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Safety of Using Risk Stratification Along With High-Sensitivity Cardiac Troponin in the Emergency Department

A Secondary Analysis

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ABSTRACT

BACKGROUND Implementation of an early rule-out pathway for myocardial infarction using high-sensitivity cardiac troponin to risk stratify patients reduces length of stay and hospital admission. Whether gains are similar in low- and intermediate-risk patients and those discharged were correctly identified as being at lower risk of future cardiovascular events is uncertain.

OBJECTIVES This study sought to evaluate the effectiveness and safety of risk stratification with high-sensitivity cardiac troponin in patients with suspected acute coronary syndrome stratified as low and intermediate risk.

METHODS In this secondary analysis of a stepped-wedge cluster-randomized controlled trial, we evaluated the effectiveness and safety of risk stratification with high-sensitivity cardiac troponin in 31,492 consecutive patients who presented with suspected acute coronary syndrome and identified as low (<5 ng/L) or intermediate (5 ng/L to 99th percentile) risk at presentation. The primary effectiveness outcome was length of hospital stay. The primary safety outcome was subsequent myocardial infarction or cardiac death at 1 year.

RESULTS Of 31,492 patients (59 ± 17 years, 45% women), 17,299 (54.9%) and 14,193 (45.1%) were low and intermediate risk, respectively. Following implementation, length of stay was reduced in low-risk (6.9 ± 3.2 vs 4.7 ± 2.8 hours: difference 2.2; 95% CI: 0.7-3.7 hours) and intermediate-risk (15.8 ± 4.7 vs 11.0 ± 4.9 hours: difference 4.8; 95% CI: 3.8-5.8 hours) patients ($P < 0.001$ for both). Discharge from the emergency department increased in low-risk (62% [4,962 of 7,941] vs 83% [7,747 of 9,358]; adjusted OR: 3.31; 95% CI: 3.06-3.57) and intermediate-risk (36% [2,445 of 6,759] vs 55% [4,095 of 7,434]; adjusted OR: 2.06; 95% CI: 1.92-2.21) patients. Following implementation, patients discharged were at lower risk of myocardial infarction or cardiac death at 1 year (1.5% [112 of 7,407] vs 1.0% [124 of 11,842]; adjusted HR [aHR]: 0.65; 95% CI: 0.50-0.86), whether stratified as low (0.6% vs 0.3%; aHR: 0.46; 95% CI: 0.26-0.83) or intermediate (3.4% vs 2.4%; aHR: 0.74; 95% CI: 0.55-0.99) risk at presentation.

CONCLUSIONS Risk stratification with high-sensitivity cardiac troponin reduced length of stay and increased discharge from the emergency department in both low- and intermediate-risk patients with suspected acute coronary syndrome. Patients discharged from the emergency department were at lower risk of subsequent myocardial infarction or cardiac death at 1 year. (High-Sensitivity Cardiac Troponin on Presentation to Rule Out Myocardial Infarction [HiSTORIC]; NCT03005158) (JACC. 2025;86:1738-1748) © 2025 by the American College of Cardiology Foundation.

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Patients with symptoms suggestive of acute coronary syndrome frequently present to the emergency department but most do not have acute myocardial infarction.[1,2] As assessment places a major burden on health care resources, effective and safe strategies to rule out myocardial infarction earlier have been developed.[3] High-sensitivity cardiac troponin (hs-cTnI) assays with improved analytical performance at low concentrations are central to risk stratification within these early rule-out pathways and are now recommended by international clinical practice guidelines.[4-6]

SEE PAGE 1749

Previous observational studies have demonstrated that high-sensitivity cardiac troponin testing at presentation can risk stratify patients with suspected acute coronary syndrome and identify a large proportion at low risk of cardiac events.[7-15] Risk stratification thresholds have since been incorporated into early rule-out pathways that triage patients as low or intermediate risk of myocardial infarction to guide the decision to discharge or perform further testing.[16-19] We demonstrated in the HiSTORIC (High-Sensitivity cardiac Troponin On presentation to Rule out myocardial InfarCtion; NCT03005158) trial[20] that implementation of high-sensitivity cardiac troponin to risk stratify patients within an early rule-out pathway reduced length of stay by 3 hours and increased discharge from the emergency department by 21%.[17,21] However, the event rate for the safety outcome at 30 days was low and noninferiority was not demonstrated. Whether implementation reduces length of stay and increases discharge in both low- and intermediate-risk patients is unknown, and whether those patients discharged were correctly identified as being at lower risk of future cardiovascular events is uncertain.

In this prespecified secondary analysis of the HiSTORIC trial, we evaluated the effectiveness and safety of implementing risk stratification with high-sensitivity cardiac troponin in patients with suspected acute coronary syndrome stratified as low and intermediate risk.

METHODS

TRIAL DESIGN, STUDY POPULATION, AND INTERVENTION. The HiSTORIC trial was a stepped-wedge cluster-randomized controlled trial of 7 acute care hospitals in Scotland and has been described previously.[7] The hospital site was the unit of randomization and therefore individual patient consent was not sought. All patients were identified by the attending clinician using an electronic form integrated into the care pathway at the time troponin was requested. Consecutive patients were included if they presented to the emergency department with suspected acute coronary syndrome and had a high-sensitivity cardiac troponin I concentration within the normal reference range (less than the sex-specific 99th centile upper reference limit) at presentation. Patients were excluded if they presented with an out-of-hospital cardiac arrest or ST-segment elevation myocardial infarction, had been admitted previously during the trial, or were not a resident in Scotland. All data were collected from the patient record and national registries, deidentified, and linked in a data repository within a Secure Data Environment (DataLoch).

ABBREVIATIONS AND ACRONYMS

ED = emergency department

hs-cTnI = high-sensitivity cardiac troponin

URL = upper reference limit

During a validation phase of at least 6 months, cardiac troponin testing was performed at presentation and was repeated 6 or 12 hours after the onset of symptoms if indicated (standard care). Myocardial infarction was ruled out when high-sensitivity cardiac troponin concentrations were less than the sex-specific 99th percentile at presentation if symptom onset was >6 hours from presentation or after serial testing 6 to 12 hours from symptom onset in those presenting earlier according to clinical guidelines at the time of enrollment.[22,23] Sites were paired based on the expected number of patients at each site and randomized to implement risk stratification with high-sensitivity troponin within an early rule-out pathway (intervention) in 1 of 3 steps during a 6-month randomization phase. Finally, all sites completed an implementation phase of 6 to 9 months calendar-matched to the validation phase where care was guided by risk stratification (Supplemental Figure 1A). The trial was approved by the Scotland Research Ethics Committee and the conduct of the trial was periodically reviewed by an independent trial steering committee.

Throughout the trial and across all sites, care was guided by the Abbott ARCHITECT$_{STAT}$ high-sensitive troponin I assay, which has an interassay coefficient of variation of <10% at 4.7 ng/L[10] and sex-specific 99th centile of 16 ng/L in women and 34 ng/L in men.[24] During the intervention, patients were risk stratified using a validated early rule-out pathway (Supplemental Figure 1B).[17] Patients were identified as low risk if cardiac troponin concentrations were <5 ng/L at presentation and they presented >2 hours from symptom onset. Patients were identified as intermediate risk if cardiac troponin concentrations were between 5 ng/L and the sex-specific 99th percentile at presentation or they presented

within 2 hours of symptom onset. Low-risk patients were eligible for discharge from the emergency department. Intermediate-risk patients underwent additional observation in the emergency department with retesting 3 hours from presentation (~2 hours from the first test) and myocardial infarction was excluded if concentrations were unchanged (<3 ng/L) and less than the sex-specific 99th centile.

STUDY OUTCOMES. The primary and secondary effectiveness outcomes were length of stay, defined as the length of time from presentation to the emergency department until discharge from the hospital, and the proportion discharged from the emergency department, respectively. The primary safety outcome was myocardial infarction (type 1, type 4b, or type 4c) or cardiac death after discharge at 1 year. Other outcomes included cardiac death, cardiovascular death, noncardiovascular death, and reattendance at the emergency department at 1 year. All events occurring within 1 year of discharge from hospital were adjudicated by a panel blind to the study phase, as previously described.[20,25]

STATISTICAL ANALYSIS. The study population was stratified as low risk or intermediate risk at presentation. Baseline characteristics were summarized in low- and intermediate-risk patients, respectively, as count (percentage) for categorical variables and mean ± SD or median (Q1-Q3) for continuous variables as appropriate. In patients who were classified as low and intermediate risk, the primary effectiveness outcome of length of stay was compared before and after implementation of risk stratification using a linear mixed-effects regression model adjusting for season, trial sites (fitted as a random effect), an indicator for whether risk stratification was implemented, age, sex, estimated glomerular filtration rate, and comorbidities including previous myocardial infarction, heart failure hospitalization, ischemic heart disease, diabetes mellitus, and cerebrovascular disease. Length of stay was log-transformed before analysis and results were expressed as a geometric mean ratio. Missing data for these variables was uncommon and therefore regression models were based on those with complete data. The secondary effectiveness outcome was compared using a logistic mixed-effects regression model adjusting for the same variables. Interaction between risk groups and the intervention was explored to assess whether the effectiveness of implementing risk stratification varied by risk groups. The primary safety and all secondary safety outcomes were compared using a cause-specific regression model adjusting for the same variables. These were compared before and after implementation in patients discharged from the emergency department and those admitted to the hospital, with stratification according to risk at presentation. An unadjusted multiple fractional polynomial cause-specific regression model was used to assess the continuous relationship between cardiac troponin at presentation and the primary safety outcome. Exploratory analyses were conducted to evaluate the impact of risk stratification on the effectiveness and safety outcomes in women and men, respectively. All analyses were performed using R version 4.2.0 (The R Foundation for Statistical Computing).

PATIENT AND PUBLIC INVOLVEMENT. The trial steering committee included patient and lay representatives who were involved in the design and conduct of this trial.

RESULTS

STUDY POPULATION. The trial enrolled 31,492 consecutive patients (59 ± 17 years, 45% women) with suspected acute coronary syndrome (Table 1). Of these, 54.9% (17,299 of 31,492) were classified as low risk and 45.1% (14,193 of 31,492) were classified as intermediate risk at presentation with a similar proportion before and after implementation. Compared with intermediate-risk patients, those classified as low risk were younger and had fewer comorbidities. Within each risk group, baseline characteristics were similar before and after implementation.

EFFECTIVENESS OUTCOMES IN PATIENTS STRATIFIED AS LOW OR INTERMEDIATE RISK. In patients classified as low risk at presentation, the primary effectiveness outcome of length of stay was reduced from 6.9 ± 3.2 to 4.7 ± 2.8 hours (difference 2.2 hours; 95% CI: 0.7-3.7 hours; $P < 0.001$) following implementation (Figure 1A). The secondary effectiveness outcome of the proportion of patients discharged from the emergency department increased following implementation from 62% (4,962 of 7,941) to 83% (7,747 of 9,358) (adjusted OR: 3.31; 95% CI: 3.06-3.57; $P < 0.001$) (Figure 1B). Consistent with these observations, the proportion of low-risk patients undergoing serial troponin measurement fell from 37% (2,946 of 7,941) to 17% (1,561 of 9,358) (Table 1).

In patients classified as intermediate risk at presentation, the length of stay was reduced from 15.8 ± 4.7 to 11.0 ± 4.9 hours (difference 4.8 hours; 95% CI: 3.8-5.8 hours; $P < 0.001$) following implementation (Figure 1A). Fewer patients identified as intermediate risk at presentation were discharged from the emergency department but following implementation, the

TABLE 1 Baseline Characteristics of Patients With Suspected Acute Coronary Syndrome Before and After Implementation of Risk Stratification

		Low Risk (n = 17,299)		Intermediate Risk (n = 14,193)	
	(N = 31,492)	Standard Care (n = 7,941)	Risk Stratification (n = 9,358)	Standard Care (n = 6,759)	Risk Stratification (n = 7,434)
Age, y	59 ± 17	54 ± 15	53 ± 15	66 ± 16	65 ± 17
Female	14,252 (45)	3,981 (50)	4,709 (50)	2,594 (38)	2,968 (40)
Presenting symptom					
Chest pain	26,590 (84)	7,147 (90)	8,290 (89)	5,419 (80)	5,734 (77)
Dyspnea	957 (3)	140 (2)	192 (2)	280 (4)	345 (5)
Palpitation	928 (3)	203 (3)	250 (3)	229 (3)	246 (3)
Syncope	1,701 (5)	186 (2)	317 (3)	513 (8)	685 (9)
Other	1,316 (4)	265 (3)	309 (3)	318 (5)	424 (6)
Medical history					
Heart failure	1,919 (6)	200 (3)	185 (2)	833 (12)	701 (9)
Myocardial infarction	2,573 (8)	489 (6)	440 (5)	882 (13)	762 (10)
Ischemic heart disease	7,346 (23)	1,433 (18)	1,305 (14)	2,401 (36)	2,207 (30)
Cerebrovascular disease	1,684 (5)	269 (3)	275 (3)	580 (9)	560 (8)
Diabetes mellitus	1,912 (6)	311 (4)	288 (3)	691 (10)	622 (8)
Previous revascularization					
PCI	2,831 (9)	592 (8)	507 (5)	942 (14)	790 (11)
CABG	452 (1)	78 (1)	75 (0.8)	162 (2)	137 (2)
Medication					
Aspirin	8,023 (25)	1,653 (21)	1,565 (17)	2,461 (36)	2,344 (32)
Dual antiplatelet therapy[a]	1,269 (4)	274 (4)	187 (2)	464 (7)	344 (5)
Statin	12,165 (39)	2,536 (32)	2,540 (27)	3,499 (52)	3,590 (48)
ACEi or ARB	9,769 (31)	1,936 (24)	2,019 (22)	2,840 (42)	2,974 (40)
β-blocker	8,548 (27)	1,754 (22)	1,869 (20)	2,408 (36)	2,517 (34)
Oral anticoagulant[b]	2,167 (7)	314 (4)	310 (3)	719 (11)	824 (11)
Electrocardiogram[c]					
Normal	12,035 (74)	3,704 (82)	3,605 (83)	2,414 (63)	2,312 (66)
Myocardial ischemia	3,288 (20)	675 (15)	620 (14)	1,081 (28)	912 (26)
ST-segment elevation	193 (1)	43 (0.9)	32 (0.7)	68 (2)	50 (1)
ST-segment depression	252 (2)	55 (1)	53 (1)	91 (2)	53 (2)
Left bundle branch block	456 (3)	53 (1)	51 (1)	189 (5)	163 (5)
T-wave inversion	1,225 (8)	198 (4)	183 (4)	423 (11)	421 (12)
Laboratory					
Hemoglobin, g/L	137±22	139±18	139±21	134±22	134±25
eGFR, mL/min	81±22	86±19	87±19	75±25	75±24
Presentation cTnI, ng/L	3 (1, 6)	2 (1, 3)	2 (1, 3)	7 (4, 12)	7 (5, 12)
Peak cTnI, ng/L	3 (1, 7)	2 (1, 3)	2 (1, 3)	8 (5, 14)	8 (5, 14)
Serial testing (≥2)	11,904 (38)	2,946 (37)	1,561 (17)	3,594 (53)	3,803 (51)
Time intervals					
Presentation to first, min	66 (45-97)	71 (50-103)	69 (47-102)	61 (42-90)	60 (39-91)
First to second, min	351 (188-553)	390 (219-552)	267 (164-441)	509 (306-626)	215 (152-389)

Values are n (%), mean ± SD, or median (Q1-Q3). [a]Two medications from aspirin, clopidogrel, prasugrel, or ticagrelor. [b]Includes warfarin or novel oral anticoagulants. [c]Proportions reported for the 16,217 (51%) participants with electrocardiogram data available.

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; cTnI = high-sensitivity cardiac troponin I; eGFR = estimated glomerular filtration rate; PCI = percutaneous coronary intervention.

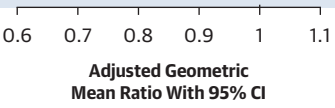
proportion increased from 36% (2,445 of 6,759) to 55% (4,095 of 7,434) (adjusted OR: 2.06; 95% CI: 1.92-2.21; $P < 0.001$) (Figure 1B). Although the proportion of intermediate-risk patients undergoing serial troponin measurement was similar at 53% (3,594 of 6,759) and 51% (3,803 of 7,434) before and after implementation, the median time interval between serial measures was reduced from 509 minutes (Q1-Q3: 306-626 minutes) to 215 minutes (Q1-Q3: 152 to 389 minutes) (Table 1).

The strength of the association between implementation of risk stratification and the reduction in

FIGURE 1 Primary and Secondary Effectiveness Outcomes in Patients With Suspected Acute Coronary Syndrome Classified as Low and Intermediate Risk at Presentation Before and After Implementation of Risk Stratification

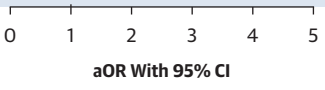
A Primary Effectiveness Outcome of Length of Stay

Groups	Standard Care, Hours Geometric Mean (SD)	Early Rule-Out, Hours Geometric Mean (SD)	Adjusted Geometric Mean Ratio (95% CI)	*P* Value
Low risk	6.9 (3.2)	4.7 (2.8)	0.67 (0.65-0.7)	<0.001
Intermediate risk	15.8 (4.7)	11 (4.9)	0.73 (0.7-0.77)	<0.001



B Secondary Effectiveness Outcome of Discharge From the Emergency Department

Groups	Standard Care, n (%)	Early Rule-Out, n (%)	aOR (95% CI)	*P* Value
Low risk	4,962/7,941 (62%)	7,747/9,358 (83%)	3.31 (3.06-3.57)	<0.001
Intermediate risk	2,445/6,759 (36%)	4,095/7,434 (55%)	2.06 (1.92-2.21)	<0.001



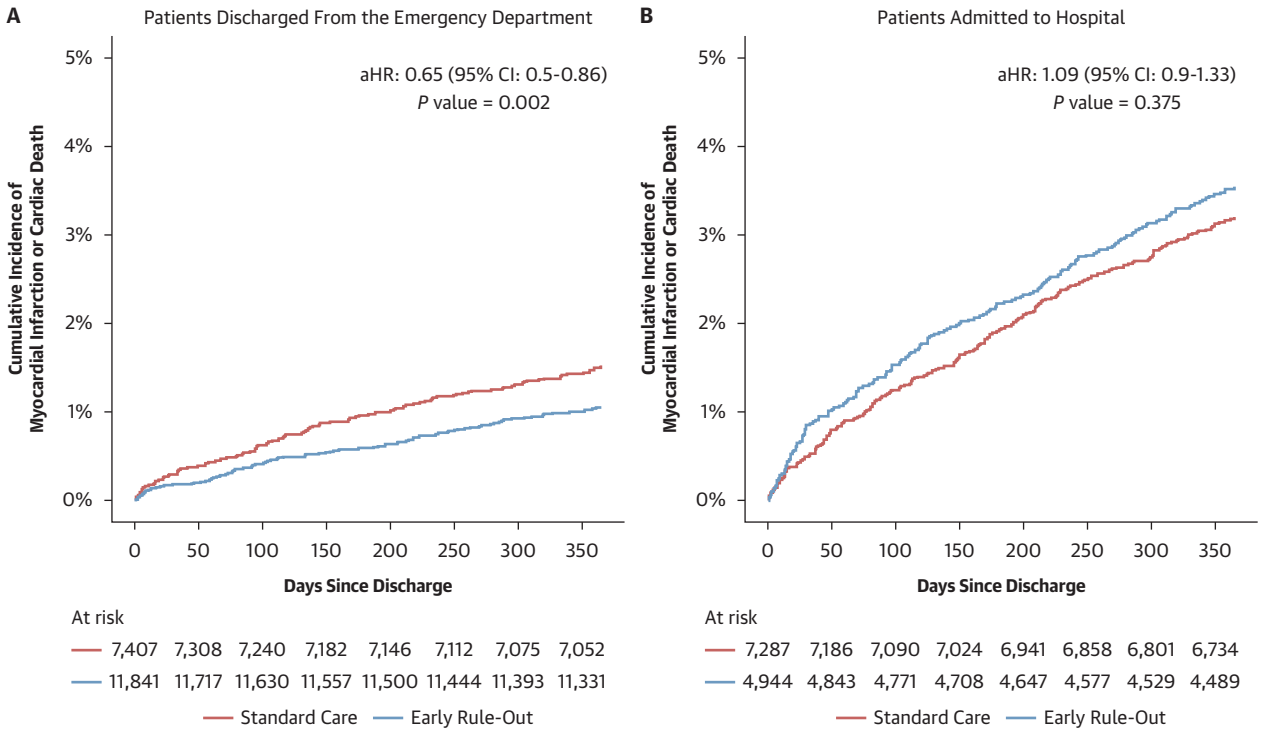
(A) Primary effectiveness outcome of length of stay in patients classified as low (green, cardiac troponin concentration <5 ng/L and >2 hours since symptom onset) and intermediate (orange, 5 ng/L to sex-specific 99th centile or ≤2 hours) risk at presentation. (B) Secondary effectiveness outcome of discharge from the emergency department in patients classified as low (green, cardiac troponin concentration <5 ng/L and >2 hours since symptom onset) and intermediate (orange, 5 ng/L to sex-specific 99th centile or ≤2 hours) risk at presentation. Mixed-effects linear and logistic regression models adjusted for season, trial sites (fitted as a random effect), an indicator variable for whether risk stratification was implemented, age, sex, eGFR, and comorbidities including previous myocardial infarction, heart failure hospitalization, ischemic heart disease, diabetes mellitus, and cerebrovascular disease, were used to compared the primary and secondary effectiveness outcomes, respectively. The regression models were performed in (A) 30,889 of 31,492 (98%) and (B) 30,900 of 31,492 (98%) patients in whom data on all variables were available.

length of stay was similar for low- and intermediate-risk groups ($P_{\text{interaction, risk group} \times \text{intervention}} = 0.176$), whereas the association between implementation and increased discharge from the emergency department was stronger in the low-risk group compared with the intermediate-risk group ($P_{\text{interaction, risk group} \times \text{intervention}} < 0.001$). Compared with standard care, implementation of risk stratification resulted in the discharge of more low-risk patients across all cardiac troponin concentrations below 5 ng/L (Supplemental Figure 2).

SAFETY OUTCOMES IN PATIENTS DISCHARGED FROM THE EMERGENCY DEPARTMENT. Patients discharged from the emergency department were younger with fewer comorbidities than those admitted to the hospital before (n = 7,407) and after (n = 11,842) implementation of risk stratification (Supplemental Table 1). In patients who were discharged, the risk of subsequent myocardial infarction or cardiac death at 1 year was lower after implementation of risk stratification (1.5% [112 of 7,407] vs 1.0% [124 of 11,842], adjusted HR [aHR]: 0.65; 95% CI: 0.50-0.86; $P = 0.002$) (Figure 2A). For comparison, the risk of myocardial infarction or cardiac death at 1 year in patients admitted to hospital was higher and similar before and after implementation of risk stratification (3.2% [233 of 7,293] vs 3.5% [175 of 4,950]; aHR: 1.09; 95% CI: 0.90-1.33; $P = 0.375$) (Figure 2B).

These observations were consistent for the secondary safety outcomes of cardiac death, cardiovascular death, and any hospital reattendance at 1 year, which occurred less often in patients discharged from the emergency department after implementation of risk stratification (Figure 3A). Following implementation, patients discharged from the emergency department were at lower risk of myocardial infarction or cardiac death at 1 year whether stratified as low risk (0.6% [28 of 4,962] vs 0.3% [25 of 7,747]; aHR: 0.46; 95% CI: 0.26-0.83; $P = 0.009$) or intermediate risk (3.4% [84 of 2,445] vs 2.4% [99 of 4,095]; aHR: 0.74; 95% CI:

FIGURE 2 **Cumulative Incidence of Myocardial Infarction or Cardiac Death Following Discharge to 1 Year in Patients Discharged From the Emergency Department and Admitted to Hospital Before and After Implementation of Risk Stratification**



Survival free from myocardial infarction or cardiac death following discharge to 1 year compared in patients who were (A) discharged from the emergency department and (B) admitted to hospital before (red) and after (blue) implementation of risk stratification using a cause-specific regression model adjusting for season, trial sites (fitted as a random effect), an indicator variable for whether risk stratification was implemented, age, sex, estimated glomerular filtration rate, and comorbidities including previous myocardial infarction, heart failure hospitalization, ischemic heart disease, diabetes mellitus, and cerebrovascular disease. The regression models were performed in 18,823 of 19,249 (98%) discharged patients and 12,066 of 12,243 (99%) admitted patients in whom data on all variables were available.

0.55-0.99; $P = 0.046$) at presentation (**Figures 3B and 3C**).

When modeled as a continuous variable, increasing cardiac troponin concentrations at presentation was strongly associated with the risk of experiencing a primary safety outcome, even though values were within the normal reference range (Supplemental Figure 3).

EFFECTIVENESS AND SAFETY OUTCOMES STRATIFIED BY SEX. In an exploratory analysis, the length of hospital stay and the proportion discharged from the emergency department were similar between women and men in both the low- and intermediate-risk groups (Supplemental Figure 4). In those discharged from the emergency department, the primary safety outcome occurred less often after implementation of risk stratification in men (aHR: 0.64; 95% CI: 0.46-0.90; $P = 0.011$) with a similar trend in women (aHR: 0.74; 95% CI: 0.48-1.14; $P = 0.169$). In those admitted to hospital, the primary safety outcome occurred at a similar frequency before and after implementation of risk stratification in women (aHR: 1.21; 95% CI: 0.88-1.68; $P = 0.239$) and in men (aHR: 1.01; 95% CI: 0.79-1.30; $P = 0.922$) (Supplemental Figure 5).

DISCUSSION

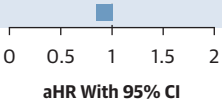
In a prespecified secondary analysis of the HiSTORIC trial, we report the effectiveness and safety of implementing risk stratification with high-sensitivity cardiac troponin in patients with suspected acute coronary syndrome stratified as low or intermediate risk at presentation (**Central Illustration**). Implementation reduced length of stay and hospital admission in both risk groups and was associated with better outcomes in patients discharged from the emergency department.

Several of our findings could inform clinical practice. First, implementation of risk stratification with high-sensitivity cardiac troponin reduced length of stay in the hospital by an average of 2.2 hours in low-

FIGURE 3 Safety Outcomes in Patients Discharged From the Emergency Department Before and After Implementation With Stratification According to Risk at Presentation

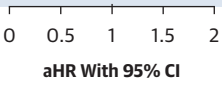
A Patients Discharged From the Emergency Department

Events	Standard Care, n (%) n = 7,407	Risk Stratification, n (%) n = 11,842	aHR (95% CI)	*P* Value
Primary outcome				
Myocardial infarction or cardiac death	112 (1.5%)	124 (1%)	0.65 (0.5-0.86)	0.002
Secondary outcomes				
Myocardial infarction	61 (0.8%)	76 (0.6%)	0.77 (0.54-1.1)	0.148
Cardiac death	54 (0.7%)	54 (0.5%)	0.55 (0.37-0.83)	0.005
Cardiovascular death	87 (1.2%)	86 (0.7%)	0.51 (0.37-0.7)	<0.001
Non-cardiovascular death	230 (3.1%)	383 (3.2%)	0.85 (0.72-1.01)	0.071
Any hospital reattendance	2,105 (28.4%)	3,710 (31.3%)	0.93 (0.88-0.98)	0.012



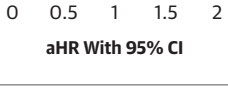
B Low-Risk Patients Discharged From the Emergency Department

Events	Standard Care, n (%) n = 4,962	Risk Stratification, n (%) n = 7,747	aHR (95% CI)	*P* Value
Primary outcome				
Myocardial infarction or cardiac death	28 (0.6%)	25 (0.3%)	0.46 (0.26-0.83)	0.009
Secondary outcomes				
Myocardial infarction	20 (0.4%)	19 (0.2%)	0.53 (0.27-1.02)	0.058
Cardiac death	8 (0.2%)	6 (0.1%)	0.35 (0.11-1.14)	0.083
Cardiovascular death	11 (0.2%)	10 (0.1%)	0.4 (0.16-1.04)	0.06
Non-cardiovascular death	69 (1.4%)	115 (1.5%)	0.87 (0.63-1.19)	0.374
Any hospital reattendance	1,446 (29.1%)	2,576 (33.3%)	0.96 (0.9-1.03)	0.245



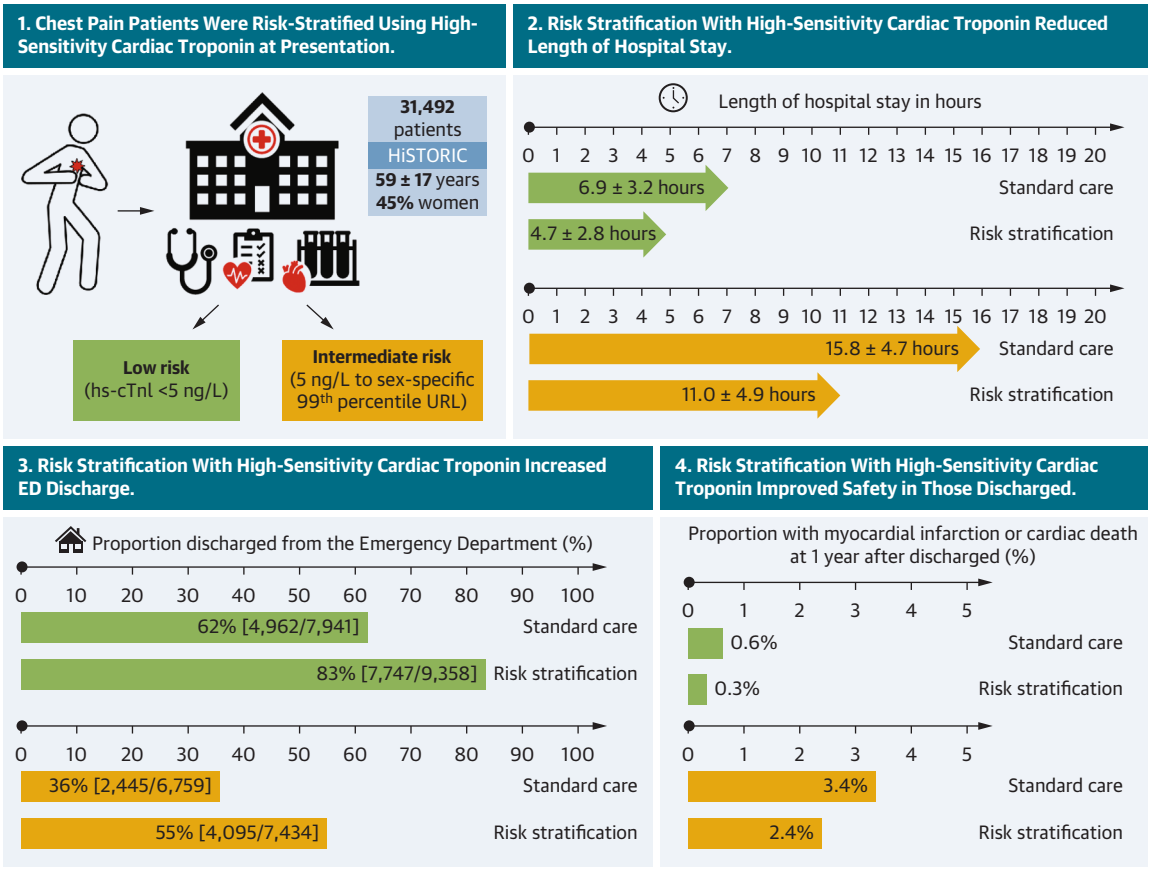
C Intermediate-Risk Patients Discharged From the Emergency Department

Events	Standard Care, n (%) n = 2,445	Risk Stratification, n (%) n = 4,095	aHR (95% CI)	*P* Value
Primary outcome				
Myocardial infarction or cardiac death	84 (3.4%)	99 (2.4%)	0.74 (0.55-0.99)	0.046
Secondary outcomes				
Myocardial infarction	41 (1.7%)	57 (1.4%)	0.92 (0.6-1.39)	0.68
Cardiac death	46 (1.9%)	48 (1.2%)	0.6 (0.39-0.92)	0.019
Cardiovascular death	76 (3.1%)	76 (1.9%)	0.54 (0.38-0.76)	<0.001
Non-cardiovascular death	161 (6.6%)	268 (6.5%)	0.88 (0.72-1.09)	0.243
Any hospital reattendance	659 (27%)	1,134 (27.7%)	0.85 (0.76-0.94)	0.002



Primary and secondary safety outcomes at 1 year in patients with suspected acute coronary syndromes discharged from the emergency department before and after implementation of risk stratification (A). Primary and secondary safety outcomes before and after implementation of risk stratification in patients discharged from the emergency department stratified as low (B) or intermediate (C) risk at presentation. All analyses used a cause-specific regression model adjusting for season, trial sites (fitted as a random effect), an indicator variable for whether risk stratification was implemented, age, sex, estimated glomerular filtration rate, and comorbidities including previous myocardial infarction, heart failure hospitalization, ischemic heart disease, diabetes mellitus, and cerebrovascular disease. The regression models were performed in 18,823 of 19,249 (98%) patients in whom data on all variables were available. Abbreviation as in Figure 2.

CENTRAL ILLUSTRATION **Safety of Risk Stratification With High-Sensitivity Cardiac Troponin in the Emergency Department: A Secondary Analysis of the HiSTORIC Trial**



Li Z, et al. JACC. 2025;86(19):1738–1748.

ED = emergency department; hs-cTnI = high-sensitivity cardiac troponin I; URL = upper reference limit.

risk and 4.8 hours in intermediate-risk patients. This was achieved by halving the number of serial cardiac troponin tests in low-risk patients and by reducing the time interval between serial measurements by two-thirds in intermediate-risk patients. Second, the use of risk stratification increased the proportion of patients discharged from the emergency department from 62% to 83% and from 36% to 55% in those stratified as low and intermediate risk, respectively. Third, those patients discharged from the emergency department were at lower risk of subsequent myocardial infarction or cardiac death after risk stratification was used to guide the selection of patients for discharge. This was consistent in both low- and intermediate-risk patients and for other safety outcomes of cardiac death, cardiovascular death, and hospital reattendance at 1 year, which occurred less often in those discharged from the emergency department after risk stratification was implemented. Exploratory analyses stratified by sex showed similar effectiveness and safety outcomes in women and men. Together our findings demonstrate that the implementation of risk stratification with high-sensitivity cardiac troponin in the emergency department is effective and safe in both low- and intermediate-risk patients with benefits for both patients and health care providers.

Although international guidelines now encourage the use of risk stratification within accelerated diagnostic pathways[26,27] and multiple pathways have been evaluated in observational studies, there are limited data on their efficacy or effectiveness from randomized trials. Two other randomized trials have reported.[28,29] The LoDED (Limit of Detection and ECG

Discharge) trial randomized 632 patients with chest pain to immediate discharge using the limit of detection of a high-sensitivity assay for risk stratification, but this approach did not significantly increase the rate of hospital discharge at 4 hours compared with standard care (46% [141 of 309] vs 37% [114 of 311]).[28] In contrast, the RAPID-TnT (Rapid Assessment of Possible Acute Coronary Syndrome in the emergency department with High-Sensitivity Troponin T) trial compared a 0/3-hour pathway without risk stratification with a 0/1-hour pathway with risk stratification using high-sensitivity cardiac troponin T in 3,378 patients, and demonstrated a reduction in length of stay of 1.2 hours and an increase in discharge from the emergency department (32% vs 45%) when care was guided by risk stratification.[29] Interestingly, the increase in the proportion of patients discharged from the emergency department when risk stratification was used to guide care was similar at 12% and 13% in LoDED and RAPID-TnT, respectively. Neither trial reported efficacy stratified into low- or intermediate-risk groups. Both sought patient consent and therefore may have been influenced by selection bias or the Hawthorne effect whereby lower-risk patients with less to gain are enrolled or direct observation of clinical care by researchers promotes adherence in both arms. Our trial evaluated effectiveness in consecutive patients in whom care was not directly overseen by the researcher. Although it is difficult to compare outcomes between trials directly as the populations enrolled and the care pathways differed, our findings add to these prior reports suggesting that risk stratification with high-sensitivity cardiac troponin can achieve important reductions in length of stay and hospital admission for both low- and intermediate-risk patients.

Accelerating care and reducing hospital admission is important for patients and health care systems, but only if this can be achieved without compromising patient safety. Although the 0/1-hour protocol in the RAPID-TnT trial was not inferior to standard care, the trial did not evaluate safety outcomes in those discharged from the emergency department. Indeed, in a secondary analysis of the RAPID-TnT trial, death or myocardial infarction at 1 year was higher in patients evaluated using the 0/1-hour pathway compared with the 0/3-hour pathway (3.7% vs 2.3%). The HiSTORIC trial did not demonstrate noninferiority for the primary safety outcome at 30 days, in part because of the very low number of events.[20,30] However, our findings from this prespecified secondary analysis are reassuring and suggest that accelerated care and reducing hospital admission does not increase subsequent myocardial infarction or cardiac death at 1 year in either low- or intermediate-risk patients. Indeed, where risk stratification was used to guide the selection of patients for discharge or admission, those discharged from the emergency department were at lower risk of subsequent myocardial infarction or cardiac death at 1 year. Reassuringly, although the absolute increase in discharge from the emergency department was substantial at ~20%, this was not associated with an increase in hospital reattendance. No excess in reattendance for any cause or noncardiovascular death was observed, suggesting that focusing on early discharge of those without myocardial infarction does not contribute to misdiagnosis of noncardiac conditions. Together these findings suggest that the use of risk stratification to guide whether or not to discharge patients from the emergency department improves the identification of those at risk compared with relying on clinical judgment and a “negative” troponin. The higher discharge rate likely reflects increased confidence among clinicians in interpreting high-sensitivity cardiac troponin with a single cardiac troponin test. In contrast, a “negative troponin” does not necessarily confer low risk and, therefore, serial testing and hospital admission is more likely.

STUDY LIMITATIONS. The HiSTORIC trial evaluated the use of a single high-sensitivity cardiac troponin I assay, and whether applying a similar approach to risk stratification using other assays would be effective is unclear.[21,31] Although observational studies suggest this approach can be applied to multiple high-sensitivity cardiac troponin assays,[17,32] the thresholds used for risk stratification are not biologically equivalent and the gains in efficiency for health care systems may differ. However, we note that the length of stay in the standard care arm of our trial was comparable to those observed in other health care settings.[33] Likewise, the HiSTORIC trial evaluated the use of risk stratification within a specific early rule-out pathway that is designed to maximize the proportion of patients discharged using a single cardiac troponin measurement at presentation. Whether similar reductions in length of stay and hospital admission can be safely achieved using other approaches to risk stratification or serial sampling pathways is under evaluation in clinical trials.[34] Unfortunately, information on care following discharge was not recorded, and we do not know whether those patients who were discharged following implementation of risk stratification were more likely to be referred to outpatient services, an important health economic consideration. Furthermore, we were not able to report the proportion of patients who

subsequently underwent coronary angiography before and after implementation of risk stratification. The role of imaging in patients discharged after myocardial infarction is excluded remains uncertain and is currently being evaluated in a randomized controlled trial of coronary computed tomography angiography.[35,36]

CONCLUSIONS

Risk stratification with high-sensitivity cardiac troponin reduced length of stay in both low- and intermediate-risk patients with suspected acute coronary syndrome. Following implementation, discharge from the emergency department increased in both groups and those discharged were at lower risk of subsequent myocardial infarction or cardiac death.

DATA AVAILABILITY The data and analysis code that support the findings of this study are available from the corresponding author on reasonable request.

TRANSPARENCY. The lead authors (Dr Li and Dr Doudesis) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

DISSEMINATION TO PARTICIPANTS AND RELATED PATIENT AND PUBLIC COMMUNITIES. Findings of this study will be shared with clinicians and patients through national and international cardiology conferences, and through social media platforms. A plain-language summary also will be disseminated through a press release.

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KEY WORDS high-sensitivity cardiac troponin, myocardial infarction, risk stratification

APPENDIX For the list of HiSTORIC trial investigators, supplemental figures and tables, HighSTEACS (High-sensitivity Troponin in the Evaluation of patients with Acute Coronary Syndrome) trial protocol, and statistical analysis plan, please see the online version of this paper.

Go to https://www.acc.org/jacc-journals-cme to take the CME/MOC quiz for this paper.