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Detectable High-Sensitivity Cardiac Troponin within the Population Reference Interval Conveys High 5-Year Cardiovascular Risk: An Observational Study

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BACKGROUND: Increased cardiac troponin I or T detected by high-sensitivity assays (hs-cTnI or hs-cTnT) confers an increased risk of adverse prognosis. We determined whether patients presenting with putatively normal, detectable cTn concentrations [> limit of detection and < upper reference limit (URL)] have increased risk of major adverse cardiovascular events (MACE) or all-cause mortality.

METHODS: A prospective 5-year follow-up of patients recruited in the emergency department with possible acute coronary syndrome (ACS) and cTn concentrations measured with hs-cTnI (Abbott) and hs-cTnT (Roche) assays. Cox regression models were generated with adjustment for covariates in those without MACE on presentation. Hazard ratios (HRs) for hs-cTn were calculated relative to the HRs at the median concentration.

RESULTS: Of 1113 patients, 836 were without presentation MACE. Of these, 138 incurred a MACE and 169 died during a median 5.8-year follow-up. HRs for MACE at the URLs were 2.3 (95% CI, 1.7–3.2) for hs-cTnI and 1.8 (95% CI, 1.3–2.4) for hs-cTnT. Corresponding HRs for mortality were 1.7 (95% CI, 1.2–2.2) for hs-cTnI and 2.3 (95 % CI, 1.7–3.1) for hs-cTnT. The HR for MACE increased with increasing hs-cTn concentration similarly for both assays, but the HR for mortality increased at approximately twice the rate for hs-cTnT than hs-cTnI. Patients with hs-cTnI ≥10 ng/L or hs-cTnT ≥16 ng/L had the same percentage of MACE at 5-year follow-up (33%) as patients with presentation MACE.

CONCLUSIONS: Many patients with ACS ruled out and putatively normal but detectable hs-cTnI concentrations are at similar long-term risk as those with MACE. hs-cTnT concentrations are more strongly associated with 5-year mortality than hs-cTnI.

Cardiac troponin is the guideline-preferred biomarker for the diagnosis of acute myocardial infarction *(1)*, and therefore, a cornerstone test in the investigation of patients presenting to the emergency department (ED)[10] with possible acute coronary syndromes (ACS). Advances in assay technology have enabled detection of lower concentrations of both cardiac troponin I and cardiac troponin T than previously possible. Plasma cardiac troponin concentrations falling above their respective 99th percentiles of a reference, presumed healthy, population, form part of the diagnostic criteria for acute myocardial infarction (AMI) *(1)*. Results below this threshold are commonly reported as normal or "negative" and are generally accepted as ruling out AMI.

Guidelines recommend that in the presence of symptoms consistent with cardiac ischemia, patients with troponin results above the 99th percentile (i.e., "positive") should be intensively managed with investigative work-up for AMI and underlying coronary artery disease *(2–8)*. Conversely, patients with troponin concentrations below the upper reference limit (URL = 99th per-

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[10] Nonstandard abbreviations: ED, emergency department; ACS, acute coronary syndrome; AMI, acute myocardial infarction; URL, upper reference limit; MACE, major adverse cardiac event; hs-cTnI, high sensitivity cardiac troponin I; hs-cTnT, high sensitivity cardiac troponin T; cTn, cardiac troponin; LoD, limit of detection; LoB, limit of blank; ICD10, International Statistical Classification of Diseases and Related Health Problems, version 2010; ADAPT, Accelerated Diagnostic Protocol to Assess Patients with Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker Trial; HR, hazard ratio; BMI, body mass index.

centile) and not otherwise meeting diagnostic criteria for AMI are likely to have less intensive investigations and management because the immediate life-threatening event has been ruled out and clinicians are generally reassured by reference to such troponin concentrations as "negative" or "normal."

However, several studies conducted in patients with and without established cardiovascular disease have demonstrated that detectable circulating cardiac troponin, within the reference interval of a high-sensitivity assay, are associated with subsequent major adverse cardiovascular events (MACE), commonly defined as MI, heart failure, and cardiovascular death *(9–17)*. A small prospective 2-year study of ED patients suggested that detectable high-sensitivity troponin T (hs-cTnT) and I (hs-cTnI) concentrations below the URL but above the limit of detection (LoD) are associated with increased rates of future MACE *(17)*. Further, a large Swedish registry-based study of patients attending an ED with no incident diagnosis of AMI suggested that hs-cTnT concentrations less than the URL but greater than the LoD are at greater risk of subsequent myocardial infarction, heart failure, and mortality over approximately 3 years *(14)*. There are no similar findings in this patient group for the hs-cTnI assay, and there been no long-term prospective study with hs-cTnT. Ultimately, it is unknown if the hs-cTn assays in routine use are differentially associated with the risk for future events.

To address this knowledge gap, we explored the relationship between 5-year outcomes and results from 2 hs-cTn assays (Abbott and Roche) of serial samples acquired during the initial ED assessment of patients with suspected ACS.

Materials and Methods

STUDY DESIGN AND OVERSIGHT

This study was a preplanned observational analysis of long-term cardiovascular events in patients with symptoms of possible ACS who attended a single ED and were enrolled in the 2-h Accelerated Diagnostic Protocol to Assess Patients with Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker Trial (ADAPT) observational study *(18)*. We assessed associations between 5-year MACE and all-cause mortality with concentrations of hs-cTnI and hs-cTnT in serial blood samples acquired during the initial ED assessment. The regional ethics committee approved the study, and all patients provided written consent.

STUDY POPULATION

Patients were enrolled in a longitudinal observational study undertaken through the ED of Christchurch Hospital, Christchurch, New Zealand, as the New Zealand cohort of the ADAPT study registered on the Australia–New Zealand Clinical Trials Registry, ACTRN12611001069943. Recruitment was extended beyond the original dates of the published ADAPT data, providing a total recruitment period from November 6, 2007, through April 13, 2010 *(19)*. The inclusion and exclusion criteria for the ADAPT study have been previously described *(19)*. In summary, eligible patients were ≥18 years old, without ST elevation AMI or likely noncoronary pathology, presented acutely from the community to the ED with symptoms thought to suggest ACS that the attending physicians planned to investigate with serial cardiac troponin tests. Participants were followed until the first of either death or survival to April 13, 2015 (survivors were followed for a minimum of 5 years). Patients were excluded if results were not available for both hs-cTnI and hs-cTnT. The primary analysis population was the subcohort of patients without an adjudicated diagnosis of AMI or other MACE at the index admission.

SAMPLING AND LABORATORY ANALYSIS

Blood was drawn into lithium-heparin tubes on presentation, and 2 h later, immediately centrifuged and stored at −80 °C for later testing. Storage times before analysis were 3.5–7 years for hs-cTnI and 4.5–8 years for hs-cTnT. Our analysis used the higher of the presentation or 2-h concentrations of hs-cTnI and hs-cTnT concentrations by measurement with 2 assays: the Abbott ARCHITECT high-sensitivity troponin I (measured on an ARCHITECT i2000; Abbott Diagnostics) and Roche 5th generation troponin T marketed outside of the US (measured on a Cobas e411, Roche Diagnostics). The hs-cTnT manufacturer-reported limit of blank (LoB) is 3 ng/L, LoD 5 ng/L, and 99th percentile 14 ng/L. These metrics are slightly different from the FDA-cleared hs-cTnT assay in the US (package insert). The hs-cTnI assay has an LoB of 0.7–1.3 ng/L, an LoD of 1.1–1.9 ng/L, and a 99th percentile of 26 ng/L and sex-specific 99th percentiles of 16 ng/L for females and 34 ng/L for males. In this analysis we used an LoD of 1.9 ng/L.

OUTCOME DEFINITIONS AND ADJUDICATION

The primary composite outcome was the first MACE following discharge. MACE was defined as cardiac arrest, cardiogenic shock, ventricular arrhythmia requiring intervention, high-degree atrioventricular block, MI (type 1 or type 2), emergency revascularization, or cardiac death [defined as (*a*) death related to ACS, (*b*) evidence of cardiac death even if unrelated to ACS, or (*c*) death without clear evidence that it was noncardiac]. Detailed definitions have been previously described *(19)*. The secondary outcome was all-cause mortality.

All hospital attendances in New Zealand can be accurately tracked through a unique national alphanumeric patient identifier. For this cohort, almost all hospital readmissions occurred locally because Christchurch Hospital is the only large general hospital within a 300-km

radius. For all readmissions to Christchurch Hospital, a cardiology research physician used medical records to identify clearly noncardiac-associated hospitalizations. For the remaining (possibly cardiac) local readmissions, 2 cardiologists independently adjudicated the outcome with a third cardiologist tiebreaker in cases of disagreement. All those involved in adjudicating outcomes were blinded to the index troponin results. ICD10 (International Statistical Classification of Diseases and Related Health Problems, version 2010) codes for all readmissions to all other New Zealand hospitals were from the national database held by the New Zealand Ministry of Health and were used to categorize the cause of admission and to define MACE. Finally, we obtained death registry data from the Ministry of Health, which were adjudicated as either noncardiac or cardiac.

Classification of MI was based on the global taskforce universal definition for MI, requiring evidence of a rise or fall in troponin, with at least 1 concentration above the 99th percentile, together with evidence of myocardial ischemia (ischemic symptoms, ECG changes, or imaging evidence) *(20)*. In this study δ was not rigidly specified, although 20% was commonly used *(21, 22)*. The reference troponin assay used for the clinical adjudication of an MI diagnosis was the assay used clinically at the time. For all index admissions and for subsequent readmissions before April 23, 2013, this assay was the Abbott contemporary cTnI assay (ARCHITECT Troponin I; for details, see the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol64/issue7). The Abbott hs-cTnI was used for readmissions after April 23, 2013. Adjudicators used sex-specific 99th percentiles.

STATISTICAL ANALYSIS

Cox regression models were constructed relating each hs-cTn to the outcomes. Because of the rightward skew of the hs-cTn concentrations, they were first log-transformed before being inserted into a restricted cubic-spline function with 4 knots at the 5%, 35%, 65%, and 95% percentiles of the hs-cTn concentrations. A restricted cubic spline was used to avoid an assumption of linearity and to retain all information from a continuous variable rather than to lose information through (arbitrary) discretization into multiple groups. As the patient group below the LoD was different with both assays, we chose to present the rate of the primary outcome observed at the median troponin concentration of each assay as the reference concentration. This enabled better comparison of risk between troponin assays. The results with the reference hazard ratio (HR = 1) set at the LoD of each assay are presented in the Material Section in the online Data Supplement.

Cox regression models were adjusted for age, sex, smoking, dyslipidemia, diabetes, hypertension, body mass index (BMI), history of cardiovascular events (prior myocardial infarction, angina, and heart failure), and plasma creatinine. Missing covariables (n = 106 for BMI, n = 7 for creatinine) were imputed with the method of multivariate imputation of chained equations with logistic regression for binary variables and linear regression by bootstrapping for numeric variables with use of the "mice" package in R *(23)*. The proportional hazards assumption was tested with the method of Grambsch et al. *(24)*. Finally, for each regression model we assessed the relative influence of each hsTn to the other variables by comparing their χ^2 minus the number of degrees of freedom of the variable values ($\chi^2 - df$). $\chi^2 - df$ is proportional to the influence of the variable on the overall model and so can be used to rank the influence of variables on the model.

We used Kaplan–Meier plots to identify the hs-cTn thresholds above which the 5-year MACE rate was the same in patients with, and in those without, an index admission MACE. A subgroup analysis was conducted that considered males and females separately. Statistical calculations were made in R version 3.2.2 (The R Foundation for Statistical Computing).

Results

STUDY POPULATION

Of 1184 patients enrolled in the primary study, 66 had insufficient sample for measurement of hs-cTn, and 5 died during the index admission (see Fig. 1 in the online Data Supplement). Therefore, 1113 patients provided data for analysis. Of these, 277 (24.9%) suffered an index MACE, leaving 836 (75.1%) in the primary analysis population. Slightly more patients were male (57%) and had a high prevalence of known coronary disease and history of previous ACS (Table 1). The first blood sample was taken a median 5.9 h (IQR, 5.3–7.8) following onset of symptoms.

The median duration of follow-up was 5.8 years (IQR, 5.1–6.6), and patients with at least one MACE numbered 138 (16.5%). The most common first follow-up MACE event was non-ST-segment elevation MI (n = 96, 69.5% of events) (Table 1). All-cause mortality totaled 169. Overall, among those without index MACE, there were more results both below the LoD (n = 305, 35.7%) and above the URL (n = 198, 23.2%) for hs-cTnT compared with hs-cTnI (n = 119, 13.9%, and n = 59, 6.9%, respectively). Median concentrations of hs-cTnT and hs-cTnI were 6.8 ng/L and 4.3 ng/L, respectively. The concordance between hs-cTnI and hs-cTnT as a function of patient group and outcomes is displayed in Fig. 2 in the online Data Supplement.

PRIMARY OUTCOME

As hs-cTn concentrations increased above the LoD, MACE HRs rose, increasing steeply above the median concentrations (Fig. 1). HRs for MACE at troponin

Table 1. Demographics and presenting features.[a]

Variable	Entire cohort (*n* = 1113)	With index admission MACE[b] (*n* = 277)	Without index admission MACE (*n* = 836)
Male	663 (59.6%)	189 (68.2%)	474 (56.7%)
Age	65.3 ± 13	69 ± 13	64 ± 12.7
Smoking	162 (14.6%)	47 (17%)	115 (13.8%)
Body mass index	28.2 ± 5.6	28 ± 5.1	28.3 ± 5.7
Creatinine, μmol/L	95.8 ± 35.8	104.7 ± 38.3	92.9 ± 34.4
mg/dL	1.08 ± 0.40	1.18 ± 0.43	1.05 ± 0.39
Potassium, mmol/L	4.1 ± 0.4	4.1 ± 0.5	4.1 ± 0.4
Hemoglobin, g/L	138 ± 16	139 ± 19	138 ± 16
Systolic blood pressure, mmHg	145 ± 27	148 ± 30	144 ± 26
Diastolic blood pressure, mmHg	80 ± 14	82 ± 16	79 ± 13
Diabetes	180 (16.2%)	55 (19.9%)	125 (15%)
Dyslipidemia	640 (57.5%)	151 (54.5%)	489 (58.5%)
Hypertension	685 (61.5%)	183 (66.1%)	502 (60%)
Previous heart failure	109 (9.8%)	26 (9.4%)	83 (9.9%)
Previous myocardial infarction	338 (30.4%)	84 (30.3%)	254 (30.4%)
Previous transient ischemic attack	66 (5.9%)	19 (6.9%)	47 (5.6%)
Peripheral vascular disease	54 (4.9%)	14 (5.1%)	40 (4.8%)
Previous angina	531 (47.7%)	122 (44%)	409 (48.9%)
Previous CABG	117 (10.5%)	35 (12.6%)	82 (9.8%)
Previous PTCA	271 (24.3%)	55 (19.9%)	216 (25.8%)
Aspirin	602 (54.1%)	151 (54.5%)	451 (53.9%)
Patients with hs-cTn > LoD			
hs-cTnI	993 (89.2%)	276 (99.6%)	717 (86.1%)
hs-cTnT	807 (72.5%)	276 (99.6%)	531 (64.4%)
Outcomes (first event)			
Patients with at least 1 MACE event during follow-up (primary composite outcome)	233 (20.9%)	95 (34.3%)	138 (16.5%)
Outcomes (n and % of outcomes)			
Cardiac death	43 (18.5%)	20 (21.1%)	23 (16.7%)
STEMI	6 (2.6%)	2 (2.1%)	4 (2.9%)
NSTEMI	164 (70.4%)	68 (71.6%)	96 (69.6%)
Ventricular arrhythmia	6 (2.6%)	2 (2.1%)	4 (2.9%)
High-degree atrioventricular block	9 (3.9%)	1 (1.1%)	8 (5.8%)
Cardiogenic shock	2 (0.9%)	1 (1.1%)	0
Cardiac arrest	4 (1.7%)	1 (1.1%)	3 (2.2%)
All-cause mortality (n and % of cohort)	262 (23.5%)	93 (33.5%)	169 (20.2%)

[a] Values are presented as mean ± standard deviation, median (lower quartile – upper quartile).
[b] MACE, major adverse cardiac event; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angiography; STEMI, ST-elevated myocardial infarction; NSTEMI, non-ST-elevated myocardial infarction, or n (%).

URLs, relative to their median concentrations, were 3.4 (95% CI, 2.5–4.5) for hsTnI and 2.7 (95% CI, 2.1–3.5) for hsTnT. After adjustment, both hs-cTns continued to show increasing HRs in the detectable range, and the HRs at the URL were 2.3 (95% CI, 1.7–3.2) for hs-cTnI and 1.8 (95% CI, 1.3–2.4) for hs-cTnT (Fig. 1). Adjustment increased the associated *c*-statistic for hs-cTnI from 0.72 (95% CI, 0.67–0.76) to 0.81 (95% CI, 0.76–0.86)

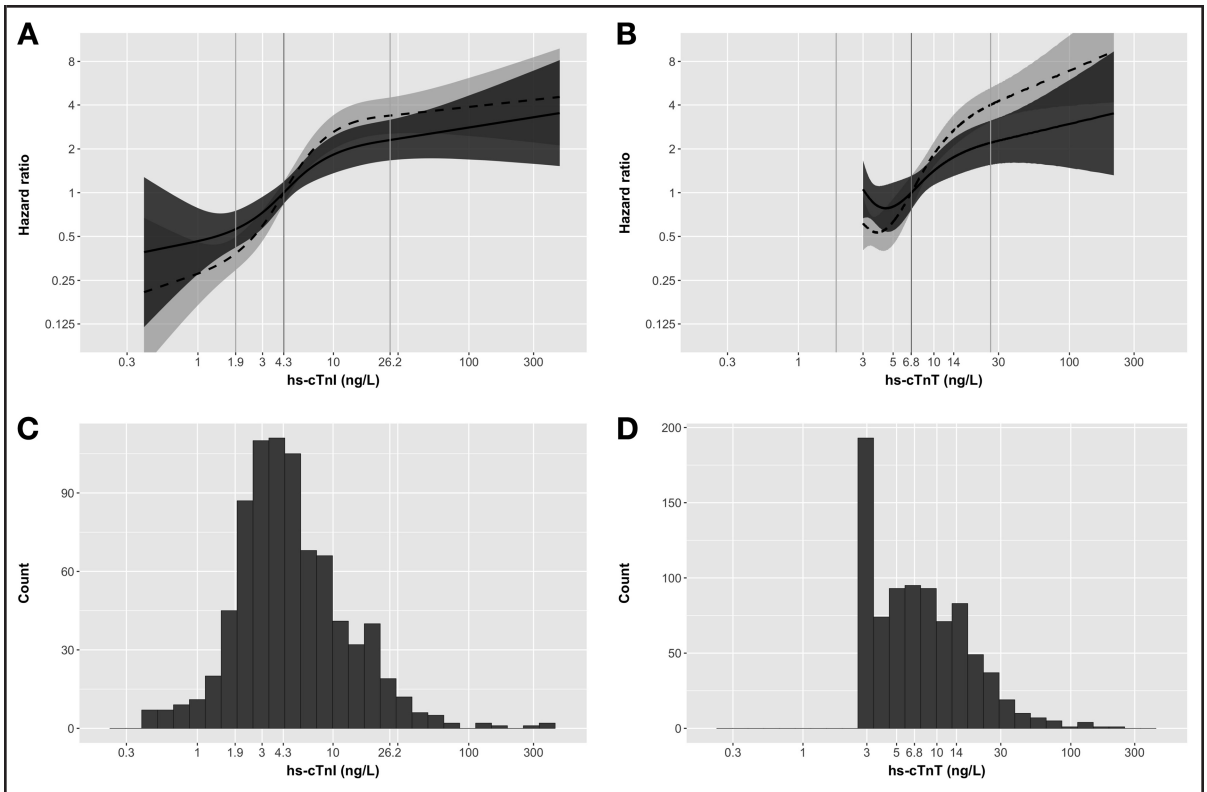

Fig. 1. The HR relative to the hazard at the median concentration for MACE as a function of hs-cTnI (A) and hs-cTnT (B).

The unadjusted (dashed line) and adjusted (solid line) models are shown with 95% CI (light-gray and dark-gray shading, respectively). (C) and (D) are histograms of hs-cTn. Graphs were truncated at 500 ng/L as there were so few concentrations >500 ng/L.

and for hs-cTnT from 0.71 (95% CI, 0.66–0.76) to 0.80 (95% CI, 0.75–0.85), indicating that adjustment improved prediction of future MACE. For the hs-cTnI model, hs-cTnI was the most influential variable in the model, whereas for the hs-cTnT model, a history of MI was marginally more influential than hs-cTnT (see Figs. 3 and 4 in the online Data Supplement).

For patients with an index admission MACE, 33% had another MACE within 5 years. An equivalent event rate occurred in patients without index admission MACE with hs-cTnI ≥10 ng/L and with hs-cTnT ≥16 ng/L (Fig. 2).

SECONDARY OUTCOME

Increasing concentrations measured by both hs-cTns were univariately associated with increasing all-cause mortality; however, the HR for hs-cTnT increased much more rapidly than that for hs-cTnI (Fig. 3). Adjustment increased the *c*-statistic associated with hs-cTnI from 0.71 (95% CI, 0.67–0.76) to 0.83 (95% CI, 0.78–0.87) and for hs-cTnT from 0.79 (95% CI, 0.75–0.84) to 0.84 (95% CI, 0.79–0.88). After adjustment, HRs at the 99th percentile relative to the median concentration were 1.7 (95% CI, 1.2–2.2) for hs-cTnI and 2.3 (95% CI, 1.7–3.1) for hs-cTnT (Fig. 3). In the adjusted model with hs-cTnI, age was the most influential variable with $\chi^2 - df = 65.1$ and hs-cTnI next at 5.8 (see Fig. 5 in the online Data Supplement). In the adjusted model with hs-cTnT, age also remained the most influential variable at $\chi^2 - df = 35.8$ and hs-cTnT next at 24.5 (see Fig. 6 in the online Data Supplement).

Fig. 4 uses the same models as for Figs. 1 and 3, but for best visual comparison of the 2 assays' predictive performance, it displays the HRs as a function of the concentration percentile. For MACE, the HRs were very similar for the 2 assays across the whole percentile range before and after adjustment (Fig. 4A). However, for all-cause mortality, the HR for hs-cTnT increased at approximately twice the rate as that for hs-cTnI, with concentrations in increasing percentiles (Fig. 4B).

SUBGROUPS

The association of increased hazard of MACE and of death with increased concentrations of both hs-cTns was seen in both sexes, with no difference observed between sexes (see Figs. 7 and 8 in the online Data Supplement).

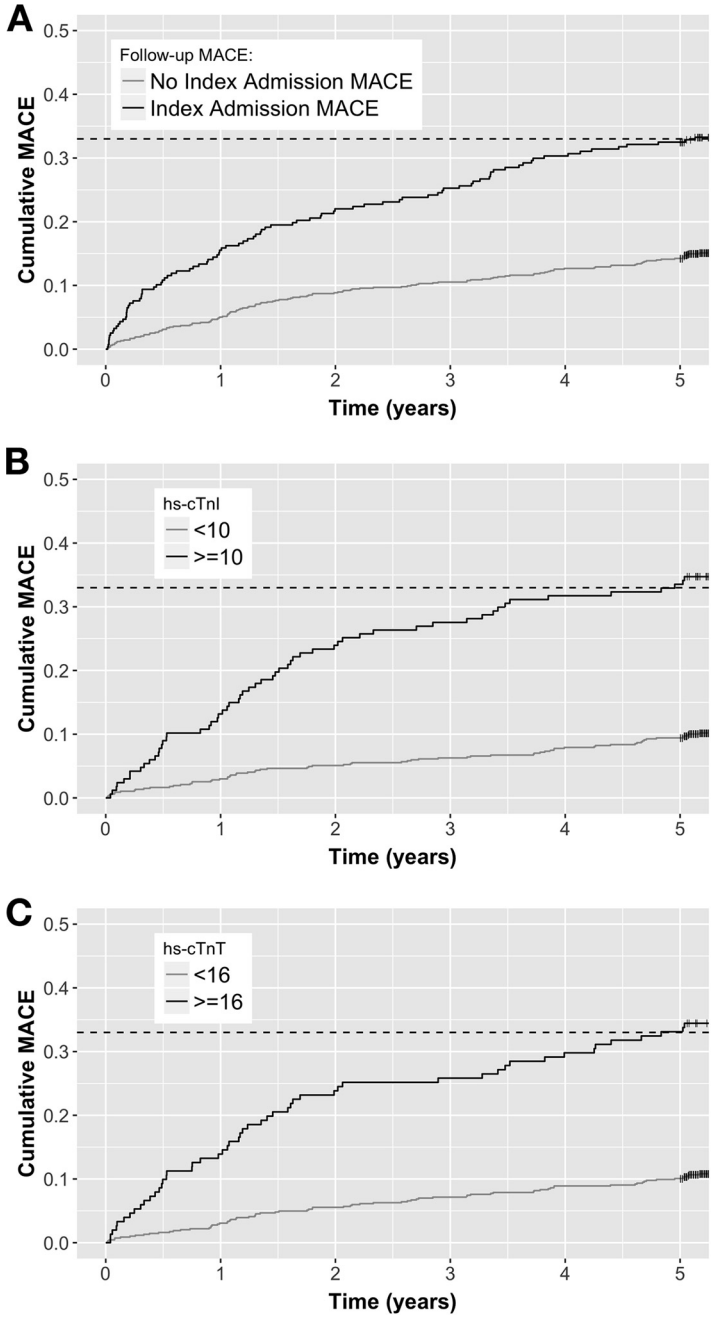

Fig. 2. Kaplan–Meier plots of cumulative MACE for patients with and without index admission MACE (A), and split according to hs-cTnI (B) and hs-cTnT (C) thresholds in patients without index admission MACE.

The hs-cTn thresholds in (B) and (C) are chosen to give at least an equivalent 5-year cumulative MACE as for patients with index admission MACE of 0.33 (33%).

Finally, relative to the LoD (i.e., HR defined as 1.0 at the LoD) for MACE, there were adjusted HRs of 3.8 (95% CI, 2.8–5.3) and 2.1 (95% CI, 1.6–2.9) at the URL for hs-cTnI and hs-cTnT, respectively (see Fig. 9 in the online Data Supplement). Similarly, for mortality there was an adjusted 2.1-fold (95% CI, 1.5–2.8) increase in the HR at the URL for hs-cTnI and 3.1-fold (95% CI, 2.3–4.3) increase for hs-cTnT (see Fig. 10 in the online Data Supplement).

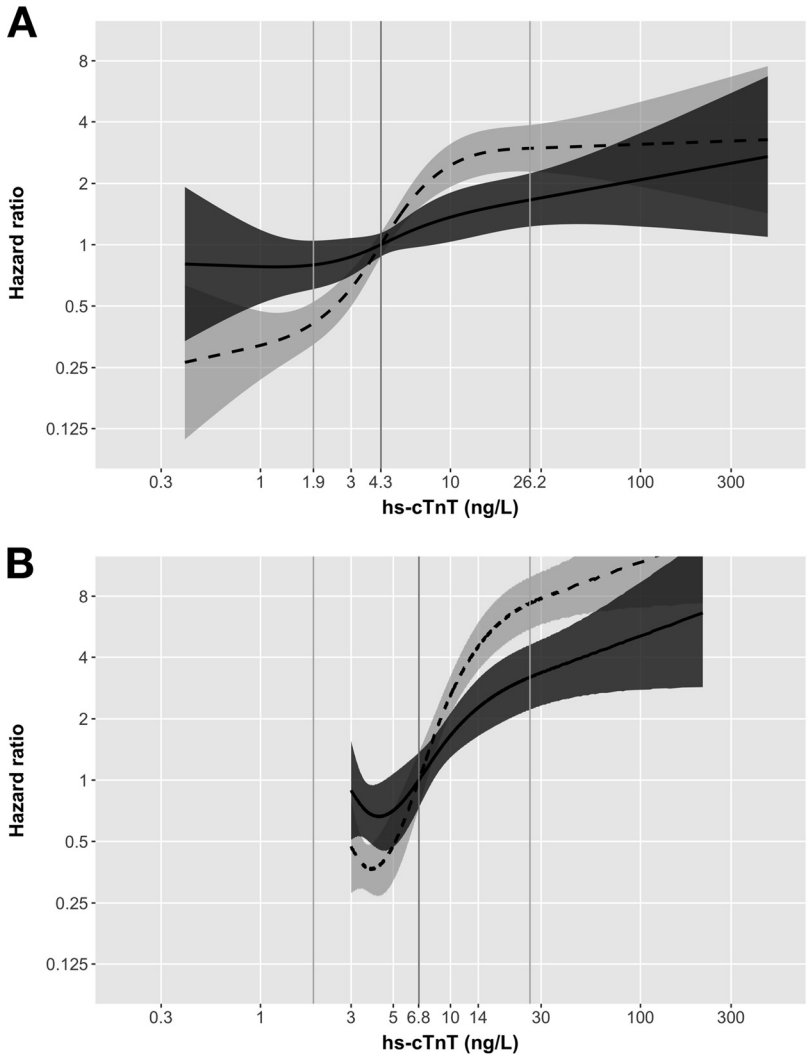

Fig. 3. The HRs relative to the hazard at the median concentration for all-cause mortality as a function of hs-cTnI (A) and hs-cTnT (B) relative to their median concentrations.

The unadjusted (dashed line) and adjusted (solid line) models are shown with 95% CI (light-gray and dark-gray shading, respectively). Graphs were truncated at 500 ng/L as there were so few concentrations >500 ng/L.

Discussion

In patients presenting to the ED with symptoms of possible ACS, we observed that with increases in concentrations of cTn, measured by each hs-cTn assay, below the URL, the risk of a subsequent MACE and all-cause mortality also increased. The associations with future MACE remained after allowing for demographic variables, and background risk factors was approximately the same for both assays. However, the association with mortality was stronger for hs-cTnT than for hs-cTnI.

Our comparison of the relative performance of 2 hs-cTn assays was made highly robust by the use of the same patient group, by adjustment for other known risk factors, by benchmarking HRs to the median concentrations, and by the use of restricted cubic splines to model hs-cTn. The restricted cubic splines model is preferable to the common methods, which categorize troponin concentrations into a limited number of intervals based on quantiles, tertiles, or similar, or at above and below threshold (e.g., LoD or URL) *(25)*, because such categorization results in reduced precision and assumes the relationship between troponin and the outcome is flat within prediction intervals but can change when an interval boundary is crossed. While it may be true that any measurable troponin concentration is worse than if un-

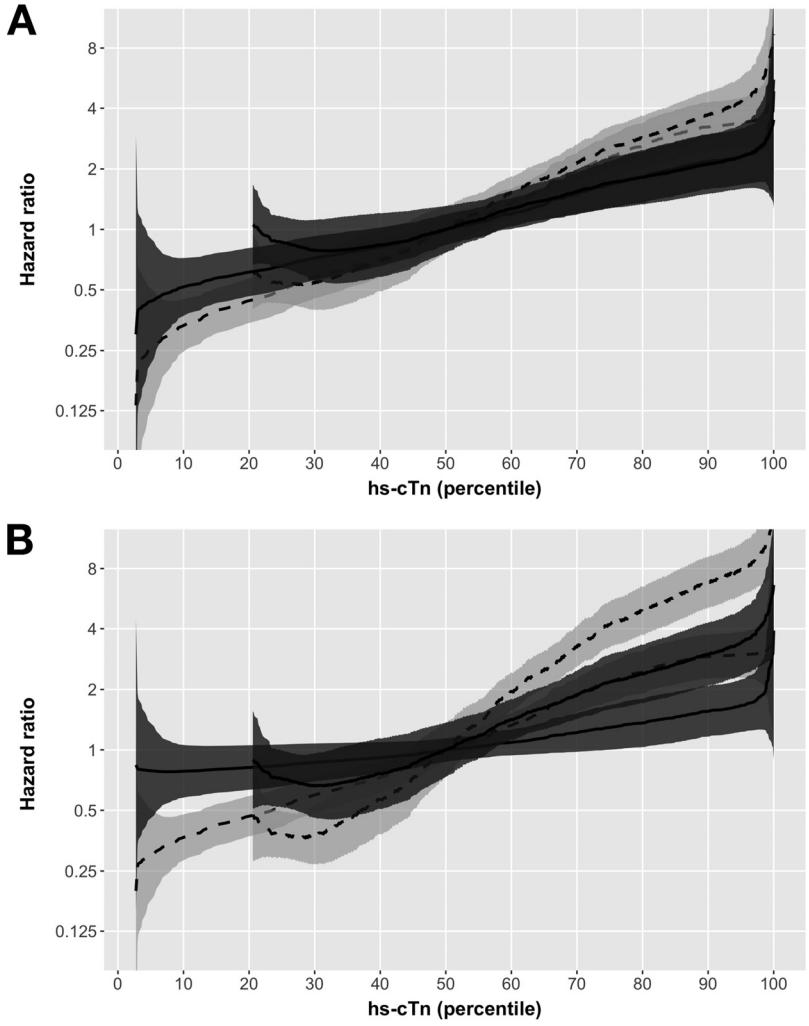

Fig. 4. The HRs for MACE (A) and all-cause mortality (B) for hs-cTnI (from approximately 4%) and hs-cTnT (from approximately 21%) as a function of hs-cTn percentile.

Light-gray is the unadjusted and dark-gray the adjusted 95% CIs. The 10%, 25%, 50%, 75%, and 90% percentiles for hs-cTnI were 1.6, 2.6, 4.3, 8.3, and 18.1 ng/L and for hs-cTnT 3.0, 3.5, 6.8, 13.3, and 22.4 ng/L.

detectable, caution must be taken not to compare assays by reference to HR rates benchmarked to the LoD. This is because the LoDs are not comparable between assays. With the methodology used, we highlighted that in this ED population, although the compared assays have different proportions of patients below the LoD and above the URL, the "normal" values are similarly associated with future MACE. The reasons for our finding a dissimilar association with future mortality when we take into account the percentile of each hs-cTn concentration are unclear.

The stronger association of hs-cTnT than hs-cTnI with mortality after adjustment in an ED population investigated for possible ACS is a novel finding. The reasons for hs-cTnT being more strongly associated with mortality than hs-cTnI in this current cohort cannot be determined by this study. The reasons may be related to biological factors. The difference may not lie simply in differences in the TnT and TnI molecules, per se, because differences in mortality have also been observed between TnI assays *(26, 27)*. Instead, differences might be in part be explained by the specific selection of antibodies that measure different protein epitopes and thus potentially different circulating troponin moieties. Increased cardiac troponin T has also been associated with injury to skeletal muscle *(28, 29)*, and diseases that affect both skeletal muscle and mortality may explain the difference in mor-

tality prediction between hs-cTnI and hs-cTnT. Unfortunately, we had insufficient data to investigate this question further in our cohort. Consistent with our mortality finding is that, in an unadjusted analysis in patients investigated for possible ACS (including those with AMI), Haaf and colleagues showed that the area under the receiver operator characteristic curve for 2-year mortality was greater for hs-cTnT than for TnI measured with either of 2 different hs-cTnI assays (Beckman and Siemens) *(26)*. In a large registry of patients without AMI, Roos and colleagues, with a mean 3.3-year follow-up, showed that after adjustment for several risk factors, hs-cTnT was associated with an increased hazard rate in 5 hs-cTn intervals relative to patients with hs-cTnT below the LoD *(14)*.

The clinical implications of this study and others in which "normal" troponin concentrations have been associated with adverse outcomes are potentially profound. Patients with troponin that is detectable but ≤99th percentile are not routinely recognized as being at increased risk and may not be reliably identified without the use of an hs-cTn assay. A discharge diagnosis of nonspecific chest pain is very common *(30)*. In the current study, 18% of nonindex MACE patients had an hs-cTnT greater than the concentration thresholds we found at which the 5-year event rate of MACE was equivalent to that of patients with an initial MI, and 20% had an hs-cTnI greater than the concentration thresholds. While these proportions may be lower in jurisdictions with ED populations that are less at risk of MI, such as Australia and the US, there are still likely to be millions of such patients worldwide annually. If hospital- and community-based healthcare professionals are unaware that there is a concentration-related gradient of increased long-term risk associated with troponin concentrations falling within the reference interval, patients may be discharged without adequate plans or guidance for further investigation. Conversely, routine investigation of all cases with detectable troponin does not have clear guidance, may result in net detriment, and may have major financial implications for health systems. The optimal diagnostic and management strategies to mitigate this risk and their cost effectiveness are not known.

Therefore, a considered consensus is needed to define and refine the appropriate management strategy for patients with detectable hs-cTn ≤ URL. The diverse pathophysiological processes underlying chronic, low-level injury and troponin release may make development of a unified strategy difficult. Some may have myocardial injury caused by plaque rupture and thrombosis while many others will have a myriad of causes for their myocardial injury. The dilemma may be further complicated by assays able to detect plasma cTn in all patients with an inevitable but uncertain crossover between truly benign measurable troponin and low concentrations reflecting pathology. Trials to confirm thresholds and to explore both the potential cost and benefit of investigations and possible treatment for cardiac ischemia or other unmasked cardiovascular disease are needed. These could determine if standardized management, either at discharge from the ED or during follow-up with primary care providers or specialists, might benefit this vulnerable population.

This study has several limitations. First, these results come from a single center and may not be generalizable, although they are consistent with the studies of Haaf and Roos. Additionally, clinical care and most case adjudication was dependent upon a contemporary (i.e., not high-sensitivity) TnI assay. Adjudication with a hs-cTn assay may have led to more diagnoses of MI. Furthermore, the use of a troponin I assay to adjudicate outcomes may affect the results for hs-cTnT, as the apparent performance of an assay may be affected by the type of troponin assay used for adjudication *(31)*. Next, patients were being investigated for ACS; therefore, some variables potentially linked to long-term cardiovascular outcomes such as C-reactive protein and lipids were not routinely collected and so were not part of the adjusted model. How risk stratification with such measurements would impact our results is unknown. We also note that index admission MACE prevalence is high by international standards because of a well-developed and well-funded primary healthcare that is effective at screening out many patients who may otherwise present to the ED. While a robust methodology was used to adjudicate the vast majority of outcomes, there were a small proportion of events at other hospitals identified through ICD10 codes. New Zealand's national patient identification system enabled the identification of all hospital admissions or deaths throughout the country. For some of the results, we present HR at the URLs. These URLs are the manufacturer-specified thresholds and are not based on any threshold derived from a New Zealand reference population, as no suitable study has been done. There is a paucity of evidence on the stability of hs-cTn in frozen (−80 °C) samples over a long period. Both hs-cTnI and hs-cTnT have been shown to be stable at −80 °C for up to 1 year even with 2 freeze–thaw cycles *(32)*. Finally, although this was a sizable cohort, there were insufficient numbers of events to allow robust subgroup analyses. In particular, we were not able to investigate if early presenters had similar outcomes as later presenters. Further research is, therefore, necessary to identify the most at-risk patient subgroups in whom more intensive management should be studied further.

In conclusion, many patients in the ED with putatively normal but detectable concentrations of cardiac troponin (I or T) below the 99th percentile are at increased long-term (5-year) risk of MACE and death. Although the 99th percentile is used to diagnose and guide management, a lower cutpoint may identify patients without AMI but at increased long-term risk and in need of more intensive inves-

tigation and management. These results suggest the need for further clinical research to ascertain the optimal threshold and approach to management of these patients.

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