Evaluating Rapid Rule-out of Acute Myocardial Infarction Using a High-Sensitivity Cardiac Troponin I Assay at Presentation

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BACKGROUND: Low concentrations of cardiac troponin (cTn) have been recommended for rapid rule-out of acute myocardial infarction (AMI). We examined the Beckman Coulter Access high-sensitivity cardiac troponin I (hs-cTnI) assay to identify a single test threshold that can safely rule out AMI.

METHODS: This analysis used stored samples collected in 2 prospective observational studies. In all, 1871 patients presenting to a tertiary emergency department with symptoms of acute coronary syndrome had blood taken for measurement of cTnI on presentation. The endpoint was type 1 myocardial infarction (T1MI). Sensitivity and negative predictive value (NPV) were calculated for hs-cTnI values below the 99th percentile.

RESULTS: Ninety-eight patients had T1MI (5.2%), and 638 (34.1%) patients had an hs-cTnI <2 ng/L (limit of detection), with sensitivity of 99.0% (95% CI, 94.4%–100%) and NPV of 99.8% (95% CI, 99.1%–100%). No hs-cTnI value above a concentration of 2 ng/L achieved sensitivity of 99%. However, an NPV of 99.5% was achieved at values <6 ng/L. A cutoff <6 ng/L enabled 1475 (78.8%) patients to be ruled out on presentation with sensitivity of 93.9% (95% CI, 87.1%–97.7%).

CONCLUSIONS: A single baseline cTn <2 ng/L measured with the Access hs-cTnI assay performed well for rule-out of AMI. This cutoff concentration identified 99% of patients with AMI and could reduce the number of patients requiring lengthy assessment. A cutoff of <6 ng/L yielded a high NPV but missed more cases of AMI than would be acceptable to clinicians.

The assessment of patients with potential acute coronary syndrome (ACS)[6] incorporates clinical history, electrocardiograms (ECGs), and cardiac troponin (cTn) testing *(1, 2)*. It is commonly thought that previous generations of cTn assays have low diagnostic sensitivity for acute myocardial infarction (AMI) on presentation. Consequently, the diagnosis of AMI requires serial sampling over 6 to 12 h *(1, 2)*. This process presents a substantial economic burden to the healthcare system *(3)* and is incongruent with the need to rapidly and safely assess patients in overcrowded emergency departments (EDs).

cTn measured with newer generations of analytically highly sensitive cardiac troponin (hs-cTn) assays has been investigated in accelerated discharge protocols on the assumption that the newer assays have an improved ability to detect and quantify cardiomyocyte injury more quickly than previous generations of cTn assays *(4)*. Using such assays, more rapid rule-out strategies over 1 to 3 h have been studied *(5–7)* and recently endorsed by the European Society of Cardiology (ESC) 2015 guidelines *(8)*. Rapid rule-out strategies using a single baseline hs-cTn have also been investigated *(9–16)*. With the Abbott hs-cTnI and Roche hs-cTnT assays, very low cTn concentrations around their respective limits of detection (LoD) have high negative predictive values (NPVs) (>99%) and moderate to high diagnostic sensitivities (>90%) for AMI *(9–16)*. However, there is wide variability in the detection capabilities of hs-cTn assays from different manufacturers *(17)*, and separate assessment of clinical performance for each assay is critical.

Beckman Coulter has released an hs-cTnI assay (Access hs-cTnI), but to date, information on the clinical performance of this assay is limited. We evaluated the diagnostic performance of a single Access hs-cTnI measurement at presentation for early rule-out of AMI. We

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[6] Nonstandard abbreviations: ACS, acute coronary syndrome; ECG, electrocardiogram; cTn, cardiac troponin; AMI, acute myocardial infarction; ED, emergency department; hs-cTn, cardiac troponin measured with a highly sensitive assay; ESC, European Society of Cardiology; LoD, limit of detection; NPV, negative predictive value; STEMI, ST-segment elevation myocardial infarction; T1MI, type 1 myocardial infarction; MACE, major adverse cardiac events; T2MI, type 2 myocardial infarction.

examined a range of presentation hs-cTnI values to identify a threshold that can be safely used to rule out AMI in patients presenting to the ED for investigation of potential ACS. We hypothesized that an hs-cTnI value below the LoD would have high sensitivity (>99%) for AMI.

Materials and Methods

STUDY DESIGN AND SETTING

This analysis used stored samples and data collected from 2 prospective studies *(18, 19)*. The studies were conducted within the same tertiary hospital in Australia, and results of the primary studies have been reported previously. The first was the Australian component of the ADAPT trial, an observational study of 986 patients presenting to the ED between November 2008 and February 2011 *(18)*. The second was an intervention trial including 1366 patients between February 2011 and March 2014 *(19)*. The study protocols were approved by the Human Research and Ethics committee (HREC2008/101 and HREC/10/QRBW/403) and complied with the Declaration of Helsinki. The evaluation of new biomarkers was included as part of the protocol for both original studies. However, the hs-cTnI concentrations were measured after completion of the study.

STUDY POPULATION

Eligible patients were recruited if they were ≥18 years of age, had ≥5 min of chest pain consistent with ACS, were undergoing investigation for potential ACS, and had provided informed consent. Pain consistent with ACS was defined using the American Heart Association definitions, including acute chest, epigastric, neck, jaw, or arm pain, or discomfort or pressure without a clear noncardiac source *(20)*. Exclusion criteria were a clear alternative cause for the suspected symptoms other than ACS, inability or unwillingness to provide informed consent, recruitment was considered inappropriate (e.g., palliative treatment), pregnancy, previous recruitment to the study within 45 days, interhospital transfer, or inability to be contacted after discharge (e.g., homeless). Patients were also excluded from this study if they met the criteria for ST-segment elevation myocardial infarction (STEMI) on presentation. Such patients are emergently referred for revascularization and do not undergo investigation for ACS in the ED. Eligible patients were recruited consecutively during working hours (8 AM to 5 PM).

All patients in the first study (the observational study) were treated according to standard care, which included ECG and cTnI measurements at presentation, followed by troponin measurements 6 h later (93.4% of all patients). A subset of patients in the second study (the intervention study) were deemed suitable for an accelerated assessment process where 0- and 2-h troponin tests were used rather than 0- and 6-h tests. Such patients included those for whom the clinician was comfortable with accelerated testing and the following features were absent: (*a*) ECG changes, (*b*) hemodynamic compromise, (*c*) syncope, or (*d*) previous percutaneous coronary intervention or coronary artery bypass grafting. All patients not eligible for accelerated testing underwent standard care including 0- and 6-h biomarkers.

METHODS OF MEASUREMENT

Research nurses collected data from patients using standardized reporting guidelines *(21)*. Baseline characteristics, past medical history, risk factors, and current medications were gathered directly from the patient. If the patient was unsure about an answer, a "no" response was recorded unless patients were taking a medication for these conditions.

ECGs and cTnI samples were taken on presentation (0 h) and 2 h later. Blood samples were collected in EDTA tubes, centrifuged, and stored at −80 °C. These plasma samples were later analyzed in a blinded fashion with the Beckman Coulter Access hs-cTnI assay on a DxI 600 analyzer (Beckman Coulter). The manufacturer claims a 99th population percentile concentration of 17.5 ng/L and an LoD of 2.3 ng/L. These values were rounded to 18 and 2, respectively, for the current analysis. Local laboratory evaluation reported an LoD of 1.5 ng/L. Intermediate precision (CV) determined over 21 days with 1 reagent lot was <10% for serum pools at a concentration ≥2.9 ng/L. At a concentration of 2.9 ng/L, the 95% CI was 2.3 to 3.4 ng/L.

OUTCOMES

The primary endpoint was type 1 myocardial infarction (T1MI) during initial hospitalization. This included patients with non-STEMI, STEMI (developing after presentation), or patients who died of a cardiac cause before hospital discharge. Local cardiologists performed adjudication for T1MI using the clinical record, ECGs, troponin results, and all subsequent investigations from standard care. This adjudication was conducted specifically for research and was not part of clinical care. A second cardiologist conducted a blind review of all patients who received a cardiovascular endpoint and 10% of cases with a noncardiovascular endpoint. In cases of disagreement, endpoints were agreed by consensus between the 2 cardiologists and an emergency physician. Cardiologists were blinded to the hs-cTnI results during endpoint adjudication. Diagnosis of T1MI was made when there was evidence of myocardial necrosis and ischemia *(1, 22)*. Evidence of ischemia could include ECG or positive imaging results from exercise tolerance testing, myocardial perfusion scan, stress echocardiography, or coronary angiography. Necrosis was diagnosed according to an increase or decrease in cTn concentration,

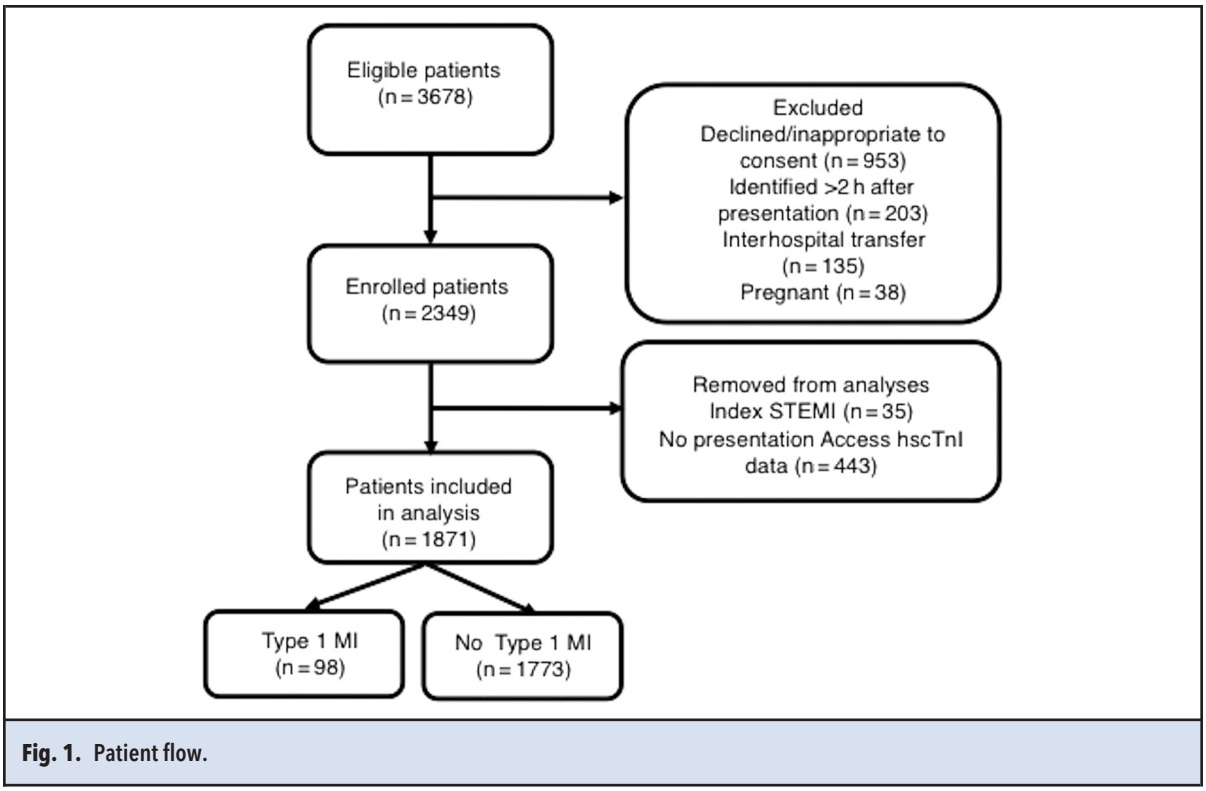

Fig. 1. Patient flow.

with at least 1 value above the 99th percentile of the healthy reference population. The troponin value used to adjudicate patient outcomes was the Beckman Coulter Enhanced AccuTnI assay, which was in routine use at the time. This assay is not regarded as an hs-cTn assay and has an LoD of 0.01 μg/L, a 99th percentile of 0.04 μg/L, and imprecision of 14% at the 99th percentile. In the observational study, 0- and 6-h troponins were used for endpoint adjudication. In the intervention study, all available troponin measurements were used. For both studies, a cTnI above the 99th percentile of a healthy reference population was used as the clinical cutoff in accordance with international guidelines *(1, 22)*.

Secondary outcomes included index AMI, 30-day T1MI, 30-day major adverse cardiac events (MACE), and 1-year mortality. Index AMI included T1MI and type 2 myocardial infarction (T2MI). Assessment for T2MI was not included in the first stage of adjudication, as this category of AMI was included in the universal definition after the protocol for the first study was developed. Thus, readjudication for T2MI occurred at a later stage. This readjudication was conducted for all patients with a sensitive troponin above the 99th percentile, including those previously diagnosed with T1MI and those diagnosed with other cardiovascular complaints. One senior emergency physician and 1 senior cardiologist conducted readjudication for T2MI. These individuals conducted separate blinded adjudication. Agreement was high ($\kappa = 0.94$; 95% CI, 0.90–0.99), and in instances of disagreement, the endpoint was determined by consensus. The definition of T2MI was determined according to the 2012 Universal Definition of Myocardial Infarction *(1)*. Clinical notes, troponin concentrations, and results of investigations up to 30 days from presentation were evaluated for all patients with increased troponin values. T2MIs were identified as a rise or fall in troponin above the 99% upper reference limit when a condition other than atherothrombosis contributed to an imbalance between myocardial oxygen supply and/or demand *(1)*. Cases of coronary spasm were diagnosed following confirmation from angiography. Underlying coronary artery disease was not required for a diagnosis of T2MI. If the troponin concentration was greater than the reference threshold without evidence of a supply/demand imbalance or atherothrombosis, the patient was considered to have another cause of myocardial injury (e.g., myocarditis).

Thirty-day MACE included patients with non-STEMI, STEMI (developing after presentation), emergency or urgent revascularization, and patients who died of a cardiovascular cause within 30 days of their presentation. All-cause mortality was assessed up to 1 year. This endpoint was available only for those patients who consented to longer-term follow-up (n = 1520). Mortality data were obtained from the national death registry, a database of all deaths occurring within Australia.

Table 1. Baseline characteristics of the sample.

Characteristic	All patients (n = 1871)
Mean age (SD)	52.9 (13.9)
Mean age, males (SD)	51.5 (14.0)
Mean age, females (SD)	54.9 (13.5)
Male sex, n (%)	1122 (60.0)
Median time to presentation, h (IQR)	3.6 (1.5–15.5)
Median time from presentation to first troponin test, h (IQR)	0.4 (0.3–0.6)
Early presenters (presentation ≤1 h), n (%)	253 (13.6)
Risk factors	
Hypertension, n (%)	823 (44.0)
Dyslipidemia, n (%)	792 (42.3)
Diabetes, n (%)	240 (12.8)
Family history of coronary artery disease, n (%)	761 (40.7)
Current or recent smoking, n (%)	520 (27.8)
Cardiovascular history	
Previous myocardial infarction, n (%)	262 (14.0)
Previous coronary artery bypass graft, n (%)	96 (5.1)
Previous angioplasty, n (%)	164 (8.8)
Previous stroke, n (%)	113 (6.0)
Previous congestive heart failure, n (%)	49 (2.6)

IQR, interquartile range.

STATISTICAL ANALYSIS

We hypothesized that the LoD would have sensitivity of >99% for AMI. Ninety-six patients with AMI were required to detect this level of sensitivity with 2% precision and confidence level of 95%. Data were analyzed using Stata (version 14; Statacorp). Baseline characteristics of the sample were reported using standard descriptive statistics. It is common practice for laboratories to round troponin values before reporting *(23)*. As such, a 99th percentile of 18 ng/L and LoD of <2 ng/L were used. hs-cTnI values <2 ng/L were considered below the LoD. Instrument results ≥2.0 ng/L were rounded to the nearest whole number. The sensitivity and NPV for T1MI (primary endpoint) and the secondary endpoints (T1MI and T2MI, 30-day T1MI, and 30-day MACE) were calculated for values <2 ng/L and then for each rounded troponin value below the 99th percentile. Exact (Clopper–Pearson) CIs were calculated, as these have more accurate coverage probability than alternative commonly used approaches (e.g., Wald and bootstrapping) across a range of proportions *(24)*. This study sought to identify a safe threshold that could be used to rule out AMI in patients on presentation to the ED. Thus, the diagnostic accuracy statistics were compared against 2 possible safe thresholds used in the literature. The first is a threshold that would maintain a minimum sensitivity of 99%, a value deemed appropriate by emergency physicians *(25)*. The second is an NPV of 99.5% in line with previous research *(10)*.

Cox proportional hazards regression was conducted to identify the relationship between low-concentration troponin values and all-cause mortality. Troponin was initially entered as a continuous variable, but residual analyses demonstrated a nonlinear relationship between troponin values and mortality. Nonlinearity was addressed by fitting fractional polynomials (see Appendix 1 in the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol64/issue5), but the reliability of the continuous model was unclear given low numbers of deaths. Thus, cTn values were categorized as <2 ng/L and ≥2 ng/L, ≤7 ng/L and >7 ng/L, and ≤18 ng/L and >18 ng/L (99th percentile). Such categories were chosen based on clinical use (LoD and 99th percentile) or because they represented groupings with similar risk of mortality. Cumulative mortality over 1 year was plotted for each troponin subcategory.

Several sensitivity analyses were conducted. The first examined the unrounded LoD (<2.3 ng/L) rather than the rounded value of <2 ng/L. Previous research has demonstrated that there is a difference in the proportion of patients below the LoD using rounded vs unrounded

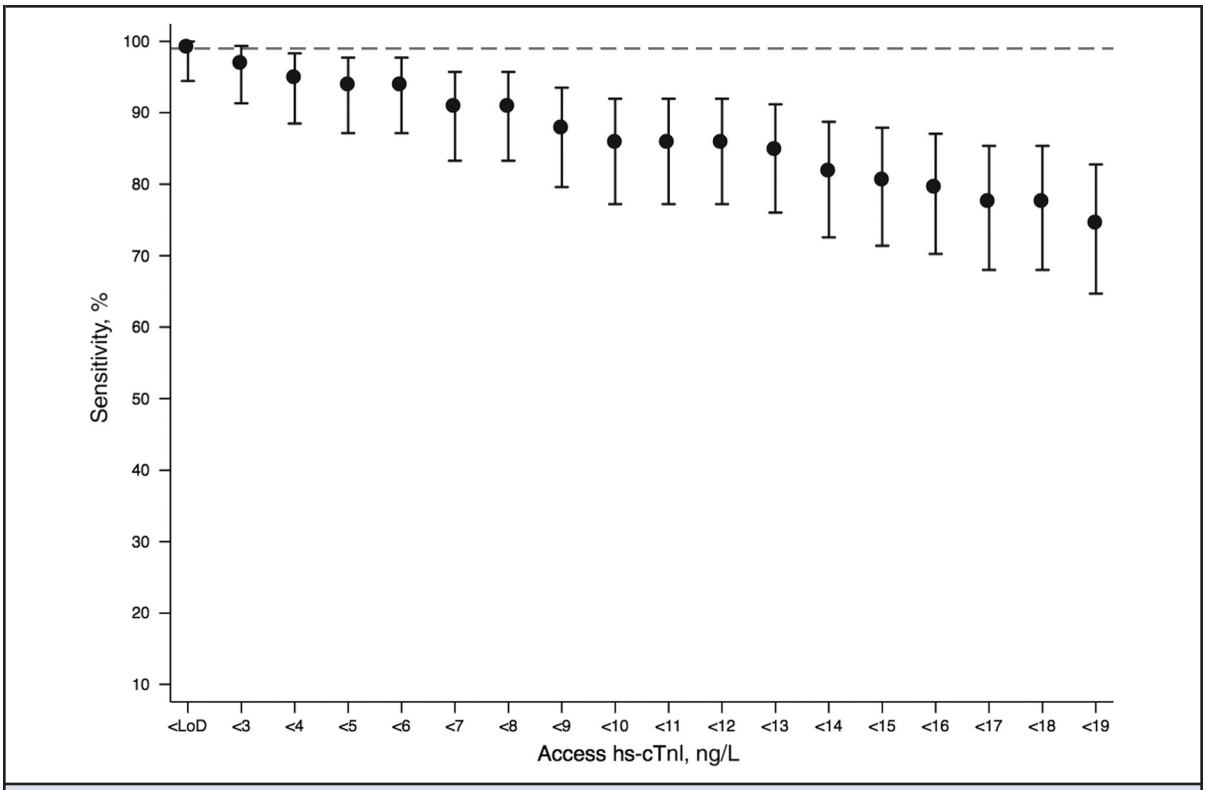

Fig. 2. Sensitivity for each troponin cutpoint.
Dotted line represents sensitivity of 99%.

values *(26)*. The second evaluated the diagnostic accuracy of each troponin value in conjunction with ECG findings; previous research has incorporated nonischemic ECGs with low-level troponin values for safe rule-out of AMI *(9, 15, 27)*. The third excluded early presenters (presenting ≤1 h of chest pain onset). This analysis was conducted based on the ESC guidelines that early rule-out strategies should apply only to individuals presenting >1 h after onset of pain *(8)*. The fourth compared diagnostic accuracy for males and females separately.

Results

Data were available for 1871 patients (Fig. 1). Ninety-eight patients met the primary endpoint of T1MI (5.2%) during their index admission, and 145 patients (7.7%) met the criteria for either T1MI (n = 98) or T2MI (n = 47) during their index admission, 99 (5.3%) for 30-day T1MI, and 118 (6.3%) for 30-day MACE. Twenty-four of 1520 (1.6%) patients were deceased at 1 year. Baseline characteristics of the cohort are provided in Table 1.

The sensitivity and NPV of each troponin cutpoint for T1MI are shown here in Figs. 2 and 3 and in Table 1 of the online Data Supplement. In all, 638 (34.1%) patients had a value <2 ng/L (LoD), of which 1 was diagnosed with AMI. Thus, sensitivity was 99.0% (95% CI, 94.4%–100%) with an NPV of 99.8% (95% CI, 99.1%–100%). No cTn value >2 ng/L achieved a sensitivity of 99%. However, an NPV of 99.5% was achieved at all cutoff values <6 ng/L. Choosing a cutoff of <6 ng/L enabled 1475 (78.8%) patients to be ruled out on presentation. Sensitivity at this cutoff was 93.9% (95% CI, 87.1%–97.7%). Details of false-negative cases are provided in Table 2 of the online Data Supplement. In addition, 152 (8.1%) patients had an hs-cTnI >99th percentile, with sensitivity of 74.5% (95% CI, 64.7%–82.8%). These data are similar to the non-hs-cTn assay in routine use (Beckman Coulter Enhanced AccuTnI), for which 146 (7.8%) patients had a value >99th percentile on presentation with sensitivity of 69.1% (95% CI, 58.9%–78.1%).

Sensitivity for T1MI alone was similar to that when both T1MI and T2MI were included (see Table 3 in the online Data Supplement). Sensitivity and NPV for 30-day T1MI and 30-day MACE are in found in Table 4 of the online Data Supplement. Values <2 ng/L had high sensitivity (99.0%; 95% CI, 94.5%–100%) for T1MI up

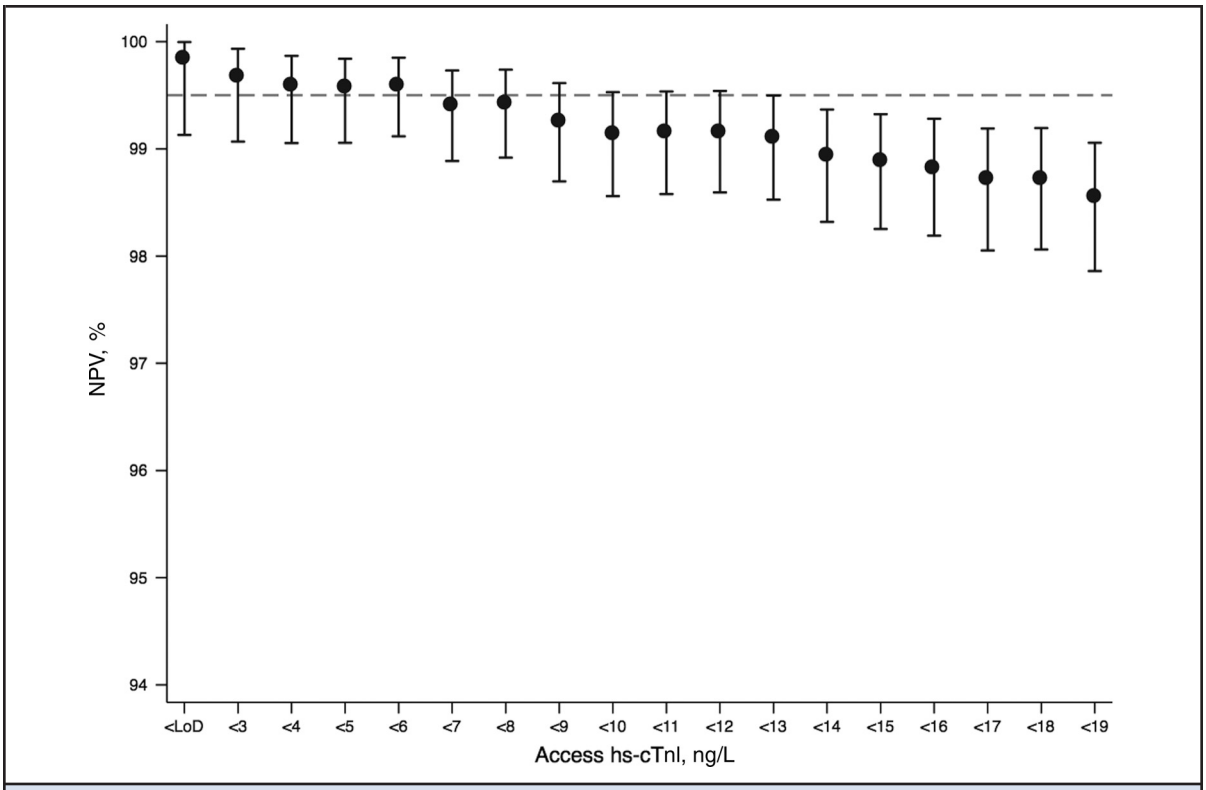

Fig. 3. NPV for each troponin cutpoint.
Dotted line represents NPV of 99.5%.

to 30 days, but had slightly lower sensitivity for 30-day MACE (97.5%; 95% CI, 92.7%–99.5%).

One-year mortality was similar when the presentation hs-cTnI was <2 ng/L or 2 to 7 ng/L (hazard ratio = 1.4; 95% CI, 0.1–15.2). Compared with patients with a presentation cTnI <2 ng/L, mortality was higher when the presentation cTnI was 8 to 18 ng/L (hazard ratio = 55.2; 95% CI, 7.1–427.7) or >18 ng/L (hazard ratio = 50.3; 95% CI, 6.4–393.3). The Kaplan–Meier failure function is provided in Fig. 4.

Using unrounded results, 836 patients (44.7%) had an initial hs-cTnI concentration below the LoD (<2.3 ng/L); of these, 2 were diagnosed with AMI. Thus, sensitivity was 98.0% (95% CI, 92.8%–99.8%) with an NPV of 99.8% (95% CI, 99.1%–100%).

Table 1 in the online Data Supplement provides data for each troponin cutoff in combination with nonischemic ECGs. The inclusion of ECG had minimal impact on the diagnostic accuracy for low-level troponin values. Sensitivity did not reach 99% at any cutoff >2 ng/L, and an NPV of 99.5% was achieved at a cutoff of <6 ng/L.

The point estimates excluding early presenters (n = 253) were similar to those for the entire cohort (Fig. 5). The median time to presentation in the cohort without early presenters was 4.9 h (interquartile range = 2.1–19.3 h). Sensitivity without early presenters was 98.9% (95% CI, 93.8%–100.0%), and NPV was 99.8% (95% CI, 99.0%–100%). Sensitivity was similar for males and females at low cutpoints (Fig. 5).

Discussion

This study sought to identify whether low values on patient presentation for hs-cTnI, as measured using the Beckman Coulter Access assay, could be used to rapidly rule out AMI. hs-cTnI concentrations <2 ng/L (the LoD) identified 99.0% of patients with AMI, and 34.1% of the cohort could be ruled out at this cutoff. Presentation troponin values as high as 5 ng/L provided a high NPV (>99.5%) and would enable rule-out of 78.8% of patients.

The ESC guidelines include provision for immediate rule-out of AMI when the presentation hs-cTn is below the LoD. Such guidelines note that a rapid rule-out strategy can be used only with clinically validated hs-cTn (Abbott, Siemens, and Roche) *(8)*. In accordance with such guidelines, our study found support for the use

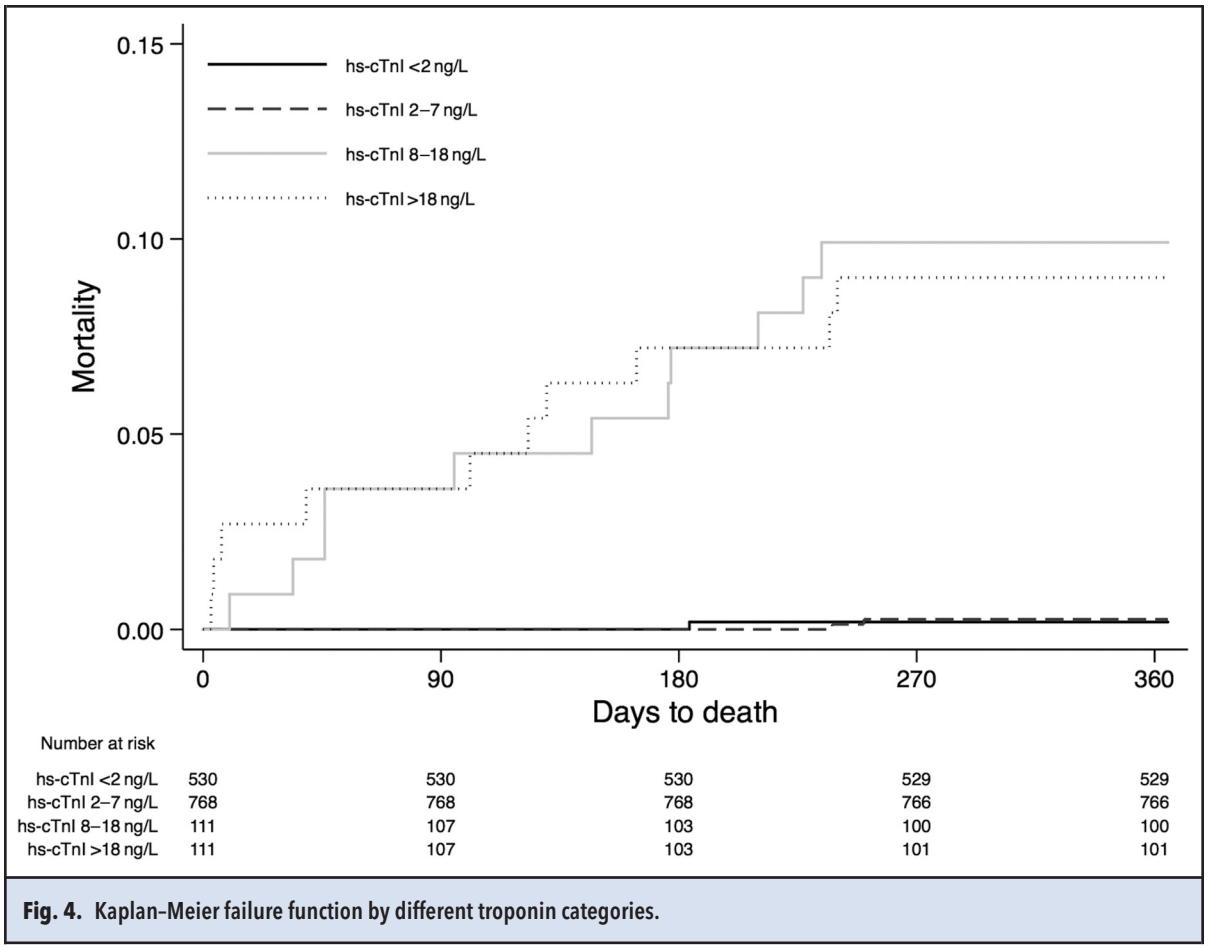

Fig. 4. Kaplan–Meier failure function by different troponin categories.

of a Beckman Coulter hs-cTnI; 1 patient ultimately diagnosed with AMI had an hs-cTnI <2 ng/L (the LoD). This strategy had an NPV higher than the 98% cited in the ESC guidelines *(8)*.

The diagnostic accuracy of the hs-cTnI at 2 ng/L (99.0% sensitivity with 34% rule-out) is similar to other hs-cTn now recommended for clinical use *(8)*. A meta-analysis of the Roche hs-cTnT reported that the pooled sensitivity for AMI at the LoD was 98.7%, with individual study results ranging from 87.9% to 100% *(11)*. For the Abbott hs-cTnI assay, previous research has reported sensitivities >99% *(9, 15, 23, 28)*. The proportion ruled out differs according to the prevalence of AMI in the population, with estimates ranging from 16% *(28)* to 27.2% for Abbott hs-cTnI *(15)* and from 3.8% to 73.5% for Roche hs-cTnT *(29)*.

Based on a high NPV, several authors have recommended the use of a troponin value cutoff slightly >2 ng/L (the LoD) using the Abbott hs-cTn I assay *(9, 10)*. A meta-analysis by Chapman and colleagues *(16)* found that an Abbott hs-cTn I <5 ng/L enabled rule-out of 49% of patients, with an NPV of 99.5% for 30-day AMI. In the current study, a cutoff of <6 ng/L on the Access hs-cTnI yielded high NPV (99.6%) and ruled out 78.8% of patients. However, sensitivity at this cutpoint was 93.9%, a value that would result in 6 missed cases of T1MI and below the acceptable miss rate for clinicians *(25)*. Thus, it is unclear whether this approach would be accepted clinically.

The issue of whether high NPV or high sensitivity is required for rule-out remains controversial. Chapman and colleagues *(30)* note that sensitivity considers only those patients with a diagnosis of AMI and does not include the target population in whom the risk stratification is being applied. They support the use of NPV for evaluating rule-out strategies. Although NPV is an important metric, it does depend critically on the prevalence of disease *(31)*. With low disease prevalence, NPV will be high, even for a test with suboptimal sensitivity. Thus, for the current study, with low disease prevalence, a focus on both NPV and sensitivity is important. The NPV of a test can be calculated for any prevalence using estimates of sensitivity and specificity *(31)*. If the NPV for the current data were calculated at an AMI prevalence of 10% or

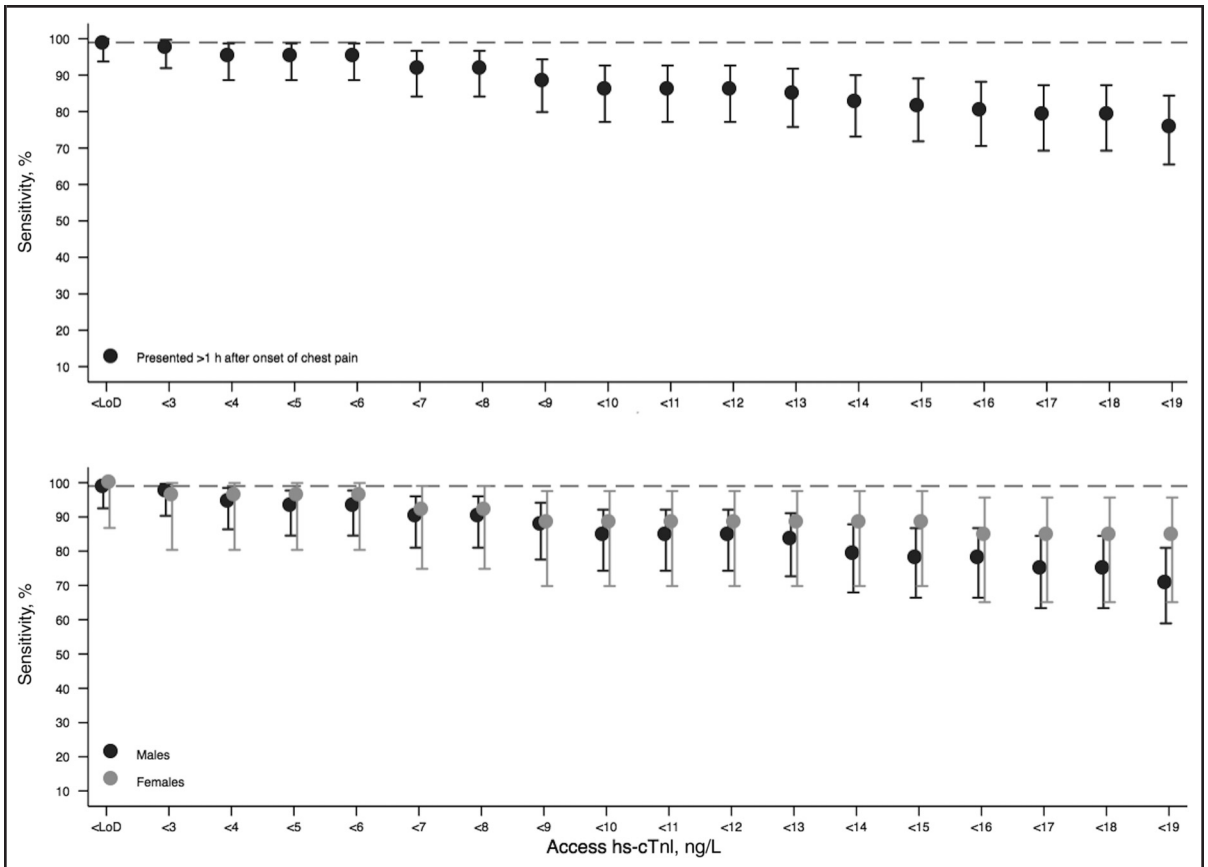

Fig. 5. Sensitivity for late presenters and by sex.

15% (similar to that seen in recent meta-analyses *(11, 16)*, the NPV would be <99.5% at all cutoffs except for the LoD. Thus, the use of a cutoff above the LoD cannot be recommended based on the available study data. Incorporation of a 1-h δ value has been shown to improve sensitivity for low-level values above the LoD *(5, 32, 33)*, and this approach may be evaluated to improve sensitivity for AMI.

In line with previous research, we found that the risk of 1-year all-cause mortality was low for patients with initial troponin results <2 ng/L *(11, 12)*. We also found a large increase in mortality risk with increasing troponin values, even those values below the 99th percentile (Fig. 4). This finding is in line with a growing body of literature indicating that patients with hs-cTn values above the LoD are at increased risk for 1-year mortality *(10, 34)*, and with data from samples of asymptomatic subjects demonstrating a relationship between troponin concentrations and mortality *(35, 36)*.

Previous research has noted that rounding affects the performance of analytically highly sensitive assays *(26)*, a finding replicated here. This is likely because of the low-risk nature of our cohort (5% AMI rate), with many individuals having low presentation troponin concentrations close to the LoD. The laboratory reporting protocol for troponin values (rounded or unrounded) should be considered when implementing rapid rule-out strategies.

This study has several limitations. Numbers of AMI and deaths were relatively low, and the results need to be validated in larger samples. This was an observational study design, and, as such, a substantial proportion of patients had further investigations for coronary artery disease. Intervention trials are recommended to determine the true impact of early rule-out strategies. All rule-out algorithms need to be implemented within the context of the clinical history. It is unclear how this would change the diagnostic accuracy reported in this article. Unstable angina pectoris was not included as an end point, as troponin values are not useful for identifying this condition. As such, patients undergoing early rule-out may still benefit from further testing for coronary artery disease. Low- and intermediate-risk patients in the IMPACT intervention study could undergo serial troponin testing over 2 h. The reduced interval for troponin

testing may mean that prevalent AMIs were missed. Thirty-day follow-up was conducted on all patients and did not reveal any cases of AMI that were missed after accelerated assessment. Only 10% of patients assigned a noncardiovascular end point underwent adjudication by a second cardiologist. Thus, some cases of AMI may have been misclassified as noncardiovascular. However, any patient with evidence of a cardiovascular complaint, including those with increased troponin values, underwent adjudication by 2 cardiologists, and the proportion of missed AMI cases is likely to be low.

In conclusion, a single baseline cTnI <2 ng/L measured with the Beckman Access high-sensitivity assay performed well for rule-out of AMI. This cutpoint identified 99% of patients with AMI and could be used to reduce the number of patients requiring lengthy assessment and inpatient admission. A cutoff of <6 ng/L yielded a high NPV but may miss more patients with AMI than is acceptable to clinicians.

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