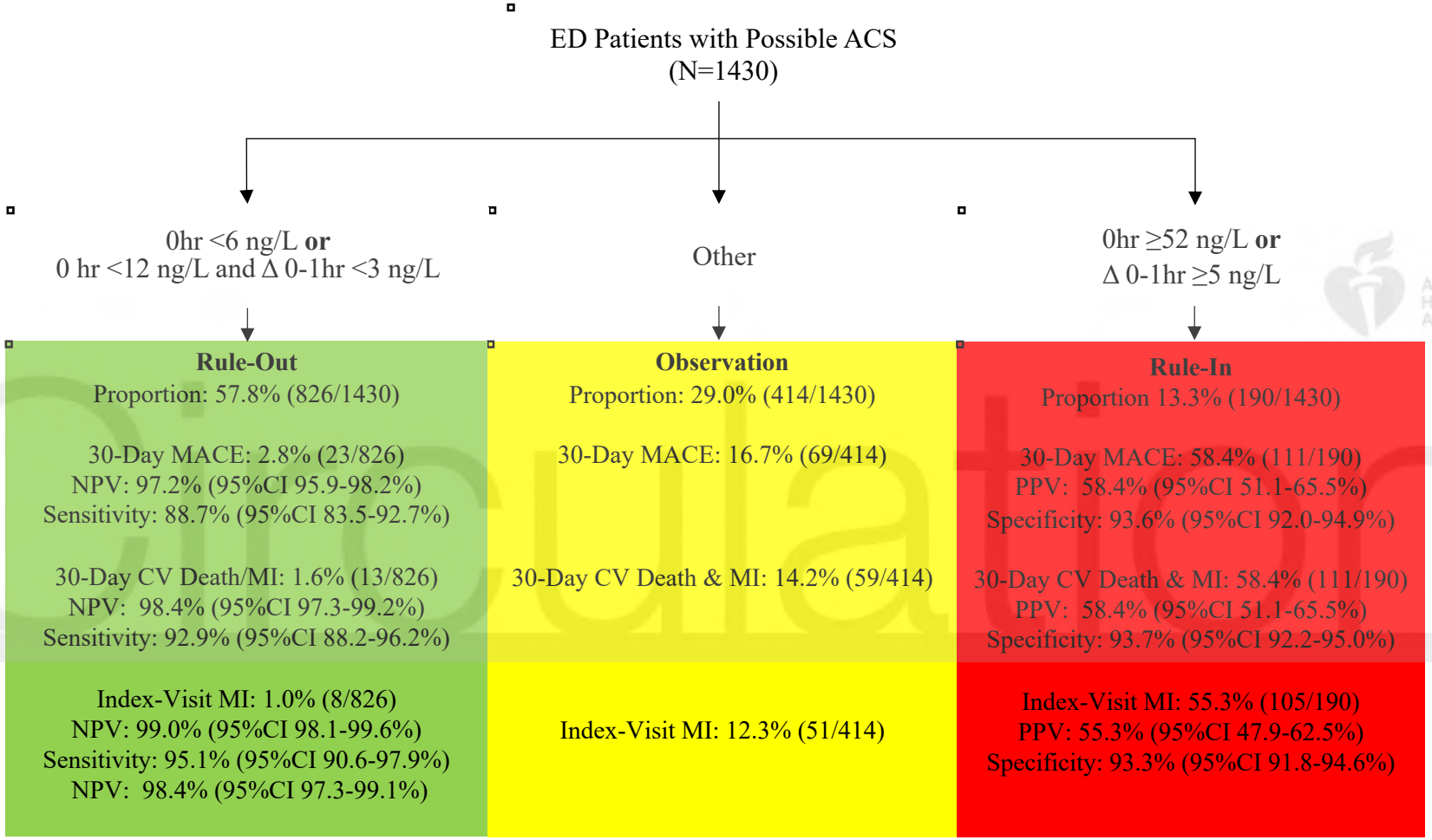
Figure 2. The 0/1-h high-sensitivity troponin algorithm for 30 Day MACE, cardiac death or MI, and index-visit MI

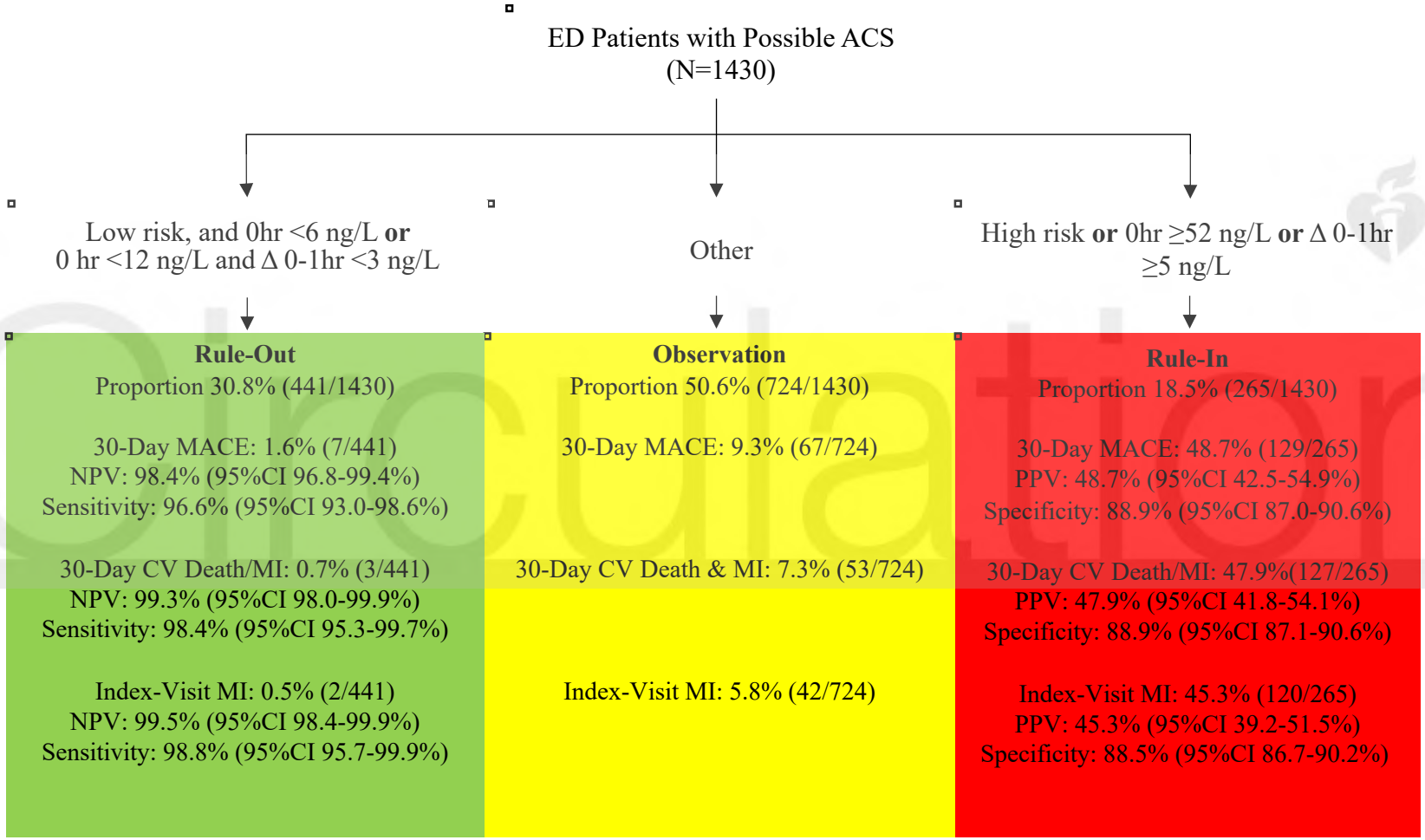
ACS = acute coronary syndrome, CV = cardiovascular, ED = emergency department, MACE= major adverse cardiac event, MI= myocardial infarction, NPV = negative predictive value, PPV = positive predictive value

Figure 3. The 0/1-h high-sensitivity troponin algorithm combined with the HEART score for 30-day MACE, cardiac death or MI, and index-visit MI

ACS = acute coronary syndrome, CV = cardiovascular, ED = emergency department, MACE= major adverse cardiac event, MI= myocardial infarction, NPV = negative predictive value, PPV = positive predictive value


Subjects enrolled:
n=1583
EXCLUDED (n=121)
Subject withdrawal (n=21)
Screen failure (n=14)
Failure to obtain study-specific sample within timeframe (n=51)
Failure to obtain serial cTn within timeframe (n=35)
Eligible for analysis:
n=1462
Lost to 30-Day Follow-Up
n=56 (3.8%)
Subjects adjudicated*:
n=417
Index Visit Outcome
MACE Present: 181 (12.4%)
• MI Diagnosis: 169
• Revascularization without MI: 11
• Cardiac/Uncertain Death: 2
30-Day Follow-Up Outcome
MACE Present: 46 (3.1%)
• MI Diagnosis: 26
• Revascularization without MI: 14
• Cardiac/Uncertain Death: 7
Primary Outcome: 30-Day MACE
MACE Present: 210 (14.4%)
• MI Diagnosis: 185
• Revascularization without MI: 24
• Cardiac/Uncertain Death: 9
Free of 30-Day MACE Outcomes:
1252 (85.6%)


ED Patients with Possible ACS
(N=1430)
0hr <6 ng/L **or**
0 hr <12 ng/L and Δ 0-1hr <3 ng/L
Other
0hr ≥52 ng/L **or**
Δ 0-1hr ≥5 ng/L
Rule-Out
Proportion: 57.8% (826/1430)
30-Day MACE: 2.8% (23/826)
NPV: 97.2% (95%CI 95.9-98.2%)
Sensitivity: 88.7% (95%CI 83.5-92.7%)
30-Day CV Death/MI: 1.6% (13/826)
NPV: 98.4% (95%CI 97.3-99.2%)
Sensitivity: 92.9% (95%CI 88.2-96.2%)
Index-Visit MI: 1.0% (8/826)
NPV: 99.0% (95%CI 98.1-99.6%)
Sensitivity: 95.1% (95%CI 90.6-97.9%)
NPV: 98.4% (95%CI 97.3-99.1%)
Observation
Proportion: 29.0% (414/1430)
30-Day MACE: 16.7% (69/414)
30-Day CV Death & MI: 14.2% (59/414)
Index-Visit MI: 12.3% (51/414)
Rule-In
Proportion 13.3% (190/1430)
30-Day MACE: 58.4% (111/190)
PPV: 58.4% (95%CI 51.1-65.5%)
Specificity: 93.6% (95%CI 92.0-94.9%)
30-Day CV Death & MI: 58.4% (111/190)
PPV: 58.4% (95%CI 51.1-65.5%)
Specificity: 93.7% (95%CI 92.2-95.0%)
Index-Visit MI: 55.3% (105/190)
PPV: 55.3% (95%CI 47.9-62.5%)
Specificity: 93.3% (95%CI 91.8-94.6%)


ED Patients with Possible ACS
(N=1430)
Low risk, and 0hr <6 ng/L or
0 hr <12 ng/L and Δ 0-1hr <3 ng/L
Other
High risk or 0hr ≥52 ng/L or Δ 0-1hr
≥5 ng/L
Rule-Out
Proportion 30.8% (441/1430)
30-Day MACE: 1.6% (7/441)
NPV: 98.4% (95%CI 96.8-99.4%)
Sensitivity: 96.6% (95%CI 93.0-98.6%)
30-Day CV Death/MI: 0.7% (3/441)
NPV: 99.3% (95%CI 98.0-99.9%)
Sensitivity: 98.4% (95%CI 95.3-99.7%)
Index-Visit MI: 0.5% (2/441)
NPV: 99.5% (95%CI 98.4-99.9%)
Sensitivity: 98.8% (95%CI 95.7-99.9%)
Observation
Proportion 50.6% (724/1430)
30-Day MACE: 9.3% (67/724)
30-Day CV Death & MI: 7.3% (53/724)
Index-Visit MI: 5.8% (42/724)
Rule-In
Proportion 18.5% (265/1430)
30-Day MACE: 48.7% (129/265)
PPV: 48.7% (95%CI 42.5-54.9%)
Specificity: 88.9% (95%CI 87.0-90.6%)
30-Day CV Death/MI: 47.9%(127/265)
PPV: 47.9% (95%CI 41.8-54.1%)
Specificity: 88.9% (95%CI 87.1-90.6%)
Index-Visit MI: 45.3% (120/265)
PPV: 45.3% (95%CI 39.2-51.5%)
Specificity: 88.5% (95%CI 86.7-90.2%)