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A Randomized Trial of a 1-Hour Troponin T Protocol in Suspected Acute Coronary Syndromes: The Rapid Assessment of Possible ACS In the Emergency Department with High Sensitivity Troponin T (RAPID-TnT) Study

Running Title: *Chew et al.; RAPID-TnT*

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Abstract

Background: High-sensitivity troponin assays promise earlier discrimination of myocardial infarction (MI). 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 multi-center study evaluated the non-inferiority of a 0/1-hour high-sensitivity troponin T (hs-cTnT) protocol compared with a 0/3-hour masked hs-cTnT protocol in suspected ACS patients presenting to the emergency department (ED).

Methods: Patients were randomized to either 0/1-hour hs-cTnT (reported to the limit of detection [<5ng/L]) versus masked hs-cTnT reported to ≤29ng/L evaluated at 0/3-hours (standard arm). The 30-day primary endpoint was all-cause death and MI. Non-inferiority was an absolute margin of 0.5% determined by poisson regression.

Results: In total, 3378 participants with an emergency presentation were randomized 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 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 (IQR 3.4.,6.4) hours versus standard arm: 5.6 (IQR 4.0,7.1) hours, p<0.001). Those randomized 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-TnT protocol was not inferior to standard care (0/1-hour arm: 17/1646 (1.0%) versus 16/1642 (1.0%), IRR 1.06, 0.53-2.11, non-inferiority 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 MI.

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

Clinical Trial Registration: URL: https://www.anzctr.org.au Unique Identifier: ACTRN12615001379505

Key Words: Troponin; Myocardial Infarction; Acute Coronary Syndromes; Emergency care Chest pain assessment; Clinical Trial

Non-standard Abbreviations and Acronyms:
ACS = Acute coronary syndrome
AF = Atrial fibrillation
BP = Blood pressure
CABG = Coronary artery bypass grafting
CAD = Coronary artery disease
CEC = Clinical events committee
CK = Creatinine kinase
CKD = Chronic kidney disease

CI = Confidence Interval
COPD = Chronic obstructive pulmonary disease
CPR = Cardiopulmonary resuscitation
CT = Computer tomography
cTnT = Cardiac troponin T
DSMB = Data safety and monitoring board
ECG = Electrocardiogram
ED = Emergency department
EST- Exercise stress test
HF = Heart failure
HR = Heart rate
Hs-TnT = High-sensitivity cardiac troponin T
IQR = Interquartile range
IRR = Incidence rate ratio
LBBB = Left bundle branch block
LOS = Length of stay
MI = Myocardial Infarction
ng/L = Nanograms per litre
Non-STEACS = non-ST segment elevation acute coronary syndrome
PCI = Percutaneous coronary intervention
STEMI = ST elevation myocardial infarction
T4MI = Type 4 myocardial infarction
T5MI = Type 5 myocardial infarction
TWI = T wave inversion
URL = Upper reference limit

Clinical Perspective

What is new?

- High-sensitivity troponin assays have promised improved diagnosis 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 hs-cTnT embedded within routine practice confirmed a low rate of 30-day death or MI for patients receiving a rule-out MI 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 ACS.
- However, use of invasive coronary investigation is increased among patients with newly identified low-concerntration troponin elevations and strategies to mitigate associated cardiac injury may require further refinements in acute coronary syndrome care.

Introduction

The introduction of high-sensitivity troponin assays, which enables detection of very low levels of myocardial injury, have 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 has not demonstrated reduction in subsequent ischaemic events.[3,4] Given 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] While 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 centres, very few employ 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 due 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, compared

with and embedded within existing practice, where the improved diagnostic precision of these assays has not been utilized, is required to evaluate the actual value of this innovation on 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 ED assessment of suspected ACS and investigating an accelerated 0/1-hour decision-rule based on high sensitivity troponin T (hs-cTnT) compared 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 Assessment of Possible ACS In the emergency Department with high sensitivity Troponin T (RAPID-TnT) trial was a prospective patient-level randomized non-inferiority evaluation of a 0/1-hour protocol using a hs-cTnT reporting format compared with a 0/3-hour protocol with troponin T results masked below 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 following 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 four metropolitan public emergency departments in Adelaide, Australia and details of its design has 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 prior to 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 unrestricted grant from Roche Diagnostics International (Rotkreuz, Switzerland). 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-TnT assay (LoD: 5ng/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. Due to 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 14ng/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 (i.e. masked, with the lower reference limit reported as "≤29ng/L" rather than to report down to the LoD [5ng/L]). The decision was made with the recognition that the 5th generation hs-cTnT assay had greater sensitivity compared with the same concentrations reported on the 4th generation assay. Specifically, in maintaining reported lower reference limit at ≤29ng/L while transitioning fromform the 4th generation to the 5th generation assay, this reduced the actual lower reference limit reported to clinicians, since a concentration of 29ng/L using the 4th generation assay equates to a concentration of ~43ng/L on the 5th generation assay. [17] The clinical implications of access to troponin concentrations between 5-29 ng/L to enable diagnostic classification consistent with international standards was then prospectively evaluated in a prior randomized trial (n=1937) showing modest differences in treatment and no

difference 12-month rates of death or recurrent acute coronary syndromes.[3] Hence, this masked reporting policy was maintained enabling a patient-level implementation of the current randomized trial. Uniquely, apart from the preliminary trial, participating EDs had therefore remained masked to troponin T concentrations below 29ng/L; thus clinicians had no prior clinical experience with hs-cTnT results below 29ng/L, nor 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 randomized to the 0/1-hour arm and the interpretation was guided by the study protocol (see below). Maintenance of the integrity of the two randomized reporting formats was managed through the single statewide pathology reporting system. After capture of baseline data, randomization in permuted blocks of four occurred 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, as the safety of early discharge is less clinically relevant in this cohort. Similarly, reliant on physician judgement at initial assessment, the study sought to include participants for whom care may be influenced by rapid triage protocols (i.e. 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; baseline electrocardiogram (ECG) interpreted as not definitive for coronary ischemia; 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 due to language or comorbidity.

Study Protocol

To maintain integrity of the troponin testing procedure, all participants were consented and randomized after senior ED physician interpretation of initial ECG, but before troponin results were available. For participants randomized 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 <5ng/L over 3 hours since the onset of symptoms, or ≤12ng/L and a change in troponin over 1 hour of <3ng/L was seen; "rule-in" with admission to hospital for management of suspected MI was recommended when the baseline troponin was ≥52ng/L or a change over 1 hour of ≥ 5ng/L was documented; Continued observation, with repeat testing and possible hospital admission was recommended when the baseline troponin was between 13-51 ng/L with a change over 1 hour of <5ng/L, or with a baseline troponin of ≤12ng/L and a change over 1 hour of 3-4ng/L.

The care of participants in the standard masked hs-cTnT arm followed the statewide chest pain protocol which 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 ≤29ng/L. Within the local standard of care, participants with an elevated troponin, ongoing chest pain or known coronary artery disease (CAD) were recommended for referral to inpatient clinical teams for consideration of admission. The standard local pathway recommendation for patients with troponin results

≤29ng/L was discharge from ED, with subsequent outpatient functional testing based on age >65 years and/or the presence of three or more cardiac risk factors. All participants were referred back to their primary care physicians for further evaluation. Clinical information required for calculation of various risk scores (i.e. the Emergency Department Assessment of Chest Pain Score [EDACS], History ECG Age Risk factors and Troponin [HEART] Score, Global Registry for Acute Coronary Events [GRACE] score and Thrombolysis In Myocardial Infarction [TIMI] score for non-STEACS was 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] While these protocols provided recommendations, clinicians retained discretion to vary management, in order 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 (e.g. stress testing [ECG, Echocardiography, Nuclear, CMR], echocardiography, CT coronary angiography (CTCA) and invasive coronary angiography and coronary revascularization), ED length of stay (LOS), total acute care LOS, and outpatient health care attendances for up to 30 days. To enhance capture of all clinical episodes, systematised interrogation of embedded data linkage methods for pathology, clinical and patient information

enabled the assessment of representation to emergency services and late troponin results, as well as re-admissions 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.[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 endpoint 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 hospital (missed MI) were considered an endpoint event. The timing and subclassification of all suspected MIs were adjudicated by a clinical events committee (CEC) consisting of 4 independent cardiologists. Each event was discussed at CEC meetings and disagreements settled by majority. CEC adjudicators were provided unmasked troponin concentrations (i.e. down to the LoD of 5ng/L) for events in both study arms (i.e. 0/1-hour hs-cTnT and standard masked hs-cTnT arms). This enabled adjudication of MI events to the 4th universal definition of MI and allowed adjudication of acute and chronic myocardial injury. For adjudication of acute injury, events required documentation of a rise and/or fall in troponin T (defined as a change >20% with a rate of change of ≥3ng/L/hr) with at least one sample above 14ng/L.[24] Subsequent sub-classification into MI type 1, type 2, type 4a and type 5 required clear evidence of ischaemia by a typical clinical history (type 1 and 2 only) or ischaemic ECG changes (except for type 5), new pathological Q waves, new wall motion abnormalities on cardiac imaging, or angiographic findings. As per the 4th universal definition, type 4a and type 5 MIs were not diagnosed if troponin concentrations were not documented to either be normal, stable or falling prior to the procedure. Furthermore, type 2 MI required evidence supply-demand ischaemia.[23] Re-

presentation to hospital or late troponin elevations with a rise and/or fall pattern without verifiable evidence of coronary ischaemia were reported as acute injury, whilst hospital presentations with troponin elevations >14ng/L not meeting the rise and/or fall criteria were reported as chronic injury. Key secondary endpoints included: components of the primary endpoint; representation 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/or demonstrated coronary stenosis>70% by visual estimation); rehospitalization for non-elective 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 BARC criteria, as well as TIMI major or minor and GUSTO 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] while in a comparable observational trial of 0/1-hour reporting it was 0.1%.[3,6] Consequently, a primary endpoint 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, since 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 >29ng/L. For comparison of care and care-associated outcome between the two study protocols, a non-inferiority margin for the comparison of all randomized patients was arbitrarily set at 0.5%, reflecting a clinical judgement that treatment under the 0/1-hour protocol was no worse than 0.5% greater than standard care (number needed to harm (NNH) 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 employed the intention-to-treat (ITT) population including all randomized participants. The primary analysis assessed the non-inferiority of the 0/1-hour arm, defined as 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 (IRR and 95% CI). Tests for superiority were undertaken only if non-inferiority was met. The key secondary analysis determined if the 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. Further, sensitivity analyses were undertaken evaluating the per-protocol population for safety of the rule-out protocol. (Supplemental Methods) Exploratory sub-analyses were confined to participants with an initial (first 2) troponin ≤29ng/L, i.e. in the range where troponin reporting format (e.g. actual concentration 5-29ng/L versus ≤29ng/L) differs between the two 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 <5ng/L, 5-29ng/L and 30+ ng/L), the study arm and cardiac testing was examined using a logistic regression model. Time to the primary outcome over 30 days for the two study arms are plotted 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-square tests. All statistical analyses were conducted using STATA 15.2 (College Station TX, USA) and a p-value of <0.05 was considered statistically significant.

Results

Patient population and procedures

In total, 3378 participants were randomized between August 2015 and April 2019. Ninety participants were deemed ineligible or withdrew consent. The remaining participants 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 two study arms, other than Killip Class. (Table 1) The median age of participants was 59 (IQR 49-70) years, while 49% were female, and 28% had a prior history of CAD. The median EDACS was 15 (IQR 9-21). The 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 >29ng/L was observed in 282/3288 (9%) of all participants. (Supplemental Table 1) 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 initial assessment. Among participants presenting with at least one troponin T concentration >14ng/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 randomized 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, while 15/1646 (1%) had insufficient information for a triage recommendation. (Supplemental Table 2) 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% C.I.: 30-47%). The positive likelihood ratio for index MI was 16.5 (95% C.I.: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 CMR/nuclear). Overall, there was no increase in invasive coronary angiography in the 0/1-hour arm compared the standard arm, but when confined to the subgroup with an initial troponin T concentration ≤29ng/L, a greater rate of coronary angiography was observed. (Table 2 & Figure 2) Similarly, there was an increase in coronary revascularization among patients presenting with an initial troponin T concentration of ≤29ng/L favouring the 0/1-hour arm: 38/1502 (2.5%) versus standard arm: 15/1493 (1.0%), odds ratio 2.53: 95% C.I. 1.36-4.98, p=0.002), but not when examined in the entire population. (Supplemental Table 3) 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).(Supplemental Figure 1) The median LOS in acute care was lower in the 0/1-hour arm compared with the standard masked hs-cTnT arm (0/1-hour arm: 5.3 (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 hospital at least once within 30 days with no difference between study arms. During these representations, further troponin testing was undertaken in 213/3288 (6.5%). Re-presentation with chest pain occurred more frequently among participants randomized to the 0/1-hour arm: 65/1646 (4.0%) versus standard arm: 44/1642 (2.7%), IRR: 1.61 (95% C.I. 1.40-1.84), p<0.001). Among all hospital representations, at least one hs-cTnT result >14ng/L was observed in 143/3288 (4.4%) cases with no difference between arms. Table 3 describes the adjudicated outcomes and myocardial injury/infarction sub-classifications of these patients based on the observed troponin profile combined with documented evidence of ischaemia. Type 1 MI occurred in 9 patients in the 0/1-hour arm and 5 patients in the standard arm and of these, 1 was observe in each arm among those discharged. Of note, there were 8 periprocedural MIs (0/1-hour: 6 vs standard arm: 2) and a further 7 episodes of acute injury (0/1-hour: 5 vs standard arm: 2) observed. (Supplemental Table 4) 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 arm16/1642 (1.0%), IRR 1.06, 0.53-2.11, non-inferiority p-value =0.006, superiority p-value: p=0.867). (Also see Supplemental Figure 2 and Supplemental Table 5 for sensitivity analysis) Kaplan-Meier event curves for 30-day death or MI and cardiovascular rehospitalization are presented in figure 3. Assessment of the myocardial injury sub-classification suggested an

increase in acute injury, Type 4a and Type 5 MIs among the participants randomized to the 0/1-hour hs-cTnT protocol (0/1-hour arm 26/1646 (1.6%) versus standard arm 17/1642 (1.0%), IRR: 1.53 (95% C.I. 1.15-2.04), p=0.004), (Supplemental Figure 3) with other outcomes similar between groups. Among all participants receiving a rule-out MI triage recommendation, the primary endpoint 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% C.I. 0.02-0.06]) experienced the primary endpoint. 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% C.I. 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 death or MI was 99.6% (95% C.I. 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 compared with clinical management based reporting practices that did not employ 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, while 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 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, while discharge from the ED occurred sooner and morefrequently, with clear implications for reducing ED congestion, clinical adoption of early discharge was cautious with many patients receiving a rule-out MI recommendation still undergoing extended observation. The rates of admission and ED LOS in this study are higher than other prospective observational studies where systems of practice have been given time to become established. The rates of subsequent events among those discharged under 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" CAD 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 ischaemia, 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, representation to the ED occurred in over 13% of the population within 30 days and was associated with a high proportion of repeat troponin testing (~50%). As seen by others, more than 6% of these participants had at least one troponin T concentration above 14ng/L reported.[4,33] These observations suggest better strategies are needed for the investigation and management of the considerable number of patients who are classified as "observe" or "rule-in MI". Notably, when implementing the Fourth Universal Definition of MI, nearly half of all these acute injury profiles observed occurred following coronary revascularization procedures, and of these, half had clear corroborating evidence of ischaemia 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 ≤29ng/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 subgroup with an initial troponin concentration ≤29ng/L was also observed. While exploratory, a slightly higher rate of peri-procedural 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 non-randomized evaluations of high-sensitivity troponin protocols without directly comparative populations and systematized troponin collection. [27] Although our data supports 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 have established their balance of risk and benefit in a prior era of troponin when test performance was substantially inferior to currently available tests.[36] Potentially, extension of the management strategies for ACS to those with low-modest troponin elevations using high-sensitivity troponin assays may not be associated with the same favourable 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 state-wide control of troponin reporting not only masked the high sensitivity troponin results ≤29ng/L for all patients receiving emergency care prior to this RCT, 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 below 29ng/L were masked and therefore clinicians were prevented from applying the current universal definition of MI which calls for MI/injury diagnosis to be applied, as opposed to unstable angina, when the troponin concentration exceeds 14ng/L with a rise and/or fall pattern. However, our previous prospective randomized comparison comparing unmasked and masked results showed no difference in death or recurrent ACS when levels below 29 ng/L were made available. 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. Further, 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 >14ng/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 suggests that generalization of the 0/1-hour protocol's rule-out MI performance to practices with higher thresholds for troponin testing (i.e. 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 suspected ACS patients 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.

Contributions

Study design and protocol development: DPC, TB, LAC, SQ, JK, CP

Sourced funding from NHMRC Australia DPC, TB, LAC, SQ, JK

Sourced funding Roche Diagnostics: DPC, CP

Study Steering Committee and Implementation: DPC, KL, AB, AS, MJRE, TB, LAC, SQ, JK, AC, AJN, DW, MH, EM, JKF, CP

Randomization: SQ

Analysis: DPC, SQ, JK

First Drafting of Manuscript: DPC, TB, LAC, SQ, JK, JKF, CP

Final Approval of Manuscript: DPC, KL, AB, AS, MJRE, TB, LAC, SQ, JK, AC, AJN, DW, MH, EM, JKF, CP

Data Safety Monitoring Board: Stephen J. Nicholls (Chair), Philip G. Aylward, Matthew Worthley, Richard Woodman (statistician)

Clinical Events Committee: John K French (Chair), Sheraz Nazir (cardiologist), Dylan Jones (cardiologist), Amera Halabi (cardiologist), Nikhil Pal (cardiologist),

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Disclosures

The authors are solely responsible for the design and conduct of this study including study analyses, the drafting and editing of the paper and its final contents. Funding was sought after the study was designed, approved by the human research ethics committee, and initiated.

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KL: None

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Table 1. Baseline Characteristics of all study particpants (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 -no. (%)		768/1642 (46.8)	771/1646 (46.8)
Hypertension -no. (%)		337/1642 (20.5)	324/1646 (19.7)
Diabetes -no. (%)		286/1642 (17.4)	260/1646 (15.8)
Dyslipidaemia-no. (%)		723/1642 (44.0)	712/1646 (43.3)
Current smoker -no. (%)		584/1642 (35.6)	570/1646 (34.6)
Family history of CAD -no. (%)		953/1612 (59.1)	992/1620 (61.2)
Prior history of CAD -no. (%)		477/1642 (29.0)	457/1646 (27.8)
Prior myocardial infarction -no. (%)		161/1642 (9.8)	170/1646 (10.3)
Prior angina -no. (%)		260/1642 (15.8)	250/1646 (15.2)
Prior heart hailure -no. (%)		93/1642 (5.7)	78/1646 (4.7)
Prior atrial fibrillation -no. (%)		154/1642 (9.4)	135/1646 (8.2)
Chronic obstructive airways disease -no. (%)		74/1642 (4.5)	77/1646 (4.7)
Prior cerebrovascular disease -no. (%)		52/1642 (3.2)	53/1646 (3.2)
Prior coronary artery bypass grafting -no. (%)		46/1642 (2.8%)	49/1646 (3.0%)
Prior percutaneous coronary intervention -no. (%)		138/1642 (8.4%)	171/1646 (10.4%)
Systolic blood pressure (mmHg, median, IQR)*		135 (122,151)	135 (121, 150)
Heart rate (bpm, median, IQR)		75 (66, 85)	74 (65, 85)
Killip class	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/1.73m^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)

Footnote:
Abbreviations: IQR: inter quartile range, CAD: coronary artery disease, EDACS: Emergency Department Assessment of Chest Pain Score, HEART: History ECG Age Risk factors and Troponin, GRACE: Global Registry for Acute Coronary Events, TIMI: Thrombolysis In Myocardial Infarction, NSTEACS: non ST-segment elevation acute coronary syndrome, CKD: chronic kidney disease
There were no significant differences ($P<0.05$) between the two groups except for Killip Class ($P = 0.04$).
*Missing data: 2 participants in standard arm did not have blood pressure recorded; 36 participants (17 in0/1-hour arm/19 in standard arm) did not have creatinine drawn. Note this effects calculation of GRACE score.
†The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Glomerular filtration rate calculated using the CKD-EPI Creatinine Equation (2009)

Table 2. Performance of Troponin Testing, Index Admission Classification, and Subsequent cardiac testing and revascularization in the ITT population and participants with initial troponin ≤29ng/L.

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

Acute Care length of stay, hrs, median (IQR)	6.3/1493 (4.8, 18.4)	5.1/1515 (3.6, 18.2)	<0.001
Exercise stress test within 30 days, no. (%)	43/1493 (2.9%)	34/1515 (2.2%)	0.27
Stress echocardiogram within 30 days, no. (%)	10/1493 (6.9%)	66/1515 (4.4%)	0.002
Cardiac MRI within 30 days, no. (%)	6/1493 (0.4%)	9/1515 (0.6%)	0.45
Functional testing within 30 days, no. (%)	152/1494 (10.2%)	107/1646 (7.1%)	0.002
Echocardiogram within 30 days, no. (%)	87/1493 (5.8%)	87/1515 (5.7%)	0.92
Coronary angiogram within 30 days, no. (%)	79/1493 (5.3%)	107/1515 (7.1%)	0.044
CT coronary angiogram within 30 days, no. (%)	4/1493 (0.3%)	5/1515 (0.3%)	0.76
Percutaneous coronary intervention within 30 days, no. (%)	13/1493 (0.9%)	30/1515 (2.0%)	0.010
Coronary artery bypass grafting within 30 days, no. (%)	2/1493 (0.1%)	8/1515 (0.3%)	0.060
Any coronary revascularization within 30 days, no. (%)	15/1493 (0.9%)	38/1515 (2.2%)	0.002
No subsequent cardiac test within 30 days, no. (%)	1219/1493 (81.6%)	1267/1515 (83.6%)	0.15

Footnote:

Abbreviations: ng/L: nanograms per litre, IQR: inter quartile range, MI: myocardial infarction, ED: emergency department, MRI: magnetic resonance imaging, CT: computer tomography, D: coronary artery disease, EDACS: Emergency Department Assessment of Chest Pain Score, HEART: History ECG Age Risk factors and Troponin, GRACE: Global Registry for Acute Coronary Events, TIMI: Thrombolysis In Myocardial Infarction, NSTEACS: non ST-segment elevation acute coronary syndrome, CKD: chronic kidney disease

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

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

Table 3. Primary and Secondary Outcomes in the overall ITT population and those with an initial troponin ≤29 ng/L

	Standard Protocol (N=1642)	**0/1-Hour Protocol** (N=1646)	IRR (95% C.I.)	p-value	Non-inferiority p-value ‡
Outcome	number of patients (percent)				
All participants					
Primary Endpoint: 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
Representation 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 representation	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					
Primary Endpoint, 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
Representation 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 representation	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	

Footnote:

Abbreviations: ng/L: nanograms per litre, BARC: Bleeding Academic Research Consortium, TIMI: Thrombolysis In Myocardial, GUSTO: Global Utilization of Strategies to open Occluded arteries.

*All troponin T results >14ng/L adjudicated according to the Fourth Universal Definition of Myocardial Infarction. A rise and/or fall pattern required a change troponin concentration of >20% and a rate of change arbitrarily defined as ≥3ng/L/hr. [23,24]

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

‡ Testing for non-inferiority assessed first, followed by testing for superiority if p value <0.05 for key outcomes. Where non-inferiority 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 (i.e. overall type 1 error for this analysis may not be preserved and results should be viewed as exploratory). .

Table 4. Primary and Secondary Endpoint at 30 days by triage category for participants (Intention to treat population)

	Standard Protocol		0/1-Hour Protocol		
Outcome	**cTnT≤29ng/L (N=1493)**	**cTnT>29ng/L (N=140)**	**MI Rule out (N=1,187)**	**MI Observe (N=308)**	**MI Rule In (N=136)**
Primary Endpoint: death and myocardial infarction	9 (0.6%)	7 (5.0%)	5 (0.4%)	7 (2.3%)	5 (3.7%)
All-cause death	2 (0.1%)	4 (2.9%)	1 (0.1%)	1 (0.3%)	0 (0.0%)
Cardiovascular death	0 (0.0%)	3 (2.1%)	1 (0.1%)	1 (0.3%)	0 (0.0%)
Myocardial infarction (Type 1, Type 2, Type 4a, Type 5)*	7 (0.5%)	3 (2.1%)	4 (0.3%)	6 (1.9%)	5 (3.7%)
Myocardial injury – acute*	6 (0.4%)	1 (0.7%)	5 (0.4%)	3 (1.0%)	3 (2.2%)
Myocardial infarction and myocardial injury – acute*	13 (0.9%)	4 (2.9%)	9 (0.8%)	9 (2.9%)	8 (5.9%)
Myocardial injury – chronic*	13 (0.9%)	8 (5.7%)	2 (0.2%)	11 (3.6%)	5 (3.7%)
Unstable angina	4 (0.3%)	0 (0.0%)	3 (0.3%)	2 (0.6%)	0 (0.0%)
All-cause death and myocardial infarction and unstable angina	11 (0.7%)	6 (4.3%)	7 (0.6%)	9 (2.9%)	5 (3.7%)
Chest pain representation	39 (2.6%)	5 (3.6%)	41 (3.5%)	22 (7.1%)	7 (5.1%)
Cardiovascular rehospitalisation†	10 (0.7%)	5 (3.6%)	9 (0.8%)	8 (2.6%)	6 (4.4%)
BARC 2, 3a, or 4	4 (0.3%)	9 (6.4%)	2 (0.2%)	2 (0.6%)	2 (1.5%)
TIMI major, minor or minimal	3 (0.2%)	6 (4.3%)	1 (0.1%)	2 (0.6%)	1 (0.7%)
GUSTO major or minor	1 (0.1%)	6 (4.3%)	1 (0.1%)	1 (0.3%)	2 (1.5%)

Footnote:

Abbreviations: BARC: Bleeding Academic Research Consortium, TIMI: Thrombolysis In Myocardial, GUSTO: Global Utilization of Strategies to open Occluded arteries.

*All troponin T results >14ng/L adjudicated according to the Fourth Universal Definition of Myocardial Infarction. A rise and/or fall pattern required a change troponin concentration of >20% and a rate of change arbitrarily defined as ≥3ng/L/hr. [22,23]

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

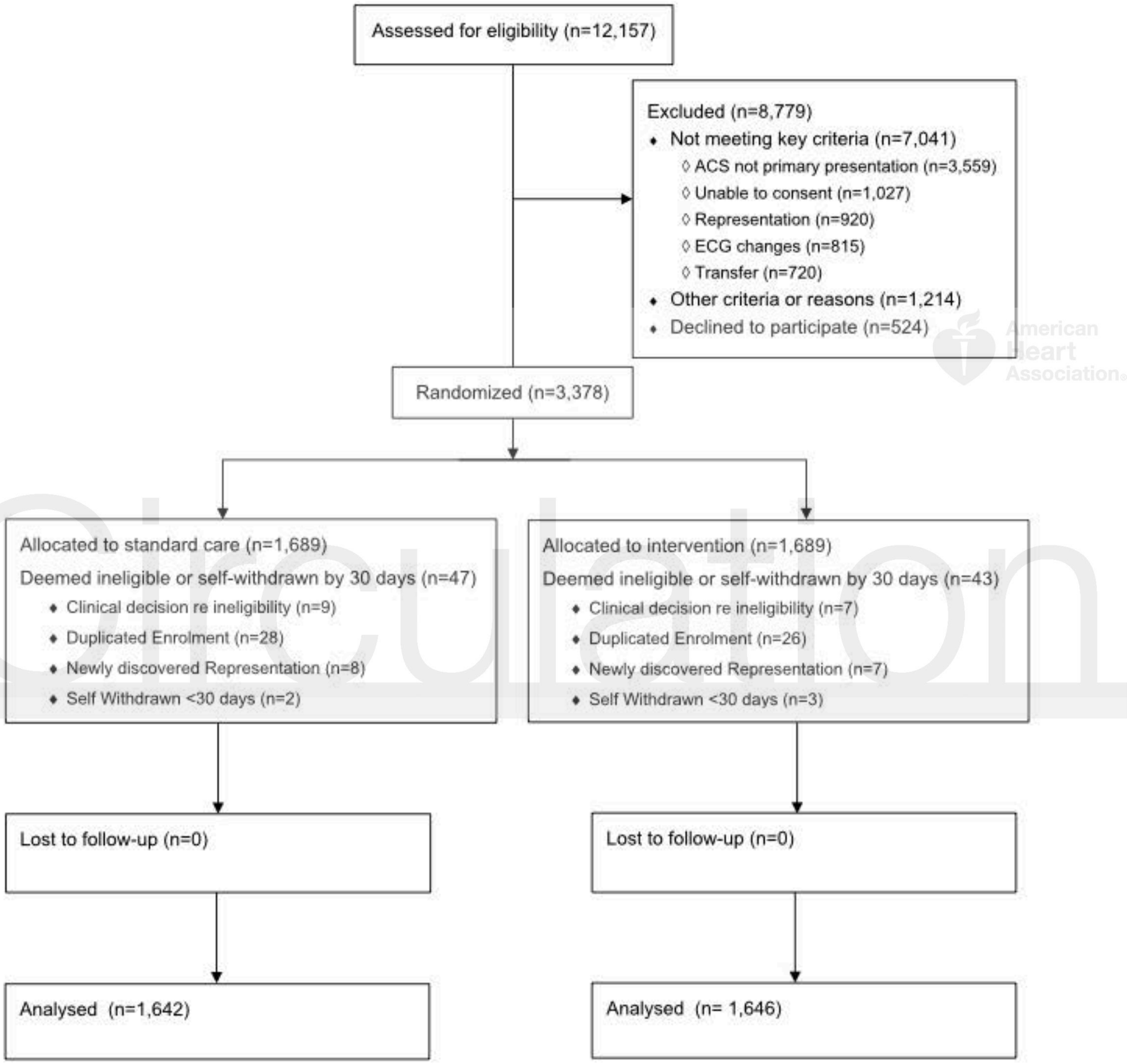
Figure Legends

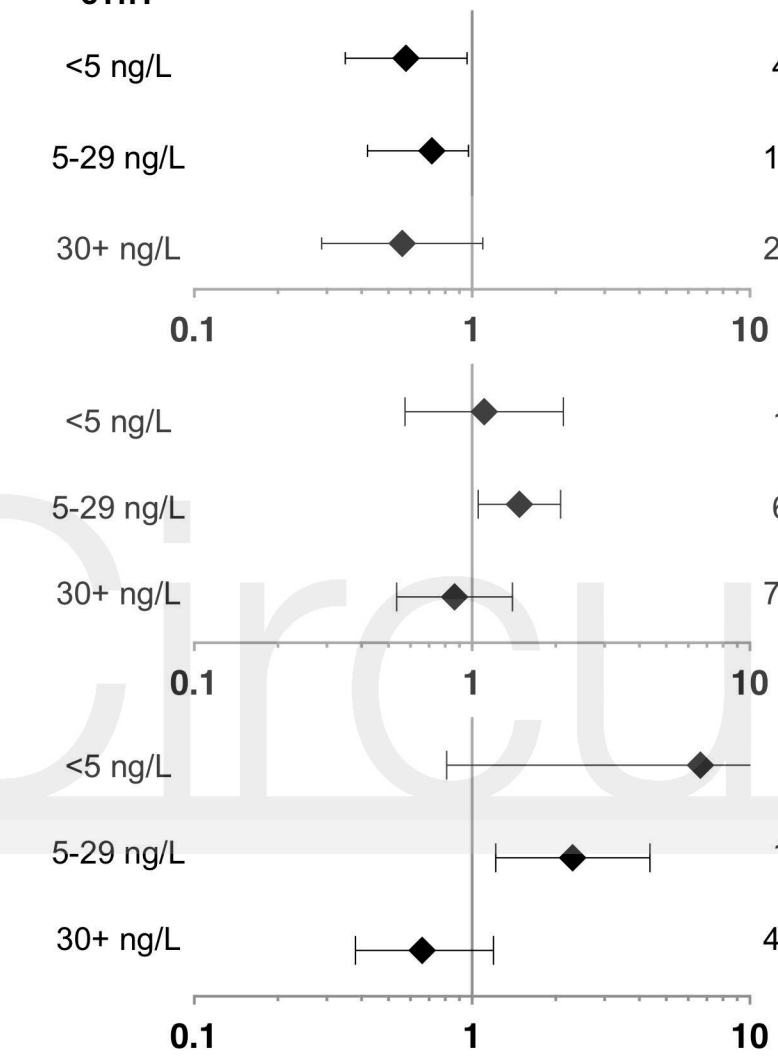
Figure 1. Screening, Eligibility, Randomization and Follow-up

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. NB: peak concentrations ≤29ng/L not observed by clinicians randomized to the standard therapy arm.

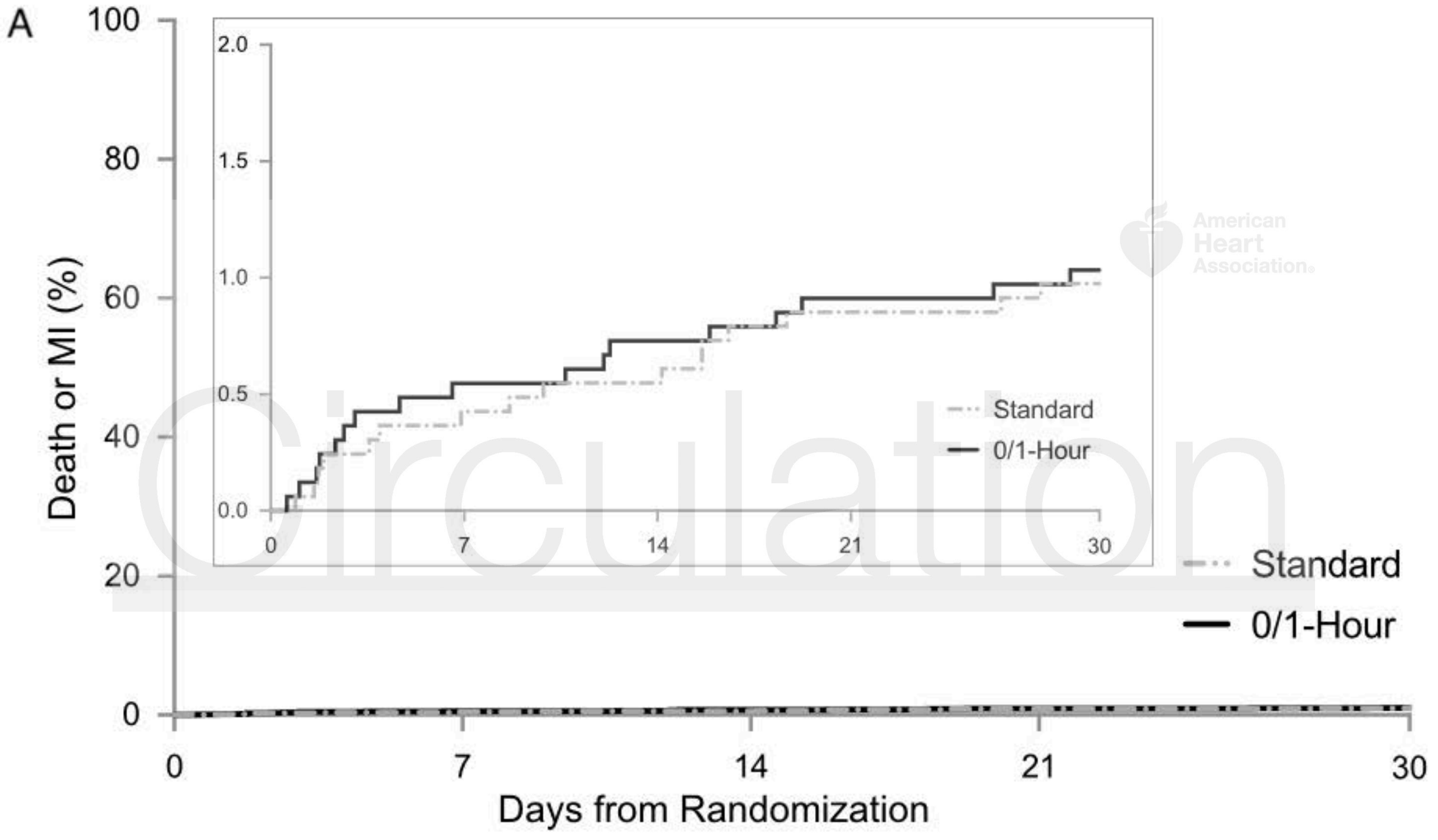
Figure 3. Clinical Outcomes within 30 days. Kaplan Meier Event Curves for (a) the primary endpoint within 30 days, and (b) cardiovascular rehospitalization within 30 days. Cardiovascular rehospitalization includes readmission for non-elective coronary revascularization, peripheral artery disease, cerebrovascular accidents; congestive cardiac failure without MI, atrial and ventricular arrhythmias.

Footnote: Standard: Masked hs-cTnT protocol; 0/1-Hour: 0/1-Hour hs-cTnT protocol





	Peak Initial cTnT	Standard (%)	0/1-hour (%)	O.R. (95% C.I.)	p-value	Interaction p-value
Functional Testing	<5 ng/L	41/620 (6.6)	26/660 (3.9)	0.58 (0.35-0.96)	0.032	
	5-29 ng/L	111/873 (12.7	81/855 (9.5)	0.72 (0.53-0.93)	0.033	0.473
	30+ ng/L	28/139 (20.1)	16/129 (12.4)	0.56 (0.29-1.09)	0.090	0.942
Angiography	<5 ng/L	17/620 (2.7)	20/660 (3.0)	1.11 (0.58-2.13)	0.758	
	5-29 ng/L	62/873 (7.1)	87/855 (10.2)	1.48 (1.05-2.08)	0.023	0.441
	30+ ng/L	74/139 (53.2)	64/129 (49.6)	0.86 (0.54-1.40)	0.553	0.550
Revascularization	<5 ng/L	1/620 (0.2)	7/660 (1.1)	6.64 (0.81-54.08)	0.077	
	5-29 ng/L	17/873 (1.6)	31/855 (3.6)	2.31 (1.22-4.37)	0.008	0.345
	30+ ng/L	41/139 (29.5)	28/129 (21.7)	0.66 (0.38-1.15)	0.146	0.037



Number at risk

Standard	1642	1635	1633	1628	1626
0/1-hour	1646	1637	1634	1631	1629

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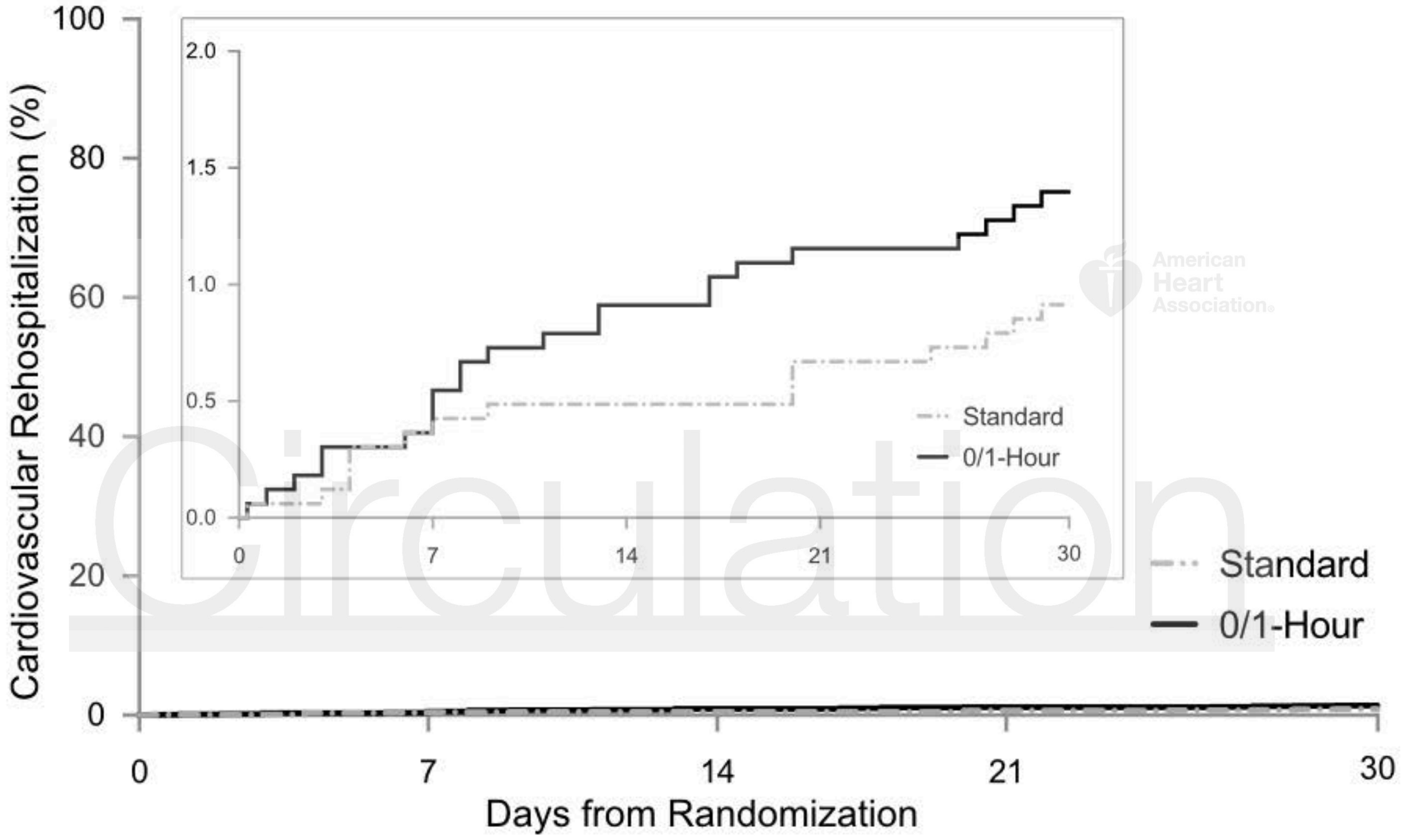

Number at					
Standard	1642	1636	1634	1631	1627
0/1-hour	1646	1640	1631	1627	1623