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ORIGINAL RESEARCH ARTICLE

# 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)

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**BACKGROUND:** High-sensitivity troponin assays promise earlier discrimination of myocardial infarction. Yet, the benefits and harms of this improved discriminatory performance when incorporated within rapid testing protocols, with respect to subsequent testing and clinical events, has not been evaluated in an in-practice patient-level randomized study. This multicenter study evaluated the noninferiority of a 0/1-hour high-sensitivity cardiac troponin T (hs-cTnT) protocol in comparison with a 0/3-hour masked hs-cTnT protocol in patients with suspected acute coronary syndrome presenting to the emergency department (ED).

**METHODS:** Patients were randomly assigned to either a 0/1-hour hs-cTnT protocol (reported to the limit of detection [<5 ng/L]) or masked hs-cTnT reported to ≤29 ng/L evaluated at 0/3-hours (standard arm). The 30-day primary end point was all-cause death and myocardial infarction. Noninferiority was defined as an absolute margin of 0.5% determined by Poisson regression.

**RESULTS:** In total, 3378 participants with an emergency presentation were randomly assigned between August 2015 and April 2019. Ninety participants were deemed ineligible or withdrew consent. The remaining participants received care guided either by the 0/1-hour hs-cTnT protocol (n=1646) or the 0/3-hour standard masked hs-cTnT protocol (n=1642) and were followed for 30 days. Median age was 59 (49–70) years, and 47% were female. Participants in the 0/1-hour arm were more likely to be discharged from the ED (0/1-hour arm: 45.1% versus standard arm: 32.3%, *P*<0.001) and median ED length of stay was shorter (0/1-hour arm: 4.6 [interquartile range, 3.4–6.4] hours versus standard arm: 5.6 (interquartile range, 4.0–7.1) hours, *P*<0.001). Those randomly assigned to the 0/1-hour protocol were less likely to undergo functional cardiac testing (0/1-hour arm: 7.5% versus standard arm: 11.0%, *P*<0.001). The 0/1-hour hs-cTnT protocol was not inferior to standard care (0/1-hour arm: 17/1646 [1.0%] versus 16/1642 [1.0%]; incidence rate ratio, 1.06 [ 0.53–2.11], noninferiority *P* value=0.006, superiority *P* value=0.867), although an increase in myocardial injury was observed. Among patients discharged from ED, the 0/1-hour protocol had a negative predictive value of 99.6% (95% CI, 99.0–99.9%) for 30-day death or myocardial infarction.

**CONCLUSIONS:** This in-practice evaluation of a 0/1-hour hs-cTnT protocol embedded in ED care enabled more rapid discharge of patients with suspected acute coronary syndrome. Improving short-term outcomes among patients with newly recognized troponin T elevation will require an evolution in management strategies for these patients.

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## Clinical Perspectives

### What Is New?

- High-sensitivity troponin assays have promised improved diagnosis of myocardial infarction, enabling more timely decision making in the emergency department.
- Resetting clinical practice to a higher level of troponin sensitivity and more rapid testing sequence may also lead to unanticipated effects, such as increased procedure-related myocardial injury and infarction.
- This patient-level prospective randomized comparison of a 0/1-hour protocol using high-sensitivity troponin T embedded within routine practice confirmed a low rate of 30-day death or myocardial infarction for patients receiving a rule-out myocardial infarction recommendation, but did not lead to a reduction in these events overall.

### What Are the Clinical Implications?

- This study supports the routine implementation of a 0/1-hour high-sensitivity troponin T protocol for the early rule-out of patients with suspected acute coronary syndrome.
- However, the use of invasive coronary investigation is increased among patients with newly identified low-concentration troponin elevations, and the strategies to mitigate associated cardiac injury may require further refinements in acute coronary syndrome care.

The introduction of high-sensitivity troponin assays, which enable detection of very low levels of myocardial injury, has promised to enhance clinical practice and improve outcomes through earlier detection of myocardial infarction (MI).[1,2] Yet, to date, prospective randomized evaluations of high-sensitivity troponin testing have not demonstrated reduction in subsequent ischemic events.[3,4]

Given that greater sensitivity translates to improved negative predictive value, these assays may allow for the exclusion of significant cardiac events more rapidly and with greater certainty, enabling earlier discharge from emergency services. Such protocols for rapid triage of patients with suspected acute coronary syndromes (ACS) have been developed and incorporated into clinical guidelines.[5–9] Although the use of high-sensitivity troponin assays in Europe is more common (>60%), uptake in North America and the Asia Pacific region is estimated to be much lower (≈20% and ≈30%, respectively) and of these centers, very few use a 0/1-hour rapid triage protocol.

However, studies supporting these protocols have yet to include contemporaneously enrolled comparative patients managed without access to the improved precision of high-sensitivity troponin and are subject to changes in decision making and clinical care that may not be attributable to the deployment of the high-sensitivity troponin assay. Furthermore, although these guidelines focus on the exclusion of MI, concerns remain regarding the implications of increased testing and coronary revascularization among those patients with low levels of myocardial injury.[10–13] Resetting clinical practice to a higher level of troponin sensitivity and more rapid testing sequence may lead to unanticipated effects, such as increased procedure-related myocardial injury and infarction. Hence, comparative randomized evaluation of a 0/1-hour protocol that relies on the diagnostic performance of high-sensitivity troponin assays, in comparison with and embedded within existing practice, where the improved diagnostic precision of these assays has not been used, is required to evaluate the actual value of this innovation in clinical decision making, downstream cardiac testing, and the balance of benefits and harms associated with any change in practice.[14] Therefore, we conducted an in-practice prospective randomized multicenter clinical trial embedded in emergency department (ED) assessment of suspected ACS and investigating an accelerated 0/1-hour decision rule based on high-sensitivity cardiac troponin T (hs-cTnT) in comparison with a 0/3-hour protocol, in which the troponin T assay's high-sensitivity performance characteristics were masked.

## METHODS

### Study Design and Funding

The design of the RAPID-TnT trial (Rapid Assessment of Possible ACS in the Emergency Department with High-Sensitivity Troponin T) was a prospective patient-level randomized noninferiority evaluation of a 0/1-hour protocol using a hs-cTnT–reporting format in comparison with a 0/3-hour protocol with troponin T results masked at <29 ng/L, in participants with suspected ACS, with respect to death or MI by 30 days. Secondarily, this study sought to confirm that participants discharged from the ED after assessment for suspected ACS in accordance with a 0/1-hour hs-cTnT protocol have a death or MI incidence rate by 30 days of <1.0%.[15] The study was conducted in 4 metropolitan public EDs in Adelaide, Australia, and details of its design have been previously published.[16] Human research ethics approval was granted by the Human Research Ethics Committee of the Southern Adelaide Local Health Network (207.15) with mutual acceptance by other participating sites, and all participants gave written informed consent before study enrollment. (Australian and New Zealand Clinical Trial Registry Registration Number ACTRN12615001379505). The study was investigator initiated and funded by the National Health and Medical Research Council of Australia (APP1124471) with supplementary support provided via an unrestricted grant from Roche Diagnostics International. Funding was secured after enrollment had commenced, and was not contingent on access

to study data or protocol modification. Data supporting the findings of this study are available from the corresponding author upon reasonable request.

## System-Level Masking of Troponin T Reporting Enabling Study Implementation

In April 2011, the Roche Diagnostics (Cobas) Elecsys 5th-generation hs-cTnT assay (limit of detection: 5 ng/L, 99th percentile: 14ng/L) was implemented as the sole troponin assay available within all public hospital EDs in South Australia via a single pathology provider. Because of the uncertainty regarding the balance between the potential increase in downstream cardiac testing versus the possible benefits of increased MI diagnosis with implementing an upper reference limit of 14 ng/L, the decision was made at adoption to numerically align the lower clinical reporting limit of the 5th-generation assay to that of the previous assay (ie, masked, with the lower reference limit reported as ≤29 ng/L rather than to report down to the limit of detection [5 ng/L]). The decision was made with the recognition that the 5th-generation hs-cTnT assay had greater sensitivity than the same concentrations reported on the 4th-generation assay. Specifically, in maintaining the reported lower reference limit at ≤29 ng/L while transitioning from the 4th-generation to the 5th-generation assay, this reduced the actual lower reference limit reported to clinicians, because a concentration of 29 ng/L using the 4th-generation assay equates to a concentration of ≈43 ng/L on the 5th-generation assay.[17]

The clinical implications of access to troponin concentrations between 5 and 29 ng/L to enable diagnostic classification consistent with international standards was then prospectively evaluated in a previous randomized trial (n=1937) showing modest differences in treatment and no difference in 12-month rates of death or recurrent ACS.[3] Hence, this masked reporting policy was maintained, enabling a patient-level implementation of the current randomized trial. Apart from the preliminary trial, participating EDs had therefore uniquely remained masked to troponin T concentrations <29 ng/L; thus, clinicians had no previous clinical experience with hs-cTnT results <29 ng/L, or with the 0/1-hour protocol. This controlled access to troponin results enabled a randomized evaluation to be embedded within routine practice. In this setting, absolute troponin T values were reported only for participants randomly assigned to the 0/1-hour arm, and the interpretation was guided by the study protocol (see below). Maintenance of the integrity of the 2 randomized reporting formats was managed through the single statewide pathology-reporting system. After capture of baseline data, randomization in permuted blocks of 4 occurring independently at each hospital was implemented by a combined envelope and web-based randomization process at study initiation.

## Study Population

This study focused on patients in whom initial clinical and ECG assessment did not provide a high diagnostic likelihood for MI, because the safety of early discharge is less clinically relevant in this cohort. Similarly, reliant on physician judgment at initial assessment, the study sought to include participants for whom care might be influenced by rapid triage protocols (ie, eligible for early ED discharge). Therefore, participants presenting to the ED were included if there was the intention to undertake troponin testing, and they had clinical features of chest pain or suspected ACS as the principal cause for investigation and a baseline ECG interpreted as not definitive for coronary ischemia, and they were ≥18 years of age and willing to give written consent. Participants were excluded if they presented for chest pain not suspected to be from a cardiac cause, presented as a result of a transfer from another hospital, presented for suspected ACS within 30 days of last presentation, required permanent dialysis, or were unable to complete the clinical history questionnaire because of language or comorbidity.

## Study Protocol

To maintain the integrity of the troponin-testing procedure, all participants were consented and randomly assigned after senior ED physician interpretation of the initial ECG, but before troponin results were available. For participants randomly assigned to the 0/1-hour hs-cTnT arm, ED management pathways for each of rule-in, observe, and rule-out were based on previous studies and were formalized in a protocol.[6,18] Specifically, rule-out with discharge to primary care with instructions regarding recurrent chest pain and primary prevention advice was recommended when the baseline troponin was <5 ng/L at >3 hours after the onset of symptoms, or ≤12 ng/L and a change in troponin over 1 hour of <3 ng/L was seen; rule-in with admission to the hospital for management of suspected MI was recommended when the baseline troponin was ≥52 ng/L or a change over 1 hour of ≥5 ng/L was documented; continued observation, with repeat testing and possible hospital admission, was recommended when the baseline troponin was between 13 and 51 ng/L with a change over 1 hour of <5 ng/L, or with a baseline troponin of ≤12 ng/L and a change over 1 hour of 3 to 4 ng/L.

The care of participants in the standard masked hs-cTnT arm followed the statewide chest pain protocol that recommended testing of troponin T at baseline and repeated at 3 hours, with discretionary further testing at 6 hours. For the implementation of the standard protocol, all troponin T concentrations were reported to a lower limit of ≤29 ng/L. Within the local standard of care, participants with an elevated troponin, ongoing chest pain, or known coronary artery disease were recommended for referral to inpatient clinical teams for the consideration of admission. The standard local pathway recommendation for patients with troponin results ≤29 ng/L was discharge from ED, with subsequent outpatient functional testing based on age >65 years or the presence of ≥3cardiac risk factors. All participants were referred back to their primary care physicians for further evaluation. Clinical information required for the calculation of various risk scores (ie, the Emergency Department Assessment of Chest Pain Score, History ECG Age Risk factors and Troponin Score, Global Registry for Acute Coronary Events score, and Thrombolysis In Myocardial Infarction score for non–ST-segment–elevation acute coronary syndrome) were collected and available to clinicians, but use was not mandated.[19–22] Education on protocol interpretation was provided at the outset and throughout study implementation. Study coordinators were comprehensively trained and were present during the initial assessment

of each patient regardless of study arm to assist in data collection and to facilitate knowledge of the protocol recommendations. Clinicians were also informed of the previously published positive and negative predictive values for rule-in MI (72%) and rule-out MI (99%) triage recommendations.[6] Although these protocols provided recommendations, clinicians retained discretion to vary management to provide inpatient or outpatient care that they deemed most appropriate for the patient.

## Data Collection and Outcome Measures

ED discharge was defined as those patients not admitted to inpatient wards or extended care facilities within the ED. Participant records were reviewed for hospital actions including subsequent cardiac testing (eg, stress testing [ECG, echocardiography, nuclear, cardiac magnetic resonance imaging], echocardiography, computed tomography coronary angiography, and invasive coronary angiography and coronary revascularization), ED length of stay (LOS), total acute care LOS, and outpatient healthcare attendances for up to 30 days. To enhance capture of all clinical episodes, systematized interrogation of embedded data linkage methods for pathology, clinical, and patient information enabled the assessment of re-presentation to emergency services and late troponin results, and readmissions and subsequent coronary revascularization procedures across the state.

The primary measure of the 0/1-hour hs-cTnT protocol was the incidence of composite all-cause mortality or new MI occurring within 30 days of randomization using the Fourth Universal Definition of MI.[16,23] Of note, MI diagnosed within 12 hours of randomization among participants continuously in-hospital was considered as the index presenting MI and not included as an end point event.[16,23] An MI documented to have commenced outside this time (recurrent MI), or within 12 hours of randomization among participants already discharged from the hospital (missed MI), were considered an end point event. The timing and subclassification of all suspected MIs were adjudicated by a clinical events committee consisting of 4 independent cardiologists. Each event was discussed at clinical events committee meetings, and disagreements were settled by the majority. Clinical events committee adjudicators were provided unmasked troponin concentrations (ie, down to the limit of detection of 5 ng/L) for events in both study arms (ie, 0/1-hour hs-cTnT and standard masked hs-cTnT arms). This enabled adjudication of MI events to the Fourth Universal Definition of MI and allowed adjudication of acute and chronic myocardial injury. For adjudication of acute injury, events required documentation of a rise or fall in troponin T (defined as a change of >20% with a rate of change of ≥3 ng·L$^{-1}$·h$^{-1}$ with at least one sample >14 ng/L.[24] Subsequent subclassification into MI type 1, type 2, type 4a, and type 5 required clear evidence of ischemia by a typical clinical history (type 1 and 2 only) or ischemic ECG changes (except for type 5), new pathological Q waves, new wall motion abnormalities on cardiac imaging, or angiographic findings. As per the Fourth Universal Definition of MI, type 4a and type 5 MIs were not diagnosed if troponin concentrations were not documented to either be normal, stable, or falling before the procedure. Furthermore, type 2 MI required evidence supply-demand ischemia.[23] Re-presentation to hospital or late troponin elevations with a rise or fall pattern without verifiable evidence of coronary ischemia were reported as acute injury, whereas hospital presentations with troponin elevations >14 ng/L not meeting the rise or fall criteria were reported as chronic injury. Key secondary end points included components of the primary end point; re-presentation for chest pain, readmission for unstable angina (defined as chest pain/discomfort with an exacerbating pattern or occurring at rest, associated with dynamic ECG changes consistent with ischemia, or functional testing consistent with ischemia, and demonstrated coronary stenosis >70% by visual estimation); rehospitalization for nonelective coronary revascularization, peripheral artery disease, cerebrovascular accidents; congestive cardiac failure without MI, atrial and ventricular arrhythmias; and bleeding events classified under the Bleeding Academic Research Consortium criteria, Thrombolysis In Myocardial Infarction major or minor, and Global Utilization of Strategies to Open Occluded Arteries major and minor bleeding criteria, as documented by hospital records within 30 days of randomization.[25]

## Statistical Analysis

The study sample size focused on observing sufficient patients with a rule-out MI recommendation and was informed by a previous randomized trial of unguided hs-cTnT reporting.[3] The event rate among those discharged directly from ED within the hs-cTnT arm of that published study was 0.3% (1/368), whereas, in a comparable observational trial of 0/1-hour reporting, it was 0.1%.[3,6] Consequently, a primary end point rate of 0.3% in the rule-out MI in the 0/1-hour arm (discharge recommendation) was assumed, and it was estimated that 1212 rule-out MI participants eligible for discharge would need to be observed to evaluate that the event rate in the 0/1-hour was below a clinically acceptable 1% absolute rate.[15] However, because randomization occurred before troponin T concentrations were available, the sample size was increased to allow for 25% of participants enrolled with a presumed low to moderate diagnostic likelihood of MI, to then have a positive troponin T concentration of >29 ng/L. For comparison of care and care-associated outcome between the 2 study protocols, a noninferiority margin for the comparison of all randomly assigned patients was arbitrarily set at 0.5%, reflecting a clinical judgment that treatment under the 0/1-hour protocol was no worse than 0.5% greater than standard care (number needed to harm of 200). Review by the Data Safety Monitoring Board in April 2019 suggested that equipoise for the performance of the rule-out MI recommendation was no longer present; thus, the decision was made to end enrollment.

Participant flow through this study is reported in the CONSORT diagram (Figure 1). The primary analysis used the intention-to-treat population including all randomly assigned participants. The primary analysis assessed the noninferiority of the 0/1-hour arm, defined as the incidence of all-cause death or MI within 30 days of randomization in the standard arm plus 0.5%, using Poisson regression with robust standard errors. This is reported as an incident rate ratio and 95% CI. Tests for superiority were undertaken only if noninferiority was met. The key secondary analysis determined if the

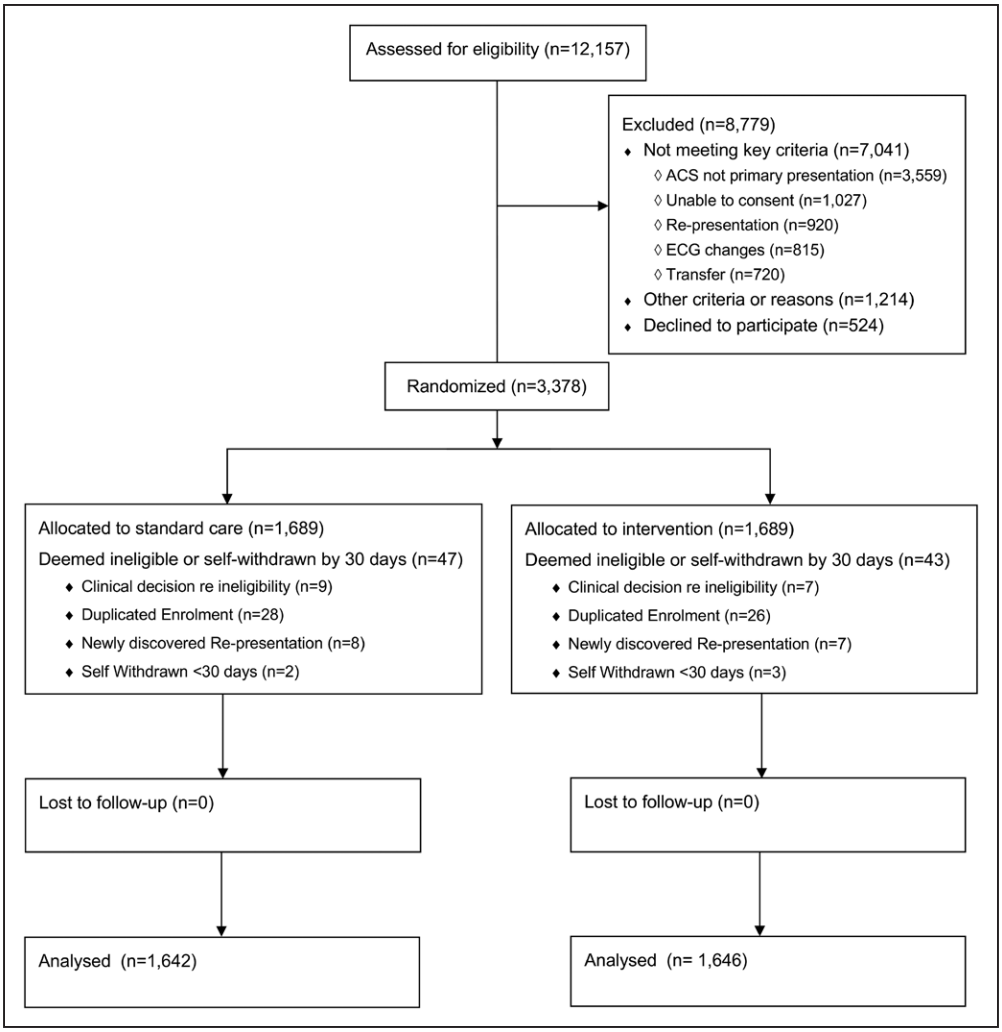


**Figure 1. Screening, eligibility, randomization, and follow-up.**
ACS indicates acute coronary syndrome.

incidence rate among the participants discharged under the 0/1-hour hs-cTnT protocol was not inferior to the accepted ED standard of 1.0% and was conducted by examining whether the 97.5% upper confidence bound crossed this value. Furthermore, sensitivity analyses were undertaken evaluating the per-protocol population for safety of the rule-out protocol (Methods in the online-only Data Supplement). Exploratory subanalyses were confined to participants with an initial (first 2) troponin ≤29 ng/L, ie, in the range where the troponin-reporting format (eg,. actual concentration 5–29 ng/L versus ≤29 ng/L) differs between the 2 study arms. Given concerns regarding the risk of periprocedural myocardial injury or infarction, these analyses are reported without adjustment for multiple testing. Aspects of subsequent care are reported as percentages and odds ratios (95% CI), and the interaction between the initial level of hs-cTnT (stratified as <5 ng/L, 5–29 ng/L, and >30 ng/L), the study arm and cardiac testing were examined using a logistic regression model. Time to the primary outcome over 30 days for the 2 study arms is plotted by using Kaplan–Meier survival curves and compared with log-rank testing. Continuous variables are reported as medians and interquartile ranges and compared by the Kruskal-Wallis test, and dichotomous and categorical variables are reported as counts and percentages and compared with $\chi^2$ tests. All statistical analyses were conducted using STATA 15.2, and a $P$ value of <0.05 was considered statistically significant.

# RESULTS

## Patient Population and Procedures

In total, 3378 participants were randomly assigned between August 2015 and April 2019. Ninety participants were deemed ineligible or withdrew consent. The remaining participants were guided by either the 0/1-hour hs-cTnT protocol (n=1646) or the 3-hour standard masked hs-cTnT protocol (n=1642) and were followed for 30 days. The baseline characteristics were well-balanced between the 2 study arms, other than Killip class (Table 1). The median age of participants was 59 (interquartile range [IQR], 49–70) years, 49% were female, and 28% had a previous history of coronary artery disease. The median Emergency Department Assessment of Chest Pain Score was 15 (IQR, 9–21). The

**Table 1. Baseline Characteristics of All Study Participants (Intention-to-Treat Population)**

| Characteristic | Standard Protocol (n=1642) | 0/1-Hour Protocol (n=1646) |
|---|---|---|
| Age, median (IQR) | 58.6 (48.8–71.2) | 58.7 (48.6–69.4) |
| Female sex, n (%) | 768/1642 (46.8) | 771/1646 (46.8) |
| Hypertension, n (%) | 337/1642 (20.5) | 324/1646 (19.7) |
| Diabetes mellitus, n (%) | 286/1642 (17.4) | 260/1646 (15.8) |
| Dyslipidemia, n (%) | 723/1642 (44.0) | 712/1646 (43.3) |
| Current smoker, n (%) | 584/1642 (35.6) | 570/1646 (34.6) |
| Family history of CAD, n (%) | 953/1612 (59.1) | 992/1620 (61.2) |
| Previous history of CAD, n (%) | 477/1642 (29.0) | 457/1646 (27.8) |
| Previous myocardial infarction, n (%) | 161/1642 (9.8) | 170/1646 (10.3) |
| Previous angina, n (%) | 260/1642 (15.8) | 250/1646 (15.2) |
| Previous heart failure, n (%) | 93/1642 (5.7) | 78/1646 (4.7) |
| Previous atrial fibrillation, n (%) | 154/1642 (9.4) | 135/1646 (8.2) |
| Chronic obstructive airways disease, n (%) | 74/1642 (4.5) | 77/1646 (4.7) |
| Previous cerebrovascular disease, n (%) | 52/1642 (3.2) | 53/1646 (3.2) |
| Previous coronary artery bypass grafting, n (%) | 46/1642 (2.8) | 49/1646 (3.0) |
| Previous percutaneous coronary intervention, n (%) | 138/1642 (8.4) | 171/1646 (10.4) |
| Systolic blood pressure, mm Hg, median (IQR)* | 135 (122–151) | 135 (121–150) |
| Heart rate, bpm, median (IQR) | 75 (66–85) | 74 (65–85) |
| Killip class, n (%) | | |
| Class 1 | 1591/1642 (96.9) | 1614/1646 (98.1) |
| Class 2 | 48/1642 (2.9) | 27/1646 (1.6) |
| Class 3 | 3/1642 (0.2) | 5/1646 (0.3) |
| Weight, kg, median (IQR) | 82 (70–96) | 83 (71–96) |
| Height, cm, median (IQR) | 170 (160–178) | 170 (160–178) |
| Body mass index, kg/m$^2$, median (IQR)† | 28.3 (24.8–32.9) | 28.7 (25.3–32.9) |
| Glomerular filtration rate, mL·min$^{-1}$·1.73 m$^{-2}$, median (IQR)*‡ | 86.0 (71.1–98.1) | 86.2 (71.6–98.2) |
| EDACS, median (IQR) | 15.0 (9.0–21.0) | 14.0 (9.0–20.0) |
| GRACE score, median (IQR)* | 75.0 (56.1–100.8) | 74.1 (55.2–97.2) |
| TIMI NSTEACS score, median (IQR) | 1.0 (0.0–3.0) | 1.0 (0.0–2.0) |
| HEART score, median (IQR) | 3.0 (2.0–4.0) | 3.0 (2.0–4.0) |

There were no significant differences ($P$<0.05) between the 2 groups except for Killip class ($P$=0.04). CAD indicates coronary artery disease; CKD, chronic kidney disease; EDACS, Emergency Department Assessment of Chest Pain Score; GRACE, Global Registry for Acute Coronary Events; HEART, History ECG Age Risk factors and Troponin; IQR, interquartile range; NSTEACS, non–ST-segment–elevation acute coronary syndrome; and TIMI, Thrombolysis In Myocardial Infarction.

*Missing data: 2 participants in the standard arm did not have blood pressure recorded; 36 participants (17 in the 0/1-hour arm/19 in the standard arm) did not have creatinine drawn. Note that this affects the calculation of the GRACE score.

†The body mass index is the weight in kilograms divided by the square of the height in meters.

‡The glomerular filtration rate is calculated using the CKD-EPI Creatinine Equation (2009).[25a]

time from first chest pain onset to presentation was <3 hours and <12 hours in 43% and 77% of participants, respectively, and was well balanced between groups. An initial troponin >29 ng/L was observed in 282/3288 (9%) of all participants (Table I in the online-only Data Supplement). Eleven percent of patients in the 0/1-hour arm received a troponin test >90 minutes after the initial sample (rule-in MI: 14%, observe: 11%, and rule-out MI: 11%) and 24% of patients in the standard arm received a troponin test >4 hours after the initial assessment. Among participants presenting with at least one troponin T concentration >14 ng/L during the index presentation, the observed frequencies of the following were: MI type 1, 124/3288 (4%); MI type 2, 39/3288 (1%); acute injury, 58/3288 (2%); and chronic injury, 479/3288 (15%). These proportions did not differ between study arms. Among participants randomly assigned to the 0/1-hour hs-cTnT protocol, 136/1646 (8%), 308/1646 (19%), and 1187/1646 (72%) were considered rule-in MI, observe, and rule-out MI, respectively, whereas 15/1646 (1%) had insufficient information for a triage recommendation (Table II in the online-only Data Supplement). The sensitivity and specificity of a rule-in recommendation for MI diagnosed within the index presentation was 88.1% and 94.7%, respectively, with a positive predictive value of 38.2% (95% CI, 30%–47%). The positive likelihood ratio for index MI was 16.5 (95% CI, 13.1–20.7) with the rule-in recommendation.

## Subsequent Care

The 0/1-hour arm was associated with a higher rate of direct discharge from the ED (0/1-hour arm, 748/1646 (45%) versus standard arm, 545/1642 (33%), odds ratio, 1.68 [95% CI, 1.45–1.93], $P$<0.001), but less frequent referral for functional testing (ECG stress testing, stress echocardiography, or perfusion cardiac magnetic resonance imaging/nuclear). Overall, there was no increase in invasive coronary angiography in the 0/1-hour arm in comparison with the standard arm, but when confined to the subgroup with an initial troponin T concentration ≤29 ng/L, a greater rate of coronary angiography was observed (Table 2 and Figure 2). Similarly, there was an increase in coronary revascularization among patients presenting with an initial troponin T concentration of ≤29 ng/L favoring the 0/1-hour arm: 38/1502 (2.5%) versus standard arm: 15/1493 (1.0%), odds ratio, 2.53 [95% CI, 1.36-4.98], $P$=0.002), but not when examined in the entire population (Table III in the online-only Data Supplement). ED LOS was shorter among those in the 0/1-hour protocol 4.6 (IQR, 3.4–6.4) hours versus 5.6 (IQR, 4.0–7.1) hours, $P$=0.001; Figure I in the online-only Data Supplement). The median LOS in acute care was lower in the 0/1-hour arm than in the standard masked hs-cTnT arm (0/1-hour arm: 5.3

**Table 2. Performance of Troponin Testing, Index Admission Classification, and Subsequent Cardiac Testing and Revascularization in the Intention-to-Treat Population and Participants With Initial Troponin ≤29 ng/L**

| Clinical Care Characteristic | Standard Protocol | 0/1-Hour Protocol | *P* Value |
|---|---|---|---|
| All participants, n | 1642 | 1646 | |
| Time between troponin testing, h, median (IQR) | 3.1 (2.9–3.5) | 1.0 (1.0–1.2) | <0.001 |
| Unallocated, n (%)* | 10/1642 (0.6) | 15/1646 (0.9) | <0.001 |
| Rule-out MI, n (%) | | 1187/1646 (72.1) | |
| Observe, n (%) | | 308/1646 (18.7) | |
| Rule-In MI, n (%) | | 136/1646 (8.3) | |
| Troponin ≤29 ng/L, n (%) | 1493/1642 (91.0) | | |
| Troponin >30 ng/L, n (%) | 139/1642 (8.5) | | |
| Incorrect troponin sensitivity reported, n (%)† | 71/1642 (4.3) | 18/1646 (1.1) | <0.001 |
| Maximum troponin T result in first 12 h, ng/L, median (IQR) | 7.0/1642 (4.0–13.0) | 7.0 (4.0–13.0) | 0.34 |
| Troponin T >14 ng/L in first 2 h, n (%) | 345/1632 (21.1) | 359/1644 (21.8) | 0.63 |
| Troponin T >30 ng/L in first 12 h, n (%) | 140/1632 (8.6) | 142/1644 (8.6) | 0.95 |
| ED working diagnosis | | | |
| Noncardiac diagnosis, n (%) | 135/1642 (8.2) | 153/1646 (9.3) | 0.620 |
| Chest pain, n (%) | 1017/1642 (61.9) | 997/1646 (60.6) | |
| Other cardiac diagnosis, n (%) | 425/1642 (25.9) | 437/1646 (26.6) | |
| Myocardial infarction, n (%) | 65/1642 (4.0) | 59/1646 (3.6) | |
| Discharged from ED, n (%) | 531/1642 (32.3) | 742/1646 (45.1) | <0.001 |
| Length of stay in ED, h, median (IQR) | 5.6 (4.0–7.1) | 4.6 (3.4–6.4) | <0.001 |
| Acute care length of stay, h, median (IQR) | 6.5 (4.9–24.3) | 5.3 (3.7–23.7) | <0.001 |
| Exercise stress test within 30 days, n (%) | 48/1642 (2.9) | 36/1646 (2.2) | 0.18 |
| Stress echocardiogram within 30 days, n (%) | 115/1642 (7.0) | 73/1646 (4.4) | 0.002 |
| Cardiac MRI within 30 days, n (%) | 19/1642 (1.2) | 17/1646 (1.0) | 0.73 |
| Functional testing within 30 days, n (%) | 180/1642 (11.0) | 123/1646 (7.5) | <0.001 |
| Echocardiogram within 30 days, n (%) | 161/1642 (9.8) | 142/1646 (8.6) | 0.24 |
| Coronary angiogram within 30 days, n (%) | 153/1642 (9.3) | 171/1646 (10.4) | 0.30 |
| CT coronary angiogram within 30 days, n (%) | 4/1642 (0.2) | 5/1646 (0.3) | 0.74 |
| Percutaneous coronary intervention within 30 days, n (%) | 46/1642 (2.8) | 53/1646 (3.2) | 0.48 |
| Coronary artery bypass grafting within 30 days, n (%) | 11/1642 (0.7) | 13/1646 (0.8) | 0.69 |
| Any coronary revascularization within 30 days, n (%) | 56/1642 (3.4) | 66/1646 (4.0) | 0.36 |
| No subsequent cardiac test within 30 days, n (%) | 1264/1642 (77.0) | 1316/1646 (80.0) | 0.038 |
| Participants with initial troponin T ≤29 ng/L, n | 1493 | 1515 | |
| ED working diagnosis | | | |
| Noncardiac diagnosis, n (%) | 128/1493 (8.6) | 148/1515 (9.8) | 0.238 |
| Chest pain, n (%) | 1012/1493 (67.8) | 996/1515 (65.7) | |
| Other cardiac diagnosis, n (%) | 345/1493 (23.1) | 355/1515 (23.4) | |
| Myocardial Infarction, n (%) | 8/1493 (0.5) | 16/1515 (1.1) | |
| Discharged from ED, n (%) | 512/1493 (34.3) | 728/1515 (48.1) | <0.001 |
| Length of stay in ED, h, median (IQR) | 5.5/1493 (4.0–7.0) | 4.5/1515 (3.4–6.2) | <0.001 |
| Acute care length of stay, h, median (IQR) | 6.3/1493 (4.8–18.4) | 5.1/1515 (3.6–18.2) | <0.001 |
| Exercise stress test within 30 days, n (%) | 43/1493 (2.9) | 34/1515 (2.2) | 0.27 |
| Stress echocardiogram within 30 days, n (%) | 10/1493 (6.9) | 66/1515 (4.4) | 0.002 |
| Cardiac MRI within 30 days, n (%) | 6/1493 (0.4) | 9/1515 (0.6) | 0.45 |
| Functional testing within 30 days, n (%) | 152/1494 (10.2) | 107/1646 (7.1) | 0.002 |
| Echocardiogram within 30 days, n (%) | 87/1493 (5.8) | 87/1515 (5.7) | 0.92 |

(*Continued*)

**Table 2. Continued**

| Clinical Care Characteristic | Standard Protocol | 0/1-Hour Protocol | *P* Value |
|---|---|---|---|
| Coronary angiogram within 30 days, n (%) | 79/1493 (5.3) | 107/1515 (7.1) | 0.044 |
| CT coronary angiogram within 30 days, n (%) | 4/1493 (0.3) | 5/1515 (0.3) | 0.76 |
| Percutaneous coronary intervention within 30 days, n (%) | 13/1493 (0.9) | 30/1515 (2.0) | 0.010 |
| Coronary artery bypass grafting within 30 days, n (%) | 2/1493 (0.1) | 8/1515 (0.3) | 0.060 |
| Any coronary revascularization within 30 days, n (%) | 15/1493 (0.9) | 38/1515 (2.2) | 0.002 |
| No subsequent cardiac test within 30 days, n (%) | 1219/1493 (81.6) | 1267/1515 (83.6) | 0.15 |

CT indicates computed tomography; cTnT, cardiac troponin T; ED, emergency department; hs-cTnT, high-sensitivity cardiac troponin T; IQR, interquartile range; MI, myocardial infarction; and MRI, magnetic resonance imaging.

*Participants with only a single uninterpretable troponin either attributable to a hemolyzed specimen, not requested, or a single assay only preventing allocation to a triage recommendation in the 0/1-hour arm.

†Represents the number of patients receiving troponin results in the format of the incorrect randomized arm (ie, hs-cTnT format in standard arm, and cTnT format in 0/1-hour arm) attributable to laboratory misreporting or direct physician request.

[IQR, 3.7–23.4] hours versus standard arm: 6.4 [IQR, 4.9–23.1] hours, *P*<0.001).

## Clinical Outcomes

Overall, 443/3288 (13.5%) participants re-presented to the hospital at least once within 30 days with no difference between study arms. During these re-presentations, further troponin testing was undertaken in 213/3288 (6.5%). Re-presentation with chest pain occurred more frequently among participants randomly assigned to the 0/1-hour arm: 65/1646 (4.0%) versus standard arm: 44/1642 (2.7%); incident rate ratio, 1.61 (95% CI, 1.40–1.84), *P*<0.001. Among all hospital re-presentations, at least one hs-cTnT result >14 ng/L was observed in 143/3288 (4.4%) cases with no difference between arms. Table 3 describes the adjudicated outcomes and myocardial injury/infarction subclassifications of these patients based on the observed troponin profile combined with documented evidence of ischemia. Type 1 MI occurred in 9 patients in the 0/1-hour arm and 5 patients in the standard arm and, of these, one was observed in each arm among those discharged. Of note, there were 8 periprocedural MIs (0/1-hour: 6 versus standard arm: 3) and a further 7 episodes of acute injury (0/1-hour: 5 versus standard arm: 2) observed (Table IV in the online-only Data Supplement). Two Type2 MIs were observed in the 0/3-hour arm. Overall, the 0/1-hour hs-cTnT protocol was not inferior to standard care with respect to death or new/recurrent MI by 30 days; however, it was not superior (0/1-hour arm: 17/1646 [1.0%] versus standard arm 16/1642 [1.0%]; incident rate ratio, 1.06 [95%, 0.53–2.11], noninferiority *P* value=0.006, superiority *P* value: *P*=0.867). (Also see Figure II in the online-only Data Supplement and Table V in the online-only Data Supplement for sensitivity analysis.) The Kaplan–Meier event curves for 30-day death or MI and cardiovascular rehospitalization are presented in Figure 3. Assessment of the myocardial injury subclassification suggested an increase in acute injury, type 4a and type 5 MIs among the participants randomly assigned to the 0/1-hour hs-cTnT protocol (0/1-hour arm 26/1646

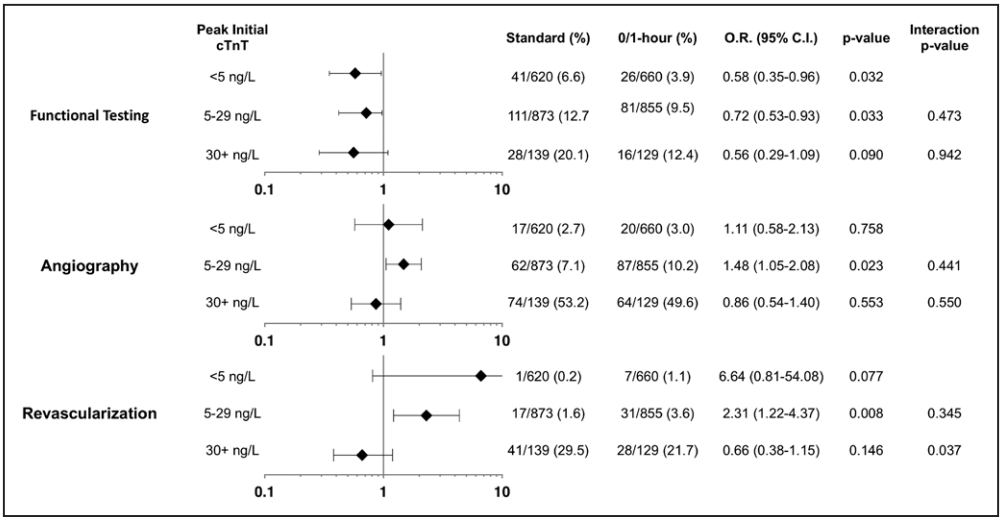


**Figure 2. Measures of clinical care.**
Odds ratio for likelihood of functional cardiac testing, coronary angiography, and coronary revascularization stratified by peak troponin concentration within initial assessment. Note: the peak concentrations ≤29 ng/L not observed by clinicians randomly assigned to the standard therapy arm. cTnT indicates cardiac troponin T; and OR, odds ratio.

**Table 3. Primary and Secondary Outcomes in the Overall Intention-to-Treat Population and Those With an Initial Troponin ≤29 ng/L**

| Outcome | Standard Protocol (n=1642) | 0/1-Hour Protocol (n=1646) | IRR (95% CI) | *P* Value | Noninferiority *P* Value* |
|---|---|---|---|---|---|
| All participants, n (%) | | | | | |
| Primary end point: death or myocardial infarction within 30 days | 16 (1.0) | 17 (1.0) | 1.06 (0.53–2.11) | 0.867 | 0.006 |
| All-cause death | 6 (0.4) | 2 (0.1) | 0.33 (0.03–3.43) | 0.355 | |
| Cardiovascular death | 3 (0.2) | 2 (0.1) | 0.67 (0.10–4.25) | 0.667 | |
| Myocardial infarction (type 1, type2, type 4a, type 5)† | 10 (0.6) | 15 (0.9) | 1.50 (0.81–2.78) | 0.197 | |
| Acute myocardial injury with/without revascularization† | 7 (0.4) | 11 (0.7) | 1.57 (1.31–1.88) | <0.001 | |
| Myocardial infarction or myocardial injury† | 17 (1.0) | 26 (1.6) | 1.53 (1.14–2.04) | 0.004 | 0.896 |
| Re-presentation with chronic myocardial injury pattern† | 21 (1.3) | 18 (1.1) | 0.85 (0.34–2.18) | 0.741 | |
| Unstable angina | 4 (0.2) | 5 (0.3) | 1.25 (0.21–7.38) | 0.807 | |
| Cardiovascular death, myocardial infarction, and unstable angina | 17 (1.0) | 21 (1.3) | 1.23 (0.71–2.14) | | 0.206 |
| Chest pain re-presentation | 44 (2.7) | 70 (4.3) | 1.61 (1.40–1.84) | <0.001 | |
| Cardiovascular rehospitalization† | 15 (0.9) | 23 (1.4) | 1.53 (1.12 –2.10) | 0.008 | |
| BARC 2, 3a, or 4 | 13 (0.8) | 6 (0.4) | 0.46 (0.26–0.82) | 0.008 | |
| TIMI major, minor, or minimal | 9 (0.5) | 4 (0.2) | | 0.163 | |
| GUSTO major or minor | 7 (0.4) | 4 (0.2) | | 0.363 | |
| Participants with initial troponin T ≤29 ng/L, n (%) | | | | | |
| Primary end point, death, or myocardial infarction within 30 days | 9 (0.6) | 10 (0.7) | 1.10 (0.39–3.11) | 0.864 | 0.001 |
| All-cause death | 2 (0.1) | 1 (0.1) | 0.49 (0.02–12.26) | 0.666 | |
| Cardiovascular death | 0 (0.0%) | 1 (0.1%) | – | – | |
| Myocardial infarction (type 1, type2, type 4a, type 5) † | 7 (0.5) | 9 (0.6) | 1.27 (0.51–3.15) | 0.609 | |
| Acute myocardial injury with/without revascularization† | 6 (0.4) | 8 (0.5) | 1.31 (0.94–1.84) | 0.109 | |
| Myocardial infarction or myocardial injury† | 13 (0.9) | 17 (1.1) | 1.29 (0.69–2.40) | | 0.512 |
| Re-presentation with chronic myocardial injury pattern† | 13 (0.9) | 13 (0.9) | 0.99 (0.27–3.62) | 0.984 | |
| Unstable angina | 4 (0.3) | 5 (0.3) | 1.23 (0.21–7.39) | 0.819 | |
| Cardiovascular death, myocardial infarction, and unstable angina | 11 (0.7) | 14 (0.9) | 1.26 (0.53–2.96) | | 0.112 |
| Chest pain re-presentation | 39 (2.6) | 61 (4.0) | 1.56 (1.43–1.70) | <0.001 | |
| Cardiovascular rehospitalization‡ | 10 (0.7) | 16 (1.1) | 1.58 (0.85–2.94) | 0.147 | |
| BARC 2, 3a, or 4 | 4 (0.3) | 3 (0.2) | 0.74 (0.36–1.52) | 0.409 | |
| TIMI major or minor bleeding | 3 (0.2) | 2 (0.1) | | 0.643 | |
| GUSTO major or minor bleeding | 1 (0.1) | 2 (0.1) | | 0.572 | |

BARC indicates Bleeding Academic Research Consortium; GUSTO, Global Utilization of Strategies to open Occluded arteries; IRR, incidence rate ratio; and TIMI, Thrombolysis In Myocardial Infarction.

*Testing for noninferiority assessed first, followed by testing for superiority if *P* value <0.05 for key outcomes. Where noninferiority is not met, the *P* value for the test for superiority is not reported with the exception of myocardial infarction and acute injury, where harm with the 0/1-hour may be evident (ie, the overall type 1 error for this analysis may not be preserved and results should be viewed as exploratory).

†All troponin T results >14 ng/L were adjudicated according to the Fourth Universal Definition of Myocardial Infarction. A rise or fall pattern required a change on troponin concentration of >20% and a rate of change arbitrarily defined as ≥3 $ng \cdot L^{-1} \cdot h^{-1}$.[23,24]

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

[1.6%] versus standard arm 17/1642 [1.0%], incident rate ratio, 1.53 [95% CI, 1.15–2.04], *P*=0.004) (Figure III in the online-only Data Supplement), with other outcomes similar between groups. Among all participants receiving a rule-out MI triage recommendation, the primary end point was observed in 5/1187 (0.4%), and among those participants discharged directly from the ED with a rule-out MI recommendation, 2/630 (0.3% [95% CI, 0.02–0.06]) experienced the primary end point. Comparable rates of 30-day death or MI were observed among those directly discharged from the ED in the standard arm (2/495; 0.4 [95% CI, 0.01–0.08]). The negative predictive value of the rule-out MI recommendation of the 0/1-hour hs-cTnT protocol for 30-day

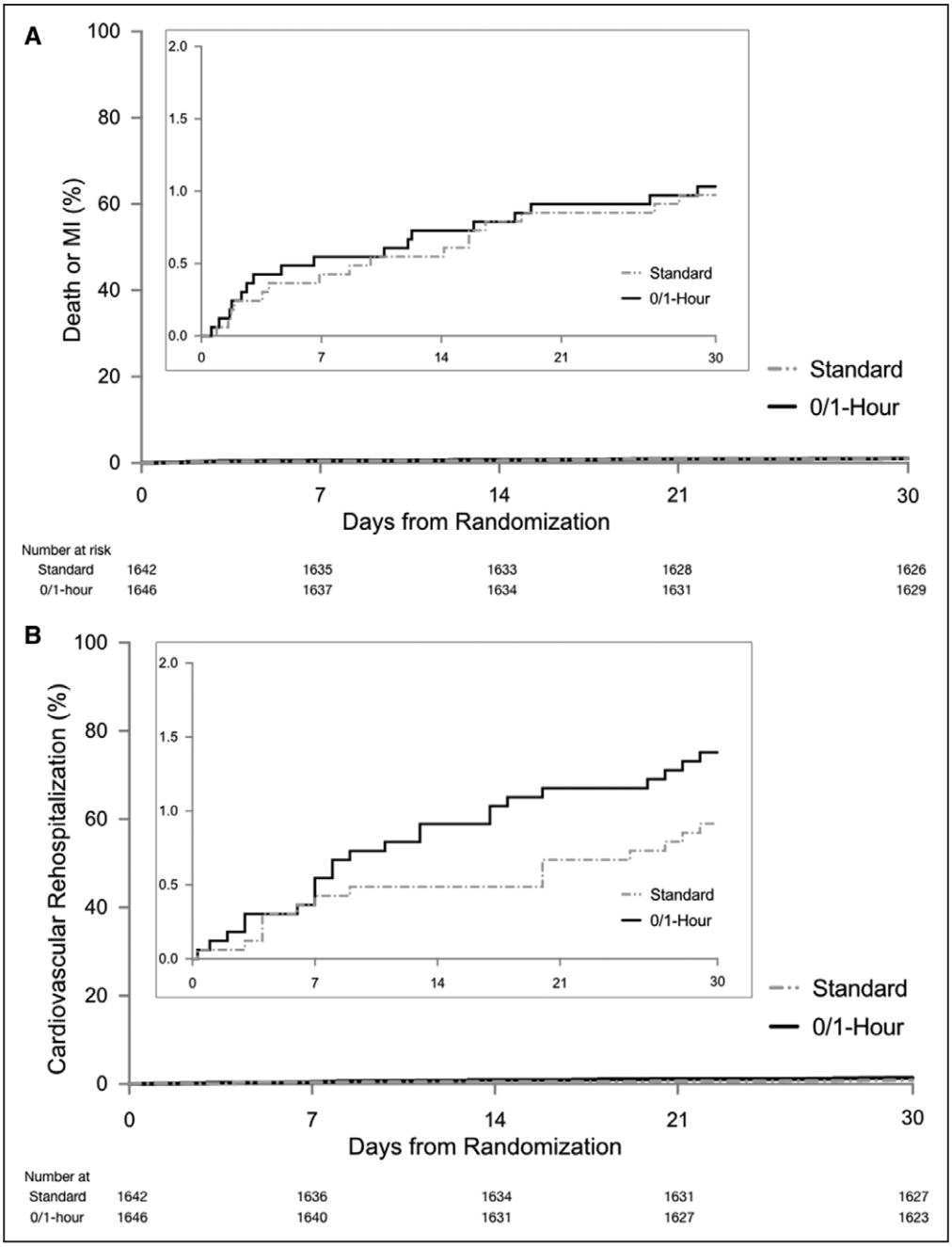


**Figure 3. Clinical outcomes within 30 days.**
Kaplan–Meier event curves for the primary end point within 30 days (**A**) and cardiovascular rehospitalization within 30 days (**B**). Cardiovascular rehospitalization includes readmission for nonelective coronary revascularization, peripheral artery disease, cerebrovascular accidents, congestive cardiac failure without MI, and atrial and ventricular arrhythmias. hs-cTnT indicates high-sensitivity cardiac troponin T; MI, myocardial infarction; Standard, masked hs-cTnT protocol; and 0/1-Hour, 0/1-hour hs-cTnT protocol.

death or MI was 99.6% (95% CI, 99.0%–99.9%; specificity 73.2%). Rates of the primary outcome and key secondary outcomes by triage categories are provided in Table 4.

## DISCUSSION

This in-practice patient-level randomized comparison of a 0/1-hour hs-cTnT protocol, observed similar overall clinical outcomes in comparison with clinical management–based reporting practices that did not use the full enhanced diagnostic performance of the hs-cTnT assay. This study confirmed an acceptable safety profile for early discharge based on a rule-out MI profile. However, although resetting the sensitivity of troponin assays to a greater level of precision has improved the negative predictive value of troponin testing, the potential for precipitating myocardial injury–associated increases in

**Table 4. Primary and Secondary End Point at 30 days by Triage Category for Participants (Intention-to-Treat Population)**

| Outcome | Standard Protocol | | 0/1-Hour Protocol | | |
|---|---|---|---|---|---|
| | cTnT≤29 ng/L (n=1493) | cTnT>29 ng/L (n=140) | MI Rule-Out (n=1187) | MI Observe (n=308) | MI Rule-In (n=136) |
| Primary end point: death and MI, n (%) | 9 (0.6) | 7 (5.0) | 5 (0.4) | 7 (2.3) | 5 (3.7) |
| All-cause death, n (%) | 2 (0.1%) | 4 (2.9%) | 1 (0.1%) | 1 (0.3%) | 0 (0.0%) |
| Cardiovascular death, n (%) | 0 (0.0) | 3 (2.1) | 1 (0.1) | 1 (0.3) | 0 (0.0) |
| MI (type 1, type 2, type 4a, type 5) , n (%)* | 7 (0.5) | 3 (2.1) | 4 (0.3) | 6 (1.9) | 5 (3.7) |
| Myocardial injury: acute, n (%)* | 6 (0.4) | 1 (0.7) | 5 (0.4) | 3 (1.0) | 3 (2.2) |
| MI and myocardial injury: acute, n (%)* | 13 (0.9) | 4 (2.9) | 9 (0.8) | 9 (2.9) | 8 (5.9) |
| Myocardial injury: chronic, n (%)* | 13 (0.9) | 8 (5.7) | 2 (0.2) | 11 (3.6) | 5 (3.7) |
| Unstable angina, n (%) | 4 (0.3) | 0 (0.0) | 3 (0.3) | 2 (0.6) | 0 (0.0) |
| All-cause death and MI and unstable angina, n (%) | 11 (0.7) | 6 (4.3) | 7 (0.6) | 9 (2.9) | 5 (3.7) |
| Chest pain re-presentation, n (%) | 39 (2.6) | 5 (3.6) | 41 (3.5) | 22 (7.1) | 7 (5.1) |
| Cardiovascular rehospitalization, n (%)† | 10 (0.7) | 5 (3.6) | 9 (0.8) | 8 (2.6) | 6 (4.4) |
| BARC 2, 3a, or 4, n (%) | 4 (0.3) | 9 (6.4) | 2 (0.2) | 2 (0.6) | 2 (1.5) |
| TIMI major, minor, or minimal, n (%) | 3 (0.2) | 6 (4.3) | 1 (0.1) | 2 (0.6) | 1 (0.7) |
| GUSTO major or minor, n (%) | 1 (0.1) | 6 (4.3) | 1 (0.1) | 1 (0.3) | 2 (1.5) |

BARC indicates Bleeding Academic Research Consortium; cTnT, cardiac troponin T; GUSTO, Global Utilization of Strategies to open Occluded arteries; MI, myocardial infarction; and TIMI, Thrombolysis In Myocardial Infarction.

*All troponin T results >14 ng/L were adjudicated according to the Fourth Universal Definition of Myocardial Infarction. A rise or fall pattern required a change in troponin concentration of >20% and a rate of change arbitrarily defined as ≥3 $ng \cdot L^{-1} \cdot h^{-1}$.[22,23]

†Cardiovascular rehospitalization includes readmission for nonelective coronary revascularization, peripheral artery disease, cerebrovascular accidents, congestive cardiac failure without MI, and atrial and ventricular arrhythmias.

coronary angiography and revascularization for those patients not receiving a rule-out MI recommendation was also observed.

Previous prospective observational studies have suggested patients with very low troponin concentrations and a small change over 1 hour have a <1% risk of subsequent 30-day events.[18,26] We confirmed in a randomized trial that patients prospectively managed under this recommendation experienced a risk tolerance of death or MI by 30 days that has been commonly considered acceptable.[15] Nevertheless, although discharge from the ED occurred sooner and more frequently, with clear implications for reducing ED congestion, clinical adoption of early discharge was cautious with many patients who received a rule-out MI recommendation still undergoing extended observation. The rates of admission and ED LOS in this study are higher than in other prospective observational studies where systems of practice have been given time to become established. The rates of subsequent events among those discharged under the rule-out recommendation was slightly higher.[27] These observations are likely the consequence of the parallel randomized pragmatic design embedded within existing practices leading to reduced clinical uptake of the protocol recommendations.[27,28]

This finding highlights the need for clinical practice to evolve in response to innovations, and suggests that even greater gains in assessment efficiency may be possible if clinical adoption of the 0/1-hour protocol is systematized as routine practice. Within our system of care, this group appeared to have lower rates of subsequent functional stress testing, as has been observed by others, suggesting higher clinical confidence in excluding ACS with hs-cTnT testing alone.[29] However, the modestly higher rates of repeat ED presentations for investigation of chest pain with the 0/1-hour hs-cTnT protocol may reflect patient expectations for subsequent cardiac testing.[30] The incremental value of testing for flow-limiting coronary artery disease very early after hs-cTnT has ruled out MI requires further clarification.[31,32]

Our findings appear to support the routine implementation of the 0/1-hour decision protocol in clinical practice to reduce ED congestion.

This study focused on the use of a rapid hs-cTnT decision tool to rule out MI among patients with suspected ACS, which is arguably where the greatest benefits of high-sensitivity troponin assays reside. Specifically, this study excluded patients with initial ECG changes highly suggestive of coronary ischemia, or those with concurrent clinical conditions that required more protracted assessment that made consideration of early discharge irrelevant. As a consequence, the rate of index MI was lower than documented in other observational studies where only patients with ST-segment elevation on the initial ECG were excluded.[27,28]

Despite the low index MI rate, re-presentation to the ED occurred in >13% of the population within 30 days and was associated with a high proportion of repeat troponin testing (≈50%). As seen by others, > 6% of

these participants had at least one troponin T concentration >14ng/L reported.[4,33]

These observations suggest that better strategies are needed for the investigation and management of the considerable number of patients who are classified as observed or rule-in MI. It is notable that, when implementing the Fourth Universal Definition of MI, nearly half of all these acute injury profiles observed occurred after coronary revascularization procedures, and of these, half had clear corroborating evidence of ischemia to establish the diagnoses of type 4a and type 5 MI, thereby highlighting the recognized risks associated with an early invasive strategy for the management of ACS.[23] Within this context, greater sensitivity for ruling-in patients was associated with greater use of invasive coronary angiography and subsequent revascularization in the subgroup of patients with an initial troponin concentration ≤29 ng/L, where the diagnostic information differed between study arms, as observed in other studies.[34,35] In this study, an increase in revascularization among the subgroups with an initial troponin concentration ≤29 ng/L was also observed. Although exploratory, a slightly higher rate of periprocedural MIs and acute injury troponin profiles was evident. No reduction in the rates of 30-day type 1 MI was documented. This observation has not been well reported within nonrandomized evaluations of high-sensitivity troponin protocols without directly comparative populations and systematized troponin collection.[27] Although our data support the routine implementation of hs-cTnT to facilitate safe early ED discharge, the enhanced detection of myocardial injury has implications for therapeutic decision making. Current strategies for the management of ACS established their balance of risk and benefit in a previous era of troponin when test performance was substantially inferior to currently available tests.[36] The extension of the management strategies for ACS to those with low-modest troponin elevations using high-sensitivity troponin assays may potentially not be associated with the same favorable profile of risk and benefit as seen in earlier ACS studies. Effective translation of the improved discriminatory capacity of high-sensitivity troponin into better outcomes for patients may require refinements in treatment approaches for these lower-risk patients.[37] Further insights into the risks and benefits of increased rates of coronary revascularization will be provided by the 12-month outcomes of this study.[16]

Nevertheless, the statewide control of troponin reporting not only masked the high-sensitivity troponin results ≤29 ng/L for all patients receiving emergency care before this randomized, controlled trial, but it also ensured that clinicians had little to no experience in interpreting hs-cTnT results allowing de novo evaluation of the impact of the new testing information on subsequent care. Our approach of embedding the study within a single health system jurisdiction's clinical data environment allowed the routine collection of all subsequent care and outcome. Moreover, it enabled the conduct of patient-level randomization in practice to provide a comparative evaluation of hs-cTnT that is necessary to fully understand the balance of benefits and any unintended consequences from the resultant changes in therapeutic decision making.

Some limitations should be considered. Within the standard arm, troponin concentrations <29 ng/L were masked; therefore, clinicians were prevented from applying the current universal definition of MI that calls for MI/injury diagnosis to be applied, as opposed to unstable angina, when the troponin concentration exceeds 14 ng/L with a rise or fall pattern. However, our previous prospective randomized comparison comparing unmasked and masked results showed no difference in death or recurrent ACS when levels <29 ng/L were made available.[3] Similarly, in this study, there are no differences in index MI rates between the study arms, suggesting that any clinical impact associated with differing troponin concentration thresholds for diagnosing MI versus unstable angina is likely to be modest. Furthermore, the standard arm also differs slightly from the published 0/3-hour protocol using a conventional assay given the use of the masked hs-cTnT assay and the absence of formal risk scoring. However, the low event rates among patients discharged in the standard arm of this study attests to the safety of this practice. The proportion of patients presenting with index MI was lower than anticipated, although the rate of recurrent presentations with associated elevated troponin T concentrations >14 ng/L was higher than expected. Not only does this likely reflect more liberal troponin-testing practices, but also highlights the potential for an increase in the frequency of clinical presentations associated with a positive test. Yet, observational data suggest that generalization of the 0/1-hour protocol's rule-out MI performance to practices with higher thresholds for troponin testing (ie, higher pretest probabilities for MI) should yield similar results.[18] Furthermore, early discontinuation of the study based on the acceptable event rate among those discharged with a rule-out MI recommendation may have prevented assessment of whether a 0/1-hour hs-cTnT protocol improves 30-day clinical outcomes. However, *superiority for the shortened protocol is not expected given the higher event rates* observed in this arm, and the true test of benefit will depend on the planned 12-month evaluation outcomes.

In conclusion, implementation of a 0/1-hour hs-cTnT protocol for the triage of patients with suspected ACS enabled more rapid decision making to discharge low-risk patients with suspected ACS. Improving short-term clinical outcomes among patients' newly recognized troponin T elevation with a hs-cTnT assay will require

evolution in the management strategies for these more frequently encountered patients.

## ARTICLE INFORMATION

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### Disclosures

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