Rapid Acute Coronary Syndrome Evaluation Over One Hour With High-Sensitivity Cardiac Troponin I

A United States-Based Stepped-Wedge, Randomized Trial

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Study objective: The real-world effectiveness and safety of a 0/1-hour accelerated protocol using high-sensitivity cardiac troponin (hs-cTn) to exclude myocardial infarction (MI) compared to routine care in the United States is uncertain. The objective was to compare a 0/1-hour accelerated protocol for evaluation of MI to a 0/3-hour standard care protocol.

Methods: The RACE-IT trial was a stepped-wedge, randomized trial across 9 emergency departments (EDs) that enrolled 32,609 patients evaluated for possible MI from July 2020 through April 2021. Patients undergoing high-sensitivity cardiac troponin I testing with concentrations less than or equal to 99th percentile were included. Patients who had MI excluded by the 0/1-hour protocol could be discharged from the ED. Patients in the standard care protocol had 0- and 3-hour troponin testing and application of a modified HEART score to be eligible for discharge. The primary endpoint was the proportion of patients discharged from the ED without 30-day death or MI.

Results: There were 13,505 and 19,104 patients evaluated in the standard care and accelerated protocol groups, respectively, of whom 19,152 (58.7%) were discharged directly from the ED. There was no significant difference in safe discharges between standard care and the accelerated protocol (59.5% vs 57.8%; adjusted odds ratio (aOR)=1.05, 95% confidence interval [CI] 0.95 to 1.16). At 30 days, there were 90 deaths or MIs with 38 (0.4%) in the standard care group and 52 (0.4%) in the accelerated protocol group (aOR=0.84, 95% CI 0.43 to 1.68).

Conclusion: A 0/1-hour accelerated protocol using high-sensitivity cardiac troponin I did not lead to more safe ED discharges compared with standard care. [Ann Emerg Med. 2024;■:1-10.]

Please see page XX for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Over 20 million individuals are evaluated for myocardial infarction (MI) in emergency departments (EDs) annually in the United States.[1] Estimates are that 5% of these individuals have an acute coronary syndrome.[2] Prior guidelines recommend measurement of biomarkers and cardiac testing.[3] The cost of this strategy is $5 to $10 billion annually in the United States, possibly contributing to ED crowding, which can lead to worse outcomes when compared to no crowding.[4-6]

Importance

High-sensitivity cardiac troponin (hs-cTn) assays allow quantification below the 99th percentile (MI threshold).[7] Observational studies show that MI evaluation protocols with measurements at 0 and 1 hours using values less than

Editor's Capsule Summary

What is already known on this topic

Diagnostic protocols for myocardial infarction using high sensitivity troponin measurements at 0 and 1 hour have high negative predictive value and low rates of 30-day adverse outcome in protocol-negative patients.

What question this study addressed

Does a 0/1-hour accelerated protocol reduce the proportion of patients safely discharged from the emergency department compared to a 0/3-hour standard care protocol?

What this study adds to our knowledge

A 0/1-hour accelerated protocol did not reduce the proportion of patients safely discharged compared to standard care but was noninferior in terms of 30-day adverse events.

How this is relevant to clinical practice

A 0/1-hour accelerated protocol safely reduced the time to rule out myocardial infarction, but other factors may be more important in determining the proportion of patients discharged.

the 99th percentile have high negative predictive value.[8,9] Nonrandomized studies implementing high-sensitivity cardiac troponin T 0/1-hour protocols show low 30-day death/MI rates.[10,11] Prospective randomized trials outside the United States evaluating accelerated protocols utilizing hs-cTn within 1 hour report low 30-day death/MI rates and demonstrate that accelerated protocols are not inferior to traditional strategies.[12-14] Recent guidelines recommend using accelerated protocols, reporting hs-cTn less than 99th percentile, and discharge of low-risk patients without further cardiac testing or application of a risk score.[15] However, there is concern that reporting hs-cTn values less than 99th percentile may lead to unnecessary revascularization procedures.[16,17]

Goals of This Investigation

To date, all randomized prospective trials evaluating accelerated protocols have been performed outside of the United States, and the real-world effectiveness and safety in this distinct practice environment are not known. The primary trial aim was to evaluate the real-world result of a 0/1-hour accelerated protocol compared to a 0/3-hour standard care protocol on the proportion of patients safely discharged from the ED (no 30-day death/MI). Secondary aims were to evaluate 30-day outcomes: death, MI, or coronary revascularization procedures in patients discharged from the ED or observation unit.

MATERIALS AND METHODS

Study Design and Population

RACE-IT (Rapid Acute Coronary Syndrome Exclusion using high-sensitivity I cardiac Troponin) was a prospective, stepped-wedge, randomized trial enrolling consecutive patients evaluated for MI in 9 EDs within Henry Ford Health in Michigan: 5 hospital-based (1 large urban, 4 suburban) and 4 free-standing suburban sites (NCT04488913). The protocol has been published.[18,19] Patients undergoing high-sensitivity cardiac troponin I (hs-cTnI) testing and an electrocardiogram were included. Exclusion criteria included: age less than 18 years, ST-segment elevation MI, hs-cTnI levels more than 18 ng/L in the ED, trauma, transfers from another facility, residence outside Michigan, and hospice. Patients were enrolled only once. The Institutional Review Board approved the trial and granted waiver of consent. Beckman Coulter funded the study. Race was self-reported. Authors are solely responsible for the design/conduct of the study, analyses, and manuscript content.

Randomization and Intervention

The order in which EDs applied the accelerated protocol was randomly assigned using a computerized random number generator. Sites had 3 phases of implementation in 3-week intervals (Table E1, available at http://www.annemergmed.com). The first phase was standard care, and data were collected. In the second phase, the accelerated protocol was introduced, but without data collection. In the third phase, use of the accelerated protocol was recommended, and data were collected.

An hs-cTnI assay (Access, Beckman Coulter) was used. This assay has a 99th percentile of 18 ng/L, limit of detection of 0.3 ng/L, and limit of quantitation of 0.8 ng/L.[20] The accelerated protocol was based on a published protocol, where MI could be excluded in three ways (Figure 1).[21] Patients who had MI excluded within 1 hour could be considered for discharge directly from the ED without use of a modified HEART score.[22] The protocol advised (but did not mandate) that further hs-cTnI testing should be considered in patients who presented less than 3 hours after symptom onset. Patients who were not ruled out within 1 hour had hs-cTnI measurement at 3 hours and could be considered for discharge if the modified HEART score was less than 4 and all hs-cTnI values were less than or equal to 18

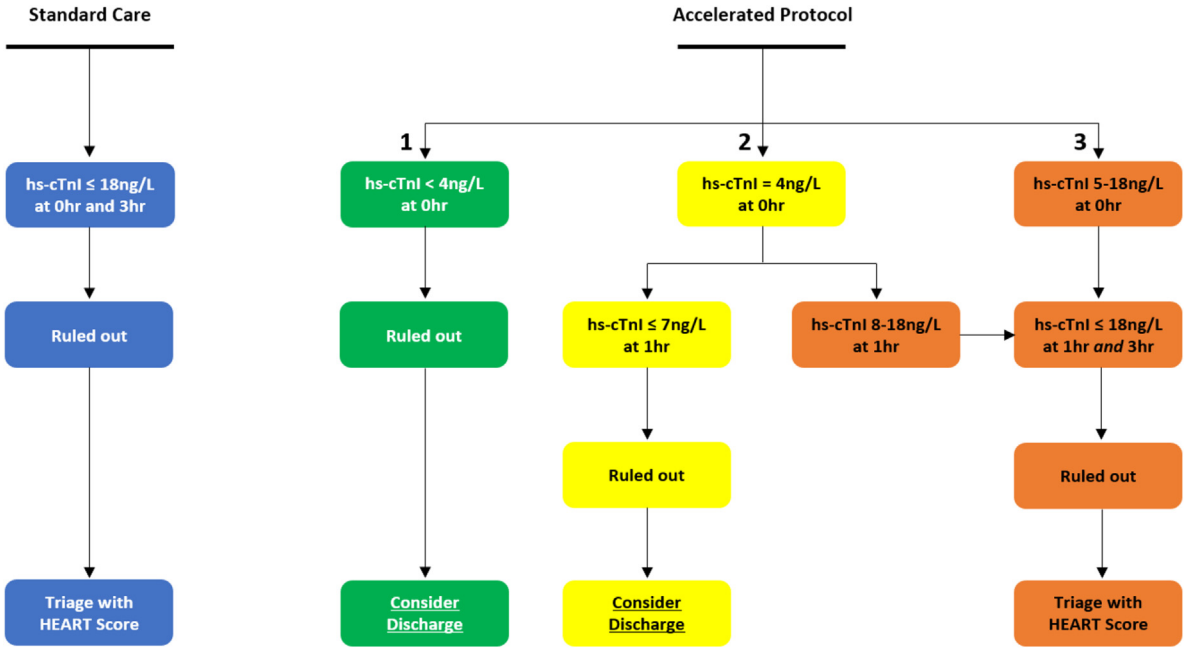

Figure 1. Suspected myocardial infarction low-risk disposition algorithms. *hr*, hour; *hs-cTnI*, high-sensitivity cardiac troponin I.

ng/L. Thus, in the accelerated protocol, only patients with intermediate hs-cTnI (5 to 18 ng/L) values required application of a modified HEART for risk stratification. Documentation of the HEART score in the medical record was not mandated.

Under standard care management, MI was excluded if hs-cTnI values were less than or equal to 18 ng/L at presentation and 3 hours. However, to be discharged without further cardiac testing, patients had to have a modified HEART score less than 4. The 3-hour time interval is consistent with guidelines when only values above the 99th percentile are reported.[3] Concentrations below 18 ng/L were not reported to clinicians in the standard care protocol. These protocols were guidelines, and clinical judgment could supersede their clinical use.

Study Outcomes

The primary endpoint was safe discharge, defined as the proportion of patients safely discharged from the ED without 30-day death/MI. Thus, the primary endpoint combined safety and effectiveness elements. We hypothesized that patients in the accelerated protocol arm would have a higher proportion of safe ED discharges. Secondary endpoints were evaluated at 30 days in those discharged from the ED or observation unit and included the composite endpoint of death or MI and coronary revascularization procedures. We hypothesized the accelerated protocol would not be inferior to standard care regarding safety (30-day death/MI). Outcomes were identified from the electronic record (Epic Systems) in patients who were discharged from the ED or observation unit and returned to any ED within 30 days. Twelve institutions in Michigan (Table E2, available at http://www.annemergmed.com) use Epic and all participate in a health information exchange.

The diagnosis of MI was adjudicated according to the Fourth Universal Definition of MI, which requires a change in cardiac troponin values with at least one value more than 99th percentile and at least one of the following: ischemic symptoms, ischemic ECG findings, new wall motion abnormality, or coronary angiographic findings.[23] Two staff clinicians (cardiologists or emergency physicians) reviewed each case, and a third was responsible for final adjudication when there was disagreement. Cardiac versus noncardiac death was determined by the reviewing physicians in accordance with a consensus document.[24] Additional deaths were determined by accessing the National Death Index (accessed April 2022). For deaths determined by the National Death Index, diagnostic codes consistent with a cardiovascular cause of death (120-125,146,149) were considered cardiac.[25]

Statistical Analysis

The binary primary endpoint (safe discharge) was analyzed using generalized linear mixed models, adjusting for ED site (random effect), time because the initial start date, age, sex, race, ethnicity, history of coronary artery disease, and group (standard care vs accelerated protocol)

indicator. The intraclass correlation coefficient from this model was reported to illustrate the importance of controlling for ED site as a random effect. The secondary endpoints (30-day death/MI) and revascularization procedures were analyzed using similar modeling adjusting for the same covariates where possible.

We performed a preplanned noninferiority analysis on the safety outcome (30-day death/MI) using the risk difference and calculated the 95% confidence interval (CI) using a bootstrapping method. Noninferiority was considered when the upper limit of the 95% CI was below a 0.5% noninferiority margin. We chose this margin based on the assumption that the overall 30-day death/MI incidence would approach 0.4%, and a noninferior protocol would require a safety outcome less than 1%. We also performed a sensitivity analysis on the primary endpoint that used the same generalized linear mixed model and included only patients without coronavirus disease 2019 (COVID-19) infection. Post-hoc analyses assessed the primary endpoint while limiting the accelerated protocol based on various rule-out categories. Assuming variable cluster size (coefficient of variance 0.4), an alpha of 0.05, and 90% power, we estimated that a sample size of 11,070 patients would be needed to test our primary endpoint with an absolute effect difference of 5% (40% safe discharge in the standard care group vs 45% safe discharge in the accelerated protocol). We present adjusted odds ratios with 95% CIs where appropriate. Mixed models were performed using PROC GLIMMIX in SAS software 9.4. We report details on model building and performance in a statistical supplement (Appendix E1, available at http://www.annemergmed.com).

RESULTS

Study Sites and Population

The study period was from July 8, 2020, to April 3, 2021. There were 32,609 eligible patients (Figure 2b). A total of 19,152 (58.7%) patients were discharged from the ED and analyzed for the primary endpoint; 22,345 (68.5%) patients were discharged from the ED or observation unit and included in secondary analyses. There were 10,264 patients admitted to the hospital. Clinical characteristics are shown in Table 1. Patients in the standard care group had more comorbidities and accelerated protocol patients more commonly had COVID-19 infection. The 2 most common chief complaints were chest pain 9,691 (29.7%) and shortness of breath 6,114 (18.8%) (Table 2).

Primary and Secondary Outcomes

In the accelerated protocol group, 11,040 (57.8%) patients had safe discharge compared to 8,037 (59.5%) patients in the standard care group (adjusted odds ratio [aOR]=1.05, 95% CI 0.95 to 1.16). When excluding patients with COVID-19, the odds of safe ED discharge were greater in the accelerated protocol (aOR=1.14, 95% CI 1.03 to 1.25) (Table 3). The intraclass correlation coefficient of the site effect was 0.26, which indicates that 26% of the variability in safe discharge was associated with the site effect.

Among those patients who had MI excluded within 1 hour using the accelerated protocol, there was a significantly higher proportion of safe ED discharges (74.1%) compared to standard care (59.5%) (aOR=1.67, 95% CI 1.48 to 1.89). Among those patients who did not have MI excluded within 1 hour, there was a significantly lower proportion of safe ED discharges using the accelerated protocol (38.1%) when compared to standard care (59.5%) (aOR=0.68, 95% CI 0.61 to 0.77). There was considerable variation across the ED sites (Table E3, available at http://www.annemergmed.com). To explore clustering by provider, a sensitivity analysis was performed on the primary outcome where first ED provider was included as a random effect. The effect estimate and 95% CIs were nearly identical.

At 30 days, there were 64 deaths (56 noncardiac, 8 cardiac) and 26 MIs among patients discharged from the ED or observation unit (Table 4). None of the 26 patients with MIs died within the 30-day follow-up period. There were 8 type 1 and 18 type 2 MIs, including more type 2 MIs in the accelerated protocol. Of the 8 type 1 MIs, 1 patient had a cardiology consult, and 1 patient had hospital admission recommended but refused. There was no significant difference in the rate of death or MI at 30 days comparing the accelerated protocol (52 events, 0.40%) to standard care (38 events, 0.40%) groups (aOR=0.84, 95% CI 0.43 to 1.68) (Table 4). The estimated adjusted risk difference between accelerated protocol and standard care was -0.068%, and the 95% bootstrap CI was (-0.43% to 0.2%), which was within our prespecified noninferiority margin of 0.50%. We report subanalyses on the secondary endpoints among those discharged from the ED (Table E4, available at http://www.annemergmed.com).

At 30 days, there were 32 revascularization procedures in patients discharged from the ED or observation unit. There was no significant difference in revascularization procedures in the accelerated protocol and standard care groups (Table 4). Similarly, there were no differences in revascularization procedures when including all admitted patients. The standard care group had 55 patients with at

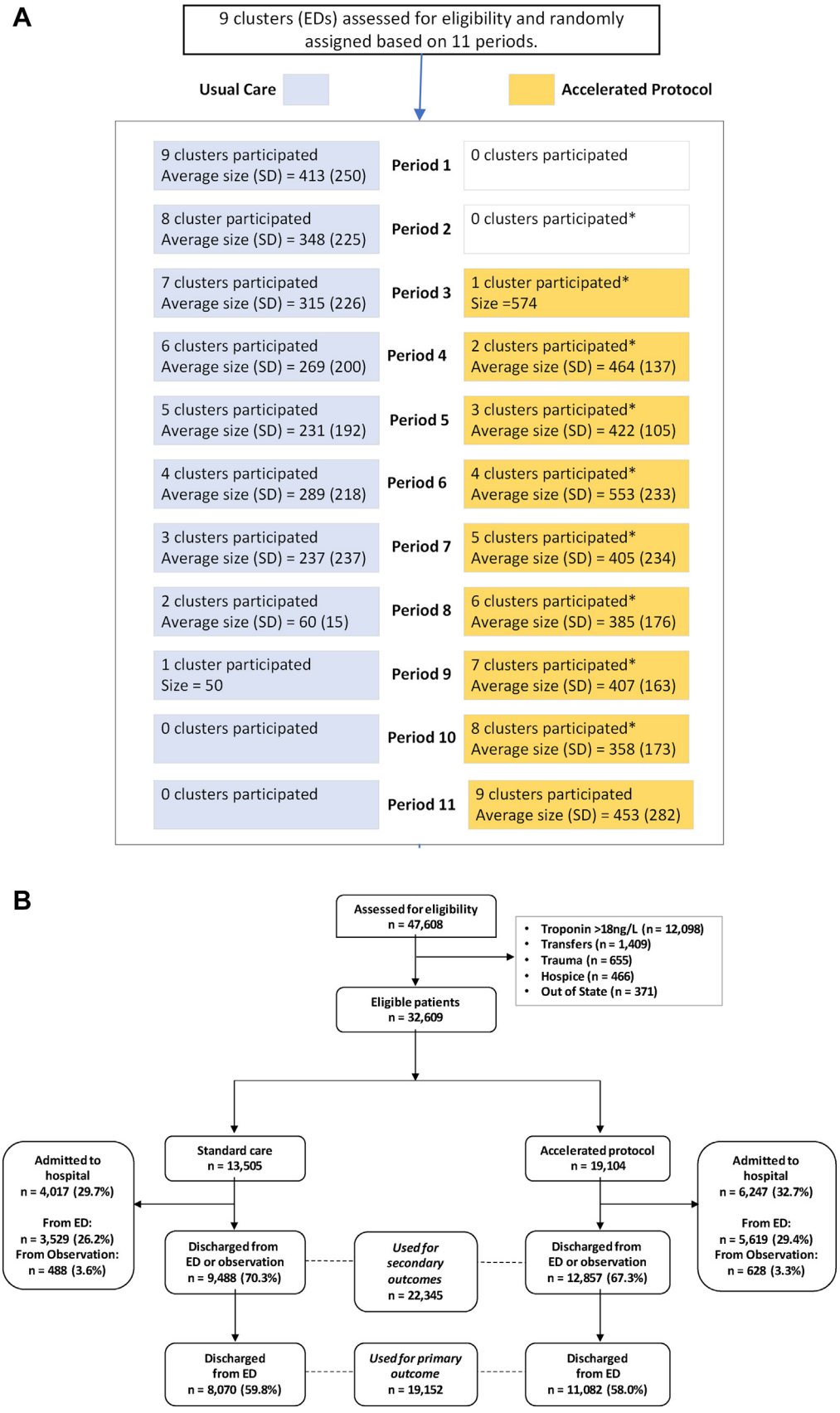

Figure 2. *A*, Consort diagram—cluster allocation. *B*, Consort diagram—intervention assignment and disposition. **ED*, emergency department.

Table 1. Entire study cohort.

Demographics	Standard Care (*N*=13,505)	Accelerated Protocol (*N*=19,104)
Age, y, median (25th, 75th percentile)	60 (46, 73)	58 (45, 71)
Sex		
Man	5,701 (42.2%)	8,198 (42.9%)
Woman	7,803 (57.8%)	10,902 (57.1%)
Unknown	1 (0.0%)	4 (0.0%)
Race		
Black	3,047 (22.6%)	6,345 (33.2%)
Other*	1,301 (9.6%)	2,500 (13.1%)
White	9,157 (67.8%)	10,259 (53.7%)
Ethnicity		
Hispanic or Latino	398 (2.9%)	860 (4.5%)
Not Hispanic/Latino	12,657 (93.7%)	17,474 (91.5%)
Unknown	450 (3.3%)	770 (4.0%)
Medical history		
Hypertension	6,733 (49.9%)	8,870 (46.4%)
Diabetes	2,959 (21.9%)	4,138 (21.7%)
Hyperlipidemia	2,595 (19.2%)	3,024 (15.8%)
Coronary artery disease	1,575 (11.7%)	2,053 (10.7%)
Peripheral vascular disease	546 (4.0%)	783 (4.1%)
Congestive heart failure	1,572 (11.6%)	1,930 (10.1%)
Abdominal aortic aneurysm	139 (1.0%)	130 (0.7%)
Atrial fibrillation	1,345 (10.0%)	1,547 (8.1%)
Chronic kidney disease	2,989 (22.1%)	3,658 (19.1%)
Chronic lung disease	2,930 (21.7%)	3,762 (19.7%)
Renal function, median (25^{th} to 75^{th} percentile)		
Serum creatinine (mg/dL)	0.88 (0.72, 1.09)	0.88 (0.72, 1.08)
eGFR (mL/min/1.73 m^2)	87 (66, 103)	88 (67, 104)
Site setting		
Suburban	12,801 (94.8%)	14,019 (73.4%)
Urban	704 (5.2%)	5,085 (26.6%)
SARS-CoV-2 PCR positive	467 (3.5%)	1,416 (7.4%)

*Further characterization of the other category is shown in Table E10 (available at http://www.annemergmed.com).

least 1 revascularization procedure (51 percutaneous coronary interventions, 5 coronary artery bypass graft surgeries, 0.41%) compared to 63 patients with at least one revascularization procedure (53 percutaneous coronary interventions, 11 coronary artery bypass graft surgeries, 0.33%) in the accelerated protocol group (accelerated protocol vs standard care, aOR=0.63, 95% CI 0.31 to 1.30).

Characteristics of the 16 patients who were not admitted but had a type 1 MI or cardiovascular death within 30 days are shown (Tables E5 and E6, available at http://www.annemergmed.com). Only 1 of the type 1 MI patients in the accelerated protocol arm had MI excluded within 1 hour, and no patients who experienced cardiac death were ruled out within 1 hour. Of the type 2 MI patients, the most common primary diagnosis was infection (8 patients); COVID-19 was diagnosed in 6 of these patients.

Effectiveness of the 0/1-Hour Protocol

In the accelerated protocol cohort, 9,015 patients (47.2 %) ruled out for MI at presentation, and 1,430 (7.5%) ruled out for MI at 1 hour (Table E7, available at http://www.annemergmed.com). Thus, 10,445 (54.7%) patients had MI excluded within 1 hour. Comorbid conditions (hypertension, diabetes mellitus, heart failure, and kidney disease) were more prevalent in EDs that did not experience an increase in safe discharges with the accelerated protocol (Table E8, available at http://www.annemergmed.com). Overall, a greater percentage of patients in the accelerated protocol group (48.5%) had only 1 hs-cTnI test ordered compared to the standard care arm (24.0%) (Table E9, available at http://www.annemergmed.com).

LIMITATIONS

Due to the large size of the cohort, we relied on review of statewide health information exchange records and the National Death Index to determine adverse events. Although we cannot be certain, this may have affected both groups similarly. Values of hs-cTnI from 4 to 18 ng/L in the standard care arm were not available, so we could not directly compare patients in the 2 groups using their actual hs-cTnI concentrations. Based on our sensitivity analysis, it appears that a higher rate of COVID-19 infection in the intervention arm may have influenced our findings, reducing the proportion of patients considered for discharge. Competing demands of the COVID-19 pandemic may have also limited clinician education and implementation of the new 0/1-hour algorithm. HEART scores were not recorded, and we cannot quantify how many more patients would have been classified as low risk using the accelerated protocol. There are health systems in the Detroit area that do not participate in the state health information exchange, and we may have had incomplete 30-day follow-up for some patients, leading to missed adverse events. The statistical model adjusted for coronary artery disease but did not factor in other comorbid

Table 2. Presenting chief complaint in entire cohort.

Chief Complaint	Number (%)
Total	32,609
Chest pain	9,691 (29.7%)
Shortness of breath	6,114 (18.8%)
Suspected COVID-19	3,424 (10.5%)
Abdominal pain	1,693 (5.2%)
Dizziness	1,478 (4.5%)
Palpitations	1,402 (4.3%)
Falls	976 (3.0%)
Nausea/Vomiting	946 (2.9%)
Fatigue	902 (2.8%)
Syncope	795 (2.4%)
High blood pressure	761 (2.3%)
Altered mental status	679 (2.1%)
Others	3,748 (11.5%)

conditions. Last, sex-specific cutoff points were not used for determination of MI, which has been recommended by some.[26]

DISCUSSION

We report 4 major findings. First, the study did not meet its primary endpoint as the accelerated protocol was not superior to standard care in the proportion of patients who were safely discharged from the ED. Excluding patients with COVID-19, however, there was an increase in the odds of safe ED discharge in the accelerated protocol compared to standard care. In addition, in those for whom MI was excluded within 1 hour using the accelerated protocol (54.7%), there was a significant increase in the proportion of safe ED discharges compared to the standard care group. These patients were eligible for ED discharge irrespective of their modified HEART score. Adverse event rates were similar in the accelerated protocol and standard of care.

In patients who did not have MI excluded within 1 hour, there was a decrease in the odds of safe ED discharge compared to the standard care group. The 0/1-hour protocol is less likely to be effective in some subsets. Diabetes mellitus, heart failure, hypertension and chronic kidney disease are associated with chronically elevated cardiac troponin levels, and such patients are less likely to have MI excluded within 1 hour. These patients are more likely to have a first hs-cTnI value in the intermediate range (5 to 18 ng/L), whereas with the prior standard care protocol, an intermediate cardiac troponin value was reported as less than 18 ng/L. Physicians may be less likely to discharge a patient with an intermediate cardiac troponin value and order further testing. Clinicians use cardiac troponin testing broadly, including patients with mental status change, dyspnea, and suspected COVID-19. Only 29.7% had chest pain as the chief complaint. This is considerably less than the 81% presenting with chest pain in a related trial of suspected MI in Scotland.[27]

Second, this study confirms that the accelerated protocol was not inferior to the standard care regarding 30-day death/MI in patients not admitted to the hospital. The 30-day death/MI rate was only 0.4% in the both groups, which is identical to the 30-day death/MI rate in the Rapid Assessment of Possible Acute Coronary Syndrome in the Emergency Department with High-Sensitivity Troponin T (RAPID-TnT) trial.[13] This supports the safety of accelerated protocols, such as the Beckman Coulter hs-cTnI assay used here, for real-world applications, which have diminished reliance on risk scores for disposition decisionmaking and are included in the American Heart Association/American College of Cardiology chest pain guidelines.[15]

Third, in those patients who had MI excluded within 1 hour, most did so at presentation. Among 10,445 patients with MI excluded within 1 hour, more than 85% were excluded at time 0. Also, in the accelerated protocol, a greater percentage of patients had only 1 hs-

Table 3. Safe emergency department discharge.

Disposition	Patients	Standard Care	Accelerated Protocol	Absolute (%) Difference (95% CI)	Adjusted OR (95% CI)
Entire cohort	*N*=32,609	*N*=13,505	*N*=19,104		
Safe discharge	19,077 (58.5%)	8,037 (59.5%)	11,040 (57.8%)	1.7 (1.697 to 1.704)	1.05 (0.95 to 1.16)
Excluding COVID-19 patients*	*N*=30,726	*N*=13,038	*N*=17,688		
Safe discharge	18,403 (59.9%)	7,837 (60.1%)	10,566 (59.7%)	0.4 (0.398 to 0.404)	1.14 (1.03 to 1.25)

CI, confidence interval; *OR*, odds ratio.

*Although the percentage of patients in the standard care arm that had a safe ED discharge was more than that of the accelerated protocol arm, after adjusting for the covariates the accelerated protocol arm had greater odds of safe ED discharge compared to the standard care arm.

cTnI drawn (48.5%) as compared to the standard care group (24.0%). This finding underscores the potential for improved efficiency within the ED. However, the large urban hospital-based ED had a greater percentage of patients with only 1 hs-cTnI assessment in the standard care arm. Patients in the urban setting more commonly had comorbidities associated with chronically elevated cardiac troponin levels. A physician may order only 1 cardiac troponin assessment when symptoms occurred many hours ago. In this case, in the standard care arm, the value would be less than or equal to 18 ng/L, and MI would be excluded. However, in patients with significant comorbidities, who were enriched in our population that included "all comers," this value could be 15 ng/L in the accelerated protocol arm and lead to further cardiac troponin testing. Thus, when using the accelerated protocol in a population with comorbidities leading to chronic cardiac troponin elevation, there may be an increase in hs-cTnI measurements that may blunt some of the beneficial effects in the lower risk patients.

Fourth, there was no difference in 30-day revascularization procedures. These findings are reassuring. Some studies consider a revascularization procedure within 30 days as an adverse event in patients not admitted.[28,29] In addition, there have been concerns that the reporting of low hs-cTn levels may lead to more revascularization procedures, some of which may be unnecessary, which we did not observe.[16,17]

This pragmatic, real-world randomized trial adds important information relevant to the use of hs-cTn assays. As some authors have noted, real-world randomized application trials are rare but important as they involve patients in whom novel protocols are used for clinical management so that both benefits and potential deficits can be probed, which cannot occur in observation trials.[30] The present study has several important strengths. It is the first randomized study to compare the safety and effectiveness a 0/1-hour to 0/3-hour protocol with a hs-cTnI assay to rule out MI. The RAPID-TnT trial was the only other randomized trial comparing a hs-cTn 0/1-hour to 0/3-hour protocol, but this study occurred outside the United States, involved only 3,378 patients, and used a high-sensitivity cardiac troponin T assay.[13] Studies of different hs-cTn assays are important as there are potentially important differences between hs-cTnI and high-sensitivity cardiac troponin T during episodes of transient ischemia.[31] We enrolled a diverse cohort of consecutive patients, which is representative of how hs-cTn testing is used in the United States, where such testing is used more broadly than in other countries. Although ST-segment elevation MI patients were excluded, those with other ischemic ECG changes were included. We included a large proportion of Black patients providing information on a population that is significantly underrepresented in non-United States-based trials. Four of the 9 sites were free-standing EDs, which have not been included in many clinical trials. Finally, we found considerable variation in the primary endpoint depending on the ED site. This suggests that the influence of the accelerated protocol likely will depend on site-specific characteristics such as practice patterns and

Table 4. Death, myocardial infarction, and revascularization procedures within 30 days (among those discharged from the ED or observation unit).

Events	All	Standard Care	Accelerated Protocol	Adjusted Odds Ratio (95% CI)
Participants, n (%)	22,345	9,488	12,857	
Myocardial infarction/all-cause death*	90 (0.40%)	38 (0.40%)	52 (0.40%)	0.84 (0.43-1.68)
All-cause death*	64 (0.29%)	33 (0.35%)	31 (0.24%)	0.65 (0.29-1.47)
Noncardiac death*	56 (0.25%)	29 (0.31%)	27 (0.21%)	0.53 (0.22-1.27)
Cardiac death†	8 (0.04%)	4 (0.04%)	4 (0.03%)	2.54 (0.42-15.48)
Myocardial infarction*	26 (0.12%)	5 (0.05%)	21 (0.16%)	1.98 (0.50-7.93)
Type 1‡	8 (0.04%)	4 (0.04%)	4 (0.03%)	0.67 (0.15-3.01)
Type 2*	18 (0.08%)	1 (0.01%)	17 (0.13%)	23.57 (2.37-234.39)
Revascularization procedure	32 (0.14%)	14 (0.15%)	18 (0.14%)	0.99 (0.25-3.87)
Coronary artery bypass surgery†	5 (0.02%)	3 (0.03%)	2 (0.02%)	1.13 (0.12-10.41)
Percutaneous coronary intervention	28 (0.13%)	12 (0.13%)	16 (0.12%)	1.02 (0.24-4.29)

CI; confidence interval.
*Model was not adjusted for site as a random effect due to limitations in model fitting for low event frequency. Logistic regression was used instead.
†Model was not adjusted for site as a random effect due to limitations in model fitting for low event frequency. Firth logistic regression (due to the very rare outcome) was used instead.
‡Model was not adjusted for time because initial start due to limitation in model fitting for low event frequency.

patient populations. Although beyond the scope of our trial's planned primary analysis, this heterogeneity suggests a need for future work on site-specific performance of accelerated protocols.

In conclusion, our application trial of a 0/1-hour accelerated protocol to exclude MI using hs-cTnI did not increase the odds of safe discharge from the ED overall. Within sensitivity analyses, there was increased odds of safe discharge in the accelerated protocol compared to standard care when excluding patients with COVID-19 and also when limiting the accelerated protocol to those who had MI excluded within 1 hour. However, in those who did not have MI excluded within 1 hour, there was a decrease in the odds of safe discharge. Finally, the introduction of the accelerated protocol was not inferior to standard care regarding 30-day rates of death or MI.

James McCord and Joseph Miller had full access to all of the data and take responsibility for the integrity of the data and accuracy of the data analysis.

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Author contributions: JiMc, JoMi, BC, NM, SM, PL, and SK conceived the study, and designed the trial. SP, KN, HK, RG, AL, MH, GP, BZ, DL, and HK adjudicated endpoints (myocardial infarction and death). SD, AT, ET, and CK provided statistical advice on study design and analyzed the data. All other authors were involved with either data collection or assisting in the implementation of the new protocol. JiMc drafted the manuscript and all authors contributed to its revision. JiMc takes responsibility for the paper as a whole. JoMi takes final responsibility of the data in the manuscript.

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