The Limit of Detection in the Emergency Department Trial (LEGEND): A Stepped-Wedge Cluster Randomized Trial to Rule Out Acute Myocardial Infarction and Reduce Hospital Length of Stay for Patients Presenting to the Emergency Department

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Study objectives: The Limit of Detection in the Emergency Department (LEGEND) rule-out strategy integrates high-sensitivity cardiac troponin assay concentrations with shared decision making to rapidly assess emergency patients with suspected acute coronary syndrome (ACS). We hypothesized that the LEGEND rule-out strategy would reduce length of stay (LOS), increase the proportion of patients safely discharged within 4 hours, reduce cardiac testing, and decrease hospital representations, while maintaining patient safety.

Methods: We conducted a stepped-wedge cluster randomized controlled trial in 4 Australian emergency departments from August 2019 to July 2020. We included adult patients presenting with suspected ACS. We randomized sites to implement the LEGEND strategy. The primary outcome was LOS. Secondary outcomes included discharge from hospital within 4 hours, cardiovascular tests, representations, index, and 30-day events.

Results: The study included 9,944 patients, 5,347 in the standard care and 4,597 in the intervention arm. For patients in the LEGEND cohort (presentation troponin $\leq$2 ng/L), the mean LOS was 3.6 hours shorter in the intervention arm than the standard care arm (95% confidence interval [CI] 2.5 to 4.6 hours). The proportion of patients safely discharged within 4 hours increased by 22.9% (95% CI 19.5% to 26.3%), and cardiac testing decreased by 7.8% (95% CI 4.6% to 11.1%). There were no differences in representations, index events, or 30-day events.

Conclusion: The LEGEND rule-out strategy safely ruled out acute myocardial infarction, reduced hospital LOS, increased the proportion of patients discharged within 4 hours, and reduced cardiac testing. [Ann Emerg Med. 2026;87:424-434.]

Please see page 425 for the Editor's Capsule Summary of this article.

Keywords: High-sensitivity troponin, Acute myocardial infarction, Shared decision making, Limit of detection, Acute coronary syndrome.

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INTRODUCTION

Background

Acute coronary syndrome (ACS) is the most common acute presentation of coronary heart disease and the largest single cause of death.[1] More than 1,200 patients present to Australian emergency departments (EDs) every day for investigation of suspected ACS, accounting for approximately 6% of the 7.8 million annual ED visits.[2] However, fewer than 15% of these cases are diagnosed with ACS.[3] Current assessment guidelines effectively exclude the severe, life-threatening condition of acute myocardial infarction (AMI) with high accuracy.[4] To achieve this, they incorporate multiple components, including clinical history, ECGs, and serial cardiac

Editor's Capsule Summary

What is already known on this topic

Chest pain evaluations are common and often take hours.

What question this study addressed

Does the Limit of Detection in the Emergency Department (LEGEND) rule-out strategy safely reduce emergency department (ED) length of stay for patients with suspected acute coronary syndrome?

What this study adds to our knowledge

In a stepped-wedge cluster randomized controlled trial in 4 Australian EDs, the intervention safely reduced the mean length of stay by 3.6 hours (95% confidence interval 2.5 to 4.6 hours).

How this is relevant to clinical practice

When validated, this shared decision making/single high-sensitivity troponin strategy may foster faster ED chest pain evaluations.

troponin testing.[5] Many patients are then referred for functional testing for myocardial ischemia or imaging for coronary atherosclerosis.[5] This process is lengthy and may contribute to ED and hospital crowding.[3]

Importance

The use of high-sensitivity cardiac troponin assays (hs-cTn) allows for expedited ACS assessment. These assays provide precise results well below the 99th percentile of healthy populations, improving the detection and quantification of cardiomyocyte injury.[6] Approximately 30% to 50% of patients have hs-cTn concentrations below the limit of detection using both laboratory and point-of-care assays, placing them at low risk for short and long-term events.[7-9] Clinicians can use this threshold to rule out AMI with a high negative predictive value (NPV, >99.5%).[7,8] However, much of the research supporting limit of detection strategies has been observational, measuring hs-cTn without guiding patient care. Implementation of a limit of detection strategy into standard care, preferably within a randomized controlled trial, is required to provide robust evidence for this strategy.

ACS assessment is protocolized and relies heavily on clinician-defined estimates of acceptable risk, often overlooking individual patient preferences. Shared decision making, where patients and physicians collaborate on care decisions, is one approach that incorporates patient preferences into chest pain assessment.[10] Combining shared decision making with an limit of detection strategy could increase protocol compliance and align assessments more closely with patients' values and preferences.

Goals of This Investigation

This paper presents a randomized controlled trial of chest pain assessment strategy applied immediately on ED presentation to rule-out AMI. The strategy, termed Limit of Detection in the Emergency Department (LEGEND), integrates hs-cTn concentrations measured on presentation with shared decision making. We hypothesized that the LEGEND rule-out strategy would reduce length of stay (LOS), increase the proportion of patients safely discharged within 4 hours, reduce cardiac testing, and reduce the number of representations to hospital, while maintaining patient safety (as evidenced by no change in AMI diagnosis).

METHODS

Study Design and Setting

We conducted a stepped-wedge, cluster randomized trial in 4 hospitals in Queensland, Australia. We used a stepped-wedge design because the intervention was implemented for the entire department rather than individual patients, making patient-level randomization unsuitable. This design also ensured that the entire eligible patient cohort was enrolled, rather than being limited to those able or willing to provide individual consent. The stepped-wedge design helped to reduce the risk of crossover contamination where the intervention becomes incorporated into the standard care arm. Importantly, the design allowed us to evaluate the intervention under real-world implementation conditions, capturing both effectiveness and feasibility across diverse hospital settings. Each hospital represented one cluster, and each cluster was randomized to a treatment sequence. The economic effect of this trial has been previously reported.[11]

Each hospital started with a usual care phase to provide data on current practice and patient outcomes. The usual care phase was followed by a 4-week implementation phase, during which education was provided to clinical teams on the clinical practice change. We continued to deliver education throughout the intervention phase. We randomized hospitals to start the implementation phase 2, 3, or 4 months after study commencement. Data were collected for 6 months at 3 hospitals and ceased earlier at 4 months for one site in response to the COVID-19 pandemic. The decision to cease data collection approximately 8 weeks earlier than planned at one hospital was due to local impacts of the COVID-19 pandemic at that site. The pandemic significantly changed

the number of participants presenting to the ED at that facility and the ability of staff to be in the department to collect data due to changes in local regulations.

At the start of the trial, we randomized hospitals to treatment sequences, where each treatment sequence defined the timing of the intervention. A statistician (JG) randomized the treatment sequences using R software. Blinding of the intervention timing was not possible. A Human Research Ethics Committee (HREC) approved the study protocol (HREC/2018/QRBW/45352). The trial was prospectively registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12618001833257). The HREC approved a waiver of consent for participants in this study as the use of early rule-out strategies based on a single troponin below the limit of detection was included in existing clinical guidelines, the intervention was implemented at the hospital level, and the shared decisionmaking component allowed patients to choose whether to undergo accelerated assessment. The trial was reported in accordance with the guidelines for stepped-wedge cluster randomized trials (Table E1, available at http://www.annemergmed.com).

Selection of Participants

We included patients if they were aged ≥18 years, and the treating physician investigated for suspected ACS. Senior research nurses reviewed all patients with troponin tests in the ED to determine whether clinicians were investigating suspected ACS. Assessments were based on troponin patterns, ECGs, other cardiac investigations, and the documented ED differential diagnoses. Patients were included even if multiple diagnoses were considered. Ambiguous cases were discussed within the research nurse team to reach consensus, ensuring consistency of inclusion.

We excluded patients if they were transferred from another hospital that had high-sensitivity troponin, or had already been recruited to the study. We included patients if they were transferred from a hospital where troponin was measured using a sensitive point-of-care assay (eg, small rural hospitals) provided that the treating hospital conducted an assessment for ACS. We collected data between August 12, 2019 and July 31, 2020. Dates for individual hospitals are provided in Table E2 (available at http://www.annemergmed.com).

Standard Care

In the usual care phase, clinicians managed patients according to standard care as per their local hospital's documented clinical pathways. These pathways differed slightly at each hospital but were all based on the Australian clinical guidelines for the management of ACS 2016.[5] This guideline included risk stratification based on clinical characteristics, serial troponin testing, and serial ECGs. Patients were then referred for further inpatient or outpatient testing. All sites used the Beckman Coulter Access cardiac troponin I high-sensitivity troponin assay. The clinical sex-specific 99th percentile upper reference limits used for the assay were 10 ng/L for women and 20 ng/L for men, with a limit of detection at 2 ng/L.[12]

Intervention

The focus of the intervention was patients with a presentation hs-cTn at or below the limit of detection (≤2 ng/L, the LEGEND cohort). For these individuals, clinicians used a shared decisionmaking form to determine whether the patient preferred early discharge or to undergo further investigation before discharge. Clinicians used the form to support collaborative decisionmaking with the patient regarding further assessment and management.

For patients who were discharged, we sent a standardized discharge summary to the patient's primary care physician. An action plan for use in case of recurrent symptoms was incorporated. Patients with ischemic ECGs were not eligible for early discharge. Patients with pain onset less than 2 hours prior to assessment could be included only if they had an hs-cTn taken 2 or more hours after symptom onset. For patients with an hs-cTn>2 ng/L, assessment occurred as per standard care. Education of hospital staff was undertaken before and during the intervention period. This education was face to face and included information about troponin testing, the cohorts who require serial troponin testing, and the risks and benefits of functional or objective testing. Most hospitals used exercise stress testing (EST) as the first-line investigation for chest pain assessment. We provided data on the risks associated with this testing and the low utility of this test for low-risk patients. To ensure consistency, the education was delivered by 2 members of the study team who jointly developed a standardized education package. This package included a single PowerPoint presentation and accompanying speaker notes, which were used at all participating hospitals to provide uniform content and messaging. Research staff worked in the participating EDs throughout the intervention period to answer staff questions and provide ongoing education.

Public and Patient Involvement

We developed a shared decision form based on existing literature.[13] This form included a pictorial representation

of the risk of having ACS given current assessment findings, the risks associated with undergoing further testing, and information about options available (no further testing, further testing, or letting the physician decide). Members of a local consumer advisory group reviewed the form. They sought the advice of patients who had undergone chest pain assessment and redesigned the form to align with patient recommendations (Figure E1, available at http://www.annemergmed.com).

Data Collection

Designated trained research staff collected data throughout the trial. With the intervention being implemented at the hospital level, we could not collect data on whether individual patients were investigated using a chest pain assessment strategy or whether they were eligible for early discharge based on the LEGEND protocol. As such, research staff reviewed the medical records for every patient with a troponin test ordered within the ED. If the research staff identified that the treating team had investigated the patient for suspected ACS, they collected clinical information for this patient. We classified patients with a troponin $\leq$2 ng/L (termed the LEGEND cohort) as the intervention group and included them in the analyses.

Research staff collected data using a standardized case report form with precisely defined variables. These staff were routinely monitored and retrained if any errors in data collection were found. Data collectors could not be blinded to study hypotheses, but none of the endpoints were subjective. We collected information on baseline demographics, cardiac risk factors, prior medical history, ECG results, troponin tests, results from anatomical or functional testing, ED and hospital LOS, disposition information, and discharge diagnosis. Where data were missing on demographics, risk factors, or medical history, data collectors either obtained this information directly from the patient during follow-up or identified the data as "unknown." A member of the study team reviewed the data collected for the first 100 patients. There was perfect agreement on the primary study endpoint (LOS).

Six months after the initial presentation, research staff reviewed the statewide hospital database to identify whether the patient had further troponin testing, outpatient cardiac investigations, or admissions to a public hospital for chest pain assessment. This database, which was reviewed for all patients, contains data for hospital presentations, laboratory results, and investigations for every presentation to a public hospital throughout the state. Within our health care system, each patient is assigned a unique study number, which we used to interrogate this database. The validity of this database for research has not been formally established. However, standardized data collection at the point of clinical care, routine quality checks, comprehensive coverage, and widespread use in clinical care and health service reporting suggest it is reliable. Where appropriate, we then phoned patients to identify whether they had visited their general practitioner, a private cardiologist, or a private hospital within 6 months. This information was obtained for 78.2% of patients. Patients were not called if they had evidence in the patient's medical record or online database of reduced mental capacity, a history of dementia, no fixed address, or previous alerts for aggression.

Outcomes

Our primary outcome was hospital LOS for patients with troponin concentrations $\leq$2 ng/L from the first sample taken in the ED. We calculated hospital LOS as the difference between the date and time of hospital discharge and hospital arrival. Prespecified secondary outcomes were as follows: (1) the proportion of patients discharged from the hospital within 4 hours of presentation without a subsequent AMI within 30 days (early discharge); (2) the number of patients with cardiovascular tests performed, defined as stress testing, echocardiography, coronary angiography, or computed tomography coronary angiography; (3) the number of representations to the hospital within 6 months; (4) a composite endpoint of all-cause mortality, AMI, or unplanned revascularization during the index admission; and (5) a composite endpoint of all-cause mortality, AMI, or unplanned revascularization within 30 days. Each outcome was considered for both patients with presentation troponin $\leq$2 ng/L and the overall cohort. Although the intervention primarily targeted low-risk patients (troponin $\leq$2 ng/L), it was implemented at the hospital level and included education about both expediting assessment for low-risk patients and the broader risks and benefits of testing. Therefore, analyzing the entire cohort provides insight into the broader effect of implementation on ED resource utilization and patient flow. Including all patients with suspected ACS captures potential spillover effects and reflects the real-world influence of system-level changes in clinical practice.

Endpoint Adjudication

A senior clinician adjudicated patients who had at least one hs-cTn concentration >99th percentile. The clinician based their adjudication on a review of all available information up to 6 months after the initial presentation. This information included 12-lead ECG, further cardiac

investigations or procedures, hs-cTn results, and clinical presentation. A second review was conducted if the clinician requested a second opinion due to the case's complexity. The diagnosis of AMI was defined according to the Fourth Universal Definition of myocardial infarction.[14] It required a rise and/or fall in cardiac troponin with at least one concentration >99th percentile (using the Beckman Coulter Access cardiac troponin I hs-cTn assay with sex-specific cutpoints). Patients with only a single troponin could be diagnosed with AMI if that concentration was >99th percentile. In addition, AMI criteria required were as follows: (1) acute ischemic symptoms, (2) development of pathological Q waves in the 12-lead ECG, (3) ECG changes indicative of new ischemia, (4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, or (5) identification of an intracoronary thrombus by angiography or autopsy.[14]

We further classified patients with AMI as type 1 or 2 myocardial infarction. Type 1 myocardial infarction is AMI related to atherosclerotic plaque disruption. Type 2 myocardial infarction is a result of ischemia caused by an imbalance between myocardial oxygen supply and demand without atherothrombosis. If no clear cause for supply/demand balance was identified, type 2 myocardial infarction was not supported. Patients with a troponin concentration >99th percentile who did not meet the criteria for type 1 myocardial infarction or type 2 myocardial infarction were defined as having an acute or chronic myocardial injury.[14]

Analysis

We anticipated recruiting an average of 3,000 patients per site, with 30% of these having a presentation troponin below the limit of detection (1,000 per site). The average LOS for patients with an hs-cTn below the limit of detection at the lead study site was 19 hours before study commencement. The target sample size was estimated to give a statistical power of >95% to detect a 4-hour reduction in LOS. This calculation used a two-sided statistical significance level, an intraclass correlation from 0.01 to 0.05, and a stepped-wedge design.

Analyses were conducted using Stata (version 17, StataCorp) and RStudio (version 4.4.1). R Coding is available from https://github.com/RWParsons/lod-edt. We modeled the primary outcome of hospital LOS for the LEGEND cohort as a count variable in a regression model with a negative binomial error structure. We conducted 2 sets of analyses. First, unadjusted regression analyses were performed, with the outcome regressed on intervention (standard care versus LEGEND). From these models, we used Stata's margins command to calculate marginal means for each group, the difference between means, and 95% confidence intervals (CIs) for the difference. In the absence of covariates, these marginal means reflect observed means. Second, an adjusted model was performed that included intervention, time since the commencement of the intervention (to model potential linear trends across time), and the interaction between intervention (standard care versus LEGEND) and time since commencement of the intervention (to model changes in the effect of time after implementation). The time since commencement of the intervention was calculated as the time of presentation minus the intervention commencement date in days, with presentations occurring before implementation assigned negative values. Age and sex were also included in the model, with age being modeled with a b-spline (with 3 degrees of freedom) to enable any nonlinear effects to be modeled based on the data. The adjusted model was specified as a mixed model, incorporating a random intercept for hospital, and a random effect for the interaction of intervention and time by hospital to account for site-level variation in protocol uptake across time. For adjusted models, marginal means for each group were calculated. The difference between marginal means with 95% CIs was reported.

We modeled secondary outcomes using regression with either a negative binomial (hospital LOS), Poisson (representations) or binomial (early discharge, cardiac tests, and mortality) error structure. Unadjusted differences were reported for all secondary outcomes. Adjusted analyses were also performed for early discharge. Adjusted analyses were performed for this secondary endpoint as it provided valuable information about the safety and efficiency of the protocol. We did not adjust the remaining secondary outcomes to avoid overfitting and model instability in a study not powered for these exploratory analyses. There were no missing data for the primary endpoint (LOS), early discharge, cardiac tests, or representation.

RESULTS

Characteristics of Study Subjects

We identified 13,679 patients who met the inclusion criterion for this study and excluded 3,735 based on predefined criteria. Thus, the final cohort included 9,944 patients, 5,347 in the standard care and 4,597 in the intervention arm (Figure 1). Table 1 shows baseline characteristics of the LEGEND cohort. Table E3 (available at http://www.annemergmed.com) provides baseline

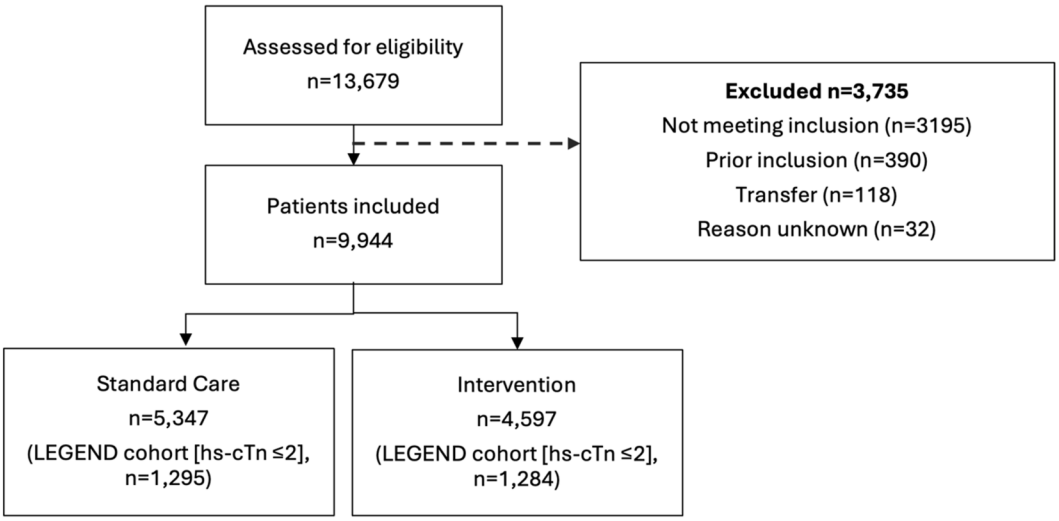

Figure 1. Patient flow.

characteristics for the overall cohort. The standard care and intervention cohorts were similar in age, sex, risk factors, and history. The proportion of Indigenous Australians (8.8% in the LEGEND cohort and 8.1% in the overall cohort) is higher than the Australian population as a whole, according to the 2021 census (3.2%).[15] The intervention cohort had a slightly higher proportion of Indigenous Australian patients (9.6%) than the standard care arm (6.8%). The proportion of women with an hs-cTn ≤2 ng/L (34.1%) was higher than that of men (18.1%).

Main Results

Figure E2 (available at http://www.annemergmed.com) provides the distribution of LOS for both cohorts. For patients in the LEGEND cohort, the mean hospital LOS (the primary endpoint) was shorter in the intervention compared with the standard care arm (mean difference 3.6 hours, 95% CI 2.5 to 4.6; see Table 2). A significant reduction in LOS remained after adjustment for time from the start of the intervention, age, and sex (mean difference: 2.2 hours, 95% CI 0.4 to 4.0 hours, see Figure 2). Additional model parameters are provided in Table E4 (available at http://www.annemergmed.com).

We observed an increase in the proportion of LEGEND patients discharged within 4 hours from 18.5% in the standard care arm to 41.4% in the intervention arm (mean probability difference 22.9%, 95% CI 19.5% to 26.3%). This difference remained significant after adjustment (mean probability difference 14.2%, 95% CI 1.6% to 26.8%). ED LOS was reduced by 97 minutes (95% CI 79 to 115 minutes).

The proportion of patients undergoing cardiac testing (Table 2) was lower in the intervention compared with the standard care group (mean probability difference 7.8%, 95% CI 4.6% to 11.1%). This difference was driven by a reduction in EST (18.2% versus 10.6%, mean probability difference 7.6%, 95% CI 4.9% to 10.3%). There were no differences between standard care and intervention groups on the number of representations within 6 months.

We found no difference between standard care and intervention groups for death, myocardial infarction, or unplanned revascularization during the index admission (mean probability difference 0.2%, 95% CI –0.1% to 3.7%), or at 30 days (mean probability difference –0.1%, 95% CI –0.5% to 0.1%; see Table 2). Table E5 (available at http://www.annemergmed.com) provides a breakdown of endpoints in each group. Two patients in the LEGEND cohort had an AMI, both were in the standard care arm (Table E6, available at http://www.annemergmed.com). Thus, a single troponin ≤2 ng/L yielded a sensitivity of 99.8% (95% CI 99.1% to 100%) and an NPV of 99.9% (95% CI 99.7% to 100%) for index events. These individuals both had ischemic changes on ECG (ST depression and biphasic T waves) and, thus, would not have been eligible for early discharge under the LEGEND protocol. Two additional patients (1 standard care and 1 intervention) had an event within 30 days. The patient in the standard care arm had UAP during their initial presentation and then returned 29 days later with type 2 myocardial infarction from coronary spasm. The patient in the intervention arm was discharged with no cause for their chest pain found. This individual had elected for further testing and underwent serial troponins in ED before being referred for outpatient EST. The patient

Table 1. Baseline characteristics for patients with troponin ≤2 ng/L (LEGEND cohort).

Characteristic	Standard Care (n=1,295)	Intervention (n=1,284)
Age (y), mean (SD)	43.6 (14.3)	44.0 (13.9)
Age range	18-86	18-85
Male, n (%)	470 (36.3%)	451 (35.1%)
Indigenous Australians, n (%)	99 (7.6%)	127 (9.9%)
Age of Indigenous Australians	40.7 (12.4)	42.2 (12.1)
Risk factors, n (%)		
Smoker	314 (24.2%)	284 (22.1%)
Family history of AMI	290 (22.4%)	245 (19.1%)
Hypertension	228 (17.6%)	248 (19.3%)
Dyslipidemia	230 (17.8%)	201 (15.7%)
Diabetes	108 (8.3%)	115 (9.0%)
Medical history, n (%)		
Prior AMI	36 (2.8%)	36 (2.8%)
Prior CAD	78 (6.0%)	69 (5.4%)
Prior CABG	7 (0.5%)	6 (0.5%)
Prior angioplasty	34 (2.6%)	28 (2.2%)
Presentation ≥2 hours, n (%)	879 (78.0%)	855 (77.7%)
Median initial troponin ng/L (IQR)	2 (1-2)	2 (1-2)
Median min to first troponin minute (IQR)	44 (28-73)	37 (23-64)
Single troponin testing, n (%)	327 (25.3%)	766 (59.7%)
Median systolic blood pressure, mmHg (IQR)	129 (118-141)	130 (118-145)
Median pulse rate, beats/min (IQR)	78 (68-89)	78 (69-88)
Median creatinine, μmol/L (IQR)	69 (59-80)	70 (60-81)

AMI, Acute myocardial infarction; *CABG*, coronary artery bypass graft; *CAD*, coronary artery disease; *IQR*, interquartile range.
There were 352 patients with unknown time of chest pain onset. There were also missing data for systolic blood pressure (n=239), pulse rate (n=225), and creatinine (n=24).

Table 2. Outcomes for patients with troponin ≤2 ng/L (LEGEND cohort).

Outcome	Standard Care (n=1,295)	Intervention (n=1,284)
Mean hospital LOS, h(SD)	14.2 (35.0)	10.7 (24.0)
Mean ED length of stay, min (SD)	427 (344)	330 (259)
Discharge within 4 h (no 30-d event), n (%)	240 (18.5%)	532 (41.4%)
Inpatient admission, n (%)	202 (15.6%)	146 (11.4%)
Number of presentations per patient, mean (SD)	0.2 (1.0)	0.2 (0.6)
Cardiac testing within 6 mo, n (%)	353 (27.3%)	249 (19.4%)
Revascularization, n (%)		
PCI	3 (0.2%)	3 (0.2%)
CABG	0 (0%)	0 (0%)
Clinical outcomes, n (%)		
Index event	2 (0.2%)	0 (0.0%)
30-d event	3 (0.2%)	1 (0.1%)
Index mortality	0 (0.0%)	0 (0.0%)
30-d mortality	0 (0.0%)	0 (0.0%)

CABG, Coronary artery bypass graft; *ED*, emergency department; *IQR*, Interquartile range; *LEGEND*, Limit of detection in the Emergency Department; *LOS*, length of stay; *PCI*, percutaneous coronary intervention.

developed ST elevation while undergoing EST 13 days later.

Overall Cohort

For the overall cohort, there was a reduction in LOS for unadjusted analyses (mean difference 3.9 hours, 95% CI 1.7 to 6.0; Table E7, available at http://www.annemergmed.com). However, this difference became nonsignificant after adjustment (mean difference 2.5 hours, –1.2 to 6.2 hours). There was an increase in the proportion of patients discharged early in both unadjusted (mean probability difference=9.6%, 95% CI 8.1 to 11.0) and adjusted analyses (mean probability difference 9.2%, 95% CI 3.0% to 15.4%; see Figure 3). ED LOS was reduced by 72 minutes (95% CI 62 to 82 minutes).

A reduction in testing was seen in the overall cohort (38.2% versus 34.8%, mean probability difference 3.5%, 95% CI 1.6% to 5.4%). This reduction was due to a reduction in EST (mean probability difference 3.6%, 95% CI 2.3% to 4.8%). There were no differences between standard care and intervention groups on the number of representations within 6 months. We found no difference between standard care and intervention groups for death, myocardial infarction, or unplanned revascularization during the index admission (mean probability difference 0.5%, 95% CI –0.6% to 1.6%), or at 30 days (mean probability difference 0.5%, 95% CI –0.7% to 1.6%).

LIMITATIONS

There were some limitations to this study. First, we ceased data collection at one site after 4 months (rather than 6 months) due to the effect of the COVID-19 pandemic. Although we consider this unlikely to have affected study results, any effect is unknown. Second, the power calculation for the primary endpoint (hospital LOS) was based on 12,000 patients, with 4,000 in the limit of

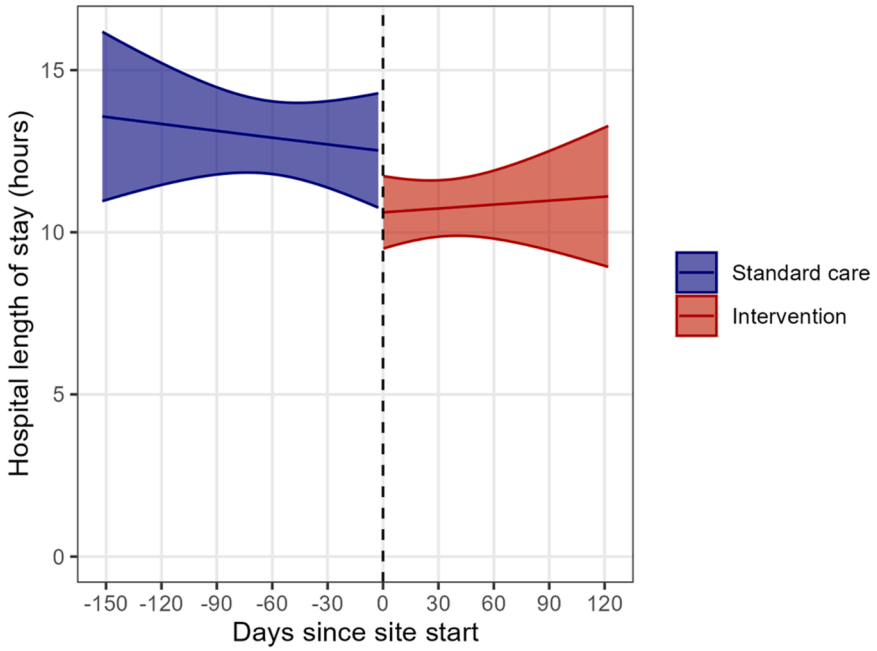

Figure 2. Hospital length of stay for the LEGEND cohort. Shaded areas represent 95% CIs. Model adjusted for age, sex, days since site start, and the interaction between time and intervention. Mean difference is 2.2 hours (95% CI 0.4 to 4.0 hours, P=.01).

detection group. The number of patients recruited was less than anticipated (2,579 limit of detection patients and 9,944 total patients). Despite this reduction in power, we still reported a significant reduction in LOS. Third, in the intervention phase, only two-thirds of the patients with troponin $\leq$2 ng/L underwent single troponin testing. As data were collected from patient medical records, we were not always able to determine whether patients had serial testing due to shared decision making, whether the patient met an exclusion criterion (eg, ECG findings), or due to

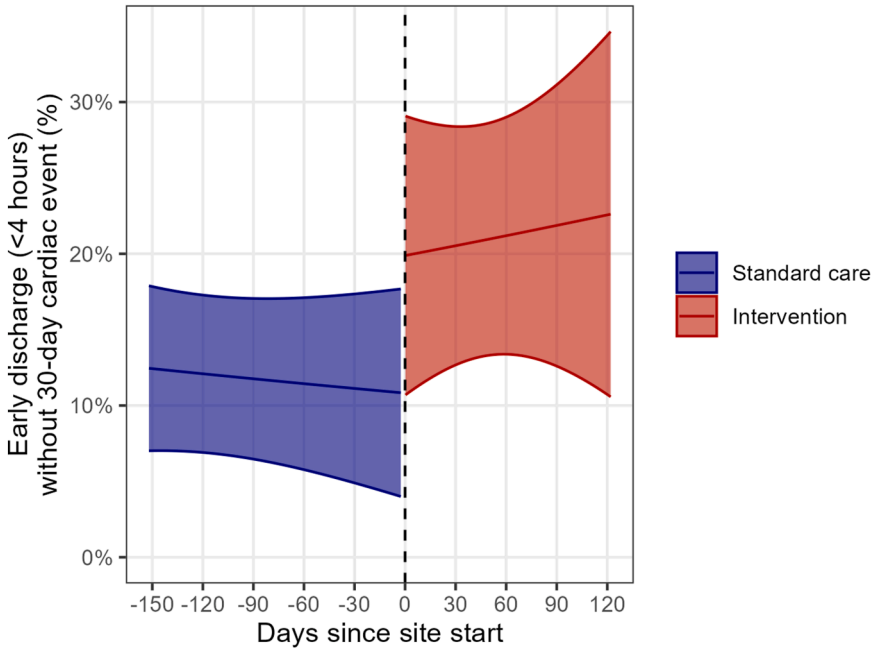

Figure 3. Early discharge within 4 hours for the entire cohort. Shaded areas represent 95% CIs. Model adjusted for age, sex, days since site start, and the interaction between time and intervention. Mean probability difference is 9.2% (95% CI 3.0% to 15.4%, P<.01).

physician noncompliance with the protocol. This means we were unable to perform a per-protocol analysis or compare differences between an intention-to-treat and a per-protocol analysis. We focused on the entire cohort of patients with a troponin ≤2 ng/L, potentially underestimating the effect of the intervention on the target group. Fourth, we did not collect detailed information on shared decision making. That is, patient-preferred decisions were not reported for all patients, and there was no systematic capture of whether clinicians used the shared decision making tool. Data were collected for a small convenience sample (n=215), and in this cohort, the form was used for 89% of patients. It is unclear whether this is representative of the entire study. Fifth, the cohort of patients enrolled is younger than the ACS populations reported in some previous research, potentially limiting the generalizability of results. However, the mean age of the cohort was 57 years, similar to previous randomized trials (mean of 59 years in Rapid assessment of possible acute coronary syndrome in the emergency department with high-sensitivity troponin T study [RAPID-TnT], 59 years in High-Sensitivity cardiac Troponin On presentation to Rule-out myocardial infarction [HiSTORIC], and 53 years in Limit of Detection and ECG Discharge [LoDED]).[16-18] Sixth, a single troponin assay was in use at all sites, potentially limiting generalizability of the study findings. Seventh, we did not collect complete data on the cultural background of our participants. Based on the Australian census data, it is likely that most of the cohort were born in Australia (68.5%), with smaller proportions from England (3.5%), New Zealand (2.3%), India (3.4%), and China (2.6%).[15] Eighth, we cannot exclude the possibility of the Hawthorne effect, whereby awareness of being observed may have influenced clinician behavior and inflated the apparent effect of the intervention.

DISCUSSION

We evaluated a rapid rule-out strategy that combined a single troponin test taken on arrival to ED with shared decision making. After implementing the LEGEND strategy across 4 sites, we observed reduced hospital LOS, a doubling in the proportion of patients discharged within 4 hours, and a decrease in downstream cardiac testing. Importantly, the LEGEND strategy was safe, with only 2 patients (0.08%) who met LEGEND criteria having an AMI within 30 days. This aligns with proportions of patients with AMI seen under standard care in previous research[19] and with previous randomized and observational trials finding that a single troponin below the limit of detection has high diagnostic accuracy for ruling out AMI.[7,17,18,20-26]

The LEGEND strategy reduced hospital LOS and doubled the proportion of patients safely discharged within 4 hours. Existing randomized trials have yielded contradictory results regarding whether rapid rule-out strategies reduce hospital LOS. Both the HiSTORIC and RAPID-TnT trials found a reduction in LOS post-implementation of a rapid rule-out pathway.[16,17] However, these trials differed from LEGEND in their use of serial testing; HiSTORIC included rule-out at 0 or 3 hours, whereas RAPID-TnT required serial testing over 1 hour. The LoDED trial is the only randomized controlled trial focusing on a 0-hour limit of detection strategy and found no increase in the proportion of patients discharged within 4 hours of presentation compared with standard care (46% versus 37%).[18] Notably, the proportion of patients discharged early in the LoDED trial was higher than in both arms of the LEGEND trial and the authors suggest that there may have been contamination, whereby patients in the standard care arm were treated under a limit of detection strategy. The high proportion discharged in the standard care arm may also suggest that limit of detection strategies were more frequently used in the UK hospitals as part of standard care compared to Australia. UK and Australian guidelines have incorporated a single high-sensitivity troponin test since 2016.[5,27] However, the number of Australian hospitals using a single troponin test before the LEGEND study was extremely low.[28] The contradictory findings of existing trials suggest that the increase in efficiency gained by using rapid rule-out strategies depends on the specific model of standard care and the type of rule-out strategy used.

Our study introduced a unique element in the use of shared decision making with a limit of detection strategy. Previous trials of rapid rule-out strategies utilize a protocolized pathway, and quality is judged according to their safety in identifying AMI. A miss rate of <1% is considered acceptable.[29] At this miss rate, the risk of iatrogenic harm from cardiac investigations (2%) outweighs the risk of having a cardiac event.[30] This information is not systematically provided to patients, and patients have limited input into their assessment process. Previous studies focusing on patients' risk tolerance have shown that patients display wide variability in their acceptance of risk.[31,32] Some patients would prefer to avoid the potential harms associated with testing and be discharged earlier with a slightly higher risk of events.[10] We incorporated shared decision making within the LEGEND strategy and found reduced exercise stress testing for low-risk patients.

Our pragmatic trial design had several strengths. First, experienced research staff reviewed charts of all patients with a troponin ordered to ensure that we enrolled the entire cohort of patients investigated for suspected ACS. This minimized the risk of selection bias, ensuring that we did not limit our findings to low-risk patients or those presenting within working hours. Second, because the intervention was implemented at the hospital level, we did not seek individual patient consent. This ensured that an unselected and representative cohort was included and allowed us to accurately determine the effect on the intervention on the health care system. The design also reduced the likelihood of contamination where a limit of detection strategy was applied in the standard care group. Third, our trial incorporated a large sample size, ensuring we had a sufficient number of events to evaluate safety.

Although this study supports the safety and efficiency of the LEGEND rule-out strategy, further research is needed to maximize its effect. Figure 2 suggests a possible return to baseline practices as more time passed after implementation. Further research is needed to determine whether this represents a genuine return to baseline (requiring ongoing education), or simply reflects greater uncertainty due to smaller sample sizes toward the end of the trial. Future studies should explore the cost-effectiveness of implementing this approach on a larger scale, particularly in diverse health care settings. Applying this protocol to lower or higher risk cohorts would likely alter the proportion of patients ruled out, thereby affecting the potential resource utilization and cost savings associated with the strategy. The development and validation of point-of-care assays could also enable the extension of early rule-out strategies beyond hospital environments, such as primary care or the out-of-hospital setting. This study incorporated shared decision making only for low-risk patients. Further studies should focus on applying the shared decision process to all patients investigated for suspected ACS. Systems issues such as departmental processes, competing clinical priorities, and access block may influence patient flow and, therefore, the effect of early rule-out strategies. Future research should explore the interplay between these factors and the ability of clinicians to discharge patients after a single troponin test.

In conclusion, implementing a rule-out strategy based on a single measurement of cardiac troponin at presentation combined with shared decision making was safe, reduced hospital LOS, increased the proportion of patients discharged within 4 hours, and reduced downstream cardiac testing. Adoption of this approach is safe and would reduce the use of resources within the health care system.

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