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High Sensitivity Troponin Outperforms Conventional Assays in Estimating Significant Adverse Cardiac Occurrences Up to Two Years Ahead in Patients with Chest Pain- A Comparative Study

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Abstract

Background- Prior research has indicated that patients with increased cardiac troponin and probable acute coronary syndromes (ACSs) are at risk for major adverse cardiovascular events (MACEs) in the future. This study compared the prognostic value of modern troponin assays with high-sensitivity troponin in these patients. **Methods:** Between November 2006 and April 2007, a total of 332 patients with suspected ACS were investigated; all patients were monitored for a period of two years. Abbott Architect troponin I, third generation (TnI 3) and Roche Elecsys high-sensitivity troponin T (hsTnT), as well as Roche Elecsys troponin T (TnT), were compared for their ability to predict MACE (composite of cardiovascular death, non-fatal myocardial infarction, and revascularization) using analysis of blood samples. **Findings:** Twenty-eight patients, or 20.5%, had a MACE between the time of discharge and two years. The area under the ROC curve (95% confidence intervals) for baseline hsTnT were 0.70 (0.63–0.76), TnI 3 0.66 (0.59–0.73), and TnT 0.61 (0.53–0.69), as determined by the receiver operating characteristic (ROC) curve. TnI 3 trended (P = 0.094) towards superiority but was equal to hsTnT (P = 0.001), which outperformed TnT. The patients who hsTnT best categorised had cumulative event rates for two-year MACE of 35.6% for levels that were above the 99th percentile, 17.9% for levels that fell between the 99th and limit of detection (LOD), and 5.4% for levels that predicted MACE at two years. Patients in this group had a very low risk of adverse outcomes since their hsTnT levels were below the lower limit of detection.

Introduction

The primary criterion for diagnosing non-ST elevation acute myocardial infarction is troponin; however, prior research has also demonstrated a correlation between elevated cardiac troponin levels in patients believed of having acute coronary syndromes (ACSs) and an increased risk of major adverse cardiovascular events (MACEs), including "low level" increases.1–7 For example, only the troponin assay with the highest analytical sensitivity was able to identify 10–12% of patients who experienced adverse events at a one-year follow-up in the Fast Revascularization during InStability in Coronary disease (FRISC) II subgroup analysis. This subgroup analysis compared the outcomes of several troponin T (TnT) and I (TnI) assays measured at an average of 37 h post-presentation. The assay's clinical sensitivity has been decreased because previously accessible troponin assays have proven unreliable at the lower end of the range. Many of these assays have been not able to attain a 10% coefficient of variation at the 99th percentile of a reference population, which is recommended in the 2007 definition of acute myocardial infarction (AMI)9.10 High-sensitivity troponin tests have recently been developed to improve the analytical and clinical sensitivity for the identification of myocardial damage.

Compared to patients usually seen in an emergency department (ED) population for chest discomfort and troponin measures obtained after a postponed time period, the patients enrolled in the FRISC trials were significantly more at risk. The objective of our research was to ascertain whether serial measurements of a high-

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sensitivity assay for TnT (samples taken at 0 and 6–24 hours post-presentation) offered prognostic utility in a cohort of patients showcasing to the emergency department (ED) with chest pain, including in those with detectable levels of troponin in the reference range (below the 99th percentile yet exceeding the limit of detection, or LOD).

Methodology

Individuals were monitored for two years following their index admission for complications (since the purpose of this study was not to evaluate the diagnostic accuracy of the assays, index admission events were excluded from the analysis of prognostic power). The New Zealand death registry, patient notes review, "National Events Search," and, in cases where information was unavailable, a phone call to the general practitioner were used to track down the patients. Events that occurred two years later were examined, and the prognostic value of each assay at baseline and follow-up was computed for detectable values within the reference range (between LOD and the 99th percentile) as well as for overt increases in troponin (≥99th percentile). It was also examined how a delta troponin—the difference in troponin levels between the baseline and follow-up samples—was used.

Results

Every result was presented through a predetermined, organised judging procedure. The American College of Cardiology (ACC) definitions of 200112 and the 20079 redefining of AMI—which included coronary angiography data and took into account patients treated in operational practice—were the main sources of information for patient risk factors and occurrences. (Table 1).

Table 1 Outcome definitions

Outcome	Definition
Cardiovascular death	Sudden cardiac death, death due to acute coronary syndrome (ACS), vascular death such as stroke, arterial embolism, pulmonary embolism, ruptured aortic aneurysm or dissection, death due to congestive cardiac failure or cardiac arrhythmia. Where cause of death was difficult to determine, an adjudication of cardiac death was made
Acute myocardial infarction (AMI)	In conjunction with the presenting symptoms of ACS, ≥1 value of troponin I (TnI) ≥ 99th percentile with no other clear explanation for the TnI elevation found. The dynamic change in TnI in those with elevated values to denote a rise and/or fall in TnI 2 as per definition of AMI[1] was actively considered; however, if no rise or fall existed but no clear alternative cause of the troponin elevation was apparent, then an adjudication of AMI was made.
Revascularization	Any percutanous coronary intervention or surgical coronary artery bypass grafting
Major adverse cardiac event (MACE)	Composite of cardiovascular deathMACE

Statistical Analysis

Troponin assay findings were evaluated using the 99th percentile and LOD cut-off points to assess their prognostic usefulness. Categorical variables are shown as numbers and percentages, whereas continuous variables are shown as medians (interquartile range). To compare the predictability of adverse occurrences, receiver operating characteristic (ROC) curves were generated and the areas under the ROC curve (AUC) were computed. Kaplan-Meier survival curves were used to measure the time to event, and the log-rank test was used to determine group differences. After determining the hazard ratios (HRs) and applying Cox proportional hazard modelling (with troponin <LOD as a reference), the HRs were further adjusted by index admission and the forward conditional technique based on the characteristics of the patients. All hypothesis testing was two-tailed and P values of less than 0.05 were considered to indicate statistical significance. All statistical analyses were performed with the use of SPSS for windows (www.spss.com, 1999–2004, Version 13.0) and MedCalc software (www.medcalc.be, 1993–2005, Version 8.1.0.0).

Results

332 patients in all, whose samples were large enough to measure every test at both time points, were examined (recruitment is indicated in Figure 1 of Aldous et al.11). In Table 2, baseline characteristics are displayed. Every individual had follow-up data accessible after two years, and Table 3 displays the side effects.

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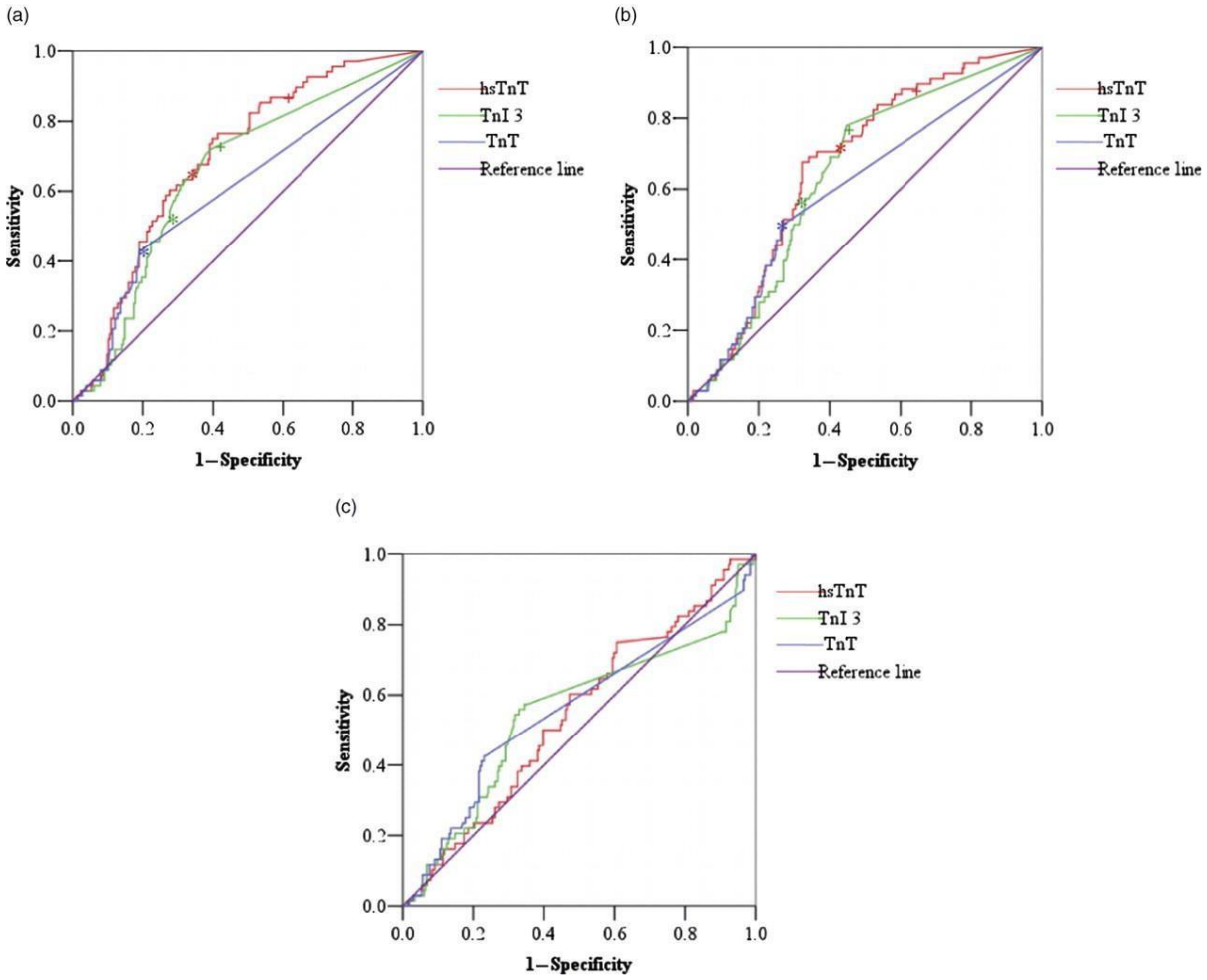

Figure 1 ROC curve analysis comparing prognostic power of troponin assays: (a) baseline troponin, (b) follow-up troponin and (c) delta troponin. ROC, receiver operating characteristic. *99th percentile; + limit of detection (NB 99th percentile and LOD are the same for TnT)

Table 2 Patient Characteristics

Characteristic (%)	**All patients, n = 332 (%)**	**Patient with MACE, n = 68**	**Patients without MACE, n = 264**	**P value**
Median age, years (interquartile range)	64.3 (52.8– 73.5)	63.6 (57.9– 76.1)	64.4 (52.0– 73.2)	>0.1
Male	200 (60.2)	38 (55.9)	162 (61.4)	>0.1
Ethnicity				
NZ/other European	282 (84.9)	58 (85.3)	224 (84.8)	>0.1
NZ Maori/Pacific Islander	20 (6.0)	3 (4.4)	17 (6.4)	>0.1
Other	30 (9.0)	7 (10.3)	23 (8.7)	N/A
Hypertension	152 (45.8)	31 (45.6)	121 (45.8)	>0.1
Diabetes	54 (16.3)	9 (13.2)	45 (17.0)	>0.1
Smoking	148 (44.6)	30 (44.1)	118 (44.7)	>0.1
Current	57 (17.2)	10 (14.7)	47 (17.8)	>0.1

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Ex	91 (27.4)	20 (29.4)	71 (26.9)	>0.1
Dyslipidaemia	126 (38.0)	27 (39.7)	121 (45.8)	>0.1
Prior ischaemic heart disease	179 (53.9)	42 (61.8)	137 (51.9)	>0.1
Family history ischaemic heart disease	132 (39.8)	28 (41.2)	104 (39.4)	>0.1

MACE, major adverse cardiovascular events; N/A, not applicable

Table 3 Adverse events at two years

Adverse events (%)	**MACE***	**Cardiac death**	**AMI**	**Revascularization**
During index admission, n = 332	124 (37.3)	3 (0.9)	110 (33.1)	61 (18.4)
Between discharge and 2 years (all patients), n = 332	68 (20.5)	20 (6.0)	54 (16.3)	24 (7.2)
Between discharge and 2 years (index admission MACE), n = 124	41 (33.1)	13 (10.5)	31 (25.0)	16 (12.9)
Between discharge and 2 years (index admission no MACE), n = 208	27 (13.0)	7 (3.4)	23 (11.6)	8 (3.8)
P value (comparing those with MACE on index admission versus those without)	<0.001	0.008	0.001	0.002

*MACE, major adverse cardiac events – composite of cardiovascular death, non-fatal AMI, revascularization; AMI, acute myocardial infarction

By thirty days, the MACE rate was 4.2%. Roche Elecsys high-sensitivity TnT (hsTnT) detected 11 of the 14 (78.6%) patients with 30-day MACE using the baseline sample and 12 (85.7%) if both samples were used when the 99th percentile was applied. Roche Elecsys TnT detected 10 (71.4%) and 11 (78.6%) patients, while Abbott Architect TnI third generation (TnI 3) identified 10 (71.4%) and 10 (71.4%) patients. After two years, the MACE rate was 20.5%. Using the baseline sample, hsTnT identified 43 (63.2%) of the 68 patients (63.2%) who experienced two-year MACE, and 47 (69.1%) if both samples were utilised. TnT 29 (42.6%) and 34 (50.0%) patients and TnI 3 34 (50.0%) and 40 (58.8%) patients, respectively, were discovered.

There were 124 patients experiencing MACE on admission, with TnI 2 adjudicating the diagnosis of AMI; 41 of these patients went on to have further MACE by two years (37 of whom had raised TnI 2). Of those 41 patients, 34 (82.9%) were identified by hsTnT, 33 (80.5%) by TnI 3 and 30 (73.1%) by TnT. Of those who did not have MACE on index admission (and therefore TnI 2 was <99th percentile), 27 went on to experience MACE; 13 (48.1%) of these TnI 2 negative patients were identified by hsTnT, 6 (22.2%) by TnI 3 and 6 (22.2%) by TnT.

ROC curve analysis

The relationship between troponin concentrations and two-year MACE are shown in Figure 1 and Table 4.

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Table 4 ROC generated AUC of biomarkers for prediction of MACE

Biomarker (95% CI)	AUC 0 h	AUC 6–24 h	AUC delta troponin
hsTnT	0.70 (0.63–0.76)	0.67 (0.60–0.73)	0.54 (0.47–0.62)
TnI 3	0.66 (0.59–0.73)	0.64 (0.57–0.71)	0.55 (0.46–0.63)
TnT	0.61 (0.53–0.69)	0.60 (0.52–0.68)	0.56 (0.47–0.64)

ROC, receiver operating characteristics; AUC, area under the curve; CI, confidence intervals; MACE, major adverse cardiovascular events

Since baseline and follow-up values did not differ significantly (P > 0.1 for all), baseline troponins were utilised in all ensuing statistical analyses due to their greater AUCs. MACE was predicted by all troponins. There was no statistically significant difference between hsTnT and TnI 3, however hsTnT outperformed TnT (P = 0.001) and TnI 3 was leaning towards superiority (P = 0.094) in the AUC for two-year MACE. The AUC for MACE of the TnI 2 assay, which was utilised to determine AMI at index admission, was 0.65 (0.57–0.72). In Table 5, the AUCs for each problem are displayed. The statistical prediction of two-year cardiovascular death was seen for all troponins. While TnT did not differ substantially from the line of non-discrimination, hsTnT and TnI 3 were predictive of non-fatal AMI and revascularization.

Table 5 ROC curve generated AUC for all adverse events using baseline troponin

Biomarker (95% CI)	Cardiovascular death	Non-fatal AMI	Revascularization
hsTnT	0.77 (0.71–0.86)	0.66 (0.59–0.73)	0.68 (0.58–0.77)
TnI 3	0.73 (0.64–0.82)	0.61 (0.53–0.68)	0.64 (0.53–0.76)
TnT	0.68 (0.55–0.80)	0.57 (0.48–0.65)	0.61 (0.49–0.73)

ROC, receiver operating characteristics; AUC, area under the curve; CI, confidence intervals; AMI, acute myocardial infarction

The baseline sample was collected from the onset of symptoms at a median time of 3.7 hours (interquartile range: 1.9–8.0). A median of 9.4 hours (interquartile range: 6.3–13.3) passed between the baseline sample and the follow-up sample. For every assay, the dynamic shift in troponin (% delta) from the baseline to the follow-up sample did not differ statistically from the non-discrimination line and, as a result, lacked predictive value (Table 4).

Kaplan–Meier event-free survival analysis Kaplan–Meier two-year MACE-free survival curves areshown in Figure 2, again demonstrating that all troponins predicted two-year MACE. All troponins also predicted death (P < 0.001 for all), non-fatal AMI (P = 0.001, 0.006 and 0.035 for hsTnT, TnI 3 and TnT, respectively) and revascularization (P = 0.035, 0.010 and 0.006, respectively). Figure 2 also demonstrates how those with troponin concentrations detectable in the reference range in assays with sufficient analytical sensitivity also predict adverse events, particularly for TnI 3, with a more graded event rate for hsTnT. This analysis could not be done for TnT as the LOD and 99th percentile are the same.

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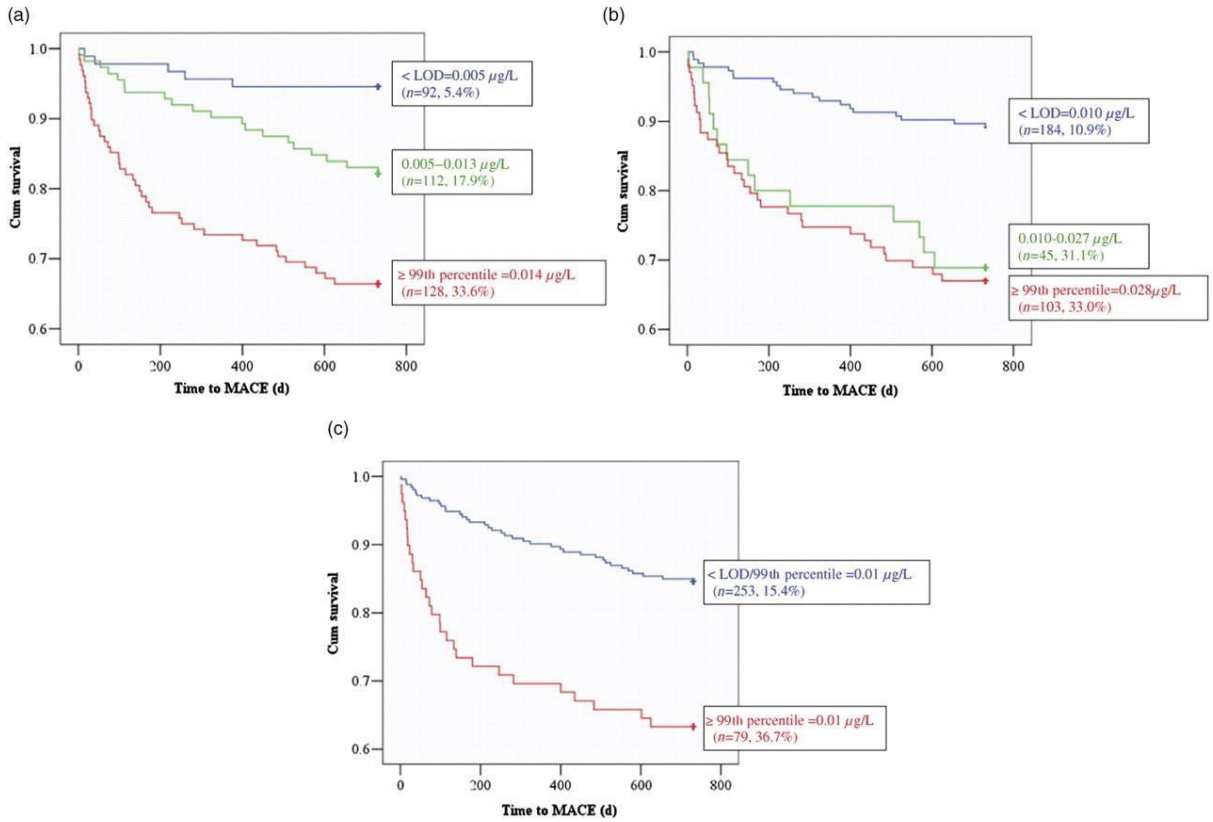

Figure 2 Two-year major adverse cardiovascular event (MACE)-free survival curves: (a) hsTnT (P < 0.001), (b)TnI 3 (P < 0.001) and (c) TnT (P < 0.001)

Cumulative event rates and hazard ratio analysis

Cumulative two-year MACE rates for overt rises (≥99th percentile), detectable levels in the reference range (between LOD and 99th percentile) and undetectable troponin (<LOD) are shown in Table 6 with their respective hazard ratios as adjusted by index admission MACE. hsTnT and TnI 3 conveyed prognostic utility even when adjusted for index admission diagnosis of MACE. TnT was trending to prognostic utility (P = 0.076). The TnI 2 assay, used for adjudication of AMI of index admission, had an HR for follow-up MACE adjusted by index admission MACE of 2.0 (0.8–4.9, P > 0.1). Again the assays were stratified by troponin values showing that even those with detectable levels in the reference range of hsTnT and TnI 3 have prognostic utility. Applying a delta criterion or a rise in troponin of ≥20% to any patient with a peak troponin ≥99th percentile was not predictive of two-year MACE (HR were not raised and P > 0.1 for all). Patients with hsTnT or TnI 3 below the LOD were less likely to have a prior history of ischaemic heart disease than those with levels above the LOD, but all other characteristics were similar.

Table 6 Cumulative event rates and adjusted hazard ratios for MACE

Troponin	Cumulative MACE rate (% ± SE)	Adjusted hazard ratio (95% CI)
hsTnT		
<LOD, n = 92	5.4 ± 2.4	Reference
LOD to 99th percentile, n = 112	17.9 ± 3.6	3.2 (1.2–8.5, P = 0.022)
≥99th percentile, n = 128	33.6 ± 4.2	5.2 (1.9–14.5, P = 0.001)
TnI 3		
<LOD, n = 184	10.9 ± 2.3	Reference

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LOD to 99th percentile, n = 45	31.1 ± 6.9	2.4 (1.2–4.7, P = 0.012)
≥99th percentile, n = 103	33.0 ± 4.6	2.7 (1.3–5.4, P = 0.007)
TnT*		
<LOD, n = 253	15.4 ± 2.3	Reference
LOD to 99th percentile, n = 0	N/A	N/A
≥99th percentile, n = 79	16.7 ± 5.4	1.7 (0.9–3.2, P = 0.076)

Discussion

We report the utility of the newer hsTnT compared with contemporary troponin assays for evaluation of prognostic utility in patients presenting to the ED with chest pain.

This is the first publication that we are aware of that shows similar findings in an ED population, despite the fact that is strong data about the predictive relevance of troponin increases in patients with ischemic heart disease,2–5,13–18 the critically ill,18,19, and in outpatient cohorts,20, 21. This data, which are consistent with previous findings in other settings, 2–5,13–18, show a graded relationship between the extent of troponin heights and prediction. These results validate for the first time the notion that even "high normal" values of these higher sensitivity troponin assays are anticipatory of afterwards coronary artery disease in these patients.

Troponin ≥99th percentile and prognosis

All the troponin assays that were looked at were predictive of MACE, which is consistent with previous studies.4,5,16,17, and 22 employing various cohorts, troponin tests, composite outcomes, and follow-up intervals. These variations in research make it difficult to directly compare tests across studies. The predictive efficacy of hsTnT above TnI 3 and TnT was amply proven by cumulative event rates, despite ROC curve study only demonstrating superiority over TnT. This could have occurred due to an inadequate sample size. Furthermore, all assays detected patients who later experienced MACE during the follow-up period but were missed by the initial TnI 2 assay, despite the fact that the troponin assay (TnI 2) was used to establish admission AMI, which contributed to identifying admission MACE. Statistical analysis confirmed that this prognostic utility was significant for hsTnT and TnI 3, suggesting that assays with high analytical sensitivity best predict adverse events long term.

There have only been a few studies that compare modern troponin assays with greater sensitivity assays, and the results have only revealed slight variations. For instance, Keller et al.21 discovered that for the 30-day composite of death, myocardial infarction, stroke, or hospital admission due to cardiovascular causes, or the need for unforeseen percutaneous coronary intervention within one month after the index incident, the Siemens Troponin I ultra above the 99th percentile had an adjusted HR of 1.96 versus a standard TnT result above the 99th percentile of 1.91. Because our patients had few short-term events (data not shown), previous research has mostly focused on short-term outcomes, which makes extrapolating differences between tests difficult. We thus focused on long-term outcomes. The adjusted HR for the composite of two-year death and non-fatal AMI was 4.37 for Beckmann Coulter AccuTnI and 4.32 for Beckmann Coulter hsTnI using the 99th percentile cut-off point, which is higher than that found in the current study for TnI 3 or TnT but lower than that found for hsTnT. These results are in comparison with a study by Kavsak et al.,15 which did have long-term follow-up. Smaller variations in troponin are more likely to have long-term importance for longer-term outcomes, even though the signal for short-term events is probably large.

Delta troponin and prognosis

In patients with a delta or rise in troponin of ≥20% and a peak troponin concentration ≥99th percentile, the use of a delta troponin has been demonstrated to improve specificity for the diagnosis of AMI17; however, this method did not yield helpful prognostic information for long-term follow-up. The degree of apparent change in troponin readings, however, might have been underestimated because there were varying intervals between the baseline and follow-up samples as well as between the presentation and baseline samples. Furthermore, the most recent research by Vasile et al. demonstrated that, for short-term changes (between 0 and 4 h), the level at which a delta in hsTnT exceeds the biological and analytical variance was 84%. This suggests that many patients achieving a 20% delta do so

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because of biological and/or analytical variation and not because of myocardial damage, which would reduce the test performance of a delta criterion.[23] Nevertheless, despite such potential limitations, these data imply that a delta troponin is unlikely to be a helpful strategy for identifying those at risk of long-term adverse events as suggested by Kavsak et al.[24] who also looked at long-term prognosis, confirming that an acute change in troponin did not appear to be prognostically informative. Conversely, Apple et al.[17] found that adding the criterion of an increase in troponin of >30% improved risk stratification for cardiac events or death in the short term.

Troponin <99th percentile and prognosis

Troponin levels have been demonstrated to be able to predict unfavourable outcomes. In this investigation, hsTnT was better at risk stratification, and even those with detectable levels in the reference range of both TnI 3 and hsTnT were predictive of two-year MACE. Apple et al.4 estimated that the group's 60-day event rates were 11.1% (relative risk 3.9), while the group with no detectable troponin had 2.8% and the group with troponin exceeding the 99th percentile had 42% (relative risk 8.9). In contrast to this study, which clearly demonstrated prognostic efficacy, Apple and Kavsak et al. both found that detectable levels in the reference range did not predict adverse events with statistical significance.15, 17 These detectable but normal results only start to show their predictive significance over an extended period of time because high-sensitivity assays only identify values within the reference range (and because of the correlation between the degree of elevations and prognosis). To fully comprehend these results and the appropriate action for these patients, more research is needed.

The main advantage of employing a high-sensitivity assay in this case appears to be that individuals lacking detectable hsTnT have an incredibly low risk for adverse events, in addition to those with elevations in hsTnT ≥99th percentile having an increased risk and, to a lesser extent, those with detectable levels in the reference range. As a result, measuring hsTnT may be used as a "rule out" method to determine which individuals are unlikely to experience negative outcomes. This method may replace more costly studies like provocative testing. Using a high-sensitivity TnI assay, Venge et al.22 shown that while no patient had readings below the median of the 99th percentile, several patients experienced mortality or AMI within a year that were not detected by this method. However, with the current expert opinion suggesting that an assay cannot be defined as high sensitivity unless at least 95% of healthy individuals have measurable troponin,[22,25] the cut-off value to identify lower-risk patients needs to be validated as the number of patients with values <LOD become fewer. In addition, the endpoints used in this study do not include unstable angina or recurrent chest pain which are an important cause of morbidity; hsTnT may not be as proficient at stratification if such factors were included.

Conclusions

When it came to predicting adverse cardiovascular events up to two years in patients who came to the emergency department (ED) complaining of chest pain, hsTnT performed better than modern TnI and TnT assays. Prognostically significant patients were also found to have detectable values for hsTnT and TnI 3 within the reference range; more specifically, patients with levels below the LOD were shown to be extremely low risk of adverse outcomes. It was revealed that delta troponins were not beneficial.

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