

Randomized Comparison of High-Sensitivity Troponin Reporting in Undifferentiated Chest Pain Assessment

Derek P. Chew, MBBS, MPH; Christopher Zeitz, MBBS, PhD; Matthew Worthley, MBBS, PhD; Hugh Grantham, MBBS; John Beltrame, MBBS, PhD; Margaret Arstall, MBBS, PhD; Penelope Coates, MBBS; Carolyn Astley, DrPH; Stephen Quinn, PhD; Julie Ratcliffe, PhD; Matthew Horsfall, RN; Philip G. Aylward, BMBCh, PhD

Background—High-sensitivity troponin T (hs-TnT) assays promise greater discrimination of evolving myocardial infarction, but the impact of unguided implementation on the effectiveness of care is uncertain.

Methods and Results—We evaluated the impact of hs-TnT reporting on care and outcome among chest pain patients presenting to 5 emergency departments within a multicenter randomized trial. Patients were allocated to hs-TnT reporting (hs-report) or standard reporting (std-report; Roche Elecsys). The primary end point was death and new or recurrent acute coronary syndrome by 12 months. A total of 1937 patients without ST-segment elevation were enrolled between July 2011 and March 2013. The median age was 61 (interquartile range, 48–74) years, and 46.3% were women. During the index hospitalization, 1466 patients (75.7%) had maximal troponin <30 ng/L within 24 hours. Randomization to hs-report format did not alter the admission rate (hs-report: 57.7% versus std-report: 58.0%; $P=0.069$). There was no difference in angiography (hs-report: 11.9% versus std-report: 10.9%; $P=0.479$). The hs-reporting did not reduce 12-month death or new/recurrent acute coronary syndrome in the overall population (hs-report: 9.7% versus std-report: 7.2% [hazard ratio, 0.83 (0.57–1.22); $P=0.362$]). However, among those with troponin levels <30 ng/L, a modest reduction in the primary end point was observed (hs-report: 2.6% versus std-report: 4.4%, [hazard ratio, 0.58; 95% confidence interval, 0.34–0.1.00; $P=0.050$]).

Conclusions—High-sensitivity troponin reporting alone is associated with only modest changes in practice. Clinical effectiveness in the adoption of high-sensitivity troponin may require close coupling with protocols that guide interpretation and care.

Clinical Trial Registration—URL: <http://www.ANZCTR.org.au>. Unique identifier: ACTRN12611000879965. (*Circ Cardiovasc Qual Outcomes*. 2016;9:542-553. DOI: 10.1161/CIRCOUTCOMES.115.002488.)

Key Words: acute coronary syndrome ■ angiography ■ clinical trial ■ myocardial infarction ■ troponin T

Although the clinical guideline–recommended management of patients presenting with high-risk features suggestive of acute coronary syndromes (ACS) is relatively well defined, the management of patients with low- and intermediate-risk chest pain is more heterogeneous.^{1–3} Nevertheless, these patients represent, by far, the greatest proportion presenting to emergency services for evaluation of suspected ACS.⁴ The efficient identification of the few patients who are in the early stages of an ACS, among the many patients presenting with noncardiac chest pain, remains a key clinical challenge.

Troponin testing has revolutionized the care of suspected ACS patients, by improving the diagnostic sensitivity and identifying those patients who derive a greater absolute benefit from potent antiplatelet agents, early angiography, and

revascularization.^{5–7} Consequently, troponin results have substantial clinical and resource implications for the patient and the healthcare system.

More recently, troponin assays with increased diagnostic precision have been developed. These assays are able to determine serum troponin levels at the 99th percentile of a reference population with <10% coefficient of variation.^{8–10} Several investigators have demonstrated increased sensitivity and high negative predictive value but reduced specificity and lower positive predictive value with these assays.^{11,12} Clinical interpretation of low levels of troponin elevation requires careful consideration of ACS likelihood.¹³ Potentially, improvement in discriminatory capacity with high-sensitivity troponin may lead to fewer missed myocardial infarction (MI)

Received November 17, 2015; accepted June 20, 2016.

From the Flinders University, Adelaide, South Australia, Australia (D.P.C., H.G., C.A., S.Q., J.R., P.G.A.); Flinders Medical Centre, Adelaide, South Australia, Australia (D.P.C., P.G.A.); University of Adelaide, Adelaide, South Australia, Australia (C.Z., M.W., J.B.); The Royal Adelaide Hospital, Adelaide, South Australia, Australia (C.Z., M.W.); The Queen Elizabeth Hospital, Adelaide South Australia, Australia (J.B.); The Lyell McEwen Hospital, Adelaide, South Australia, Australia (M.A.); SA Pathology, SA Health Adelaide, South Australia, Australia (P.C.); Heart Foundation, South Australia, Australia (C.A.); and SA Health, Adelaide, Australia (M.H.).

The Data Supplement is available at <http://circoutcomes.ahajournals.org/lookup/suppl/doi:10.1161/CIRCOUTCOMES.115.002488/-/DC1>.

Correspondence to Derek P. Chew, MBBS, MPH, Flinders Medical Centre, Flinders Dr, Bedford Park, South Australia, 5042, Australia. E-mail derek.chew@flinders.edu.au

© 2016 American Heart Association, Inc.

Circ Cardiovasc Qual Outcomes is available at <http://circoutcomes.ahajournals.org>

DOI: 10.1161/CIRCOUTCOMES.115.002488

WHAT IS KNOWN

- Studies have suggested that high-sensitivity troponin assays have superior performance for the diagnosis and exclusion of myocardial infarction when compared with previous generation troponin assays.

WHAT THE STUDY ADDS

- Whether this improved assay performance alone translates to superior care and outcome among patients presenting to the emergency department with suspected ACS remains uncertain.
- This study is a prospective randomized evaluation of the impact of high-sensitivity troponin T reporting on care and outcome among patients presenting to the emergency department.
- Within a patient-level, randomized trial of high-sensitivity troponin versus standard troponin reporting, only modest changes in overall practice and clinical outcomes by 12 months were observed.
- Translating high-sensitivity troponin testing into superior patient outcomes, and more efficient care may require integration of these assays into prospectively validated protocols that guide clinical decision making.

and enable rapid discharge of patients without evolving ACS, but the concern that these benefits may be offset by the possible risks associated with the overinvestigation of patients with elevated troponin results not related to ACS remains. To explore whether there is greater risk discrimination with impact on cardiac investigations, management, and outcome, we conducted a randomized study examining the effects of unguided troponin reporting down to levels achievable with a high-sensitivity troponin T assay on in-hospital clinical care and death or recurrent ACS admission by 12 months among a broad population of patients presenting with undifferentiated chest pain.

Methods

Study Design and Patient Population

This study was a prospective multicenter trial comparing serum troponin levels reported at either levels consistent with a standard troponin T assay or at levels achievable with a high-sensitivity assay, randomized in a 1:1 ratio at the patient level.¹⁴ Patients were screened and enrolled in the emergency departments (ED) at 5 metropolitan hospitals in Adelaide and followed up for a duration of 12 months after randomization. Each of these hospitals provided emergency services 24 hours per day, and all but one had dedicated chest pain assessment units. The study was approved by each hospital's human research ethics committee, and all participants provided written informed consent. (Australian New Zealand Clinical Trials Registry [<http://www.anzctr.org.au/>] registration number ACTRN12611000879965.)

Patients presenting to the ED with clinical features of chest pain or suspected ACS (chest pain or overwhelming shortness of breath (>10 minutes at rest <24 hours from the time of presentation) in whom the treating physician deemed a measurement of the serum troponin was required were eligible. Patients were excluded if they were <18 years of age; had evidence of ST-segment elevation on presenting ECG; required permanent dialysis; had suspected ACS secondary to other

causes (severe anaemia, sepsis, etc); were unable to complete a clinical history questionnaire because of language or comorbidity; or were unable or unwilling to provide written informed consent. Patients were prospectively subclassified by the National Heart Foundation ACS Guidelines risk classification using clinical characteristics such as hemodynamic compromise, ECG changes, biomarker elevation, presence of previous coronary disease, and diabetes mellitus (Table I in the [Data Supplement](#)), with this information made available to the treating physician.¹⁵ Randomization was blocked by hospital and Heart Foundation clinical risk strata, evaluated using a standardized questionnaire completed by trial staff. Clinical components of the Global Registry of Acute Cardiac Events risk score and Thrombolysis In Myocardial Infarction risk were also documented but not used in randomization.^{16,17}

Randomization Allocation and Intervention

Patients undergoing troponin testing were identified soon after presentation, before samples were sent for pathology testing to limit delays of usual patient assessment. Within the hours of 9 AM to 5 PM, dedicated study nurses stationed within the ED ensured that the initial ECG did not demonstrate ST-segment elevation and then approached each patient. Outside these times, patients were not included. After written informed consent, the clinical risk strata was determined, and patients were randomized to troponin testing reported to either standard troponin T levels (std-report; actual level 30 ng/L [ie, levels below 29 ng/L reported as <29] and above [<29 ng/L: normal, 30–100 ng/L: borderline abnormal, and >100 ng/L: myocardial injury]) or high-sensitivity format (hs-report: actual level >3 ng/L [normal: ≤14 ng/L and >14 ng/L: myocardial injury]) using sequentially numbered sealed envelopes. Preprepared blood request forms within each sealed envelope were then used to inform the state-wide pathology service of the randomized allocation and the required reporting format. All patients underwent troponin testing at ED presentation and 3 and 6 hours after presentation unless discharged before these time points at clinical discretion. Troponin testing outside protocol-defined time points was permitted at the treating clinicians discretion, but reporting of the result was restricted to the allocated format for the index admission. Physicians receiving reports in the std-report format were not permitted to request results in the hs-report. No recommendations regarding repeat testing and specific care were provided in the report and all subsequent care was determined by the treating clinicians. Only standardized advice about interpretation of the tests (sensitivity of the test and upper limited of the reference range) was provided by the pathology service. Standard reporting was maintained for all patients not enrolled for the entire duration of the study and subsequent admissions for study participants. To minimize the risk of contamination and crossover between study arms associated with the use of separate conventional and high-sensitivity assays, all troponin tests were performed using the Elecsys Troponin T high-sensitive (TnT-hs)-cobas (Roche Diagnostics), and only the reporting was changed for the study patients.

Measures of Care and Clinical Outcomes

Measures of Care

Clinical care was measured by the frequency of functional testing, echocardiography, invasive angiography, and revascularization by 12 months, and the use of guideline-recommended therapies. In addition, patients were assessed for ED length of stay, total length of stay, and readmission for cardiovascular causes. Late outcomes were captured through a state-wide universal hospital administrative system that includes all readmissions and is linked to the death registry, enabling evaluation of late survival. The details of readmissions were then sourced from the treating hospitals. Patients were also contacted at 30 days, 6 months, and 12 months, to assess for vital status, rehospitalizations, and quality of life.

Clinical Outcomes

The primary outcome was the cumulative composite end point of all-cause mortality and new or recurrent ACS (beyond the first 24

hours of enrollment) ≤12 months. The end point of new or recurrent ACS was defined as MI with a rise or fall in cardiac biomarkers or a new myocardial defect on cardiac imaging, and consistent with the Universal Definition¹⁸ (using troponin levels >30 ng/dL); or unstable angina defined as chest pain/discomfort with a crescendo pattern or occurring at rest, associated with: dynamic ECG changes consistent with ischemia; or functional testing consistent with ischemia; and/or demonstrated coronary stenosis >70% by visual estimation. All index presentations and outcomes were independently adjudicated by cardiologists without involvement in the care of patient. Through this process, MI diagnosed within the first 24 hours of presentation was considered as an index event and was not included in the primary outcome. Secondary outcomes included cardiovascular mortality; individual components of the primary end point; cerebrovascular accidents with cerebral imaging; atrial or ventricular arrhythmias; congestive cardiac failure without MI; representation for chest pain; and significant bleeding assessed using the Bleeding Academic Research Consortium (BARC) definitions (definition 2–5).¹⁹

A Clinical Event Committee, chaired by an experienced cardiologist and managed by an independent member of the data-management group, provided blinded evaluation of all components of the primary end point including index (within 24 hours of initial presentation) and subsequent MI. A Data and Safety Monitoring Board assessed the study safety through the evaluation of all in-hospital and postdischarge (≤7 days) clinical events including representations to hospital.

Statistical Analysis

Because randomization occurred before troponin testing, the primary analysis population included all randomized patients regardless of the initial troponin level, and all analyses were conducted as intention to treat. Subsequent analyses were also confined to patients with maximal peak troponin levels within 24 hours of <30 ng/L where differences in the reporting format existed between the 2 study arms. Baseline clinical characteristics were presented for all patients and by troponin report type. Continuous variables are expressed as medians with interquartile ranges, whereas categorical and count variables are presented as frequency (percentage). Patient baseline characteristics, inpatient investigation, therapies, and outcomes between the randomized groups were compared using χ^2 or Fisher

exact tests for categorical variables and using Kruskal–Wallis tests for continuous variables.

The rates of death and new/recurrent ACS at 12 months and the composite primary end point at 30 days were examined in the entire population and stratified by maximal in-hospital troponin (<5 ng/L [below level of detection], 5–14 ng/L [LoD to hs-TnT upper reference limit {URL_{hsTnT}}], 15–29 ng/L [URL_{hsTnT} to standard report reference limit {URL_{std}}], 30–100 ng/L [URL_{std} to older MI thresholds], and >100 ng/L) and by clinical risk strata. The primary analysis compared the time to first occurrence of the primary end point between the high-sensitivity and standard troponin format study arms using univariable Cox model with hospital random effects (shared frailty model) to account for correlated readings within hospitals. Twelve-month freedom from mortality, recurrent MI, and cardiac readmission was also assessed using the same methods. Time to event curves were plotted for the entire population and among those with a peak troponin <30 ng/L within the first 24 hours using a cumulative incidence function.

To explore whether the troponin reporting format may influence decisions to admit or discharge patients from the ED when the Heart Foundation risk strata were also considered, a logistic regression model, with ED discharge as the dependent variable and report type, risk strata, and interaction terms for each risk strata by hs-report type as independent variables, was used. Similarly, the influence of the level of peak troponin within the first 24 hours and the randomized reporting format on the provision of cardiac investigations, coronary revascularization, and recommended pharmacologies were explored within logistic models. Within these models, the investigation or therapy was modeled as the dependent variable, with the troponin strata, the reporting format, and an interaction term for each troponin strata by hs-report type modeled as independent variables.

Sample Size Estimation

Assuming the correct management of these patients translates to reduction in death or ACS admissions, from 8.6% to 5.1%, a sample size of 828 patients per arm (power of 80% at an alpha of 0.05) was required for the primary analysis. The planned sample size was 2000 patients. A probability of <0.05 is considered statistically significant. All analyses were performed using Stata 13.1 (College Station, TX).

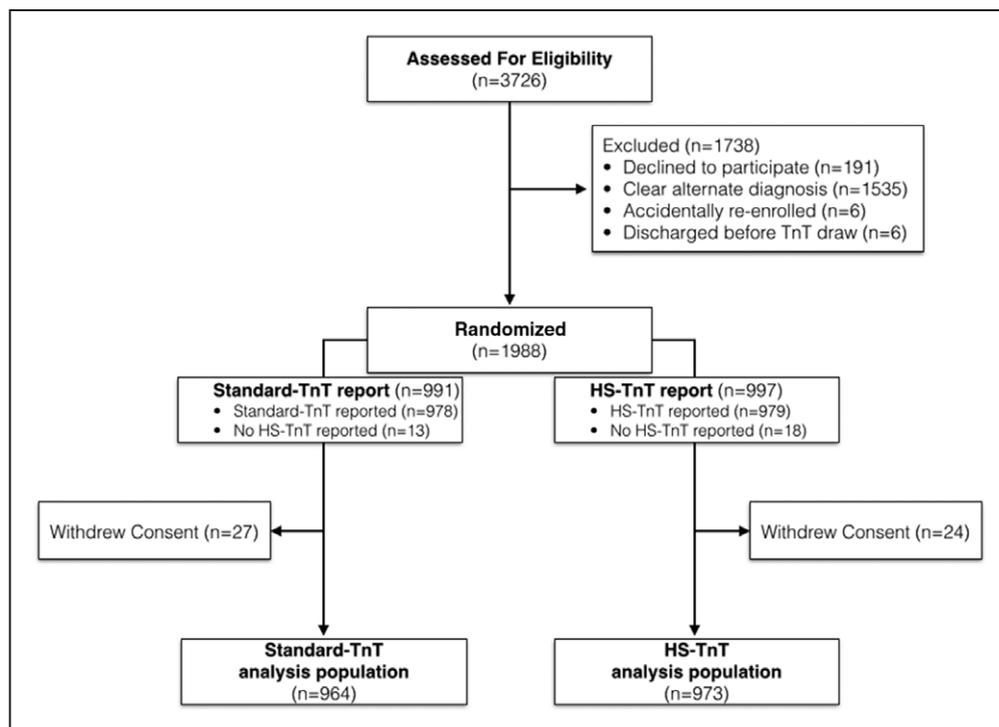


Figure 1. CONSORT diagram describing patient flow. Hs-TnT indicates high-sensitivity troponin T.

Results

In total, 1988 patients (53% of the screened population) were randomized in the study between July 2011 and March 2013. Among these patients, 51 patients withdrew consent during the follow-up period, leaving 1937 patients for analysis (973 receiving a high-sensitivity report and 964 patients receiving the standard report). Reflecting the pragmatic nature of

the study, 31 patients had hemolyzed blood samples without repeat troponin testing requested, and these patients have been retained in the intention-to-treat analysis. A summary of patient flow and exclusions is provided in Figure 1. Risk stratification criteria observed that 1421 patients (73.4%) were at either intermediate or high risk, whereas 1466 patients (75.7%) had a peak troponin level <30 ng/L, and 230 patients

Table 1. Baseline Clinical Characteristics by Troponin Report Type

Characteristic	Total (n=1937)	High-Sensitivity Troponin Report (n=973)	Standard Troponin Report (n=964)	P Value
Age, y, median (IQR)	61.3 (48.6–73.9)	61.6 (48.7–73.8)	60.7 (48.3–74.3)	0.804
Female sex	46.3%	47.3%	45.3%	0.391
Presentation with chest pain or shortness of breath	89.1%	88.8%	89.3%	0.684
Time to presentation, h, median (IQR)	2.2 (0.7–5.5)	2.1 (0.6–5.2)	2.5 (0.8–5.8)	0.237
Time from presentation to consent, min, median (IQR)	30 (16–51)	30 (16–50)	30 (17–53)	0.657
Heart rate, mm Hg, median (IQR)	76 (66–88)	76 (66–88)	76 (66–88)	0.899
Systolic blood pressure, mm Hg, median (IQR)	140 (124–155)	139 (123–154)	140 (125–156)	0.240
SD on ECG	13.3%	12.6%	14.0%	0.376
Baseline creatinine, mmol/L, median (IQR)	75 (64–89)	75 (64–89)	74 (63–89)	0.269
Heart foundation classification				0.509
High risk	33.7%	35.0%	32.5%	
Intermediate risk	39.7%	39.1%	40.3%	
Low or no risk	26.6%	27.3%	26.0%	
GRACE score, median (IQR)	78 (56–108)	79 (56–110)	78 (57–107)	0.489
TIMI risk score, median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	0.446
Current smoker	18.4%	18.3%	18.6%	0.574
Known hypertension (n, %)	51.8%	51.2%	52.4%	0.596
Known hyperlipidemia (n, %)	52.4%	52.3%	52.4%	0.974
Diabetes mellitus (n, %)	18.6%	19.2%	18.0%	0.471
Family history of IHD (n, %)	54.1%	53.4%	54.8%	0.325
Previous myocardial infarction (n, %)	17.3%	16.7%	18.0%	0.438
Previous coronary intervention (n, %)	15.2%	16.3%	14.1%	0.171
Previous CABG (n, %)	8.3%	8.2%	8.3%	0.951
Previous cerebrovascular disease (n, %)	7.9%	7.7%	8.1%	0.760
Previous chronic lung disease (n, %)	9.9%	10.0%	9.8%	0.902
Peripheral vascular disease (n, %)	7.3%	6.9%	7.7%	0.515
Known malignancy (n, %)	10.3%	10.1%	10.5%	0.769
Impaired activities of daily living (n, %)	3.4%	3.1%	3.8%	0.425
Morbid obesity (n, %)	11.0%	10.6%	11.3%	0.611
Maximal troponin strata (n=1906)				0.400
Undetectable	31.0%	32.5%	29.6%	
5–14 ng/L	33.8%	32.0%	35.7%	
15–29 ng/L	12.1%	12.8%	11.4%	
30–100 ng/L	18.7%	18.4%	18.9%	
>100 ng/L	4.4%	4.3%	4.5%	

Categorical variables compared by χ^2 test. Continuous variables compared by Kruskal–Wallis test. CABG indicates coronary artery bypass grafting; GRACE, Global Registry of Acute Cardiac Events; IHD, ischemic heart disease; IQR, interquartile range; and TIMI, thrombolysis in myocardial infarction.

Table 2. Investigations and Management by Troponin Report Type During Index Presentation

Characteristic	Total (n=1937)	High-Sensitivity Troponin Report (n=973)	Conventional Troponin Report (n=964)	P Value	
ED disposition					
Admitted	57.9%	57.7%	58.0%	0.067*	
Discharged	41.1%	41.8%	40.4%		
Left at own risk	1.0%	0.5%	1.6%		
Discharge (TnT <30 ng/L)	46.0%	49.1%	46.4%	0.045	
Echocardiography	18.5%	18.8%	18.2%	0.711	
Functional study	22.6%	22.2%	23.0%	0.663	
Angiogram by 12 mo	11.4%	11.9%	10.9%	0.479	
Revascularization by 12 mo	5.4%	5.2%	3.8%	0.138	
Medications at discharge					
Aspirin	35.8%	36.1%	35.5%	0.771	
Other antiplatelet agent	14.0%	13.7%	14.2%	0.723	
Statin	42.6%	42.7%	42.6%	0.994	
ACE-I or ARB	37.8%	36.5%	39.1%	0.234	
β-Blocker	26.3%	26.1%	26.5%	0.862	
ED LOS, h (IQR)	5.4 (3.7–7.5)	5.4 (3.7–7.6)	5.4 (3.6–7.3)	0.330	
Hospital LOS, d (IQR)	0.9 (0.2–2.0)	0.9 (0.2–2.0)	0.9 (0.2–2.0)	0.958	
Final index admission diagnosis					
Undiagnosed chest pain	38.0%	37.0%	39.0%	0.084	
Stable angina	2.2%	2.7%	1.7%		
Unstable angina	4.8%	3.8%	5.8%		
Myocardial infarction	4.1%	4.2%	3.3%		
Heart failure	1.8%	2.0%	1.7%		
Arrhythmia	7.4%	8.8%	6.0%		
Pericardial disease	1.2%	1.1%	1.4%		
Other noncardiac	40.5%	40.4%	40.6%		
Coronary diagnosis	11.1%	10.7%	11.4%		0.612
Noncoronary cardiac diagnosis	10.5%	11.9%	9.0%		0.037
Patients With TnT <30 ng/L Within 24 h					
Total (n=1466) High-Sensitivity Troponin Report (n=738) Conventional Troponin Report (n=728) P Value					
Discharged	46.0%	49.1%	46.4%	0.045	
Echocardiography	14.7%	15.6%	13.7%	0.318	
Functional study	22.7%	21.4%	24.0%	0.230	
Angiogram by 12 mo	7.1%	7.6%	7.6%	0.458	
Revascularization by 12 mo	2.2%	2.3%	2.1%	0.750	
Medications at discharge					
Aspirin	32.2%	33.1%	31.2%	0.430	
Other antiplatelet agent	110.9%	10.7%	11.1%	0.512	
Statin	38.1%	38.9%	37.2%	0.512	
ACE-I or ARB	35.0%	34.3%	35.7%	0.565	
β-Blocker	21.8%	22.6%	20.9%	0.417	

Categorical variables compared by χ^2 test or Fisher exact test. Continuous variables compared by Kruskal–Wallis test. Noncoronary cardiac diagnosis includes heart failure, arrhythmia, or pericardial disease. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; coronary diagnosis, myocardial infarction, unstable angina, or stable angina; ED, emergency department; IQR, interquartile range; LOS, length of stay; and TnT, troponin T.

*Fisher exact test.

(12.1%) had a troponin level between 14–29 ng/L within the first 24 hours. The median time from symptom onset to ED presentation and presentation to consent was 2.2 hours (range, 0.7–5.6) and 30 minutes (range, 16–51), respectively. Baseline clinical characteristics are presented in Table 1.

In-Hospital Care and Discharge Diagnosis

Overall, there was no difference in the proportion of patients discharged home directly from the ED with high-sensitivity reporting (hs-report: 406 of 971 patients (41.8%) versus std-report: 389 patients (40.1%); $P=0.514$). However, among patients classified as low or no risk by Heart Foundation Criteria, a higher rate of discharge from the ED was observed in the hs-report group (hs-report: 168 of 253 patients (66.4%) versus std-report: 148 of 263 patients (56.3%); $P=0.010$), although discharge rates were nonsignificantly lower in the moderate risk and no different in the high risk groups, respectively, with the hs-report (moderate risk: hs-report: 131/380 (34.5%) versus std-report: 155 of 262 patients (40.2%), $P=0.068$; high-risk: hs-report: 108 of 340 patients (31.8%) versus std-report: 86 of 313 patients (27.5%), $P=0.488$; interaction P value=0.029). There was no difference in subsequent inpatient cardiac investigations and management. Specifically, there was a nonsignificant increase coronary angiography among patients randomized to the hs-report, with a nonsignificant increase in revascularization was evident by 12 months. Antiplatelet therapy and statin therapy were prescribed in the same frequency in both treatment groups. The overall use of cardiac investigations and management stratified by troponin reporting is presented in the Table 2. However, among patients

with a peak troponin of 14 to 29 ng/L within 24 hours, there was a significant interaction between the use of the hs-report and the prescription of aspirin (hs-report: 55.4% versus std-report 34.0%, $P=0.006$; interaction P value=0.007) and statins (hs-report: 65.6% versus std-report 5.0%, $P=0.017$; interaction P value=0.005) at discharge (Figure 2). A nonsignificant increase in revascularization was observed in this group, and there was no significant interaction between the reporting format, the troponin level, and the prescription of the other pharmacotherapies.

The Clinical Event Committee–determined final diagnosis is shown in Table 2. There was no increase in the proportion of patients with the diagnosis of MI within the first 24 hours of admission. There was a significant increase in the proportion of patients discharged with a noncoronary cardiac diagnosis. The proportion of patients discharged with a noncardiac diagnosis was similar between the 2 groups.

Troponin Level and Clinical Events

There was a strong association between the maximal in-hospital troponin level within 24 hours and the risk of subsequent clinical events (Figure 3). For patients with a troponin level below the reportable limit (<5 ng/L), there were no deaths and 2 ACS events (1 MI and 1 unstable angina) observed within the first 30 days of follow-up. By 12 months, there was 1 death and 5 ACS events (3 MIs and 2 unstable angina) observed in this group. Nevertheless, there remained a substantial number of hospital representations in this group, largely driven by representations with chest pain. With modest elevations in either the initial troponin or the maximal observed troponin level,

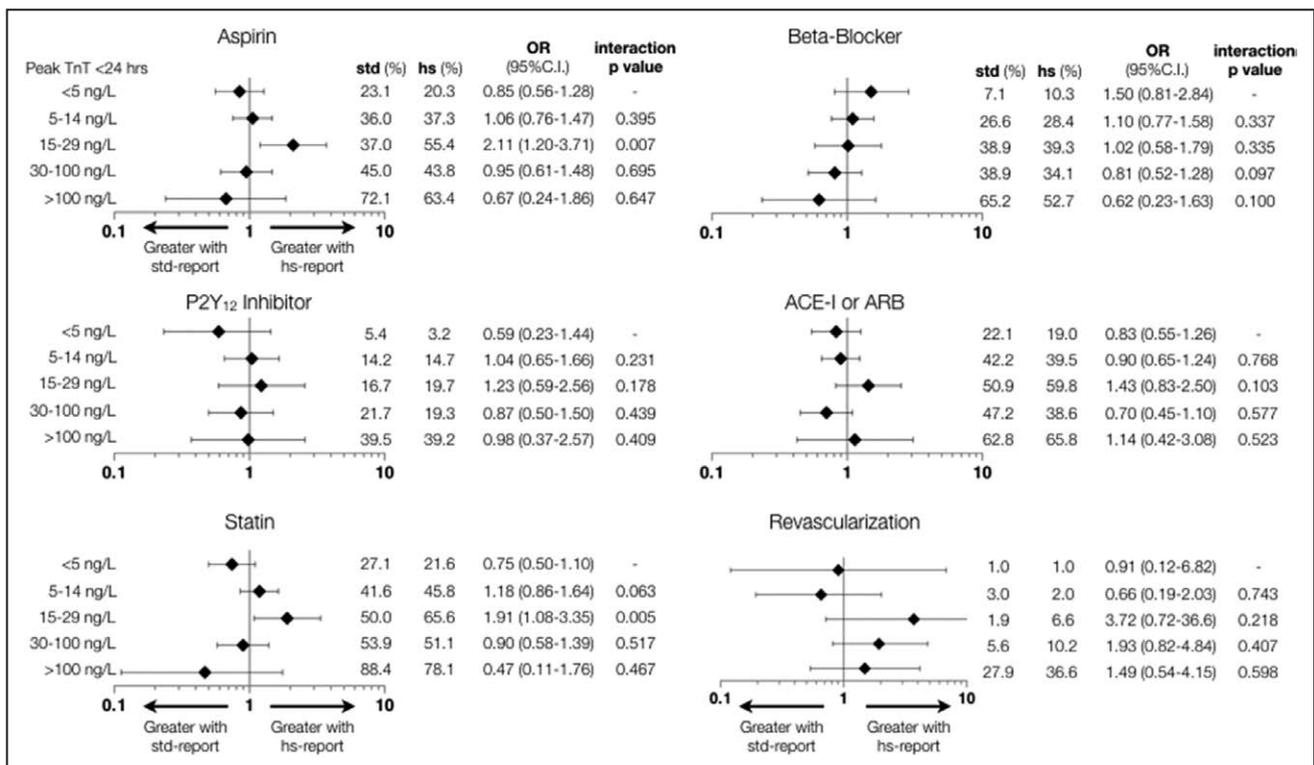


Figure 2. Interaction between troponin reporting type, peak troponin level within 24 h, and the use of ACS guideline–advocated therapies. ACE-I indicates angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CI, confidence interval; hs, high-sensitivity; OR, odds ratio; std, standard; and TnT, troponin T.

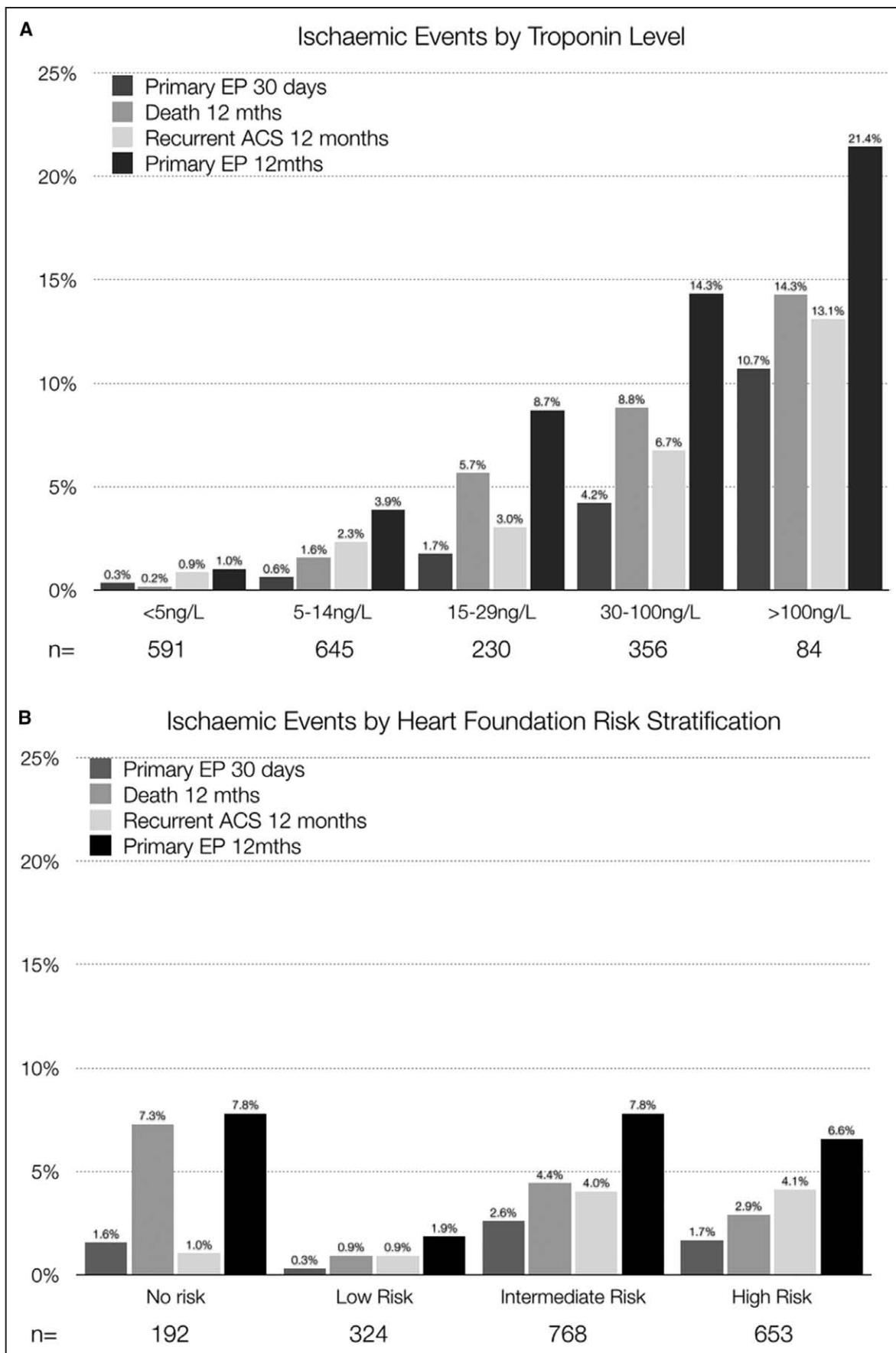


Figure 3. Clinical outcomes stratified by (A) maximal troponin level during index presentation and (B) National Heart Foundation Risk Classification. EP indicates end point.

there was an increased rate of 30-day and 12-month mortality, new or recurrent MI, and admissions for heart failure. This increased risk was observed among patients with levels of between 5 and 14 ng/L, considered within the normal range, with a clear linear trend of increased risk associated with elevations beyond this level. In contrast, stratification by the risk criteria demonstrated poor discrimination for 30-day and 12-month events.

Clinical Events by Troponin Reporting

Overall, there were no differences in the primary end point at 12 months for patients randomized to the high-sensitivity troponin report compared with the standard troponin report (hs-report: 57 of 973 patients (9.7%) versus std-report: 69 out of 964 patients (7.2%) [hazard ratio {HR}, 0.83 {0.57–1.22}; $P=0.362$]; Table 3). However, the composite death and repeat cardiovascular admissions (ie, representations for chest pain, recurrent MI, cerebrovascular accidents, major bleeding, heart failure, or cardiac arrhythmia) were increased at 30 days in the overall population (hs-report: 94 of 973 patients (9.7%) versus std-report: 69 of 964 patients (7.2%) [HR, 1.37 (1.00–1.89); $P=0.047$]) and when confined to patients with troponin levels <30 ng/L. This was driven by an increase in early noncoronary representations and was no longer significant at 12 months. Among patients with a maximal level

<30 ng/L, randomization to the high-sensitivity report was associated with a reduction in the primary end point at 30 days (hs-report: 1 of 738 patients (0.1%) versus std-report: 9 of 728 patients (1.2%); HR, 0.11 [95% confidence interval, 0.02–0.76]; $P=0.034$) and at 12 months (hs-report: 19 of 738 patients (2.6%) versus std-report: 32 of 728 (4.4%); HR, 0.58 [95% CI, 0.34–0.10]; $P=0.05$; Table 4). A modest reduction in the risk of death (hs-report: 7 of 738 patients (1.0%) versus std-report: 17 of 728 patients (2.3%); HR, 0.44 [95% confidence interval, 0.17–0.97]; $P=0.044$) remained evident at 12 months, and all of these deaths were adjudicated to be of cardiac cause. Figure 4 shows the Kaplan–Meier event curves for the overall population and patients with troponin level <30 ng/L within 24 hours.

Discussion

This study is the first to evaluate the impact of unguided troponin T reporting to levels capable with a high-sensitivity troponin T assay, on clinical care and outcome within a randomized clinical trial embedded within routine ED care. Within this heterogeneous study cohort, a substantial number of clinical events are evident by 12 months. Furthermore, clear gradient of increased risk for new or recurrent ACS events and mortality are observed at 30 days and 12 months with increased levels of peak troponin observed within the first 24 hours, even

Table 3. Event Rates and Hazard Ratios at 30 Days and 12 Months, by Troponin Report Type Among All Randomized Patients

Characteristic	High-Sensitivity Troponin Report (n=973)	Standard Troponin Report (n=964)	Hazard Ratio (95% CI)	P Value
Clinical outcomes at 30 d				
Primary end point	1.54 (0.09–2.54)	2.07 (1.34–3.20)	0.74 (0.45–1.50)	0.379
Death	0.62 (0.03–0.14)	0.83 (0.04–1.65)	0.74 (0.26–2.11)	0.580
Myocardial infarction	0.82 (0.41–1.64)	0.93 (0.49–1.79)	0.88 (0.61–1.27)	0.500
Unstable angina	0.31 (0.01–1.0)	0.41 (0.02–1.10)	0.74 (0.15–3.69)	0.716
CVA	0.51 (0.21–1.23)	0.52 (0.02–1.24)	0.99 (0.52–1.90)	0.980
Major bleeding	2.26 (1.49–3.41)	1.24 (0.71–2.18)	1.82 (0.78–4.3)	0.166
Readmission for chest pain	4.53 (3.38–6.03)	3.53 (2.53–4.90)	1.29 (0.83–2.01)	0.263
Readmission for heart failure	1.03 (0.55–1.90)	0.41 (0.16–1.10)	2.48 (0.72–7.92)	0.124
Readmission for arrhythmia	1.34(0.78–2.29)	0.52 (0.22–1.24)	2.59 (0.92–7.26)	0.071
Any CV event	9.66 (7.96–11.69)	7.16 (5.70–8.98)	1.37 (1.00–1.89)	0.047
Clinical outcomes at 12 mo				
Primary end point	5.86 (4.55–7.35)	7.05 (5.60–8.86)	0.83 (0.57–1.22)	0.362
Death	3.08 (2.17–4.38)	4.15 (3.06–5.61)	0.74 (0.50–1.10)	0.135
Myocardial infarction	2.06 (1.43–3.17)	2.18 (1.43–3.23)	0.94 (0.64–1.40)	0.768
Unstable angina	1.23 (0.70–2.16)	1.14 (0.63–2.05)	1.08 (0.62–1.87)	0.781
CVA	1.08 (0.54–2.16)	1.45 (0.86–2.44)	0.78 (0.44–1.36)	0.380
Major bleeding	4.01 (2.94–5.45)	2.49 (1.68–3.69)	1.56 (0.84–2.88)	0.166
Readmission for chest pain	13.46 (11.47–15.77)	13.28 (11.29–15.59)	0.98 (0.78–1.25)	0.908
Readmission for heart failure	3.70 (2.68–5.09)	2.90 (2.01–4.18)	1.23 (0.75–2.00)	0.414
Readmission for arrhythmia	4.73 (3.56–6.26)	4.88 (3.69–6.44)	0.97 (0.65–1.46)	0.902
Any CV event	24.67 (22.08–27.50)	24.07 (21.49–26.89)	1.04 (0.87–1.25)	0.639

Kaplan–Meier failure rates (expressed as percentage and 95% CI). Comparisons using univariate random-effects Cox model (shared frailty: enrolling hospital) for hazard ratio, 95% confidence bounds, and P value. CI indicates confidence interval; CV, cardiovascular; and CVA, cerebrovascular accident.

among patients with detectable levels considered within the normal range for the assay studied. However, we observed only modest impact on clinical practice considering the greater degree of information offered by the high-sensitivity troponin result, with only minor reduction in the rate of discharge from hospital, and a nonsignificant increases in hospital admissions and revascularization overall. An increased use of aspirin and statins was seen among patients with a peak troponin level of 14 to 29 ng/L within 24 hours. Nevertheless, a modest reduction in death and recurrent ACS was observed within 30 days and by 12 months, with a reduction in mortality also observed at 12 months. Further realizing the promise of greater risk discrimination by informing the better selection of patients for cardiac investigations and treatments through hs-troponin testing may require a commensurate adaptive change of clinical decision making. Adoption of hs-TnT reporting should be clinically integrated with robust protocols validated in appropriately designed randomized clinical trials.

The proportion of patients within this cohort with an initial troponin level of <15 ng/L within 24 hours was 64% and is comparable to other large-scale, population-based samples.⁴ However, we observed a higher absolute risk of all-cause death and/or recurrent ACS at both 30 days and 12 months than reported in these other studies potentially reflecting differing clinical thresholds for troponin testing in the ED.⁴ The gradient of increasing risk of cardiac events that is evident even at levels within the described reference limits is also consistent with several population-based studies, suggesting the potential opportunities for proven cardiac investigation and therapies to improve outcomes if extended to this large patient population.²⁰

Despite the increased interest, reporting of the troponin T level without integration with clinical protocols had a relatively little impact on admission and cardiac investigations, with modest differences in discharge rates among patients at low and intermediate risk based on other clinical criteria.

Nonsignificantly higher rates of coronary angiography and coronary revascularization were seen and an increase in the use of aspirin and statins was observed among the patients with modest peak troponin levels documented within 24 hours. These data are in contrast to a previously reported observational study examining the impact of implementing a troponin I assay with greater sensitivity performance.²¹ Potential factors contributing to the discordant results in that observational study include a greater difference in the information being provided to the clinician resulting from a much greater difference in assay performance between the 2 troponin I tests assessed; the post hoc exclusion of patients with an alternate noncardiac diagnosis; and the impact of secular changes in clinical practice that is difficult to control for when conducting a before and after comparisons of healthcare innovations.

Given the limited impact on care, the modest reduction in recurrent cardiac events and mortality should be interpreted with caution, especially considering the multiple comparisons and the lack of difference seen for the primary outcome analysis. Nevertheless, subtle differences in practice, particularly among patients with other noncoronary cardiac conditions, may account for differences in outcomes observed. The overall higher representation rate for patients receiving hs-TnT testing requires further explanation and is potentially related to identification of modest elevations in troponin during the index presentation leading to an increase in noncoronary cardiac diagnoses and subsequent care in addition to the modest differences in pharmacology observed. Knowledge of these diagnoses may influence patient behavior and outcome after initial presentation, highlighting the need for studies of diagnostic testing to evaluate late outcomes beyond the initial diagnostic process. Nevertheless, effective implementation of hs-TnT testing is also likely to require strategies that incorporate better management of patients with nonischemic causes of myocardial injury.

Table 4. Event Rates and Hazard Ratios at 30 Days and 12 Months, by Randomized Troponin Report Type Among Patients With Peak Troponin Level <30 ng/L Within 24 H

Clinical Outcomes at 30 D (Peak Troponin <30 ng/L)	High-Sensitivity Troponin Report (n=738)	Standard Troponin Report (n=728)	Hazard Ratio (95% CI)	P Value
Primary end point	0.14 (0.02–0.01)	1.24 (0.7–2.36)	0.11 (0.02–0.76)	0.034
Death	0.14 (0.02–0.096)	0.41 (0.1–1.27)	0.33 (0.03–3.16)	0.335
Myocardial infarction	0	0.41 (0.01–1.27)	...	0.081
Unstable angina	0	0.41 (0.01–1.27)	...	0.081
Major bleeding	1.08 (0.54–2.16)	0.82 (0.37–1.83)	1.31 (0.46–3.79)	0.613
Any CV event	7.32 (5.65–9.45)	4.67 (3.36–6.47)	1.59 (1.04–2.44)	0.034
Clinical outcomes at 12 mo				
Primary end point	2.57 (1.65–4.01)	4.40 (3.13–6.16)	0.58 (0.34–1.00)	0.050
Death	0.95 (0.45–1.98)	2.34 (1.46–3.73)	0.40 (0.17–0.97)	0.044
Myocardial infarction	0.68 (0.30–1.62)	0.96 (0.5–2.01)	0.70 (0.22–2.22)	0.548
Unstable angina	0.95 (0.45–1.98)	1.10 (0.55–2.19)	0.86 (0.31–2.37)	0.772
Major bleeding	2.30 (1.35–3.56)	2.20 (1.35–3.56)	1.05 (0.53–2.07)	0.894
Any CV event	21.41 (18.62–24.55)	19.51 (16.81–22.57)	1.12 (0.90–1.41)	0.313

Kaplan–Meier failure rates (expressed as percentage and 95% CI). Comparisons using univariate random-effects Cox model (shared frailty: enrolling hospital) for hazard ratio, 95% confidence bounds, and P value. CI indicates confidence interval; and CV, cardiovascular.

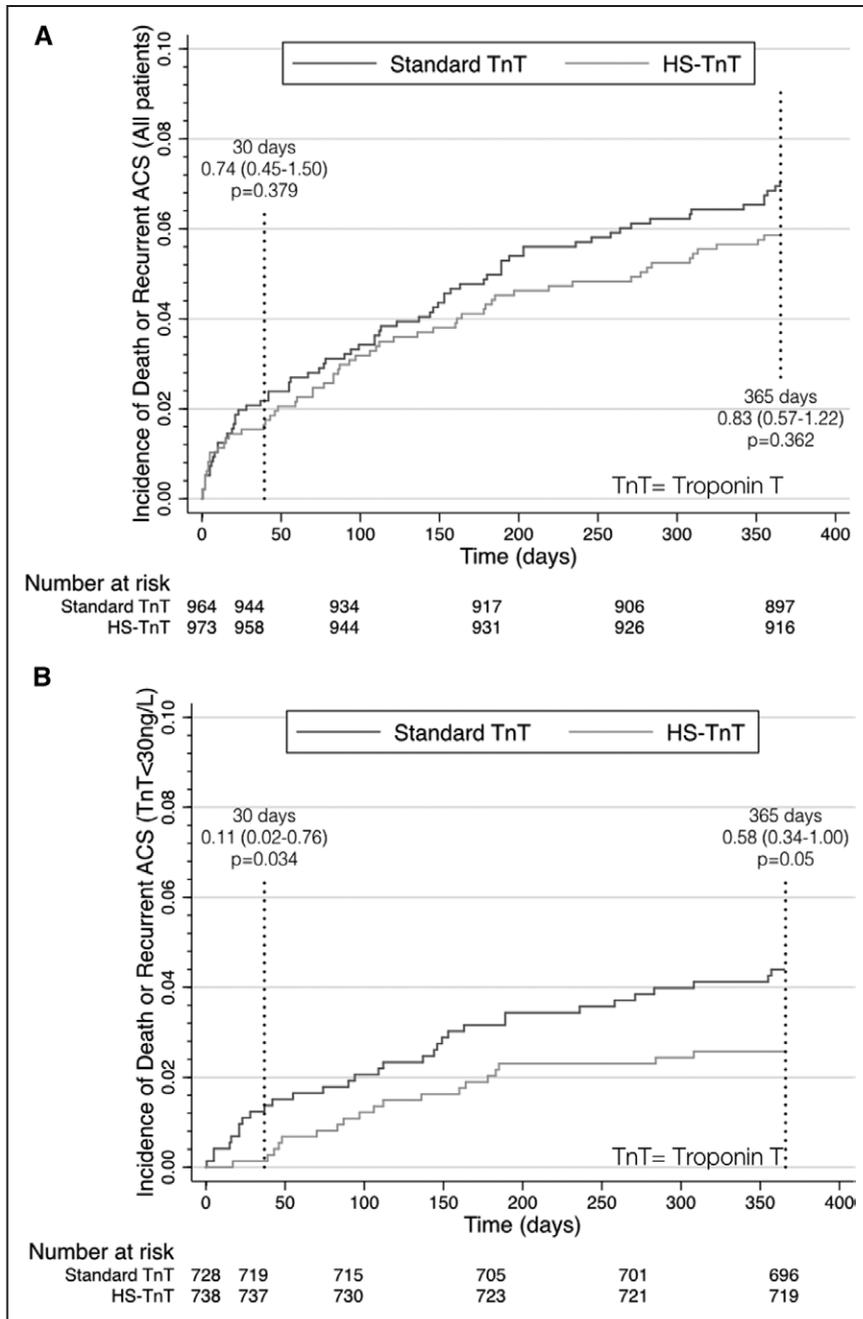


Figure 4. Kaplan-Meier failure function for (A) overall population and (B) patients with troponin level <30 ng/L within 24 h stratified by type of troponin reporting. ACS indicates acute coronary syndrome; and TnT, Troponin T.

The routine use of hs-TnT assays incorporated into protocols of care is currently advocated in ACS guidelines, particularly for identifying patients suitable to early discharge.³ This study highlights the inertia of clinical decision making in response to the adoption of new diagnostic and therapeutic innovations. Availability of troponin results with greater diagnostic precision alone did not substantially improve the effectiveness or efficiency of care, particularly among patients with low or no detectable troponin T. The modest change in practice may reflect many factors, including a lack of clinical appreciation of the increased risk for future events associated with low-level elevations in troponin or the lack of mature decision making and established investigative/management pathways for the care of patients with and without evidence of low-grade myocardial injury. Of significance is that

hs-TnT assays are yet to be approved by the Food and Drug Administration for routine use in the United States, whereas HealthPACT (Australian Health Technology Assessment Agency) and the Canadian Agency for Drug and Technologies in Health currently recommend against routine use as recently as in 2011 and 2013, respectively.^{22,23} Recent publications from the National Institute for Health and Care Excellence in the United Kingdom reinforce these recommendations calling for more research evaluating the true clinical and health service impacts of this diagnostic innovation and the design of clinical protocols to effectively optimize their use.²⁴ Several noncomparative observational series and small-scale randomized feasibility studies have been performed.²⁵⁻²⁸ This study suggests the routine use of hs-TnT reporting may be associated with reduced mortality and recurrent ACS. However,

for widespread use of hs-TnT testing in routine practice to be advocated, the incremental gains in clinical effectiveness of new hs-troponin-based protocols should be demonstrated within appropriately designed randomized clinical trials, as called for in international guidelines.³

Conclusions

High-sensitivity troponin provides useful risk information, but routine reporting without integration within protocols is associated with only modest changes in practice. Nevertheless, beyond the diagnostic process, routine use may improve late outcomes. Adoption of high-sensitivity troponin testing is likely to require coupling with management protocols that guide interpretation and care if the benefits of greater diagnostic discrimination are to be harnessed. Such protocols should be validated in comparative clinical trials.

Acknowledgments

We would like to thank Marleesa Ly for her editorial support. All Authors were involved with the study design and implementation. D.P. Chew and M. Horsfall were responsible for the data collection and analysis. The initial draft of the manuscript was written by D.P. Chew and reviewed by each of the authors. D.P. Chew had full access to all the data in the study and takes responsibility for the integrity and accuracy of the data analysis.

Sources of Funding

This study was supported by the National Health & Medical Research Council of Australia (grant number APP1024008) and the South Australian Department of Health.

Disclosures

None.

References

- Chew DP, Aroney CN, Aylward PE, Kelly AM, White HD, Tideman PA, Waddell J, Azadi L, Wilson AJ, Ruta LA. 2011 Addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes (ACS) 2006. *Heart Lung Circ.* 2011;20:487–502.
- Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ; ACC/AHA Task Force Members; Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;130:2354–2394. doi: 10.1161/CIR.0000000000001133.
- Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Baumgartner H, Gaemperli O, Achenbach S, Agewall S, Badimon L, Baigent C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cuisset T, Erol C, Fitzsimons D, Halle M, Hamm C, Hildick-Smith D, Huber K, Iliodromitis E, James S, Lewis BS, Lip GY, Piepoli MF, Richter D, Rosemann T, Sechtem U, Steg PG, Vrints C, Luis Zamorano J. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2016;37:267–315. doi: 10.1093/eurheartj/ehv320.
- Bandstein N, Ljung R, Johansson M, Holzmann MJ. Undetectable high-sensitivity cardiac troponin T level in the emergency department and risk of myocardial infarction. *J Am Coll Cardiol.* 2014;63:2569–2578. doi: 10.1016/j.jacc.2014.03.017.
- Heeschen C, Hamm CW, Goldmann B, Deu A, Langenbrink L, White HD. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. PRISM Study Investigators. Platelet Receptor Inhibition in Ischemic Syndrome Management. *Lancet.* 1999;354:1757–1762.
- Morrow DA, Cannon CP, Rifai N, Frey MJ, Vicari R, Lakkis N, Robertson DH, Hille DA, DeLuca PT, DiBattiste PM, Demopoulos LA, Weintraub WS, Braunwald E; TACTICS-TIMI 18 Investigators. Ability of minor elevations of troponins I and T to predict benefit from an early invasive strategy in patients with unstable angina and non-ST elevation myocardial infarction: results from a randomized trial. *JAMA.* 2001;286:2405–2412.
- Newby LK, Ohman EM, Christenson RH, Moliterno DJ, Harrington RA, White HD, Armstrong PW, Van De Werf F, Pfisterer M, Hasselblad V, Califf RM, Topol EJ. Benefit of glycoprotein IIb/IIIa inhibition in patients with acute coronary syndromes and troponin t-positive status: the paragon-B troponin T substudy. *Circulation.* 2001;103:2891–2896.
- Apple FS, Collinson PO; IFCC Task Force on Clinical Applications of Cardiac Biomarkers. Analytical characteristics of high-sensitivity cardiac troponin assays. *Clin Chem.* 2012;58:54–61. doi: 10.1373/clinchem.2011.165795.
- Apple FS, Wu AH. Myocardial infarction redefined: role of cardiac troponin testing. *Clin Chem.* 2001;47:377–379.
- Apple FS. A new season for cardiac troponin assays: it's time to keep a scorecard. *Clin Chem.* 2009;55:1303–1306. doi: 10.1373/clinchem.2009.128363.
- Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, Biedert S, Schaub N, Buerge C, Potocki M, Noveanu M, Breidhardt T, Twerenbold R, Winkler K, Bingisser R, Mueller C. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med.* 2009;361:858–867. doi: 10.1056/NEJMoa0900428.
- Januzzi JL Jr, Bamberg F, Lee H, Truong QA, Nichols JH, Karakas M, Mohammed AA, Schlett CL, Nagurny JT, Hoffmann U, Koenig W. High-sensitivity troponin T concentrations in acute chest pain patients evaluated with cardiac computed tomography. *Circulation.* 2010;121:1227–1234. doi: 10.1161/CIRCULATIONAHA.109.893826.
- Diamond GA, Kaul S. How would the Reverend Bayes interpret high-sensitivity troponin? *Circulation.* 2010;121:1172–1175. doi: 10.1161/CIR.0b013e3181d839e8.
- Astley CM, Beltrame JF, Zeitz C, Worthley M, Coates P, Murray A, Arstall M, Grantham H, Dunn R, Quinn S, Aylward PE, Chew DP. Study design of embracing high-sensitivity troponin effectively: the value of more information: a randomized comparison. *Contemp Clin Trials.* 2014;39:183–190. doi: 10.1016/j.cct.2014.08.012.
- Aroney C, Aylward P, Kelly A, Chew D, Clune E. National Heart Foundation of Australia Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes 2006. *Med J Aust.* 2006;184:S1–S35.
- Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, Avezum A, Goodman SG, Flather MD, Anderson FA Jr, Granger CB. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ.* 2006;333:1091. doi: 10.1136/bmj.38985.646481.55.
- Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA.* 2000;284:835–842.
- Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Thygesen K, Alpert JS, White HD, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA, Chaitman BR, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow JJ, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghide M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasileva EJ, Mendis S, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Morais J, Aguiar C, Almahmeed W, Arnar DO, Barili F, Bloch KD, Bolger AF, Botker HE, Bozkurt B, Bugiardini R, Cannon C, de Lemos J, Eberli FR, Escobar E,

- Hlatky M, James S, Kern KB, Moliterno DJ, Mueller C, Neskovic AN, Pieske BM, Schulman SP, Storey RF, Taubert KA, Vranckx P, Wagner DR; Joint ESC/ACCF/AHA/WHF Task Force for Universal Definition of Myocardial Infarction; Authors/Task Force Members Chairpersons; Biomarker Subcommittee; ECG Subcommittee; Imaging Subcommittee; Classification Subcommittee; Intervention Subcommittee; Trials & Registries Subcommittee; Trials & Registries Subcommittee; Trials & Registries Subcommittee; ESC Committee for Practice Guidelines (CPG); Document Reviewers. Third universal definition of myocardial infarction. *J Am Coll Cardiol*. 2012;60:1581–1598. doi: 10.1016/j.jacc.2012.08.001.
19. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123:2736–2747. doi: 10.1161/CIRCULATIONAHA.110.009449.
 20. Chew DP, Briffa TG, Alhammad NJ, Horsfall M, Zhou J, Lou PW, Coates P, Scott I, Brieger D, Quinn SJ, French J. High sensitivity-troponin elevation secondary to non-coronary diagnoses and death and recurrent myocardial infarction: an examination against criteria of causality. *Eur Heart J Acute Cardiovasc Care*. 2015;4:419–428. doi: 10.1177/2048872614564083.
 21. Mills NL, Churchhouse AM, Lee KK, Anand A, Gamble D, Shah AS, Paterson E, MacLeod M, Graham C, Walker S, Denvir MA, Fox KA, Newby DE. Implementation of a sensitive troponin I assay and risk of recurrent myocardial infarction and death in patients with suspected acute coronary syndrome. *JAMA*. 2011;305:1210–1216. doi: 10.1001/jama.2011.338.
 22. Forel D. *Technology Brief: High Sensitivity Troponin Assays for the Diagnosis of Myocardial Infarction (Version 1.0)*. Brisbane, Queensland: Health Policy Advisory Committee on Technology Australia and New Zealand; 2012:1–13.
 23. *Recommendations for the Use of Troponin Assays for the Rapid Diagnosis of Acute Coronary Syndrome in the Emergency Department*. Canadian Agency for Drugs and Technologies in Health; 2013:1–10.
 24. Myocardial infarction (acute). *Early Rule Out Using High-Sensitivity Troponin Tests (Elecsys Troponin T High-Sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 Assays): NICE Diagnostic Guidance (DG15)*. UK Diagnostic Advisory Committee NICE; 2014:1–53.
 25. Cullen L, Mueller C, Parsonage WA, Wildi K, Greenslade JH, Twerenbold R, Aldous S, Meller B, Tate JR, Reichlin T, Hammett CJ, Zellweger C, Ungerer JP, Rubini Gimenez M, Troughton R, Murray K, Brown AF, Mueller M, George P, Mosimann T, Flaws DF, Reiter M, Lamanna A, Haaf P, Pemberton CJ, Richards AM, Chu K, Reid CM, Peacock WF, Jaffe AS, Florkowski C, Deely JM, Than M. Validation of high-sensitivity troponin I in a 2-hour diagnostic strategy to assess 30-day outcomes in emergency department patients with possible acute coronary syndrome. *J Am Coll Cardiol*. 2013;62:1242–1249. doi: 10.1016/j.jacc.2013.02.078.
 26. Than M, Aldous S, Lord SJ, Goodacre S, Frampton CM, Troughton R, George P, Florkowski CM, Ardagh M, Smyth D, Jardine DL, Peacock WF, Young J, Hamilton G, Deely JM, Cullen L, Richards AM. A 2-hour diagnostic protocol for possible cardiac chest pain in the emergency department: a randomized clinical trial. *JAMA Intern Med*. 2014;174:51–58. doi: 10.1001/jamainternmed.2013.11362.
 27. Reichlin T, Schindler C, Drexler B, Twerenbold R, Reiter M, Zellweger C, Moehring B, Ziller R, Hoeller R, Rubini Gimenez M, Haaf P, Potocki M, Wildi K, Balmelli C, Freese M, Stelzig C, Freidank H, Osswald S, Mueller C. One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. *Arch Intern Med*. 2012;172:1211–1218. doi: 10.1001/archinternmed.2012.3698.
 28. Body R, Carley S, McDowell G, Pemberton P, Burrows G, Cook G, Lewis PS, Smith A, Mackway-Jones K. The Manchester acute coronary syndromes (MACS) decision rule for suspected cardiac chest pain: derivation and external validation. *Heart*. 2014;100:1462–1468. doi: 10.1136/heartjnl-2014-305564.

Randomized Comparison of High-Sensitivity Troponin Reporting in Undifferentiated Chest Pain Assessment

Derek P. Chew, Christopher Zeitz, Matthew Worthley, Hugh Grantham, John Beltrame, Margaret Arstall, Penelope Coates, Carolyn Astley, Stephen Quinn, Julie Ratcliffe, Matthew Horsfall and Philip G. Aylward

Circ Cardiovasc Qual Outcomes. 2016;9:542-553; originally published online August 9, 2016;
doi: 10.1161/CIRCOUTCOMES.115.002488

Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272
Greenville Avenue, Dallas, TX 75231

Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7705. Online ISSN: 1941-7713

The online version of this article, along with updated information and services, is located on the
World Wide Web at:

<http://circoutcomes.ahajournals.org/content/9/5/542>

Data Supplement (unedited) at:

<http://circoutcomes.ahajournals.org/content/suppl/2016/09/13/CIRCOUTCOMES.115.002488.DC1>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Cardiovascular Quality and Outcomes* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation: Cardiovascular Quality and Outcomes* is online at:
<http://circoutcomes.ahajournals.org//subscriptions/>

SUPPLEMENTAL MATERIAL

National Heart Foundation Australia ACS guidelines: risk classification ¹

<i>Suspected Non ST elevation ACS* with high risk features</i>	Persistent or dynamic ECG† changes Transient ST elevation (>1mm) ST depression > 0.5mm or new deep T wave in version (> 1mm) or pseudonormalisation of T waves in more than 2 contiguous leads Hemodynamic compromise: killip class > 1 and/or new onset mitral regurgitation and/or syncope Presence of known diabetes Ongoing chest pain at rest without persistent ST elevation of 1mm in 2 or more contiguous leads New or presumed new bundle branch block pattern on initial ECG not meeting definition of ST elevation MI‡
<i>Suspected Non ST elevation ACS with intermediate risk features</i>	Age ≥ 65 years Known coronary artery disease Prior MI Prior revascularisation Known coronary lesion > 50% Pathological Q-waves 2 or more of hypertension, family history, smoking or hyperlipidemia Aspirin use
<i>Suspected Non ST elevation ACS with low risk features</i>	1 risk factor of hypertension, family history, active smoking or hyperlipidemia
<i>Atypical presentation</i>	Presentation with chest pain features considered not typical of ACS

*ACS= acute coronary syndrome, †ECG= electrocardiogram, ‡MI= myocardial infarction

Reference

¹Aroney C, Aylward P, Kelly A, Chew D, Clune E. National Heart Foundation of Australia Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes 2006. Medical Journal of Australia. 2006;184:S1–S35