Circulation

ORIGINAL RESEARCH ARTICLE

Late Outcomes of the RAPID-TnT Randomized Controlled Trial

0/1-Hour High-Sensitivity Troponin T Protocol in Suspected ACS

Kristina Lambrakis, BSc; Cynthia Papendick, MBBS; John K. French, MBChB, PhD; Stephen Quinn, PhD; Andrew Blyth, MBChB, PhD; Anil Seshadri, MBBS; Michael J.R. Edmonds, MBBS; Anthony Chuang, MBBS, MMed; Ehsan Khan, MBBS, MMed; Adam J. Nelson, MBBS, PhD; Deborah Wright, MNSc; Matthew Horsfall, RN; Erin Morton, PhD; Jonathan Karnon, PhD; Tom Briffa, PhD; Louise A. Cullen, MBBS, PhD; Derek P. Chew, MBBS, MPH, PhD

BACKGROUND: High-sensitivity troponin assays are increasingly being adopted to expedite evaluation of patients with suspected acute coronary syndromes. Few direct comparisons have examined whether the enhanced performance of these assays at low concentrations leads to changes in care that improves longer-term outcomes. This study evaluated late outcomes of participants managed under an unmasked 0/1-hour high-sensitivity cardiac troponin T (hs-cTnT) protocol compared with a 0/3-hour masked hs-cTnT protocol.

METHODS: We conducted a multicenter prospective patient-level randomized comparison of care informed by unmasked 0/1-hour hs-cTnT protocol (reported to <5 ng/L) versus standard practice masked hs-cTnT testing (reported to ≤29 ng/L) assessed at 0/3 hours and followed participants for 12 months. Participants included were those presenting to metropolitan emergency departments with suspected acute coronary syndromes, without ECG evidence of coronary ischemia. The primary end point was time to all-cause death or myocardial infarction using Cox proportional hazards models adjusted for clustering within hospitals.

RESULTS: Between August 2015 and April 2019, we randomized 3378 participants, of whom 108 withdrew, resulting in 12-month follow-up for 3270 participants (masked: 1632; unmasked: 1638). Among these, 2993 (91.5%) had an initial troponin concentration of ≤29 ng/L. Deployment of the 0/1-hour hs-cTnT protocol was associated with reductions in functional testing. Over 12-month follow-up, there was no difference in invasive coronary angiography (0/1-hour unmasked: 232/1638 [14.2%]; 0/3-hour masked: 202/1632 [12.4%]; *P*=0.13), although an increase was seen among patients with hs-cTnT levels within the masked range (0/1-hour unmasked arm: 168/1507 [11.2%]; 0/3-hour masked arm: 124/1486 [8.3%]; *P*=0.010). By 12 months, all-cause death and myocardial infarction did not differ between study arms overall (0/1-hour: 82/1638 [5.0%] versus 0/3-hour: 62/1632 [3.8%]; hazard ratio, 1.32 [95% CI, 0.95–1.83]; *P*=0.10). Among participants with initial troponin T concentrations ≤29 ng/L, unmasked hs-cTnT reporting was associated with an increase in death or myocardial infarction (0/1-hour: 55/1507 [3.7%] versus 0/3-hour: 34/1486 [2.3%]; hazard ratio, 1.60 [95% CI, 1.05–2.46]; *P*=0.030).

CONCLUSIONS: Unmasked hs-cTnT reporting deployed within a 0/1-hour protocol did not reduce ischemic events over 12-month follow-up. Changes in practice associated with the implementation of this protocol may be associated with an increase in death and myocardial infarction among those with newly identified troponin elevations.

REGISTRATION: URL: https://www.anzctr.org.au; Unique identifier: ACTRN12615001379505.

Key Words: acute coronary syndrome ■ diagnostic testing ■ high-sensitivity troponin ■ myocardial infarction ■ randomized trial

Clinical implementation of troponin assays with improved analytic precision have enabled more rapid assessment of patients with suspected acute coronary syndrome (ACS), and safe discharge of patients deemed to be at low risk on the basis of these protocols.[1,2] Similarly, the greater sensitivity

Correspondence to: Derek P. Chew, MBBS, MPH, PhD, Flinders University, Flinders Drive, Bedford Park, South Australia, 5042, Australia. Email derek.chew@flinders.edu.au
This work was presented as an abstract at the American College of Cardiology's Scientific Session, May 15–17, 2021.
The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.121.055009.
For Sources of Funding and Disclosures, see page 124.

Circulation is available at www.ahajournals.org/journal/circ

ORIGINAL RESEARCH ARTICLE

Clinical Perspective

What Is New?

- Although the use of a 0/1-hour high-sensitivity cardiac troponin T protocol expedited discharge of patients presenting to the emergency department with a low event rate at 30 days, an increase in death or myocardial infarction was observed at 1 year in those with unmasked high-sensitivity cardiac troponin T concentrations.
- Among those with intermediate cardiac troponin concentrations, where care was informed by a 0/1-hour unmasked high-sensitivity cardiac troponin T protocol, increases in revascularization and reductions in noninvasive cardiac investigation were observed.
- These changes in practice that result from the use of rapid discharge protocols may potentially be associated with an increase in all-cause death or myocardial infarction by 12 months among those low-level troponin elevations.

What Are the Clinical Implications?

- Observations from this study may suggest the ongoing utility of downstream cardiac testing to diagnose unrecognized coronary artery disease among low-risk patients presenting with suspected acute coronary syndrome.
- Randomized trials are required to robustly assess downstream investigative and therapeutic strategies for those with intermediate cardiac troponin concentrations, especially given the large proportion of patients with myocardial injury not attributable to type 1 myocardial infarction.
- More sophisticated clinical decision support approaches may improve outcomes and need to be prospectively validated in clinical practice.

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
CAD	coronary artery disease
ED	emergency department
hs-TnT	high-sensitivity cardiac troponin T
MI	myocardial infarction
RAPID-TnT	Rapid Assessment of Possible ACS in the Emergency Department With High-Sensitivity Troponin T trial

of these assays coupled with the ability to observe small temporal changes in troponin can be used to define acute and chronic injury patterns.[3,4] However, to date, no prospective randomized trials have demonstrated that the increased detection of myocardial injury associated with high-sensitivity troponin assays leads to a reduction in cardiovascular outcomes over the longer term.[5,6]

In a study cohort with a low suspicion for ACS, unmasking the values <30 ng/L using a high-sensitivity cardiac troponin T (hs-cTnT) assay within a 0/1-hour chest pain assessment protocol, the RAPID-TnT trial (Rapid Assessment of Possible ACS in the Emergency Department With High-Sensitivity Troponin T trial), observed a 0.5% rate of death or myocardial infarction (MI) within 30 days among patients receiving a MI rule-out recommendation.[7] Care was guided by the unmasked 0/1-hour protocol and was found to be noninferior at 30 days compared with the standard 0/3-hour protocol with troponin results <30 ng/L masked to the clinician.[7] However, consistent with other nonrandomized comparisons, clinical reporting of actual low-level troponin concentrations was associated with a reduction in the use of early functional testing and an increase in coronary angiography.[8,9] This increase in early coronary investigations was associated with an overall increase in myocardial injury, without a commensurate increase in the diagnosis of type 1 MI (ie, atherosclerotic plaque disruption) at the initial presentation.[7] Furthermore, given the low risk profile of this patient population, the initial 30-day noninferiority analysis of this trial was not designed to adequately examine the long-term safety associated with the changes in practice resulting from the clinical unmasking of low-level troponin concentrations. Therefore, as planned and prespecified in the design of this study, we followed this prospectively randomized cohort to evaluate the effect of 0/1-hour unmasked hs-cTnT versus 0/3-hour masked hs-cTnT protocol on all-cause mortality and recurrent MI events over 12 months, with particular interest in those participants with initial hs-cTnT concentrations within the previously clinically masked range <29 ng/L.

METHODS

Study Design

The design of the RAPID-TnT trial has been described in detail elsewhere.[10] In brief, this was a prospective patient-level randomized evaluation of a 0/1-hour protocol using unmasked hs-cTnT reporting compared with standard care 0/3-hour testing, where troponin T values were masked <29 ng/L. This study enrolled participants with suspected ACS who were potentially eligible for early discharge and for whom initial ECG did not suggest coronary ischemia from 4 metropolitan public emergency departments (EDs) in Adelaide, South Australia. Given the dual and potentially competing clinical goals of rapid ED chest pain assessment, specifically safe early discharge and effective diagnosis and treatment of coronary presentations to prevent late cardiovascular events, this trial planned 2 analyses. The initial safety-based noninferiority assessment of the 30-day outcomes has been previously reported.[7] As planned, this analysis examined the association between the changes in practice resulting from a 0/1-hour unmasked hs-cTnT protocol and subsequent improvements in 12-month clinical outcomes. The

Southern Adelaide Clinical Human Research Ethics Committee provided approval (207.15) (URL: https://www.anzctr.org.au; Unique identifier: ANZCTRN12615001379505). The data that support the findings of this study and other potential analyses are available from the corresponding author on request.

System-Level Troponin T Masking

A single pathology provider services all public hospitals in South Australia. In April 2011, the Roche Diagnostics (Cobas) Elecsys fifth generation hs-cTnT assay (limit of detection: 5 ng/L; 99th percentile: 14 ng/L) was implemented as the sole troponin assay available within all South Australia public hospitals. At the time of deployment, the lower reporting limit was aligned to that of the previous-generation assay (ie, lower reference limit reported as ≤29 ng/L rather than down to 5 ng/L) because of concerns over the possible increase in invasive cardiac assessments if lower reference limits were used.[6] Access to unmasked concentrations was possible only through trial enrollment, thus enabling single-blind study implementation.

Study Population

This study focused on patients for whom there may be greater incremental diagnostic yield from hs-cTnT reporting and therefore aimed not to enroll patients for whom protracted care was likely to be required. Therefore, eligible participants were those (1) with clinical features of suspected ACS as the principal cause of presentation; (2) without definitive evidence of coronary ischemia on baseline ECG; (3) who were ≥18 years old; and (4) who willing to give written informed consent. We excluded patients who (1) had chest pain believed to be of noncardiac origin; (2) were transferred in from another hospital; (3) had received suspected ACS assessment within the previous 30 days; (4) were receiving permanent dialysis; or (5) had a comorbidity or language barrier leading to the inability to complete essential trial documentation.

Study Protocol

Consent and randomization using permuted blocks of 4, stratified by participating hospital, occurred after the initial ECG had been taken and interpreted, but before troponin values were clinically available. For participants randomized to the 0/1-hour hs-cTnT arm, ED management was guided by the following protocol: rule-out with discharge to primary care if the baseline troponin value was <5 ng/L and it had been >3 hours since symptom onset, or where the baseline was ≤12 ng/L with a change over 1 hour of <3 ng/L; rule-in with hospital admission recommended for suspected MI if the baseline troponin value was ≥52 ng/L or a change of ≥5 ng/L over 1 hour was seen regardless of the baseline concentration; observe (ie, gray zone) with repeat testing recommended when the baseline troponin values were between 13 and 51 ng/L with a change over 1 hour of <5 ng/L, or when the baseline troponin value was ≤12 ng/L with a change over 1 hour of 3 to 4 ng/L.[1,2,10]

Care in the standard arm followed the South Australia statewide chest pain protocol, which recommends troponin T testing at baseline and at 3 hours, with discretionary further testing at 6 hours. In the standard arm, all troponin T values were reported to a lower limit of ≤29 ng/L. Within the local standards, those with a troponin value >29 ng/L and ongoing symptoms, ECG changes, or known coronary artery disease (CAD) were recommended for inpatient assessment. Patients with troponin values ≤29 ng/L and without ongoing pain or known CAD were recommended for discharge, with subsequent outpatient functional testing determined by age >65 years and the presence of ≥3 cardiac risk factors. Clinicians retained the discretion to use other risk assessment tools such as risk scores and to vary management as they deemed appropriate. Indications for coronary angiography and possible coronary revascularization were not stipulated by either protocol and were provided on the basis of local clinical judgment.

Data Collection and Outcome Measures

All representations were assessed for repeat cardiac investigations. This included all ECGs, troponin tests, echocardiography, stress testing (ECG, echocardiography, nuclear scanning, cardiac magnetic resonance imaging), computerized tomography coronary angiography, invasive coronary angiography, and coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft). This was achieved through systematic interrogation of statewide hospital and administrative data and utilization of data linkage methods. Similarly, for consenting participants, data linkage with Medicare and Pharmaceutical Benefits Scheme data were used to capture downstream medical consultations and cardiac investigations conducted in outpatient settings.

The primary outcome for this study was the time to all-cause mortality and MI adjudicated to the Fourth Universal Definition of MI evaluated up to 12 months of follow-up, with MIs identified during the index in-hospital assessment (≤12 hours) excluded.[10,11] Index admissions and subsequent events were adjudicated by at least 2 independent cardiologists with disagreements assessed by a third senior cardiologist, all of whom were blinded to the randomization arm, and each primary end point event was reviewed at a clinical events committee meeting. To meet the classification of acute injury, the documentation of a rise or fall in troponin T (defined as a change >20%) with at least 1 sample >14 ng/L was required. Subsequent subclassification into MI types 1, 2, 4a, and 5 required definitive supporting evidence of coronary ischemia by the documentation of a typical clinical history or ischemic ECG changes, new wall motion abnormalities on cardiac imaging, or angiographic findings. In addition, applying the classification of type 2 MI required documented evidence of physiological supply–demand imbalance deemed sufficient to confer coronary ischemia. Late serial troponin values with a rise or fall pattern in the absence of myocardial ischemia were reported as acute myocardial injury, and troponin elevations >14 ng/L not meeting the rise or fall criteria were reported as chronic myocardial injury. Troponin T concentrations down to 5 ng/L were available to the adjudicators. Key secondary outcomes included individual components of the primary end point; unstable angina, peripheral vascular revascularization, and cerebrovascular accidents; congestive cardiac failure, and atrial and ventricular arrhythmias; and bleeding events classified by the Bleeding Academic Research Consortium criteria in the 12 months after randomization.[12]

Statistical Analysis

Baseline characteristics, index diagnoses, and components of subsequent care are reported as counts and percentages (%), compared with χ^2 tests, with continuous variables reported as

medians and interquartile ranges and compared with Mann-Whitney *U* tests where appropriate. The flow of participants is reported in Figure 1. The analyses used the intention-to-treat principle. For this analysis, the time to first component of primary composite end point between the 2 randomized groups was compared using Cox proportional hazards models without covariate adjustment. To account for clustering between hospitals, shared frailty and robust variance estimators were used, with these methods demonstrating the smallest deviation in proportional hazards reported. The key prespecified subgroup, for which the study was originally powered, were those participants with an initial troponin concentration of 5 to 29 ng/L on their first 2 samples (ie, below the standard masked troponin concentration where there was a reporting difference between the 2 study arms). The primary composite end points by randomized arm were similarly compared without covariate adjustment, whereas covariate-adjusted models are presented in Table III in the Data Supplement. The proportional hazards assumption was tested and found to be valid in all models. Because of suspicion of increased risk, these analyses are considered exploratory and are not adjusted for multiple testing. Similarly, analyses exploring the time to other events were considered exploratory and are reported without adjustment for multiple testing. Time to the events over 12 months of follow-up for the 2 study arms are plotted using Kaplan–Meier survival curves, and a landmark analysis was undertaken at 30 days to evaluate for a difference between early and longer-term relative hazards as a consequence of baseline differences in downstream treatments. Furthermore, given the suspicion of an increase in events within the 0/1-hour arm, subsequent clinical care and event rates by triage recommendation in the 0/1-hour unmasked hs-cTnT arm were explored in contrast with that of the 0/3-hour masked hs-cTnT arm among participants with an initial troponin T concentration ≤29 ng/L. Additional analyses of care and

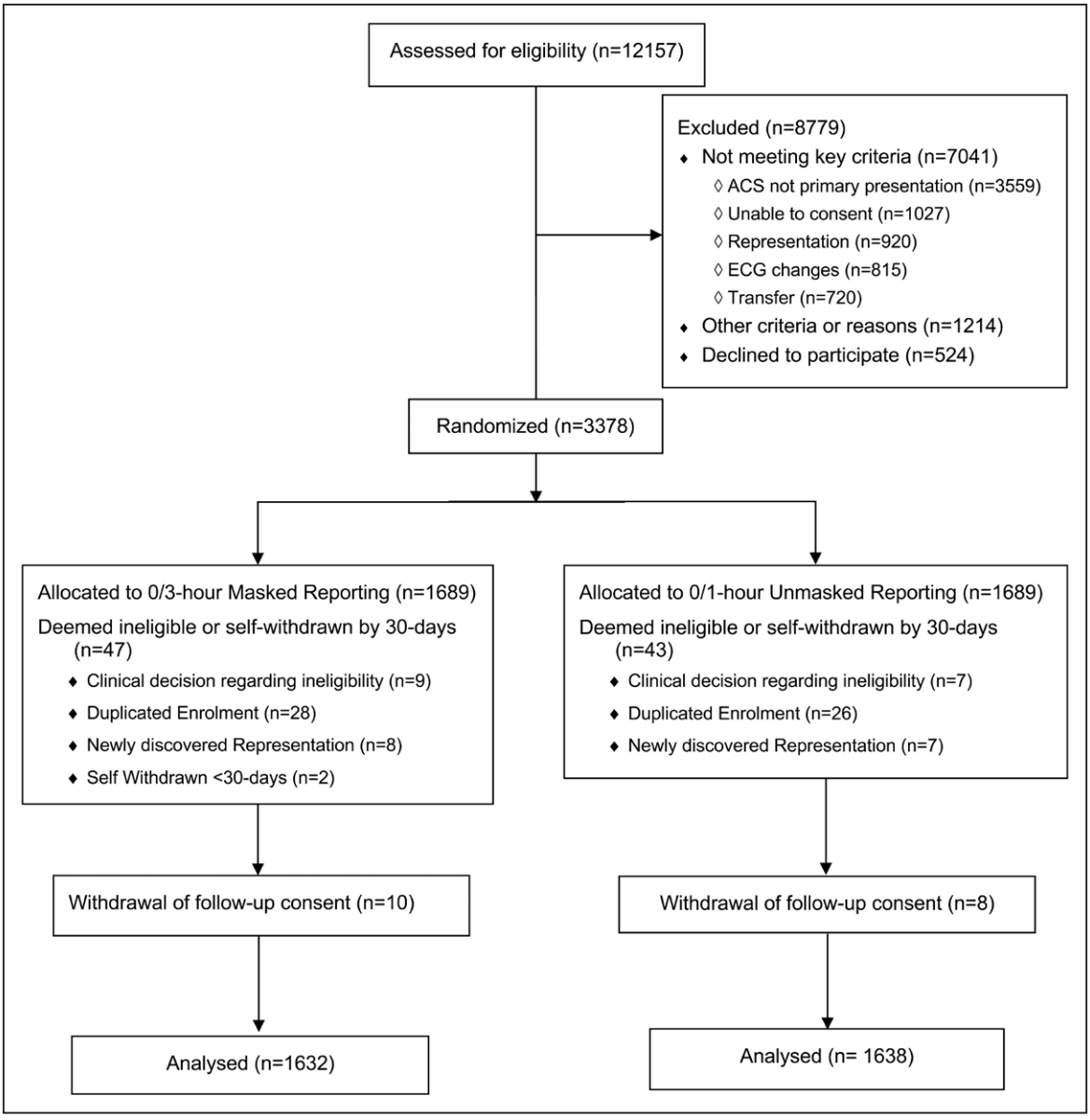

Figure 1. Screening, eligibility, randomization. and follow-up.
ACS indicates acute coronary syndrome.

events over 12 months by the highest troponin concentration observed during initial assessment stratified as <5 ng/L, 5 to 51 ng/L, and ≥52 ng/L were undertaken. The association between troponin profiles adjudicated to the Fourth Universal Definition of MI, and late outcomes, specifically all-cause mortality, acute coronary events (MI and unstable angina), and cardiovascular rehospitalizations not related to acute coronary events (heart failure, arrhythmias, cerebrovascular and peripheral vascular disease), were also explored using the Cox proportional hazards models with shared frailty, adjusting for baseline differences in age, sex, renal function, cardiovascular risk factors, and previous cardiovascular disease.

As previously described, the decision to end enrollment in April 2019 was made after Data Safety and Monitoring Board review, which suggested there was no longer equipoise on rule-out MI recommendation performance (ie, discharge under the 0/1-hour protocol was associated with a <1% rate of 30-day death or MI). All statistical analyses were conducted using STATA 16.0 (College Station, TX), and a *P* value of <0.05 (2-tailed) was considered statistically significant.

RESULTS

Patient Population and Procedures

Between August 2015 and April 2019, 3378 participants presenting to 4 metropolitan EDs were enrolled. Of these, 90 participants either did not meet inclusion criteria or withdrew initial consent, and a further 18 participants withdrew consent for late follow-up, leaving 3270 participants (0/1-hour arm: n=1638; 0/3-hour arm: n=1632), who were followed for 12 months (Figure 1). Participants with an initial troponin T concentration within the masked range of ≤29 ng/L constituted 2993/3327 (91.5%) of the total cohort. The 2 study arms were well balanced for baseline characteristics in the overall cohort (Table 1) and among those with initial results ≤29 ng/L (Table I in the Data Supplement), with a modest difference in Killip class noted. Nearly half the participants were female (47%), and the median age was 59 (interquartile range, 49–70) years. The population had a low estimated risk with a median History ECG Age Risk Factors and Troponin (HEART) score of 3 (interquartile range, 2–4), and 28% had a previous history of CAD. Diagnosis of type 1 MI on initial assessment was made in 124/3270 (4%) of the population and did not differ between study arms. Type 2 MI and acute myocardial injury was observed in 39/3270 (1%) and 61/3270 (2%), respectively. In contrast, 469/3270 (14.3%) of the cohort exhibited elevated troponin concentrations in the initial 12 hours, which had a profile consistent with chronic myocardial injury.

Clinical Care and Resource Use

Participants randomized to the 0/1-hour unmasked hs-cTnT protocol were discharged directly from the ED with greater frequency compared with the 0/3-hour arm (45.0% versus 32.3%; *P*<0.001) and were discharged earlier (median ED length of stay among directly discharged participants, 0/1-hour arm: 3.8 [IQR, 3.1–4.7] hours; 0/3-hour arm: 4.2 [IQR, 3.1–5.7] hours; *P*<0.001). Randomization to the 0/1-hour unmasked protocol was also associated with a lower rate of functional testing (Tables 2 and 3). In the overall cohort, 241/3270 (7.4%) of participants received invasive coronary angiography. This increased to 434/3270 (13.3%) by 12 months, with no difference in study arms (0/1-hour arm: 232/1638 [14.2%]; 0/3-hour arm: 202/1632 [12.4%]; *P*=0.13). However, among patients with an initial troponin ≤29 ng/L, there was a modest increase in the number of

Table 1. Baseline Characteristics of All Study Participants in the Intention-to-Treat Population

Characteristic	Standard protocol (N=1632)	0/1-h protocol (N=1638)
Age, y	58.6 (48.8–71.2)	58.7 (48.6–69.4)
Female sex	762 (46.7)	767 (46.8)
Hypertension	334 (20.5)	322 (19.7)
Diabetes	285 (17.5)	257 (15.7)
Dyslipidemia	719 (44.1)	711 (43.4)
Current smoker	582 (35.7)	566 (34.6)
Family history of coronary artery disease	951 (59.4)	987 (61.2)
Previous history of coronary artery disease	473 (29.0)	456 (27.8)
Previous myocardial infarction	161 (9.9)	170 (10.4)
Previous angina	257 (15.7)	249 (15.2)
Previous heart failure	92 (5.6)	77 (4.7)
Previous atrial fibrillation	153 (9.4)	134 (8.2)
Chronic obstructive airways disease	73 (4.5)	77 (4.7)
Previous cerebrovascular disease	51 (3.1)	53 (3.2)
Previous coronary artery bypass grafting	45 (2.8)	49 (3.0)
Previous percutaneous coronary intervention	138 (8.5)	171 (10.4)
Killip class >1*	50 (3.1)	32 (2.0)
Glomerular filtration rate (mL/min/1.73 m^2)†‡	86.0 (71.4–98.0)	86.2 (71.6–98.2)
Emergency Department Assessment of Chest Pain Score	15.0 (9.0–21.0)	14.0 (9.0–20.0)
Global Registry for Acute Coronary Events score*	75.0 (56.1–100.7)	74.1 (55.3–97.2)
Thrombolysis in Myocardial Infarction non–ST-segment–elevation acute coronary syndrome score	1.0 (0.0–3.0)	1.0 (0.0–2.0)
History ECG Age Risk Factors and Troponin score	3.0 (2.0–4.0)	3.0 (2.0–4.0)

Values indicate n (%) or median (interquartile range).

*There were no significant differences (*P*<0.05) between the 2 groups except for Killip class (*P*=0.04).

†Missing data: 2 participants in the standard arm did not have blood pressure recorded; 36 participants (17 in the 0/1-h arm and 19 in the standard arm) did not have creatinine drawn. Note that this affects the calculation of the Global Registry for Acute Coronary Events score.

‡The glomerular filtration rate was calculated using the 2009 CKI–EPI (Chronic Kidney Disease–Epidemiology Collaboration) creatinine equation.

Table 2. Adjudicated Index Diagnosis, Troponin Profile, and Coronary Artery Disease Management by Study Arm Within the Overall Population

Clinical care characteristic	Standard protocol (N=1632)	0/1-Hour protocol (N=1638)	*P* value
Final discharge diagnosis			
Type 1 myocardial infarction	65 (4.0)	59 (3.6)	0.81
Type 2 myocardial infarction	19 (1.2)	20 (1.3)	
Other cardiac diagnoses	164 (10.0)	149 (9.1)	
Chest pain	1004 (61.5)	991 (60.5)	
Troponin profiles during index hospitalization			
No cardiac injury	1294 (79.3)	1283 (78.3)	0.44
Acute cardiac injury pattern	116 (7.1)	108 (6.6)	
Chronic cardiac injury pattern	222 (13.6)	247 (15.1)	
Coronary investigation and management			
Functional testing within 30 d	178 (10.9)	122 (7.4)	<0.001
Coronary angiogram within 30 d	115 (7.0)	126 (7.7)	0.48
Percutaneous coronary intervention within 30 d	46 (2.8)	53 (3.2)	0.49
Coronary artery bypass graft within 30 d	9 (0.6)	9 (0.5)	0.99
Revascularization within 30 d	54 (3.3)	62 (3.8)	0.46
Coronary angiogram within 12 mo	202 (12.4)	232 (14.2)	0.13
Percutaneous coronary intervention within 12 mo	70 (4.3)	77 (4.7)	0.57
Coronary artery bypass graft within 12 mo	19 (1.2)	22 (1.3)	0.65
Revascularization within 12 mo	88 (5.4)	94 (5.7)	0.67
Therapies after hospitalization			
$P2Y_{12}$ inhibitor	195 (11.9)	209 (12.8)	0.48
Statin therapy	612 (37.5)	603 (36.8)	0.68
Other lipid-lowering agents	129 (7.9)	144 (8.8)	0.36
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	615 (37.7)	619 (37.8)	0.95
β-Blockers	384 (23.5)	383 (23.4)	0.92

Values indicate n (%).

coronary angiograms undertaken in the unmasked protocol (0/1-hour arm: 168/1507 [11.2%]; 0/3-hour arm: 124/1486 [8.3%], *P*=0.010) (time to angiography is presented in Figure I in the Data Supplement). Within 30 days, 116/3270 (3.6%) received coronary revascularization, increasing to 182/3270 (5.6%) by 12 months. There was no difference in the rate of revascularization between study arms within the overall population (0/1-hour arm: 94/1638 [5.7%]; 0/3-hour arm: 88/1632 [5.4%]; *P*=0.666), and similarly among those with an initial troponin ≤29 ng/L (0/1-hour arm: 62/1507 [4.1%]; 0/3-hour arm: 43/1486 [2.9%]; *P*=0.070). There was no difference in the rate of statin use or other secondary prevention medications between the 2 study arms. Tables 2 and 3 describe the rates of therapies for CAD by study arm.

Clinical Outcomes

Over the 12-month follow-up, 611 representations to a hospital with at least 1 troponin concentration >14 ng/L were observed. Most of these episodes were associated with a chronic injury troponin profile. Tables 4 and 5 describe clinical events and the rate of first representations with MI or injury using the Fourth Universal Definition of MI, and Table II in the Data Supplement describes the total number of these events over a 12-month follow-up by randomized arm.[11]

Within 30 days, 34/3270 (1.0%) participants experienced the primary end point of all-cause death or subsequent MI, and by 12 months, this increased to 144/3270 (4.4%). There was no difference between study arms within the overall population (0/1-hour arm: 82/1638 [5.0%]; 0/3-hour arm: 62/1632 [3.8%]; hazard ratio, 1.32 [95% CI, 0.95–1.83]; *P*=0.10). There was no difference in primary end point between study arms among participants with an initial troponin >29 ng/L (0/1-hour arm: 27/131 [20.6%]; 0/3-hour arm: 28/146 [19.2%]; hazard ratio, 1.05 [95% CI, 0.62–1.78]; *P*=0.859). However, among participants with initial troponin concentrations ≤29 ng/L, care informed by the unmasked

Table 3. Adjudicated Index Diagnosis, Troponin Profile, and Coronary Artery Disease Management by Study Arm in Participants With Initial Troponin ≤29 ng/L

Clinical care characteristics	Standard protocol (N=1486)	0/1-h protocol (N=1507)	*P* value
Functional testing within 30 d	150 (10.1)	106 (7.0)	0.003
Coronary angiogram within 30 d	47 (3.2)	70 (4.6)	0.037
Percutaneous coronary intervention within 30 d	13 (0.9)	30 (2.0)	0.010
Coronary artery bypass graft within 30 d	1 (0.1)	4 (0.3)	0.18
Revascularization within 30 d	14 (0.9)	34 (2.3)	0.004
Coronary angiogram within 12 mo	124 (8.3)	168 (11.1)	0.010
Percutaneous coronary intervention within 12 mo	34 (2.3)	51 (3.4)	0.071
Coronary artery bypass graft within 12 mo	9 (0.6)	13 (0.9)	0.41
Revascularization within 12 mo	43 (2.9)	62 (4.1)	0.07
Therapies after hospitalization			
$P2Y_{12}$ inhibitor	135 (9.1)	168 (11.1)	0.06
Statin therapy	517 (34.8)	519 (34.4)	0.84
Other lipid-lowering agents	107 (7.2)	128 (8.5)	0.19
Angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker	537 (36.1)	547 (36.3)	0.93
β-Blockers	305 (20.5)	312 (20.7)	0.90

Values indicate n (%).

protocol was associated with an increase in death or MI by 12 months (0/1-hour arm: 55/1507 [3.6%]; 0/3-hour arm: 34/1486 [2.3%]; hazard ratio, 1.60 [95% CI, 1.05–2.46]; *P*=0.030; interaction *P* value=0.036). This observed increase in risk persisted within analyses adjusted for key baseline clinical characteristics (Table III in the Data Supplement). There was no difference in the rates of subsequent cardiovascular rehospitalization in the overall cohort or among those with initial troponin concentrations ≤29 ng/L (Figure 2). Landmark analysis of the primary end point among those with an initial troponin concentration ≤29 ng/L did not demonstrate a difference in the relative hazard of care under the 0/1-hour unmasked protocol compared with the 0/3-hour masked protocol within 30 days. However, this analysis shows an increase in the late risk of death or MI at 12 months in those without an event at 30 days (hazard ratio, 1.68 [95% CI, 1.08–2.61]; *P*=0.021) (Figure 3).

Table 6 describes the investigative tests, management, and event rates by triage recommendation in the 0/1-hour unmasked arm contrasted with the 0/3-hour masked arm among participants with an initial troponin concentration ≤29 ng/L. Among patients with unmasked troponin results, event rates appeared disproportionately greater among those within the observe and rule-in categories with a small excess in overall events evident. Exploratory analysis of patients stratified by the highest troponin concentration observed during initial assessment demonstrates similar care and a low rate of recurrent ischemic events among patients with an initial troponin level of <5 ng/L. There were no deaths observed over the 12 months of follow-up among patients with a troponin concentration in this subgroup. In the subgroup of patients with troponin concentrations between 5 and 51 ng/L, a lower rate of functional testing and a higher rate of angiography over 12-month follow-up were observed in the 0/1-hour arm, without a significant difference in clinical events. Among patients with troponin concentrations ≥52 ng/L, there was no significant difference in outcomes (Table IV in the Data Supplement).

Clinical Outcomes by Fourth Universal Definition of MI at Presentation

Clinical events over 12 months follow-up by classification of myocardial injury on the basis of the Fourth Universal Definition of MI determined at index presentation are described in Table V in the Data Supplement. After adjusting for age, sex, and coronary risk factors, presentation with all classifications of myocardial injury or infarction were associated with an increase in mortality compared with presentations without cardiac injury. However, participants presenting with type 1 MI experienced a higher risk of recurrent MI and unstable angina that was not evident among participants who presented with myocardial injury not classified as type 1 MI. In contrast, participants presenting with acute injury, type 2 MI, or a chronic injury profile experienced a risk of subsequent rehospitalization for noncoronary cardiac diagnoses such as heart failure and arrhythmias, comparable with those with initial type 1 MI. The hazard ratios of representation over 12 months by index diagnostic classification of troponin profile are described in Figure II in the Data Supplement.

DISCUSSION

Among patients presenting with suspected ACS, troponin testing is a cornerstone of risk assessment.[13] This patient-level randomized evaluation of unmasked hs-cTnT within a 0/1-hour protocol for the clinical assessment of suspected ACS has previously supported the clinical safety of early discharge among patients with low and nondynamic hs-cTnT profile.[7,14,15] However, by 12 months, this study did not demonstrate an overall reduction in death or MI. When compared with care informed by masked hs-cTnT, a modest increase in invasive coronary angiography and a reduction in function testing were evident when low-level hs-cTnT concentrations were unmasked and reported clinically. However, although there remains the substantial possibility that

Table 4. Primary and Secondary Outcomes at 12 Months in the Overall Intention-to-Treat Population

Outcome, all participants	Standard protocol (N=1632), n (%)	0/1-h protocol (N=1638), n (%)	Hazard ratio (95% CI)	*P* value
Primary end point, death or myocardial infarction	62 (3.8)	82 (5.0)	1.32 (0.95–1.83)	0.10
All–cause death	31 (1.9)	39 (2.4)	1.25 (0.91–1.72)	0.17
Cardiovascular death	12 (0.7)	9 (0.5)	0.75 (0.39–1.42)	0.38
Myocardial infarction (types 1, 2, 4a, 5)	33 (2.0)	47 (2.9)	1.43 (1.08–1.87)	0.011
Acute myocardial injury with or without revascularization*	23 (1.4)	33 (2.0)	1.43 (0.99–2.07)	0.056
Representation with chronic myocardial injury pattern	128 (7.8)	134 (8.2)	1.04 (0.76–1.43)	0.79
Cardiovascular death or myocardial infarction	44 (2.7)	54 (3.3)	1.23 (1.11–1.35)	<0.001
Death, myocardial infarction and unstable angina	73 (4.5)	98 (6.0)	1.35 (1.04–1.74)	0.025
Cardiovascular rehospitalization†	64 (3.9)	65 (4.0)	1.01 (0.57–1.79)	0.96
Bleeding Academic Research Consortium 2, 3a, or 4	81 (5.0)	82 (5.0)	1.00 (0.80–1.27)	0.57

*All troponin T results >14 ng/L adjudicated according to the Fourth Universal Definition of Myocardial Infarction. A rise or fall pattern required a change troponin level of >20% and a rate of change arbitrarily defined as ≥3 ng/L per hour.

†Cardiovascular rehospitalization includes readmission for peripheral artery disease, cerebrovascular accidents, congestive cardiac failure without myocardial infarction, and atrial and ventricular arrhythmias.

the increase in all-cause death or MI in the 0/1-hour unmasked hs-cTnT arm is a chance finding, the influence of unmasked reporting on early cardiac assessment strategies requires careful consideration and re-evaluation in prospective randomized studies. Further, in a study cohort where ischemic changes were excluded on initial ECG, unmasked reporting of hs-cTnT concentrations did not increase the diagnosis of type 1 MI at index presentation. By excluding patients with obvious ischemia on ECG, this study may have targeted a patient group for whom there is little benefit associated with unmasked troponin T testing. However, unmasking of troponin results in this cohort identified a large proportion of patients manifesting a chronic myocardial injury pattern with substantial burden of recurrent cardiac events, most of which were not associated with MI. Overall, these observations suggest that although the improved diagnostic performance of high-sensitivity troponin testing for evolving MI is useful for determining a large proportion of patients for whom early discharge is safe, the influence of assays with superior diagnostic precision on subsequent clinical practice may not necessarily translate to superior clinical outcomes. Systemwide deployment of high-sensitivity troponin will require considered evolution of subsequent cardiac testing strategies and may also identify opportunities to explore treatments for other forms of myocardial injury that are recognized with increased frequency, to prevent the burden of heart failure and arrhythmia-associated representations observed among these patients.

Table 5. Primary and Secondary Outcomes at 12 Months in the Intention-to-Treat Population With an Initial Troponin ≤29 ng/L

Outcome, all participants	Standard protocol (N=1486), n (%)	0/1-h protocol (N=1507) n (%)	Hazard ratio (95% CI)	*P* value
Primary end point, death or myocardial infarction	34 (2.3)	55 (3.6)	1.60 (1.05 –2.46)	0.030
All-cause death	12 (0.8)	25 (1.7)	2.06 (1.27–3.34)	0.003
Cardiovascular death*	1 (0.1)	6 (0.4)	5.93 (0.87–40.33)	0.069
Myocardial infarction (types 1, 2, 4a, 5)	23 (1.5)	32 (2.1)	1.38 (1.15 –1.66)	0.001
Acute myocardial injury with or without revascularization†	17 (1.1)	19 (1.3)	1.10 (0.89–1.37)	0.38
Representation with chronic myocardial injury pattern	95 (6.4)	98 (6.5)	1.02 (0.76–1.36)	0.91
Cardiovascular death or myocardial infarction	24 (1.6)	36 (2.4)	1.49 (1.14–1.94)	0.003
Death, myocardial infarction and unstable angina	44 (3.0)	70 (4.6)	1.58 (1.30–1.92)	<0.001
Cardiovascular rehospitalization‡	46 (3.1)	48 (3.2)	1.03 (0.66–1.62)	0.89
Bleeding Academic Research Consortium 2, 3a, or 4	63 (4.2)	61 (4.0)	0.95 (0.69–1.31)	0.77

*Cardiovascular deaths: standard protocol (1 cerebrovascular accident); 0/1-h protocol: (1 cerebrovascular accident, 2 aortic aneurysm, 3 acute coronary syndrome/sudden death.

†All troponin T results >14 ng/L adjudicated according to the Fourth Universal Definition of Myocardial Infarction. A rise or fall pattern required a change troponin level of >20% and a rate of change arbitrarily defined as ≥3 ng/L per hour.

‡Cardiovascular rehospitalization includes readmission for peripheral artery disease, cerebrovascular accidents, congestive cardiac failure without myocardial infarction, and atrial and ventricular arrhythmias.

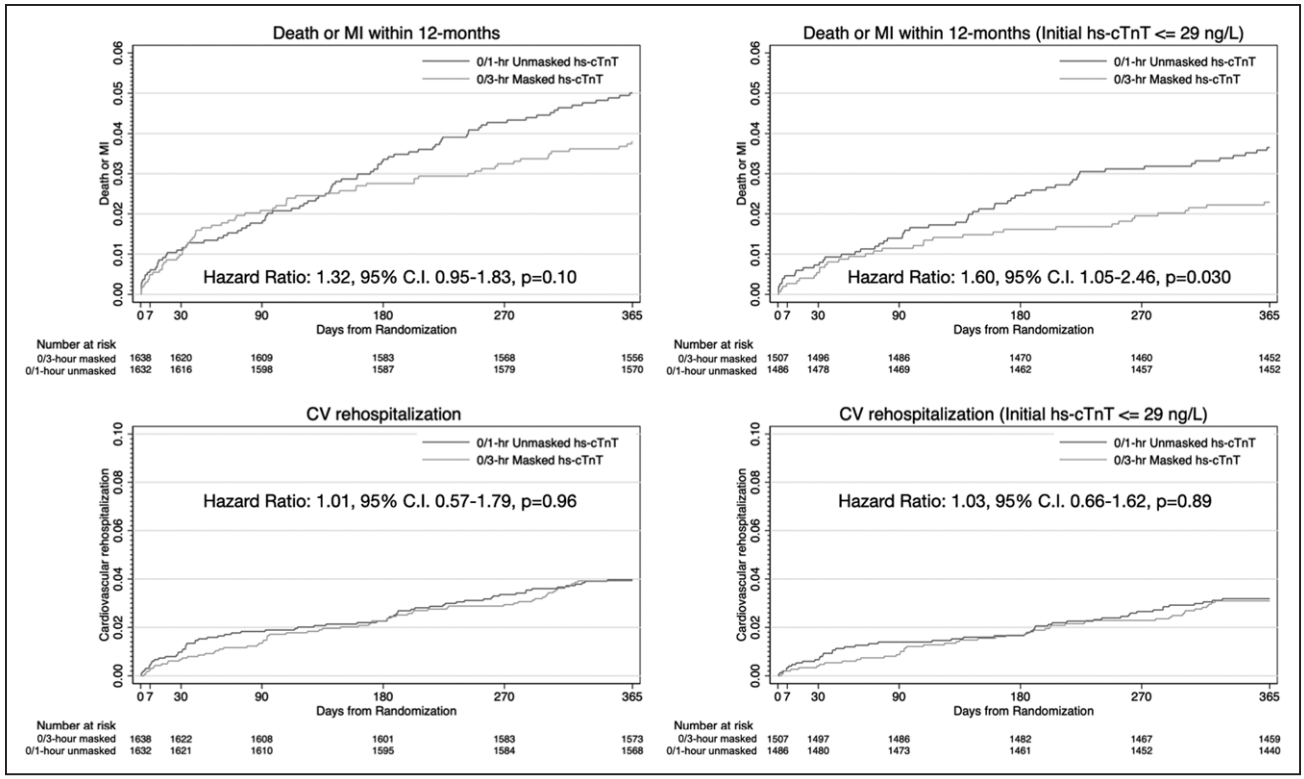

Figure 2. Primary outcome and CV rehospitalisation at 12 months by randomization arm in the overall population and in those with an initial troponin ≤29ng/L.

Kaplan-Meier event curves by masked and unmasked study arms for primary composite end point and cardiovascular rehospitalization in the overall population and patients with an initial troponin ≤29 ng/L. CV indicates cardiovascular; hs-cTnT, high-sensitivity cardiac troponin T; and MI, myocardial infarction.

A large body of evidence now suggests that the likelihood of evolving MI is low, and early discharge is safe among those with low troponin concentrations and nondynamic temporal profiles when using high-sensitivity troponin assays.[2,14] However, although this allows for a resetting of the threshold for discharge, it also identifies a greater proportion of patients with an elevated troponin concentration, for whom a greater risk of recurrent cardiac events is also observed.[16] In those with modest troponin elevations, where care was informed by unmasked hs-cTnT, small increases in invasive coronary angiography and revascularization and reductions in noninvasive cardiac investigative practices were observed. Such changes have been seen in other studies, but this did not translate to a reduction in death or MI at 12 months in this large patient-level randomized trial.[9,17–19]

Although this study did not demonstrate an excess of type 4 or type 5 MI, the shift in investigative strategy toward more coronary angiography among patients with an initial troponin concentration ≤29 ng/L was not associated with a reduction in recurrent ACS or cardiovascular mortality. These data potentially lend further support to previous observations that invasive coronary investigations among patients with suspected ACS at low overall ischemic risk are not necessarily associated with a lower rate of recurrent ischemic events.[17,20] These findings may also call for careful consideration in implementing current ACS guideline recommendations, which advocate for early invasive management among those presenting with troponin elevation, because the evidence for this recommendation was acquired in an era of less sensitive troponin assays, and thus thresholds for reporting elevated troponin were at higher concentrations.[20–23]

In addition, the reduction in functional testing in those with low-level troponin concentrations observed in this study suggests that the rule-out recommendation provided confidence in the exclusion of evolving MI/unstable angina and stable angina. However, although such rapid troponin testing protocols facilitate safe ED discharge, late outcomes evident within this study may also suggest an ongoing role for subsequent ambulatory testing for the diagnosis of latent coronary artery disease together with the initiation of preventative therapies. Such findings of inferior late outcomes associated with changes in care with the deployment of high-sensitivity troponin tests have been observed by others in the context of large-scale observational series.[24] It is possible that a shift from functional testing among higher-risk patients may account for some of the excess risk observed in this study.

These observations highlight the need for reconsideration of the investigative approaches for patients presenting with modestly elevated troponin concentrations.[25,26] It

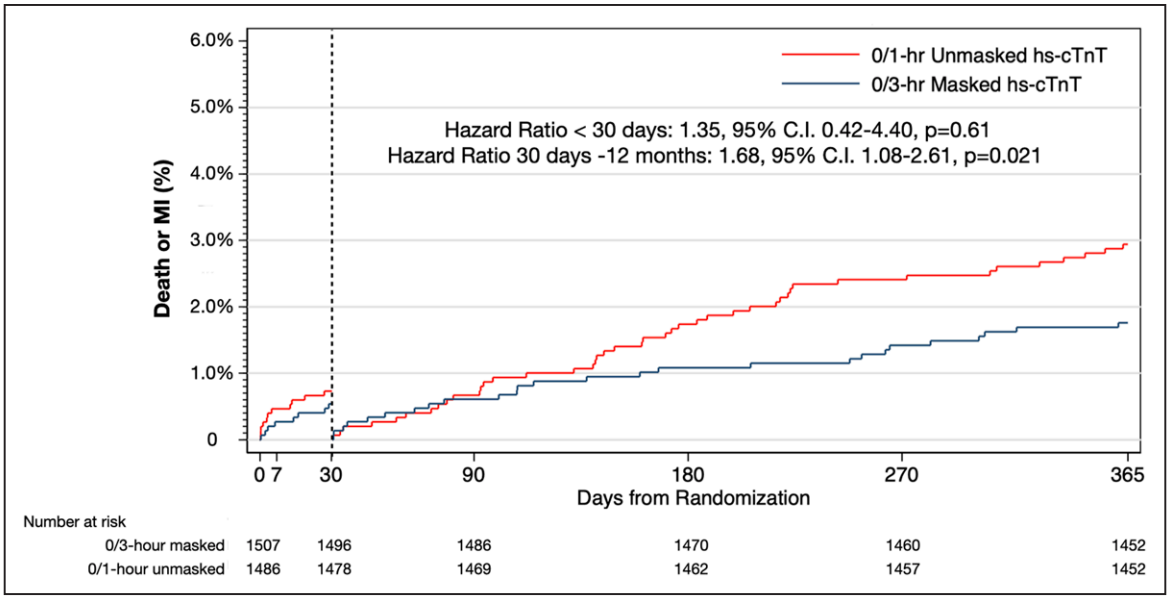

Figure 3. Landmark analysis at 30 days by randomization arm in participants with an initial troponin ≤29ng/L.
Landmark analysis up to 30 days and from 30 days to 12 months, showing increased risk of death or myocardial infarction (MI) in early and late follow-up in the 0/1-hour unmasked high-sensitivity cardiac troponin T (hs-cTnT) arm, among participants with an initial troponin T ≤29 ng/L.

is possible that by uncoupling the diagnosis of CAD from the immediate impetus to revascularize, alternative initial investigative strategies such as computerized tomography coronary angiography may provide a more risk-appropriate approach to the investigation of those with low-level troponin elevations.[27,28] Furthermore, with the deployment of unmasked hs-cTnT in the ED, this analysis highlights the disproportionate increase in patients presenting with a troponin profiles consistent with acute and chronic myocardial injury compared with that of type 1 MI.[16] Of particular note, although all forms of myocardial injury are associated with a greater risk of mortality and have a similar rate of noncoronary cardiovascular rehospitalizations over 12 months, those presenting with type 2 MI and acute and chronic injury do not appear to experience a greater risk of acute coronary events in contrast with patients with type 1 MI.[29,30] Given the often high burden of competing risk among these patients, the risk/benefit balance of coronary investigation requires further delineation.[31]

These observations represent an opportunity for the refinement of investigative work-up and highlight the need for more clinical research into the use of existing and emerging therapies among those with troponin elevations that are not a result of type 1 MI to prevent late cardiovascular morbidity and mortality. Establishing an evidence base for the treatment of these patients would realize the true promise of high-sensitivity troponin assays. Despite our need to transition to unmasked reporting of hs-cTnT in local clinical practice, translating increased precision in investigative testing into improvements in patient outcomes may require more experienced and sophisticated diagnostic resources within the ED setting. The real challenge for many health systems, however, is deployment of this expertise at scale. Integrating health data with artificial intelligence techniques to better assimilate clinical information shows some promise in supporting early diagnostic decision-making, although prospective validation when embedded within clinical practice has yet to be demonstrated.[32,33]

Limitations

In this study, several limitations should be considered. First, although all recurrent events were adjudicated using unmasked hs-cTnT concentrations, when participants presented with recurrent events, clinicians at the point of care remained masked to troponin concentrations ≤29 ng/L in both arms of the study. These perceived normal results may have led to fewer investigations and a lower rate of representations that met the trial's cardiovascular event definitions. Although this reduces the power to detect a difference in this study, it does not introduce bias between study arms. Second, observations among those within the masked range are exploratory and may be subject to type 1 error given the lack of difference in the overall study. Care and outcomes among these participants (ie, where there was an actual difference in the information afforded by hs-cTnT reporting) were clearly the primary interest of the study, and were therefore prespecified and formed the basis of the initial sample size estimation. This analytic approach was made necessary because randomization occurred before any troponin results were clinically revealed, and therefore, the primary analysis focused on the intention-to-treat population. These participants constituted >90% of the study population and remained balanced between study arms for key clinical characteristics.

Table 6. Investigations, Management, and Clinical Outcomes by Triage Category Among Participants With Initial Troponin Concentrations ≤29 ng/L

Investigations and management	0/3-h masked	0/1-h unmasked			*P* value
	≤29 ng/L (N=1486)	Rule-out (N=1182)	Observe (N= 270)	Rule-in (N=42)	
Length of stay, h	6.3 (4.8–18.3)	4.6 (3.5–7.6)	9.9 (5.1–32.5)	29.2 (7.8–54.7)	<0.0001
Discharged from emergency department	511 (34.4)	626 (53.0)	79 (29.3)	7 (16.7)	<0.0001
Functional testing within 30 d	150 (10.1)	61 (5.2)	36 (13.3)	7 (16.7)	<0.0001
Coronary angiogram within 30 d	47 (3.2)	35 (3.0)	24 (8.9)	11 (26.2)	<0.0001
Percutaneous coronary intervention within 30 d	13 (0.9)	11 (0.9)	13 (4.8)	6 (14.3)	<0.0001
Coronary artery bypass graft within 30 d	1 (0.1)	1 (0.1)	2 (0.7)	1 (2.4)	0.0008
Revascularization within 30 d	14 (0.9)	12 (1.0)	15 (5.6)	7 (16.7)	<0.0001
Coronary angiogram within 12 mo	124 (8.3)	98 (8.3)	52 (19.3)	18 (42.9)	<0.0001
Percutaneous coronary intervention within 12 mo	34 (2.3)	23 (1.9)	20 (7.4)	8 (19.0)	<0.0001
Coronary artery bypass graft within 12 mo	9 (0.6)	7 (0.6)	5 (1.9)	1 (2.4)	0.14
Revascularization within 12 mo	43 (2.9)	28 (2.4)	25 (9.3)	9 (21.4)	<0.0001
Therapies after hospitalization					
$P2Y_{12}$ inhibitor	135 (9.1)	94 (8.0)	58 (21.5)	14 (33.3)	<0.0001
Statin therapy	517 (34.8)	338 (28.6)	150 (55.6)	26 (61.9)	<0.0001
Other lipid-lowering agents	107 (7.2)	81 (6.9)	38 (14.1)	8 (19.0)	<0.0001
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	537 (36.1)	364 (30.8)	147 (54.4)	28 (66.7)	<0.0001
β-Blockers	305 (20.5)	189 (16.0)	104 (38.5)	15 (35.7)	<0.0001
Clinical outcomes					
Primary end point, death or myocardial infarction	34 (2.3)	26 (2.2)	26 (9.6)	3 (7.2)	<0.001
All-cause death	12 (0.8)	9 (0.8)	15 (5.6)	1 (2.4)	<0.001
Cardiovascular death	1 (0.7)	1 (0.8)	5 (1.9)	0	0.001
Myocardial infarction (types 1, 2, 4a, 5)	23 (1.6)	17 (1.4)	13 (4.8)	2 (4.8)	0.006
Acute myocardial injury with or without revascularization	17 (1.1)	12 (1.0)	6 (2.2)	1 (2.4)	0.345
Representation with chronic myocardial injury pattern	95 (6.4)	18 (1.5)	72 (26.7)	8 (19.1)	<0.001
Death, myocardial infarction, and unstable angina	44 (3.0)	38 (3.2)	29 (10.7)	3 (7.1)	<0.001
Cardiovascular rehospitalization	46 (3.1)	20 (1.7)	26 (9.6)	2 (4.8)	<0.001

Values indicate n (%) or median (interquartile range). Thirteen patients were unallocated because of hemolyzed or incomplete troponin sampling.
P values calculated using the Fisher exact test given the small event rates in some cells.

Furthermore, the persistent difference in adjusted analyses and the lack of difference in noncoronary cardiovascular events argues against, but does not exclude, a chance finding. Third, interpretation of the frequency of myocardial injury not attributable to type 1 MI is subject to the enrollment criteria and local investigative practices. Despite the large burden of secondary events and chronic injury representations, this study focused on patients presenting to EDs with suspected ACS where a 0/1-hour hs-cTnT protocol would have been expected to impact their clinical management (ie, patients without obvious ischemia on initial assessment). Consequently, this study focused on a patient population with a lower likelihood of evolving ACS at initial presentation. The findings do not apply to patients with suspected ACS with clear ischemic changes on ECG, and therefore, the potential benefits of high-sensitivity troponin assays may not have been realized. Nevertheless, the cohort enrolled in this study represents a substantial volume of presentations; however, the selection criteria were likely to provide an underestimate of the true incidence and prevalence of myocardial injury in the community.

CONCLUSIONS

Among patients with suspected ACS randomized to unmasked hs-cTnT troponin results in a 0/1-hour protocol, no reduction in death or MI was observed over 12-month follow-up. An excess risk observed among patients with troponin concentrations within the previously masked range warrants further study. Translating improvements in the performance of high-sensitivity troponin assays into improvements in patient outcomes may require reconsideration of the downstream investigative and therapeutic strategies. Recognition of the persistent risk asso-

ciated with modest troponin elevations among the many patients with presentations not attributable to type 1 MI represents an opportunity to explore strategies to impact future cardiovascular events.

ARTICLE INFORMATION

Received March 29, 2021; accepted April 29, 2021.

Affiliations

College of Medicine and Public Health, Flinders University of South Australia, Adelaide (K.L., A.B., A.S., A.C., E.K., E.M., J.K., D.P.C.). South Australian Health and Medical Research Institute, Adelaide (D.P.C.). South Australian Department of Health, Adelaide (K.L., C.P., A.B., A.S., M.J.R.E., A.C., E.K., A.J.N., D.W., M.H., D.P.C.). School of Medicine, University of Adelaide, Australia (C.P., A.J.N.). Department of Cardiology, Liverpool Hospital, University of New South Wales, Sydney, Australia (J.K.F.). Department of Statistics, Data Science and Epidemiology (S.Q.), Swinburne University of Technology, Melbourne, Australia. School of Population and Global Health, University of Western Australia, Perth (T.B.). Emergency and Trauma Centre, Royal Brisbane and Women's Hospital, Australia (L.A.C.). School of Public Health, Queensland University of Technology, Brisbane, Australia (L.A.C.). School of Medicine, University of Queensland, Brisbane, Australia (L.A.C.).

Acknowledgments

The authors acknowledge the support and collaboration from Dr Penny Coates and team from South Australia Pathology for their role maintaining the statewide troponin reporting policy and facilitating access to the troponin results required for the implementation of the study.

Sources of Funding

Funding was provided by the National Health and Medical Research Council of Australia (Canberra, Australian Capital Territory, GNT1124471) with supplementary support from an unrestricted grant from Roche Diagnostics International (Rotkreuz, Switzerland).

Disclosures

The authors were solely responsible for the design and conduct of this study, including study analyses, the drafting and editing of the article, and its final contents. Funding was sought after the study was designed, approved by the human research ethics committee, and initiated. Neither funder has requested any modification of the protocol nor access to the data on completion. L.A.C. received research grants from Abbott Diagnostics, Siemens, and Beckman Coulter; and speaker honoraria from Siemens, Abbott Diagnostics, Novartis, and AstraZeneca. D.P.C. received speaker honoraria from AstraZeneca Australia and Roche Diagnostic, and unrestricted grants from Edwards Life Sciences and Roche Diagnostic (this study). The other authors declare no conflicts.

Supplemental Materials

Data Supplement Materials
Data Supplement Tables I–V
Data Supplement Figures I and II

REFERENCES

1. Mueller C, Giannitsis E, Christ M, Ordóñez-Llanos J, deFilippi C, McCord J, Body R, Panteghini M, Jernberg T, Plebani M, et al; TRAPID-AMI Investigators. Multicenter evaluation of a 0-hour/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac troponin T. *Ann Emerg Med*. 2016;68:76–87.e4. doi: 10.1016/j.annemergmed.2015.11.013
2. Twerenbold R, Neumann JT, Sörensen NA, Ojeda F, Karakas M, Boeddinghaus J, Nestelberger T, Badertscher P, Rubini Giménez M, Puelacher C, et al. Prospective validation of the 0/1-h algorithm for early diagnosis of myocardial infarction. *J Am Coll Cardiol*. 2018;72:620–632. doi: 10.1016/j.jacc.2018.05.040
3. Mueller M, Biener M, Vafaie M, Doerr S, Keller T, Blankenberg S, Katus HA, Giannitsis E. Absolute and relative kinetic changes of high-sensitivity cardiac troponin T in acute coronary syndrome and in patients with increased troponin in the absence of acute coronary syndrome. *Clin Chem*. 2012;58:209–218. doi: 10.1373/clinchem.2011.171827
4. Reichlin T, Irfan A, Twerenbold R, Reiter M, Hochholzer W, Burkhalter H, Bassetti S, Steuer S, Winkler K, Peter F, et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. *Circulation*. 2011;124:136–145. doi: 10.1161/CIRCULATIONAHA.111.023937
5. Shah A, Anand A, Sandoval Y, Lee KK, Smith SW Adamson PD, Chapman AR, Langdon T, Sandemam D, Vaswani A, et al. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. *Lancet*. 2016;386:2481–2488. doi: 10.1016/S0140-6736(15)00391-8
6. Chew DP, Zeitz C, Worthley M, Grantham H, Beltrame J, Arstall M, Coates P, Astley C, Quinn S, Ratcliffe J, et al. Randomized comparison of high-sensitivity troponin reporting in undifferentiated chest pain assessment. *Circ Cardiovasc Qual Outcomes*. 2016;9:542–553. doi: 10.1161/CIRCOUTCOMES.115.002488
7. Chew DP, Lambrakis K, Blyth A, Seshadri A, Edmonds MJR, Briffa T, Cullen LA, Quinn S, Karnon J, Chuang A, et al. A randomized trial of a 1-hour troponin T protocol in suspected acute coronary syndromes: the Rapid Assessment of Possible Acute Coronary Syndrome in the Emergency Department With High-Sensitivity Troponin T Study (RAPID-TnT). *Circulation*. 2019;140:1543–1556. doi: 10.1161/CIRCULATIONAHA.119.042891
8. Twerenbold R, Jaeger C, Rubini Gimenez M, Wildi K, Reichlin T, Nestelberger T, Boeddinghaus J, Grimm K, Puelacher C, Moehring B, et al. Impact of high-sensitivity cardiac troponin on use of coronary angiography, cardiac stress testing, and time to discharge in suspected acute myocardial infarction. *Eur Heart J*. 2016;37:3324–3332. doi: 10.1093/eurheartj/ehw232
9. Melki D, Lugnegård J, Alfredsson J, Lind S, Eggers KM, Lindahl B, Jernberg T. Implications of introducing high-sensitivity cardiac troponin T into clinical practice: data from the SWEDEHEART Registry. *J Am Coll Cardiol*. 2015;65:1655–1664. doi: 10.1016/j.jacc.2015.02.044
10. Papendick C, Blyth A, Seshadri A, Edmonds MJR, Briffa T, Cullen L, Quinn S, Karnon J, Chuang A, Nelson AJ, et al. A randomized trial of a 1-hour troponin T protocol in suspected acute coronary syndromes: design of the Rapid Assessment of Possible ACS in the Emergency Department With High Sensitivity Troponin T (RAPID-TnT) study. *Am Heart J*. 2017;190:25–33. doi: 10.1016/j.ahj.2017.05.004
11. Thygesen K, Alpert JS, Jaffe AS, Morrow DA, White HD, Mickley H, Crea F, de Werf Van F, Bucciarelli-Ducci C, Katus HA, et al. Fourth universal definition of myocardial infarction (2018). *Eur Heart J*. 2019;40:237–269. doi: 10.1093/eurheartj/ehy462.
12. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, et al. 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
13. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2020;37:267. doi:10.1093/eurheartj/ehaa575
14. Pickering JW, Greenslade JH, Cullen L, Flaws D, Parsonage W, Aldous S, George P, Worster A, Kavsak PA, Than MP. Assessment of the European Society of Cardiology 0-Hour/1-Hour algorithm to rule-out and rule-in acute myocardial infarction. *Circulation*. 2016;134:1532–1541. doi: 10.1161/CIRCULATIONAHA.116.022677
15. Neumann JT, Twerenbold R, Ojeda F, Sörensen NA, Chapman AR, Shah ASV, Anand A, Boeddinghaus J, Nestelberger T, Badertscher P, et al. Application of high-sensitivity troponin in suspected myocardial infarction. *N Engl J Med*. 2019;380:2529–2540. doi: 10.1056/NEJMoa1803377
16. Chapman AR, Adamson PD, Shah ASV, Anand A, Strachan FE, Ferry AV, Ken Lee K, Berry C, Findlay I, Cruikshank A, et al. High-sensitivity cardiac troponin and the universal definition of myocardial infarction. *Circulation*. 2020;141:161–171. doi:10.1161/CIRCULATIONAHA.119.042960
17. Eggers KM, Lindahl B, Melki D, Jernberg T. Consequences of implementing a cardiac troponin assay with improved sensitivity at Swedish coronary care units: an analysis from the SWEDEHEART registry. *Eur Heart J*. 2016;37:2417–2424. doi: 10.1093/eurheartj/ehw029
18. Odqvist M, Andersson PO, Tygesen H, Eggers KM, Holzmann MJ. High-sensitivity troponins and outcomes after myocardial infarction. *J Am Coll Cardiol*. 2018;71:2616–2624. doi: 10.1016/j.jacc.2018.03.515
19. Shah ASV, Anand A, Strachan FE, Ferry AV, Lee KK, Chapman AR, Sandeman D, Stables CL, Adamson PD, Andrews JPM, et al; High-STEACS Investigators. High-sensitivity troponin in the evaluation of patients with suspected

acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial. *Lancet*. 2018;392:919–928. doi: 10.1016/S0140-6736(18)31923-8
20. Foy AJ, Liu G, Davidson WR, Sciamanna C, Leslie DL. Comparative effectiveness of diagnostic testing strategies in emergency department patients with chest pain: an analysis of downstream testing, interventions, and outcomes. *JAMA Intern Med*. 2015;175:428–436. doi:10.1001/jamainternmed.2014.7657
21. O'Donoghue M, Boden WE, Braunwald E, Cannon CP, Clayton TC, de Winter RJ, Fox KA, Lagerqvist B, McCullough PA, Murphy SA, et al. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. *JAMA*. 2008;300:71–80. doi: 10.1001/jama.300.1.71
22. Fox KA, Poole-Wilson PA, Henderson RA, Clayton TC, Chamberlain DA, Shaw TR, Wheatley DJ, Pocock SJ; Randomized Intervention Trial of unstable Angina Investigators. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. *Lancet*. 2002;360:743–751. doi: 10.1016/s0140-6736(02)09894-x
23. Eggers KM, Jernberg T, Lindhagen L, Lindahl B. High-sensitivity cardiac troponin T levels identify patients with non-ST-segment elevation acute coronary syndrome who benefit from invasive assessment. *JACC Cardiovasc Interv*. 2018;11:1665–1667. doi: 10.1016/j.jcin.2018.03.027
24. Bandstein N, Ljung R, Lundbäck M, Johansson M, Holzmann MJ. Trends in admissions for chest pain after the introduction of high-sensitivity cardiac troponin T. *Int J Cardiol*. 2017;240:1–7. doi: 10.1016/j.ijcard.2017.04.028
25. Tomaszewski CA, Nestler D, Shah KH, Sudhir A, Brown MD. American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Suspected Non–ST-Elevation Acute Coronary Syndromes: clinical policy: critical issues in the evaluation and management of emergency department patients with suspected non-ST-elevation acute coronary syndromes. *Ann Emerg Med*. 2018;72:e65–e106. doi:10.1016/j.annemergmed.2018.07.045
26. Sun BC, Redberg RF. Cardiac testing after emergency department evaluation for chest pain: time for a paradigm shift? *JAMA Intern Med*. 2017;177:1183–1184. doi: 10.1001/jamainternmed.2017.2439
27. Dedic A, Lubbers MM, Schaap J, Lammers J, Lamfers EJ, Rensing BJ, Braam RL, Nathoe HM, Post JC, Nielen T, et al. Coronary CT angiography for suspected ACS in the era of high-sensitivity troponins: randomized multicenter study. *J Am Coll Cardiol*. 2016;67:16–26. doi: 10.1016/j.jacc.2015.10.045
28. Gray AJ, Roobottom C, Smith JE, Goodacre S, Oatey K, O'Brien R, Storey RF, Na L, Lewis SC, Thokala P, et al. The RAPID-CTCA trial (Rapid Assessment of Potential Ischaemic Heart Disease with CTCA) - a multicentre parallel-group randomised trial to compare early computerised tomography coronary angiography versus standard care in patients presenting with suspected or confirmed acute coronary syndrome: study protocol for a randomised controlled trial. *Trials*. 2016;17:579. doi: 10.1186/s13063-016-1717-2
29. McCarthy CP, Vaduganathan M, Januzzi JL Jr. Type 2 myocardial infarction-diagnosis, prognosis, and treatment. *JAMA*. 2018;320:433–434. doi: 10.1001/jama.2018.7125
30. Chuang A, Hancock DG, Horsfall M, Alhammad NJ, Zhou J, Cullen L, French J, Chew DP. The predictive value of high sensitivity-troponin velocity within the first 6h of presentation for cardiac outcomes regardless of acute coronary syndrome diagnosis. *Int J Cardiol*. 2016;204:106–111. doi: 10.1016/j.ijcard.2015.11.132
31. Chuang AM, Hancock DG, Halabi A, Horsfall M, Vaile J, De Pasquale C, Sinhal A, Jones D, Brogan R, Chew DP. Invasive management of acute coronary syndrome: interaction with competing risks. *Int J Cardiol*. 2018;269:13–18. doi: 10.1016/j.ijcard.2018.07.078
32. Al-Zaiti S, Besomi L, Bouzid Z, Faramand Z, Frisch S, Martin-Gill C, Gregg R, Saba S, Callaway C, Sejdić E. Machine learning-based prediction of acute coronary syndrome using only the pre-hospital 12-lead electrocardiogram. *Nat Commun*. 2020;11:3966. doi: 10.1038/s41467-020-17804-2
33. Than MP, Pickering JW, Sandoval Y, Shah ASV, Tsanas A, Apple FS, Blankenberg S, Cullen L, Mueller C, Neumann JT, et al. Machine learning to predict the likelihood of acute myocardial infarction. *Circulation*. 2019;140:899–909. doi:10.1161/CIRCULATIONAHA.119.041980