Association of Early Noninvasive Cardiac Stress Testing With Acute Myocardial Infarction and Mortality

Aniket A. Kawatkar, PhD, MS*; Aileen S. Baecker, PhD; Adam L. Sharp, MD, MS; Rita F. Redberg, MD, MSc; Ming-Sum Lee, MD, PhD; Maros Ferencik, MD, PhD; Steve Goodacre, PhD; Praveen Thokala, PhD; Yi-Lin Wu, MS; Chengyi Zheng, PhD; Ernest Shen, PhD; Benjamin C. Sun, MD, MPP

*Corresponding Author. E-mail: aniket.a.kawatkar@kp.org.

Study objective: The evaluation for suspected acute coronary syndrome is a common and high-risk presentation in emergency departments (EDs). After exclusion of acute myocardial infarction (MI), patients often undergo early (within 72 hours) noninvasive cardiac testing. We evaluated the association between early noninvasive testing and death/acute MI in ED patients suspected of acute coronary syndrome.

Methods: We used a retrospective cohort study design within the adult ED patient population (from October 2015 to December 2020) in whom MI was ruled out, belonging to a large integrated health care delivery system. Using data on history (H), electrocardiogram (E), age (A), risk factors (R), and troponin (T), we computed the HEART risk score. We stratified the cohort into low (score 0 to 3), intermediate (score 4 to 6), and high (score $\geq$7) risk and followed them up to 1-year after ED discharge. The association between noninvasive testing within 3 days of the ED visit and composite risk of death/acute MI within 1-year of discharge was evaluated by propensity score analysis.

Results: The cohort included 174,917 patients (61% low risk [age 53; women 58%; noninvasive testing 5%], 36% intermediate risk [age 71; women 52%; noninvasive testing 18%], and 3% high risk [age 74, women 45%; noninvasive testing 23%]). The risk reduction in death/acute MI associated with early noninvasive testing was −1.54% (−1.95% to −1.12%) number needed to treat (NNT)=65; −4.93% (−5.66% to −4.20%) NNT=20, and −8.98% (95% confidence interval -11.32% to −6.64%) NNT=11; and, in the low, intermediate, and high-risk respectively.

Conclusion: Early noninvasive testing was associated with reduced risk of 1-year death or acute MI across all risk groups. [Ann Emerg Med. 2025;86:311-323.]

Please see page 312 for the Editor's Capsule Summary of this article.

Keywords: Acute coronary syndrome, Exercise test, Risk assessment, Heart disease risk factors.

Readers: click on the link to go directly to a survey in which you can provide feedback to Annals on this particular article.
A **podcast** for this article is available at www.annemergmed.com.

0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2025.02.024

SEE EDITORIAL, P. 324.

INTRODUCTION

Background

Chest pain, a symptom that often triggers an evaluation for suspected acute coronary syndrome (ACS), is the second most frequent reason for all United States emergency department (ED) visits and accounts for more than 7 million annual encounters.[1] The minority (13%) of ED chest pain visits are related to ACS, and accurate diagnosis is challenging with high clinical and medico-legal stakes.[2] To minimize missed ACS, emergency physicians will often order early (within 72 hours) noninvasive testing, such as a stress test or coronary computed tomography angiography, after electrocardiogram and cardiac biomarkers have excluded acute myocardial infarction (MI).

Importance

Professional guidelines from the American Heart Association/American College of Cardiology (AHA/ACC), European Society of Cardiology (ESC), and the American College of Emergency Physicians (ACEP) emphasize the importance of risk stratification to inform further testing, including noninvasive testing and invasive angiography.[3-5] However, there are varying recommendations on how to use such information to guide subsequent management after MI has been excluded by electrocardiogram and

Editor's Capsule Summary

What is already known on this topic

The appropriate follow-up of emergency department (ED) patients who are ruled out for acute myocardial infarction remains uncertain.

What question this study addressed

What is the benefit of early follow-up visits and noninvasive testing when stratified by pre-test HEART risk score?

What this study adds to our knowledge

Early noninvasive testing was associated with a reduced risk of 1-year all-cause and cardiovascular causes of death across risk groups. It is unclear whether noninvasive testing or engaging patients in risk-reduction strategies are most impactful.

How this is relevant to clinical practice

Rapid post ED care matters after acute myocardial infarction, but the specific ideal steps are unclear.

cardiac biomarkers. The 2021 AHA/ACC Guideline for the Evaluation and Diagnosis for Chest Pain suggests that noninvasive testing is not routinely needed for low-risk patients, whereas intermediate to high pretest patients may benefit most from cardiac testing.[3] The 2020 ESC Guidelines for the Management of ACS in patients presenting without persistent ST-segment elevation state that "stress testing with imaging or coronary computed tomography angiography will be the best option in patients with low-to-moderate clinical likelihood of unstable angina."[4] The AHA/ACC and ESC Guidelines do not provide further guidance on the timing or setting of subsequent testing after MI. Finally, the 2018 ACEP Critical Issues in the Evaluation and Management of Emergency Patients with Suspected Non-ST-Elevation Acute Coronary Syndromes recommends against routine noninvasive testing prior to discharge in low-risk patients.[5]

These professional guidelines reveal uncertainty about the optimal approach to risk stratification. The efficacy of early noninvasive testing on clinical outcomes is unclear, and no prior research has assessed effect modification by pretest risk.

Goals of This Investigation

We previously reported a small reduction in 30-day death/acute MI associated with early noninvasive testing.[6] In this study, we further develop our prior work to assess association of early noninvasive testing on 1-year outcomes stratified by pretest risk using the extensively validated history (H), electrocardiogram (E), age (A), risk factors (R) and troponin (T) (HEART) score.[7-15] Specifically, our primary objective was to evaluate the association of early noninvasive testing on the 1-year composite risk of all-cause death and acute MI stratified by pretest HEART risk score. Secondary outcomes included independent risk of all-cause mortality, coronary vascular disease (CVD)-specific mortality, and acute MI. Lastly, we also evaluated if relative risk ratio of noninvasive testing differs across HEART score strata, which could indicate differential benefits of noninvasive testing, independent of patients baseline risk.

METHODS

Study Design, Population, and Settings

We conducted a retrospective cohort study within the member population of Kaiser Permanente Southern California, an integrated health care organization with more than 8,000 physicians, 15 hospitals, and 196 medical offices. Kaiser Permanente Southern California provides comprehensive health care to more than 4.9 million racially and socio-economically diverse members residing within 7 counties of Southern California. Health care at Kaiser Permanente Southern California is coordinated through region-wide electronic medical records that capture detailed information on care provided to members.

Kaiser Permanente Southern California hospitals provide care to more than 1 million ED patients per year (study sites ranging from approximately 25,000 to 95,000 ED visits per year). Of these ED visits, approximately 80% are health plan members. During the study period, all sites used the same troponin laboratory assay (Beckman Coulter Access AccuTnI+3) as well as a uniform 0·5 ng/mL MI threshold. Physicians were asked to document the history and ECG findings discretely in the medical record, to be combined with age, risk factors, and troponin level to calculate a HEART score for appropriate patients.[16] Emergency physicians can order noninvasive testing as part of the evaluation and discharge plan of patients with suspected ACS.

The study was approved by the institutional review board of Kaiser Permanente Southern California. The study design and reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines for cohort studies.

Selection of Participants

We included all Kaiser Permanente Southern California members aged 18 years or more between October 1, 2015, and December 31, 2020, presenting at 13 EDs operated by Kaiser Permanente Southern California and who had valid HEART score documentation. We required all patients to have continuous health plan enrollment in the 12 months prior to as well as 12 months after discharge from their index ED visit unless they died during follow-up.

We excluded patients if: (1) MI was diagnosed in them (based on International Classification of Diseases 9 or 10 codes), or they had an initial troponin level more than 0.5 ng/dl during the index ED encounter; (2) they died in the ED at index event; (3) they were transferred from an outside facility; (4) they were under institutional facility care or end-of-life care; or (5) they had documented "do not resuscitate" order in the electronic medical records.

Measurements

Outcomes, intervention, and covariates measurement.

Primary Outcome

The primary outcome was composite event of all-cause death or acute MI event during 1-year follow-up from the ED discharge date.

Secondary Outcomes

Secondary clinical outcomes included composite death or acute MI within 30 days, composite death or acute MI within 31 to 365 days, and individual event rates of all-cause death within 1 year, cardiovascular cause of death within 1 year, and acute MI during the 1-year follow-up after the index chest pain visit.

Interventions

The exposure was performance of noninvasive cardiac testing within 3 days of the ED visit. Noninvasive testing included any of the following: stress electrocardiogram, stress echocardiogram, stress nuclear myocardial perfusion, or coronary computed tomography (CT) angiogram that were identified by current procedural terminology codes or electronic medical records order entry.

Covariates

Covariates included patient demographics and clinical history. We used the health plan's administrative records to obtain information on age (years), sex, and race. We obtained clinical data from the electronic medical records. We defined comorbidities and cardiac risk factors using laboratory values, medication use, and diagnostic or procedure codes along with the Elixhauser index. The details of the procedure and diagnostic codes have been described elsewhere.[6,17-19] Body mass index (BMI) was measured from ED intake documentation or the most recently available visit, whereas smoking and family history of coronary artery disease or stroke were self-reported electronic medical records fields. Those with a history of percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) were considered to have had prior coronary revascularization.

Explanatory Causal Variables

To explore the mechanism of the potential benefit associated with noninvasive testing, we measured coronary revascularization procedures and pharmacological treatment consistent with medical management of coronary artery disease risk. Cardiac procedures, including CABG, PCI, and invasive angiography, were measured during 2 time periods 1) during the index ED visits, 2) from discharge to 30 days post discharge, and from 31 to 365 days after ED discharge. Additionally, we also identified prescription medication use during the 1-year post ED discharge for the following classes of medications: 1) antidiabetic, 2) antithrombotic, 3) antihyperlipidemic, and 4) antihypertensive.

Analysis

We first stratified the cohort into low-risk (score 0 to 3), intermediate-risk (score 4 to 6), and high-risk (score $\geq$7) subcohorts based on the patient's HEART score. Within each subcohort, we used propensity score analysis, specifically inverse probability of treatment weight models, to evaluate the association of early noninvasive testing on the composite outcome of death/acute MI.[20] The inverse probability of treatment weight analysis combined a 2-step procedure where we first estimated the probability of receiving early noninvasive testing using a logit model with sociodemographic, cardiac comorbidities, and noncardiac comorbid conditions as predictors (see Supplemental Methods for details, available at http://www.annemergmed.com). Next, we used the estimated inverse-probability weights to compute weighted averages of the outcomes for each exposure level. Lastly, the contrast of these weighted averages provided estimates of the risk difference of the primary outcome (and each secondary outcome evaluated separately). We then computed the number needed to treat (NNT) to benefit from early noninvasive testing as the inverse of the absolute risk difference for each outcome.

To evaluate if the benefit of early noninvasive testing differed by baseline risk, we compared relative risk ratios estimated from Poisson regression models stratified by HEART risk and specifying robust estimates of variance. These Poisson models adjusted for same covariates as

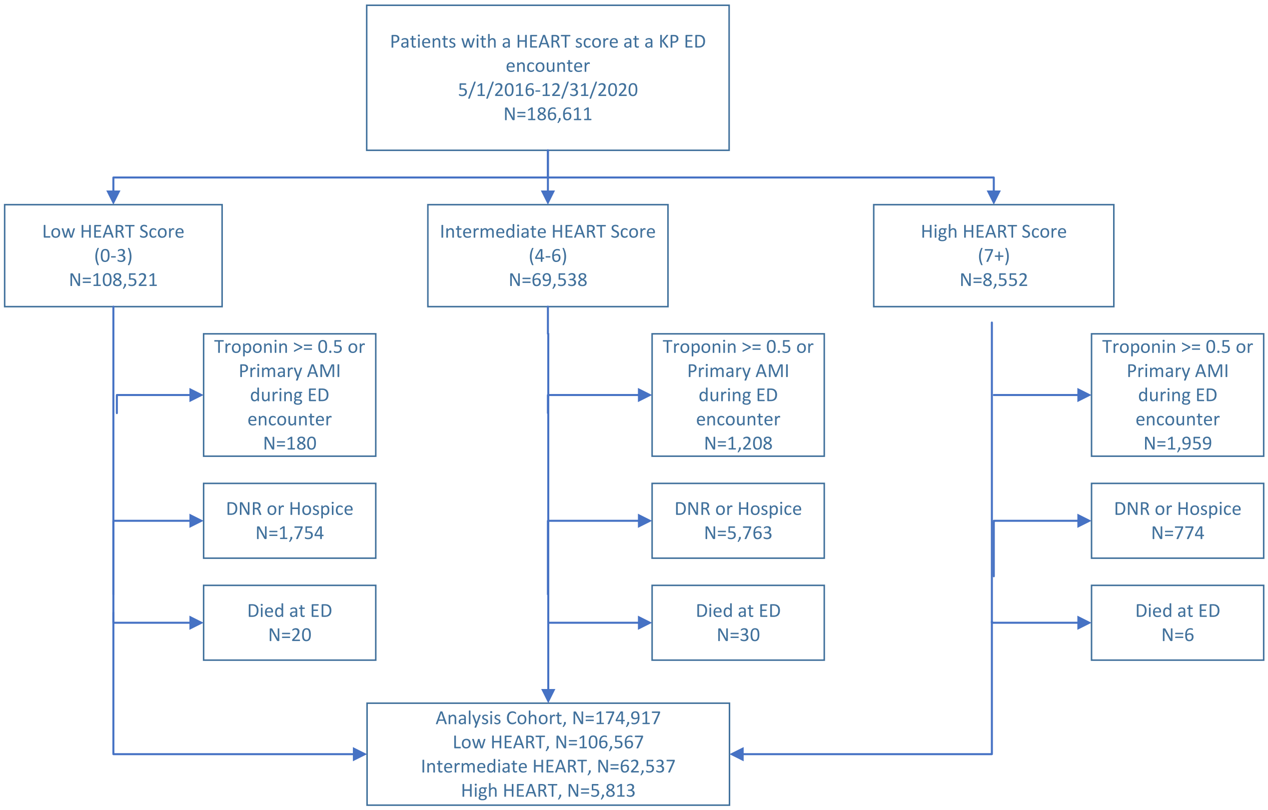


Figure 1. Study patient flowchart. Patients presenting with chest pain to an emergency department and patients included in the analysis. *KP*, Kaiser Permanente.

specified in the inverse probability of treatment weight model (see Supplemental Methods for details).

As exploratory analysis to understand the mechanism of benefit attributable to early noninvasive testing, we evaluated differences between cardiac procedures and prescription medication use between those who had early noninvasive testing versus those who did not have early noninvasive testing using inverse probability of treatment weight models. These inverse probability of treatment weight models were similar to our primary inverse probability of treatment weight analysis using a logit model with sociodemographic, cardiac comorbidities, and noncardiac comorbid conditions as predictors to obtain probability of early noninvasive testing and then contrasted the weighted averages to obtain the risk differences.

For the inverse probability of treatment weight model, we checked balancing of the covariates based on raw and weighted standardized differences in proportion and variance of each covariate. To ensure that our inferences were robust to the choice of statistical modeling, we performed extensive sensitivity analysis to account for functional form and unobserved confounding bias (see Supplemental Methods for details). All hypothesis tests were 2-sided with an apriori type I error set at 5%. Data were analyzed using Stata or MP version 15 software (Stata Corp LLC, College Station, TX).

RESULTS

Characteristics of Study Subjects

Between May 2016 and December 2020, we identified a total number (N) of 186,611 Kaiser Permanente Southern California patients who had an ED visit and had a HEART score (Figure 1). After applying the exclusions based on primary MI, death at the index ED visit, do not resuscitate, or hospice status, the final analytic cohort included 174,917 patients. Based on HEART score, the majority of the included cohort was categorized as low risk (61%) (N=106,478 [mean age, 53 years; women, 58%; early noninvasive testing, 5%]), followed by 36% categorized as intermediate risk (N=63,037 [mean age, 71; women, 52%; early noninvasive testing, 18%]), and 3% categorized as high risk (N=5,402 [mean age, 74; women, 45%; early noninvasive testing, 23%]) (Table 1 and

Table 1. Sociodemographic and clinical characteristics by HEART Risk.

	Total Cohort		HEART Category: Low (HEART Score 0-3)		HEART Category: Intermediate (HEART Score 4-6)		HEART Category: High (HEART Score 7-10)	
	No NIT within 3 days	NIT within 3 days	No NIT within 3 days	NIT within 3 days	No NIT within 3 days	NIT within 3 days	No NIT within 3 days	NIT within 3 days
Characteristic	**(N=157,433)**	**(N=17,484)**	**(N=101,347)**	**(N=5,131)**	**(N=51,917)**	**(N=11,120)**	**(N=4,169)**	**(N=1,233)**
Age (y) at ED, mean (SD)	59.4 (17.12)	63.9 (12.61)	52.4 (15.58)	55.1 (11.37)	72.1 (11.39)	66.9 (11.30)	73.6 (10.95)	73.6 (8.50)
Women, n (%)	88,271 (56.1)	8,935 (51.1)	59,509 (58.7)	2,730 (53.2)	26,932 (51.9)	5,620 (50.5)	1,830 (43.9)	585 (47.4)
Race, n (%)								
Alaska Native/Pacific Islander	2,670 (1.7)	329 (1.9)	1,754 (1.7)	78 (1.5)	853 (1.6)	228 (2.1)	63 (1.5)	23 (1.9)
Asian	16,215 (10.3)	1,911 (10.9)	10,382 (10.2)	577 (11.2)	5,435 (10.5)	1,211 (10.9)	398 (9.5%)	123 (10.0)
Black	22,812 (14.5)	2,274 (13.0)	13,332 (13.2)	648 (12.6)	8,422 (16.2)	1,452 (13.1)	1,058 (25.4)	174 (14.1)
Others	28,997 (18.4)	2,858 (16.3)	21,153 (20.9)	1,069 (20.8)	7,324 (14.1)	1,643 (14.8)	520 (12.5)	146 (11.8)
White	86,739 (55.1)	10,112 (57.8)	54,726 (54.0)	2,759 (53.8)	29,883 (57.6)	6,586 (59.2)	2,130 (51.1)	767 (62.2)
Smoking status, n (%)								
Active	9,186 (5.8)	1,012 (5.8)	6,352 (6.3)	291 (5.7)	2,629 (5.1)	659 (5.9)	205 (4.9)	62 (5.0)
Never	95,683 (60.8)	10,396 (59.5)	65,519 (64.6)	3,437 (67.0)	28,114 (54.2)	6,317 (56.)	2,050 (49.2)	642 (52.1)
Passive	748 (0.5)	58 (0.3)	584 (0.6)	14 (0.3)	153 (0.3)	36 (0.3)	11 (0.3)	*
Quit	46,215 (29.4)	5,728 (32.8)	23,940 (23.6)	1,240 (24.2)	20,421 (39.3)	3,973 (35.7)	1,854 (44.5)	515 (41.8)
BMI category, n (%)								
Underweight	2,528 (1.6)	122 (0.7)	1,270 (1.3)	27 (0.5)	1,149 (2.2)	82 (0.7)	109 (2.6)	13 (1.1)
Normal	34,691 (22.0)	3,332 (19.1)	20,676 (20.4)	915 (17.8)	12,874 (24.8)	2,167 (19.5)	1,141 (27.4)	250 (20.3)
Overweight	48,303 (30.7)	5,922 (33.9)	30,159 (29.8)	1,702 (33.2)	16,743 (32.2)	3,780 (34.0)	1,401 (33.6)	440 (35.7)
Obese	63,309 (40.2)	7,538 (43.1)	42,028 (41.5)	2,234 (43.5)	19,835 (38.2)	4,801 (43.2)	1,446 (34.7)	503 (40.8)
HEART history, n (%)								
Slightly suspicious	133,549 (84.8)	6,755 (38.6)	95,627 (94.4)	3,916 (76.3)	37,458 (72.1)	2,800 (25.2)	464 (11.1)	39 (3.2)
Moderately suspicious	188,54 (12.0)	7,450 (42.6)	5,573 (5.5)	1,130 (22.0)	12,153 (23.4)	6,031 (54.2)	1,128 (27.1)	289 (23.4)
Highly suspicious	5,030 (3.2)	3,279 (18.8)	147 (0.1)	85 (1.7)	2,306 (4.4)	2,289 (20.6)	2,577 (61.8)	905 (73.4)
HEART ECG, n (%)								
Normal	102,928 (65.4)	8,982 (51.4)	85,035 (83.9)	4,126 (80.4)	17,779 (34.2)	4,813 (43.3)	114 (2.7)	43 (3.5)
Nonspecific repolarization changes	51,949 (33.0)	7,958 (45.5)	16,225 (16.0)	986 (19.2)	33,310 (64.2)	6,037 (54.3)	2,414 (57.9)	935 (75.8)
Significant ST deviation	2,556 (1.6)	544 (3.1)	87 (0.1)	19 (0.4)	828 (1.6)	270 (2.4)	1,641 (39.)	255 (20.7)

Table 1. Continued.

	HEART Category							
	Total Cohort		Low (HEART Score 0-3)		Intermediate (HEART Score 4-6)		High (HEART Score 7-10)	
	No NIT within 3 days	NIT within 3 days	No NIT within 3 days	NIT within 3 days	No NIT within 3 days	NIT within 3 days	No NIT within 3 days	NIT within 3 days
Characteristic	**(N=157,433)**	**(N=17,484)**	**(N=101,347)**	**(N=5,131)**	**(N=51,917)**	**(N=11,120)**	**(N=4,169)**	**(N=1,233)**
HEART age (y), n (%)								
<45	32,761 (20.8)	1,162 (6.6)	32,080 (31.7)	928 (18.1)	670 (1.3)	234 (2.1)	11 (0.3)	*
Between 45 to 64	59,330 (37.7)	7,611 (43.5)	48,749 (48.1)	3,347 (65.2)	9,908 (19.1)	4,149 (37.3)	673 (16.1)	115 (9.3%)
≥65	65,342 (41.5)	8,711 (49.8)	20,518 (20.2)	856 (16.7)	41,339 (79.6)	6,737 (60.6)	3,485 (83.6)	1,118 (90.7)
HEART risk, n (%)								
No risk factors	34,264 (21.8)	1,229 (7.0)	33,986 (33.5)	1,093 (21.3)	274 (0.5)	135 (1.2)	*	*
1-2 risk factors	78,060 (49.6)	7,266 (41.6)	60,777 (60.0)	3,551 (69.2)	17,115 (33.0)	3,645 (32.8)	168 (4.0)	70 (5.7)
≥3 risk factors or atherosclerotic disease	45,109 (28.7)	8,989 (51.4)	6,584 (6.5)	487 (9.5)	34,528 (66.5)	7,340 (66.0)	3,997 (95.9)	1,162 (94.2)
Initial troponin, n (%)								
Normal	148,488 (94.3)	16,098 (92.1)	100,260 (98.9)	4,986 (97.2)	46,110 (88.8)	10,317 (92.8)	2,118 (50.8)	795 (64.5)
1-3 times normal limit	6,686 (4.2)	998 (5.7)	990 (1.0)	127 (2.5)	4,760 (9.2)	621 (5.6)	936 (22.5)	250 (20.3)
≥3-times normal limit	2,259 (1.4)	388 (2.2)	97 (0.1)	18 (0.4)	1,047 (2.0)	182 (1.6)	1,115 (26.7)	188 (15.2)
Clinical characteristics and comorbidities								
CAD (1), n (%)	23,492 (14.9)	3,881 (22.2)	5,468 (5.4)	283 (5.5)	15,890 (30.6)	2,988 (26.9)	2,134 (51.2)	610 (49.5)
Stroke (1), n (%)	6,190 (3.9)	471 (2.7)	2,342 (2.3)	56 (1.1)	3,578 (6.9)	352 (3.2)	270 (6.5)	63 (5.1)
CABG in year prior to ED admission (1), n (%)	561 (0.4)	46 (0.3)	87 (0.1)	*	417 (0.8)	33 (0.3)	57 (1.4)	*
PTCA in year prior to ED admission (1), n (%)	1,093 (0.7)	165 (0.9)	223 (0.2)	16 (0.3)	711 (1.4)	128 (1.2)	159 (3.8)	21 (1.7)
Family history of CAD (1), n (%)	51,237 (32.5)	6,735 (38.5)	32,712 (32.3)	1,881 (36.7)	17,172 (33.1)	4,362 (39.2)	1,353 (32.5)	492 (39.9)
Family history of stroke (1), n (%)	31,791 (20.2)	3,600 (20.6)	21,413 (21.1)	1,058 (20.6)	9,635 (18.6)	2,311 (20.8)	743 (17.8)	231 (18.7)
Elixhauser comorbidity index, mean (SD)	3.8 (3.05)	3.8 (2.70)	2.8 (2.49)	2.4 (2.13)	5.6 (3.09)	4.2 (2.65)	6.3 (3.27)	5.6 (2.91)
Congestive heart failure, n (%)	16,084 (10.2)	1,400 (8.0)	3,783 (3.7)	100 (1.9)	10,901 (21.0)	1,052 (9.5)	1,400 (33.6)	248 (20.1)
Cardiac arrhythmia, n (%)	30,749 (19.5)	3,310 (18.9)	12,007 (11.8)	515 (10.0)	17,099 (32.9)	2,377 (21.4)	1,643 (39.4)	418 (33.9)
Valvular disease, n(%)	10,316 (6.6)	964 (5.5)	3,109 (3.1)	122 (2.4)	6,425 (12.4)	677 (6.1)	782 (18.8)	165 (13.4)
Pulmonary circulation disorders, n(%)	6,400 (4.1)	448 (2.6)	2,332 (2.3)	52 (1.0)	3,692 (7.1)	323 (2.9)	376 (9.0)	73 (5.9)
Peripheral vascular disorders, n(%)	47,311 (30.1)	5,741 (32.8)	14,930 (14.7)	582 (11.3)	29,689 (57.2)	4,426 (39.8)	2,692 (64.6)	733 (59.4)
Hypertension uncomplicated, n(%)	73,674 (46.8)	10,460 (59.8)	36,674 (36.2)	1,998 (38.9)	34,283 (66.0)	7,544 (67.8)	2,717 (65.2)	918 (74.5)
Hypertension complicated, n(%)	19,479 (12.4)	1,722 (9.8)	5,332 (5.3)	154 (3.0)	12,675 (24.4)	1,297 (11.7)	1,472 (35.3)	271 (22.0)

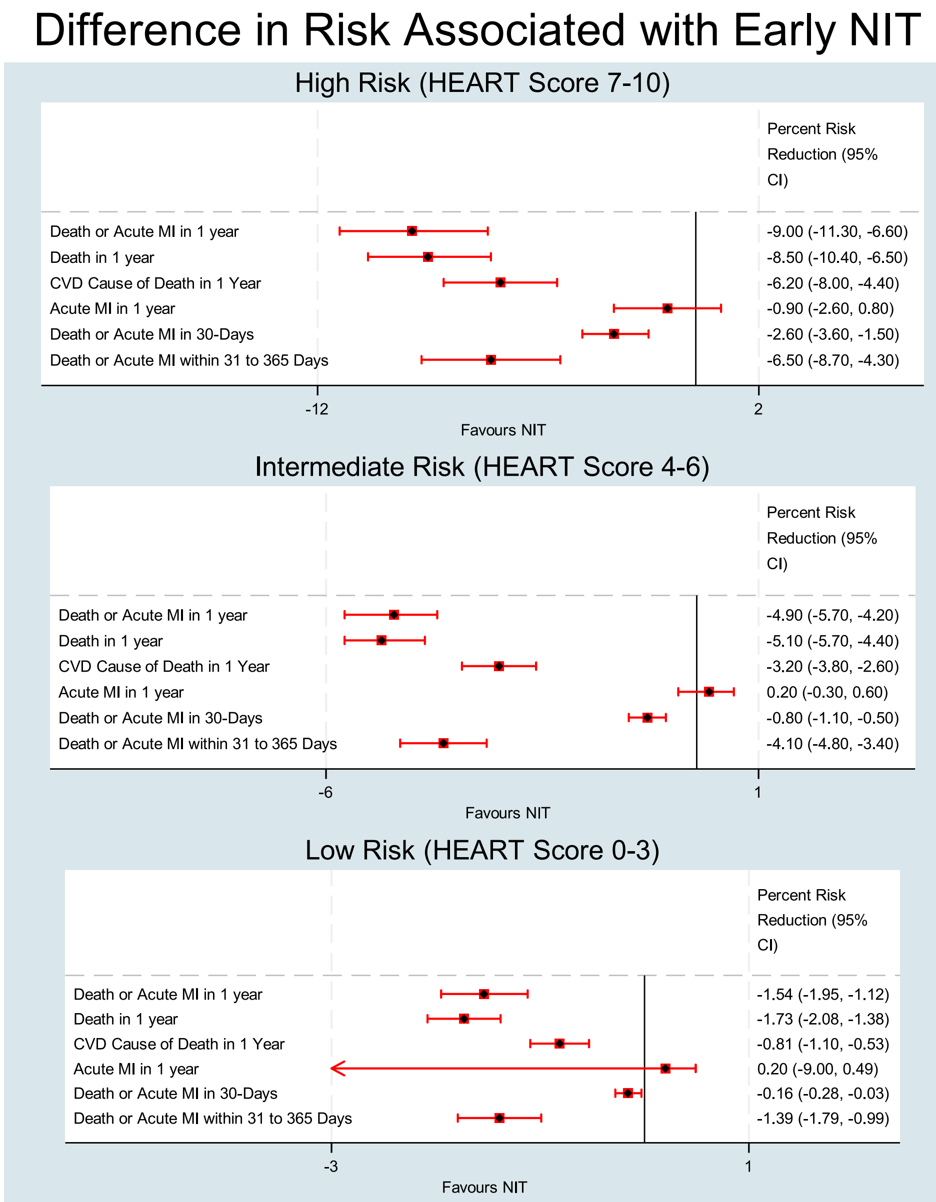
Paralysis, n(%)	2,112 (1.3)	164 (0.9)	996 (1.0)	38 (0.7)	1,038 (2.0)	105 (0.9)	78 (1.9)	21 (1.7)
Other neurologic disorders, n(%)	10,095 (6.4)	782 (4.5)	4,458 (4.4)	126 (2.5)	5,201 (10.0)	573 (5.2)	436 (10.5)	83 (6.7)
Chronic pulmonary disease, n(%)	37,716 (24.0)	3,772 (21.6)	20,988 (20.7)	867 (16.9)	15,501 (29.9)	2,575 (23.2)	1,227 (29.4)	330 (26.8)
Diabetes uncomplicated, n(%)	23,135 (14.7)	3,802 (21.7)	10,870 (10.7)	684 (13.3)	11,275 (21.7)	2,765 (24.9)	990 (23.7)	353 (28.6)
Diabetes complicated, n(%)	37,558 (23.9)	4,809 (27.5)	15,181 (15.0)	686 (13.4)	20,482 (39.5)	3,572 (32.1)	1,895 (45.5)	551 (44.7)
Hypothyroidism, n(%)	19,989 (12.7)	2,412 (13.8)	10,319 (10.2)	542 (10.6)	9,016 (17.4)	1,659 (14.9)	654 (15.7)	211 (17.1)
Renal failure, n(%)	27,023 (17.2)	3,059 (17.5)	8,384 (8.3)	337 (6.6)	16,836 (32.4)	2,275 (20.5)	1,803 (43.2)	447 (36.3)
Liver disease, n(%)	16,167 (10.3)	1,826 (10.4)	9,936 (9.8)	532 (10.4)	5,820 (11.2)	1,168 (10.5)	411 (9.9)	126 (10.2)
Peptic ulcer disease excluding bleeding, n(%)	2,174 (1.4)	217 (1.2)	1,012 (1.0)	38 (0.7)	1,066 (2.1)	155 (1.4)	96 (2.3)	24 (1.9)
Metastatic cancer, n(%)	4,230 (2.7)	264 (1.5)	2,013 (2.0)	41 (0.8)	2,065 (4.0)	193 (1.7)	152 (3.6)	30 (2.4)
Solid tumor without metastasis, n(%)	10,947 (7.0)	1,177 (6.7)	4,800 (4.7)	199 (3.9)	5,685 (11.0)	864 (7.8)	462 (11.1)	114 (9.2)
Rheumatoid arthritis/collagen, n(%)	7,561 (4.8)	788 (4.5)	3,928 (3.9)	182 (3.5)	3,365 (6.5)	529 (4.8)	268 (6.4)	77 (6.2)
Coagulopathy, n(%)	9,613 (6.1)	761 (4.4)	3,772 (3.7)	113 (2.2)	5,285 (10.2)	528 (4.7)	556 (13.3)	120 (9.7)
Weight loss, n(%)	10,046 (6.4)	668 (3.8)	3,960 (3.9)	105 (2.0)	5,503 (10.6)	475 (4.3)	583 (14.0)	88 (7.1)
Fluid and electrolyte disorders, n(%)	28,217 (17.9)	2,369 (13.5)	12,685 (12.5)	392 (7.6)	14,228 (27.4)	1,703 (15.3)	1,304 (31.3)	274 (22.2)
Blood loss anemia, n(%)	3,479 (2.2)	243 (1.4)	1,411 (1.4)	47 (0.9)	1,867 (3.6)	153 (1.4)	201 (4.8)	43 (3.5)
Deficiency anemia, n(%)	14,205 (9.0)	1,269 (7.3)	7,474 (7.4)	309 (6.0)	6,091 (11.7)	821 (7.4)	640 (15.4)	139 (11.3)
Alcohol abuse, n(%)	7,113 (4.5)	676 (3.9)	4,447 (4.4)	194 (3.8)	2,477 (4.8)	433 (3.9)	189 (4.5)	49 (4.0)
Drug abuse, n(%)	8,793 (5.6)	793 (4.5)	5,886 (5.8)	225 (4.4)	2,711 (5.2)	533 (4.8)	196 (4.7)	35 (2.8)
Psychoses, n(%)	2,506 (1.6)	179 (1.0)	1,489 (1.5)	41 (0.8)	946 (1.8)	126 (1.1)	71 (1.7)	12 (1.0)
Depression, n(%)	43,226 (27.5)	4,675 (26.7)	26,946 (26.6)	1,260 (24.6)	15,195 (29.3)	3,081 (27.7)	1,085 (26.0)	334 (27.1)

NIT, Noninvasive testing; *BMI,* body mass index; *CAD*, coronary artery disease; *CABG*, coronary artery bypass graft; *ED*, emergency department; *PTCA,* percutaneous transluminal coronary angioplasty.
*Masked because cell size is $<$10.

Table 2. Descriptive statistics of clinical outcomes, medication use and procedures by HEART risk.

	HEART Category					
	Low (HEART Score 0-3)		Intermediate (HEART Score 4-6)		High (HEART Score 7-10)	
	No NIT	NIT	No NIT	NIT	No NIT	NIT
Clinical Outcomes, Medications and Procedures	(N=10,1347)	(N=5,131)	(N=51,917)	(N=11,120)	(N=4,169)	(N=1,233)
Clinical outcomes						
1-y after discharge						
Death or acute MI within 365 d of hospital discharge, n (%)	2,800 (2.8)	56 (1.1)	5,858 (11.3)	398 (3.6)	848 (20.3)	113 (9.2)
Death within 365 d of hospital discharge, n (%)	2,428 (2.4)	27 (0.5)	5,023 (9.7)	233 (2.1)	652 (15.6)	62 (5.0)
CVD cause of death within 365 d of hospital discharge, n (%)	1,298 (1.28)	17 (0.33)	3,461 (6.67)	161 (1.45)	506 (12.14)	50 (4.06)
Acute MI within 365 d of hospital discharge, n (%)	452 (0.5)	30 (0.6)	1,087 (2.1)	190 (1.7)	264 (6.3)	61 (5.0)
Within 30-d						
Death or acute MI within 30 d of hospital discharge, n (%)	355 (0.4)	12 (0.2)	844 (1.6)	74 (0.7)	177 (4.2)	22 (1.8)
Death within 30 d of hospital discharge, n (%)	279 (0.3)	*	601 (1.2)	12 (0.1)	84 (2.0)	*
CVD cause of death within 30 d of hospital discharge, n (%)	156 (0.15)	*	378 (0.73)	10 (0.09)	68 (1.63)	*
Acute MI within 30 d of hospital discharge, n (%)	82 (0.1)	11 (0.2)	257 (0.5)	64 (0.6)	99 (2.4)	17 (1.4)
Within 31-365 d						
Death or acute MI within 31-365 d of hospital discharge, n (%)	2,451 (2.4)	44 (0.9)	5,056 (9.7)	330 (3.0)	681 (16.3)	92 (7.5)
Death within 31-365 d of hospital discharge, n (%)	2,149 (2.1)	26 (0.5)	4,422 (8.5)	221 (2.0)	568 (13.6)	57 (4.6)
CVD cause of death within 31-365 d of hospital discharge, n (%)	1,142 (1.13)	16 (0.31)	3,083 (5.94)	151 (1.36)	438 (10.51)	46 (3.73)
Acute MI within 31-365 d of hospital discharge, n (%)	370 (0.4)	19 (0.4)	830 (1.6)	126 (1.1)	165 (4.0)	44 (3.6)
Medication use						
Medication use within 1-y						
Antidiabetic medication, n (%)	16,089 (15.9)	803 (15.6)	16,666 (32.1)	3,329 (29.9)	1,435 (34.4)	450 (36.5)
Antithrombotic medication, n (%)	11,966 (11.8)	523 (10.2)	18,579 (35.8)	3,018 (27.1)	2,035 (48.8)	573 (46.5)
Antihyperlipidemic medication, n (%)	32,569 (32.1)	2,091 (40.8)	36,648 (70.6)	7,992 (71.9)	3,083 (74.0)	1,018 (82.6)
Antihypertension medication, n (%)	45,174 (44.6)	2,496 (48.6)	42,399 (81.7)	8,737 (78.6)	3,582 (85.9)	1,125 (91.2)
Procedures						
Procedures within 30-d						
CABG within 30 d of hospital discharge, n (%)	18 (0.0)	*	58 (0.1)	23 (0.2)	28 (0.7)	*
PTCA within 30 d of hospital discharge, n (%)	41 (0.0)	15 (0.3)	107 (0.2)	40 (0.4)	27 (0.6)	*
Invasive angiography within 30 d of hospital discharge (1), n (%)	288 (0.3)	66 (1.3)	533 (1.0)	191 (1.7)	78 (1.9)	38 (3.1)
Procedures within 31-365 d						
CABG within 31-365 d of hospital discharge (1), n (%)	91 (0.1)	*	206 (0.4)	62 (0.6)	40 (1.0)	17 (1.4)
PTCA within 31-365 d of hospital discharge (1), n (%)	160 (0.2)	11 (0.2)	311 (0.6)	87 (0.8)	72 (1.7)	24 (1.9)
Invasive angiography within 31-365 d of hospital discharge (1), n (%)	1,073 (1.1)	111 (2.2)	1,906 (3.7)	488 (4.4)	288 (6.9)	91 (7.4)

MI, myocardial infarction; *CVD*, cardiovascular disease.
*Masked because cell size is <10.



Estimates are based on inverse of treatment probability models where receipt of early NIT was modeled as a logit function of age, sex, race, Hispanic ethnicity, income quintiles, insurance type, BMI categories, smoking status, cardiac co-morbidities (CAD, stroke, past history of CABG or PCI, family history of CAD, family history of stroke, arrhythmia, CHF, complicated hypertension, uncomplicated hypertension, valvular disease, pulmonary circulation disorders, and peripheral vascular disorders) and non-cardiac co-morbid condition based on the Elixhauser co-morbidity index.

Figure 2. Risk difference forest plot. Difference in risk associated with early noninvasive testing and number needed to treat.

Table 3. Differences in cardiac procedures and prescription medication use.

Procedures and Medications	Low Risk (HEART Score 0-3) (%)	Intermediate Risk (HEART Score 4-6) (%)	High Risk (HEART Score 7-10) (%)
Procedures			
CABG at index ED visit	0.05 (−0.02 to 0.12)	0.24 (0.07 to 0.41)*	−1.02 (−1.86 to −0.17)*
CABG in 30 d	0.15 (0.03-0.27)*	0.03 (−0.04 to 0.10)	−0.47 (−0.86 to −0.08)*
CABG within 31-365	0.07 (−0.06 to 0.20)	0.31 (0.07-0.55)*	0.33 (−0.42 to 1.09)
CABG discharge to 365 d	0.22 (0.05-0.40)*	0.34% (0.09-0.59)*	−0.14% (−0.98 to 0.71)
PTCA at index ED visit	0.18 (0.04-0.31)*	0.30 (0.13-0.48)*	−0.33 (−1.49 to 0.83)
PTCA in 30 d	0.18 (0.06-0.30)*	0.10 (−0.02 to 0.23)	−0.31 (−0.71 to 0.10)
PTCA within 31-365 d	0.04 (−0.09 to 0.16)	0.42 (0.12-0.71)*	0.27 (−0.69 to 1.23)
PTCA discharge to 365 d	0.22 (0.04-0.40)*	0.52 (0.20-0.84)*	−0.03 (−1.07 to 1.00)
Revascularization at index ED visit	0.23 (0.07 to 0.38)*	0.54 (0.30-0.78)*	−1.33 (−2.73 to 0.06)
Revascularization in 30 d	0.33 (0.16-0.51)*	0.13 (−0.02 to 0.27)	−0.77 (−1.33 to −0.21)
Revascularization within 31-365 d	0.12 (−0.07 to 0.30)	0.64 (0.29-0.99)*	0.73 (−0.48 to 1.93)
Revascularization discharge to 365 d	0.45 (0.20-0.70)*	0.77 (0.40-1.14)*	-0.02 (−1.33 to 1.30)
Invasive angiography at index ED visit	0.85 (0.55-1.15)*	1.30 (0.90-1.69)*	−2.96 (−5.08 to −0.85)*
Invasive angiography in 30 d	0.76 (0.48-1.04)*	0.48 (0.21-0.75)*	1.22 (0.07-2.38)*
Invasive angiography within 31-365 d	1.25 (0.76-1.73)*	1.21 (0.66-1.76)*	1.24 (−0.73 to 3.22)
Invasive angiography discharge to 365 d	2.01 (1.45-2.56)*	1.69 (1.09-2.29)*	2.47 (0.24-4.70)*
Medications			
Antidiabetic medication use in 1-y	1.22 (0.06-2.38)*	0.16 (−0.89 to 1.22)	3.38 (0.17-6.60)*
Antithrombotic medication use in 1-yr	−0.95 (−1.95 to 0.05)	-2.05 (−3.13 to −0.97)*	1.37 (−1.97 to 4.7)
Antihyperlipidemic medication use in 1 y	7.75 (6.39-9.11)*	4.37 (3.38-5.37)*	7.86 (5.16-10.56)*
Antihypertensive medication use in 1 y	3.39 (2.15-4.63)*	1.15 (0.41-1.88)*	5.50 (3.61-7.38)*

PCI, Percutaneous coronary intervention.
Estimates are based on inverse of treatment probability models where receipt of early noninvasive testing was modeled as a logit function of age, sex, race, Hispanic ethnicity, income quintiles, insurance type, BMI categories, smoking status, cardiac comorbidities (CAD, stroke, past history of CABG or PCI, family history of CAD, family history of stroke, arrythmia, congestive heart failure, complicated hypertension, uncomplicated hypertension, valvular disease, pulmonary circulation disorders, and peripheral vascular disorders) and noncardiac comorbid condition based on the Elixhauser comorbidity index.
*Data indicate statistically significant differences.

Figure 1). The unadjusted proportion of composite outcome of death or acute MI increased by HEART risk, increased as the duration of follow-up increased, and was consistently higher in the no-early noninvasive testing group compared with those who received early noninvasive testing (Table 2).

Main Results

For the primary outcome of all-cause death or acute MI within 1-year of ED discharge, early noninvasive testing was associated with reduced mortality which varied according to risk category; −1.54% (95% confidence interval [CI] −1.95 to −1.12) NNT = 65 (95% CI 51 to 89); −4.93% (95% CI −5.66 to −4.20) NNT=20 (95% CI 18 to 24); and −8·98% (95% CI −11.32 to −6.64) NNT=11 (95% CI 9 to 15) risk reduction in the low-risk, intermediate risk, and high-risk subcohorts, respectively (Figure 2). These differences were primarily due to risk reduction in all-cause mortality of −1.73% (95% CI −2.08 to −1.38); −5.07% (95% CI −5.73 to −4.41); and −8.47% (95% CI −10.43 to −6.51); in the low-risk, intermediate risk, and high-risk subcohorts, respectively.

The risk difference in cardiovascular cause of death was −0.81% (95% CI −1.09 to −0.53), −3.20% (95% CI −3.81 to −2.59), and −6.17% (95% CI −7.98 to −4.35) in the low-risk, intermediate risk, and high-risk subcohorts, respectively. The risk difference in acute MI alone was not statistically significant in any subcohort. In the secondary composite outcome of death or acute MI within 30-days early noninvasive testing was associated risk reduction ranging from −0.16% (95% CI −0.28 to −0.03), NNT = 625 (95% CI 357 to 3,333) in the low-risk cohort to −2.55% (95% CI −3.57 to −1.52), NNT=39 (95% CI 28 to 66), in the high-risk subcohort. Over a longer follow-up from 31 to 365 days, the risk reduction increased in magnitude and ranged from −1.39% (95% CI −1.79 to −0.99), NNT = 72 (95% CI 56 to 101) in the low-risk subcohort to −6.53% (95% CI −8.71 to −4.34), NNT= 15 (95% CI 11 to 23) in the high-risk subcohort.

The relative risk estimates obtained from adjusted Poisson regression models were similar with incidence rate ratio of 0.53 (95% CI 0.41 to 0.69); 0.50 (95% CI 0.45 to 0.56); and 0·55 (95% CI 0.46 to 0.67) in the low-risk, intermediate risk, and high-risk subcohorts respectively.

Mechanism of Benefit. We explored the potential mechanisms for the decrease in mortality among patients undergoing noninvasive testing. We found a consistent increase in invasive coronary angiography in all risk categories (absolute increase in 30 days after the ED discharge 0·48% to 1·22% and in 365 days after the ED discharge 1.69% to 2.47%) (Table 3). A small absolute increase in revascularizations (PCI or CABG) was present only 365 days after the ED discharge among patients of low risk (0.45%) and intermediate risk (0.77%). We observed that there was a moderate increase in the use of antihyperlipidemic (4.37% to 7.86%) and antihypertensive (1.15% to 5.50%) medications in all risk categories. The increase of the antidiabetic medications was noted in patients of low risk (1.22%) and high risk (3.38%). Lastly, we found that the use of antithrombotic medications decreased among patients of low risk (0.95%) and intermediate risk (−2.05%).

Sensitivity Analyses. Based on the ratio of variance of weighted standardized difference, we found that the 2 arms were well balanced on observed covariates in the inverse probability of treatment weight model (Appendix E1 [e.Table 1-e.Table 3], available at http://www.annemergmed.com). The exposure probability density graphs did not demonstrate violation of the overlap assumption underlying the inverse probability of treatment weight model.

Sensitivity analyses of primary outcome using multivariable logistic or probit models, doubly robust augmented inverse probability-weighted regression adjustment, and generalized method of moments instrumental variables models all indicate that early noninvasive testing was associated with statistically significant benefit in each subcohort of HEART category (Appendix E1 [e.Table 4-e.Table 6]).

LIMITATIONS

Because of the observational nature of the study, we cannot rule out residual confounding and that clinicians have expert clinical judgment and ordered early noninvasive testing for a healthier cohort of patients, especially as the benefit on mortality was several points higher than changes in medication use or revascularization patterns. These findings highlight the need for large randomized controlled trials of early noninvasive testing versus no testing.

Our patient population was geographically limited to Southern California and belonged to an integrated and capitated health care system. Health plan members had ready access to outpatient care. Differences in access to primary care, specialists, noninvasive testing, and prescription medications may limit generalizability to other health care systems. We included all-cause rather than cardiac mortality in our primary outcome, as our study team found it difficult to accurately assign cause of death for out-of-hospital deaths. It is possible some deaths were unrelated to the index ED visit. Our study was conducted prior to adoption of high sensitivity troponin assays, which may identify more patients with MI at the index visit.[21] Lastly, due to the observational and retrospective nature of the study, confounding by indication cannot be ruled out completely. Although the analysis was stratified by HEART score, within strata differences explaining receipt of noninvasive testing may remain.

DISCUSSION

In this large cohort of ED patients suspected of ACS with HEART risk score data, we report that early noninvasive testing was associated with decreased one-year death or acute MI in low-, intermediate-, and high-risk groups. Our analysis shows that noninvasive testing provides a similar relative risk reduction across the HEART risk groups, but when this is applied to the varying baseline risk, it produces a greater absolute risk reduction for patients with a higher baseline HEART risk (NNT: low=65; intermediate=20, high=11). This suggests that noninvasive testing is associated with benefit across risk groups, but the benefit itself may be proportional to the baseline risk. Determination of whether the benefits of noninvasive testing outweigh the harms and justify the costs will depend on the baseline risk. To our knowledge, this is the first study to assess the effectiveness of early noninvasive testing by pretest risk at a population level.

There are several possible explanations for the apparent benefit of early noninvasive testing on mortality. Prior studies have suggested that closer outpatient follow-up, as occurs with patients who receive early noninvasive testing, is associated with better outcomes.[22-24] In the early noninvasive testing arm, there was increased use of guideline-directed therapies, including antidiabetic, antihyperlipidemic, and antihypertensive medication. These results are consistent with the results of a meta-analysis, which showed an increase in the use of preventive measures (antihyperlipidemic and antihypertensive medications, exercise, and dietary changes) in patients with abnormal noninvasive testing, such as after testing for the presence of coronary atherosclerosis with noncontrast CT.[23] Use of noninvasive testing and detecting abnormalities on the test may have offered additional opportunities for prescribing antiplatelet therapy and lipid-lowering therapy. The results of the Scottish Computed Tomography of the HEART (SCOT-HEART) trial demonstrated 4-fold increase in guideline-directed preventive therapies (antihyperlipidemic and antithrombotic) medications in stable chest pain patients who received coronary computed tomography angiography.[24] In the trial, the decrease in death and myocardial infarction was observed more than 50 days after the test and was associated with changes in medical therapies rather than in invasive coronary angiography or revascularization. Our results also suggest larger absolute changes in preventive medication use than in interventional/revascularization procedures. Therefore, we postulate a hypothesis that increased follow-up and preventive treatment play a role in improved outcomes after noninvasive testing.

Our findings have important clinical management implications. All patients, regardless of risk, should follow up with an outpatient provider to optimize medical management of cardiovascular risk factors. The results of noninvasive testing need to be effectively communicated to outpatient settings so appropriate preventive measures are implemented in patients with abnormal noninvasive testing. For low-risk patients, early noninvasive testing was associated with a small reduction in 30-day death/MI (−0.16% absolute risk, NNT=625) and incremental increase in revascularization (0.33%). Routine early noninvasive testing in this subgroup is unlikely to be cost effective if we only consider it from a short-term ED decisionmaking perspective. However, over a longer follow-up, noninvasive testing may lead to treatment intensification and improve medication adherence in patients with abnormal test results, which could be considered in the outpatient setting. Hence, we believe further guidelines are necessary to help clinicians integrate noninvasive testing results into their preventive strategies in outpatient settings.

This study has several methodologic strengths. We analyze a large, multicenter cohort of suspected ACS patients presenting to an ED. The cohort belongs to one of the largest integrated health care systems in the United States, with significant racial-ethnic and sociodemographic diversity. We address the data limitations of prior reports by combining extensive clinical information from the electronic medical records, HEART score data collected at the time of the ED evaluation, and comprehensive outcomes data, including hospitalizations at out-of-system hospitals and death registries. Finally, our results are robust to multiple analytic approaches, including an instrumental variable analysis to mitigate unobserved confounding.

In conclusion, we found that early noninvasive testing was associated with significant risk reduction of 1-year all-cause death and 1-year cardiovascular cause of death in low, intermediate, and high-risk patients as stratified by HEART score. The relative risk ratio was similar across the 3 HEART score groups, indicating that clinical benefit depends on the baseline risk. Our exploratory analysis of the mechanism of benefit was consistent with prior studies that have suggested that closer outpatient follow-up and medical management, as occurs with patients who receive early noninvasive testing, could be driving better outcomes.

Supervising editor: Tyler W. Barrett, MD, MSCI. Specific detailed information about possible conflicts of interest for individual editors is available at https://www.annemergmed.com/editors.

Author affiliations: From the Department of Research and Evaluation (Kawatkar, Baecker, Sharp, Wu, Zheng, Shen), Kaiser Permanente Southern California, Pasadena, CA; Bernard J. Tyson School of Medicine (Kawatkar, Sharp), Kaiser Permanente, Pasadena, CA; Division of Cardiology (Redberg), University of California, San Francisco, San Francisco, CA; Division of Cardiology (Lee), Los Angeles Medical Center, Kaiser Permanente Southern California, Los Angeles, CA; Knight Cardiovascular Institute (Ferencik), Oregon Health and Science University, Portland, OR; School of Health and Related Research (ScHARR) (Goodacre, Thokala), The University of Sheffield, Regent Court, Regent Street, Sheffield, United Kingdom; Department of Emergency Medicine (Sun), Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, PA.

Author contributions: BS, AK, AS, RR, MF, and ML conceived the study, designed the study, and obtained research funding. BS, AK, AB, RR, MF, AS, CZ, PT, SG, ES, and ML supervised the conduct of the study and data collection. AK, YL-W, and AB managed the data creation analysis, including quality control. AK conducted the analysis; BS chaired the data analysis committee. AK drafted the manuscript, and all authors contributed substantially to its revision. AK takes responsibility for the paper as a whole.

Data sharing statement: Because of the sensitive nature of the electronic medical record data and administrative agreements on mortality data source used in the cohort study, requests to access the electronic medical records based data set is not available. Additional details are available from the corresponding author upon reasonable request.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding and support: By *Annals*' policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). Benjamin C. Sun is a consultant for Medtronic, has received research support from Roche, expert witness for Fish and Richardson, expert witness for Winston and Strawn. Maros Ferencik has received research support from AHA and National Institutes of Health, consulting fees from Siemens Healthineers, HeartFlow, and Elucid, and stock options from Elucid. The rest of the authors have stated that no such relationships exist. This study was funded by The National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) under the R01 grant mechanism (Award: R01HL134647). The funding organization (NHLBI/NIH) had no role in (1) the design and conduct of the study; (2) collection, management, analysis, and interpretation of the data; (3) preparation, review, or approval of the manuscript; and (4) decision to submit the manuscript for publication.

Publication dates: Received for publication August 22, 2024. Revision received February 7, 2025. Accepted for publication February 27, 2025.

REFERENCES

1. CDC. National hospital ambulatory medical care survey: 2010 emergency department summary tables. Accessed October 16, 2024. https://archive.cdc.gov/www_cdc_gov/nchs/data/ahcd/nhamcs_emergency/2010_ed_web_tables.pdf
2. CDC/NCHS. Emergency department visits for chest pain and abdominal pain: United States, 1999–2008. Accessed October 16, 2024. http://www.cdc.gov/nchs/data/databriefs/db43.pdf
3. Writing Committee Members; Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *J Am Coll Cardiol*. 2021;78(22):e187-e285. https://doi.org/10.1016/j.jacc.2021.07.053
4. Collet JP, Thiele H, Barbato E, et al; ESC Scientific Document Group. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42(14):1289-1367. https://doi.org/10.1093/eurheartj/ehaa575
5. American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Suspected Non–ST-Elevation Acute Coronary Syndromes: Tomaszewski CA, Nestler D, Shah KH, et al. Clinical policy: critical issues in the evaluation and management of emergency department patients with suspected non-ST-elevation acute coronary syndromes. *Ann Emerg Med*. 2018;72(5):e65-e106. https://doi.org/10.1016/j.annemergmed.2018.07.045
6. Kawatkar AA, Sharp AL, Baecker AS, et al. Early noninvasive cardiac testing after emergency department evaluation for suspected acute coronary syndrome. *JAMA Intern Med*. 2020;180(12):1621-1629. https://doi.org/10.1001/jamainternmed.2020.4325
7. Sun BC, Laurie A, Fu R, et al. Comparison of the HEART and TIMI risk scores for suspected acute coronary syndrome in the emergency department. *Crit Pathw Cardiol*. 2016;15(1):1-5. https://doi.org/10.1097/HPC.0000000000000066
8. Backus BE, Six AJ, Doevendans PA, et al. Prognostic factors in chest pain patients: a quantitative analysis of the HEART score. *Crit Pathw Cardiol*. 2016;15(2):50-55. https://doi.org/10.1097/HPC.0000000000000075
9. Mahler SA, Riley RF, Hiestand BC, et al. The HEART pathway randomized trial: identifying emergency department patients with acute chest pain for early discharge. *Circ Cardiovasc Qual Outcomes*. 2015;8(2):195-203. https://doi.org/10.1161/CIRCOUTCOMES.114.001384
10. Leite L, Baptista R, Leitão J, et al. Chest pain in the emergency department: risk stratification with Manchester triage system and HEART score. *BMC Cardiovasc Disord*. 2015;15:48. https://doi.org/10.1186/s12872-015-0049-6
11. Six AJ, Cullen L, Backus BE, et al. The HEART score for the assessment of patients with chest pain in the emergency department: a multinational validation study. *Crit Pathw Cardiol*. 2013;12(3):121-126. https://doi.org/10.1097/HPC.0b013e31828b327e
12. Backus BE, Six AJ, Kelder JC, et al. A prospective validation of the HEART score for chest pain patients at the emergency department. *Int J Cardiol*. 2013;168(3):2153-2158. https://doi.org/10.1016/j.ijcard.2013.01.255
13. Mahler SA, Hiestand BC, Goff DC Jr, et al. Can the HEART score safely reduce stress testing and cardiac imaging in patients at low risk for major adverse cardiac events? *Crit Pathw Cardiol*. 2011;10(3):128-133. https://doi.org/10.1097/HPC.0b013e3182315a85
14. Backus BE, Six AJ, Kelder JC, et al. Chest pain in the emergency room: a multicenter validation of the HEART score. *Crit Pathw Cardiol*. 2010;9(3):164-169. https://doi.org/10.1097/HPC.0b013e3181ec36d8
15. Six AJ, Backus BE, Kelder JC. Chest pain in the emergency room: value of the HEART score. *Neth Heart J*. 2008;16(6):191-196. https://doi.org/10.1007/BF03086144
16. Sharp AL, Broder B, Sun BC. Improving emergency department care for low-risk chest pain. *NEJM Catalyst*. 2018. https://catalyst.nejm.org/doi/full/10.1056/CAT.18.0204
17. Natsui S, Sun BC, Shen E, et al. Evaluation of outpatient cardiac stress testing after emergency department encounters for suspected acute coronary syndrome. *Ann Emerg Med*. 2019;74(2):216-223. https://doi.org/10.1016/j.annemergmed.2019.01.027
18. Sharp AL, Baecker AS, Shen E, et al. Effect of a HEART care pathway on chest pain management within an integrated health system. *Ann Emerg Med*. 2019;74(2):171-180. https://doi.org/10.1016/j.annemergmed.2019.01.007
19. Sharp AL, Wu YL, Shen E, et al. The HEART score for suspected acute coronary Syndrome in U.S. emergency departments. *J Am Coll Cardiol*. 2018;72(15):1875-1877. https://doi.org/10.1016/j.jacc.2018.07.059
20. Holland P. Statistics and causal inference. *J Am Heart Assoc*. 1986;81(396):945-960. https://doi.org/10.2307/2289064
21. Shah ASV, Anand A, Strachan FE, et al. High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial. *Lancet*. 2018;392(10151):919-928. https://doi.org/10.1016/S0140-6736(18)31923-8
22. Roifman I, Han L, Koh M, et al. Clinical effectiveness of cardiac noninvasive diagnostic testing in patients discharged from the emergency department for chest pain. *J Am Heart Assoc*. 2019;8(21):e013824. https://doi.org/10.1161/JAHA.119.013824
23. Gupta A, Lau E, Varshney R, et al. The identification of calcified coronary plaque is associated with initiation and continuation of pharmacological and lifestyle preventive therapies: a systematic review and meta-analysis. *JACC Cardiovasc Imaging*. 2017;10(8):833-842. https://doi.org/10.1016/j.jcmg.2017.01.030
24. Williams MC, Hunter A, Shah ASV, et al. Use of coronary computed tomographic angiography to guide management of patients with coronary disease. *J Am Coll Cardiol*. 2016;67(15):1759-1768. https://doi.org/10.1016/j.jacc.2016.02.026