Journal of the American Heart Association

ORIGINAL RESEARCH

Prospective Validation and Comparative Analysis of Coronary Risk Stratification Strategies Among Emergency Department Patients With Chest Pain

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BACKGROUND: Coronary risk stratification is recommended for emergency department patients with chest pain. Many protocols are designed as "rule-out" binary classification strategies, while others use graded-risk stratification. The comparative performance of competing approaches at varying levels of risk tolerance has not been widely reported.

METHODS AND RESULTS: This is a prospective cohort study of adult patients with chest pain presenting between January 2018 and December 2019 to 13 medical center emergency departments within an integrated healthcare delivery system. Using an electronic clinical decision support interface, we externally validated and assessed the net benefit (at varying risk thresholds) of several coronary risk scores (History, ECG, Age, Risk Factors, and Troponin [HEART] score, HEART pathway, Emergency Department Assessment of Chest Pain Score Accelerated Diagnostic Protocol), troponin-only strategies (fourth-generation assay), unstructured physician gestalt, and a novel risk algorithm (RISTRA-ACS). The primary outcome was 60-day major adverse cardiac event defined as myocardial infarction, cardiac arrest, cardiogenic shock, coronary revascularization, or all-cause mortality. There were 13 192 patient encounters included with a 60-day major adverse cardiac event incidence of 3.7%. RISTRA-ACS and HEART pathway had the lowest negative likelihood ratios (0.06, 95% CI, 0.03–0.10 and 0.07, 95% CI, 0.04–0.11, respectively) and the greatest net benefit across a range of low-risk thresholds. RISTRA-ACS demonstrated the highest discrimination for 60-day major adverse cardiac event (area under the receiver operating characteristic curve 0.92, 95% CI, 0.91–0.94, $P<0.0001$).

CONCLUSIONS: RISTRA-ACS and HEART pathway were the optimal rule-out approaches, while RISTRA-ACS was the best-performing graded-risk approach. RISTRA-ACS offers promise as a versatile single approach to emergency department coronary risk stratification.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03286179.

Key Words: acute coronary syndrome ■ emergency department ■ risk score

Chest pain is the second leading reason for emergency department (ED) visits in the United States, with an estimated annual cost upwards of 5 billion dollars.[1] While up to 20% of patients may have a cardiac cause of their chest pain, few have life-threatening conditions and the majority are

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Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.020082

For Sources of Funding and Disclosures, see page 15.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Both the HEART [History, ECG, Age, Risk Factors, and Troponin] Pathway and a novel coronary risk algorithm (RISTRA-ACS) accurately identify emergency department patients with chest pain at very low risk (<0.5% incidence) of a major adverse cardiac event in the following 60 days.
- RISTRA-ACS had higher discrimination for overall 60-day major adverse cardiac event risk as compared with the HEART score, a troponin-only approach, or unstructured physician gestalt.

What Are the Clinical Implications?

- The HEART Pathway is a well-validated means of assigning a very low major adverse cardiac event risk designation, and thus can identify emergency department patients who have chest pain and who are unlikely to benefit from further cardiac testing.
- RISTRA-ACS may be an optimal tool for a graded-risk approach to emergency department chest pain evaluation and treatment, but external validation is needed.

Nonstandard Abbreviations and Acronyms

eCDS	electronic clinical decision support
EDACS-ADP	Emergency Department Assessment of Chest Pain Score Accelerated Diagnostic Protocol
HEART	History, ECG, Age, Risk Factors and Troponin
LOQ	level of quantitation
MACE	major adverse cardiac event
MACE-CR	major adverse cardiac event excluding percutaneous or surgical coronary revascularizations
RISTRA	Risk Stratification

ultimately diagnosed with noncardiac pain.[2] Despite the low incidence of mortality and morbidity, patients presenting to EDs with chest pain historically have had among the largest variations in hospital admission rates, largely driven by guideline recommendations to secure objective cardiac testing for possible acute coronary syndrome (ACS) before or within 72 hours of hospital discharge.[3–6] This recommendation has been repeatedly challenged in light of evidence that only 1% to 4% of patients without diagnostic ECGs and/or cardiac biomarkers have angiographic evidence of significant coronary artery disease.[7–9] Accordingly, a recent clinical policy from the American College of Emergency Physicians has recommended against routine objective cardiac testing in the ED for patients at low risk for ACS.[10]

Accurate identification of patients with chest pain at low risk of ACS is paramount to this recommendation. This goal has been the focus of decades of research, facilitated by improvements in cardiac biomarker testing characteristics, with the current state-of-the-art favoring the use of risk stratification protocols over unstructured physician judgment, given a propensity for risk overestimation with the latter (albeit less so if determined after troponin and ECG testing).[10–13] Many of these protocols function as binary "rule-out" strategies (differentiating between low- and non-low-risk patients) designed to maximize sensitivity and negative predictive value (NPV) for downstream major adverse cardiac events (MACE). Two well-validated rule-out protocols are the History, ECG, Age, Risk Factors, and Troponin Pathway (HEART Pathway) and the Emergency Department Assessment of Chest Pain Score Accelerated Diagnostic Protocol (EDACS-ADP), which have specificities ranging from 40% to 60% in achieving NPVs >99% for 30- to 45-day MACE.[14–18] However, a non-low-risk designation fails to discriminate between marginally at-risk patients and moderate- or high-risk patients.[19] A more graded-risk approach could identify patients who may still be considered low (ie, 1%–2%) risk and appropriate for outpatient management as well as those at low-moderate risk (eg, 2%–5% risk) in whom expedited outpatient or observation unit management may be preferred to hospital ward admission.[20]

To improve risk stratification among these marginally at-risk patients, we designed an algorithm to predict 60-day MACE risk among ED patients with chest pain with possible ACS. This algorithm (RISTRA-ACS) utilizes a combination of HEART and EDACS score elements, alongside early peak troponin values, to generate several levels of estimated 60-day MACE risk (<0.5%, 1%, 2%, 3%, 5%, 7%, and >7%) based on analyses of a large retrospective database of ED patients with chest pain in an integrated health system.[21] We subsequently implemented RISTRA-ACS in 13 EDs within the same integrated health system using an electronic clinical decision support (eCDS) tool embedded within the electronic health record (EHR). The goals of this investigation are to internally validate RISTRA-ACS, externally validate the embedded component risk scores (HEART score, HEART pathway, EDACS-ADP) and compare the diagnostic performance of RISTRA-ACS and these risk

scores against each other as well as troponin-only approaches and unstructured physician gestalt for ACS.

METHODS

Study Design, Setting, and Subjects

This prospective cohort study enrolled patients presenting between January 1, 2018 and December 31, 2019 to 13 medical center EDs within Kaiser Permanente Northern California (KPNC), a private not-for-profit integrated health system of over 4 million members representing 33% of the region's population. The study was part of a pragmatic trial (Clinicaltrials.gov NCT03286179) examining the impact of a novel coronary risk algorithm (RISTRA-ACS) among adult (age 18 years or over) ED patients with both a chief complaint of chest pain and serum troponin level measurement in the ED. All arenas of care (inpatient, outpatient, and emergency) within KPNC utilize a single integrated EHR (Epic, Verona, WI). RISTRA-ACS was incorporated as a module in a web-based eCDS interface referred to as RISTRA (Risk Stratification), which is nested within the EHR and has previously been described for several other use cases.[22,23] The study was approved by the KPNC Institutional Review Board with a waiver of informed consent. Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to KPNC at kpnc.irb@kp.org.

Physicians were educated about RISTRA-ACS in advance of the study and reminded monthly about its availability along with feedback on their personal frequency of RISTRA-ACS use. Real-time prompts to ED physicians were provided via automated text messaging whenever serum troponin results became available for an adult patient under their care with a chief complaint of chest pain or discomfort.[24] Physicians confirmed upon activation of the RISTRA-ACS module that the following appropriateness criteria were met: (1) age ≥18 years; (2) chief complaint of chest pain or chest discomfort; and (3) clinical concern for ACS.

ED patient encounters were included in this analysis if they met the following criteria: age ≥18 years, serum troponin measurement within 6 hours of ED arrival, active health plan membership, and complete RISTRA-ACS data collection, including recommended troponin testing (see below). Encounters were excluded if there was a previously included encounter by the same patient within 60 days prior (because of a 60-day outcome period, see below), there was an ED diagnosis of ST-segment–elevation myocardial infarction or a discharge against medical advice, there were <9 out of 12 months of active health plan membership before the encounter (to improve capture of historical data populated from the EHR), or if there were <60 days of continuous active health plan membership following the encounter (for outcome capture) except in cases of death.

Serum troponin values at all sites were obtained using a fourth-generation troponin I assay, the Access AccuTnI+3 (Beckman-Coulter, Brea, CA). The 99th percentile for this assay is 0.04 ng/mL per local institutional reporting guidelines and reference literature.[25] The coefficient of variation at the 99th percentile is <10%, and the limits of blank, detection, and quantitation are <0.01, 0.01, and 0.02 ng/mL, respectively.

Data Collection and Serum Troponin Testing

RISTRA-ACS imported relevant structured data from the EHR (eg, past medical history), which was modified and/or validated by the clinician, followed by user input of subjective elements from the clinical history as detailed in Data S1. Following initial data entry, RISTRA-ACS calculated both EDACS and HEART scores to determine a binary classifier for each (low-risk versus non-low-risk) based on the corresponding protocols (EDACS-ADP and HEART pathway, Tables 1 and 2). One key difference was that a history of coronary artery disease was not considered an independent non-low-risk criterion for the HEART score component of RISTRA-ACS, in contrast to the HEART pathway.[26] Serum troponin measurements were then imported from the EHR and further troponin

Table 1. Emergency Department Assessment of Chest Pain Score (EDACS)

- Age (y)
  - 18–45 (add 2 points)
  - 46–50 (add 4 points)
  - 51–55 (add 6 points)
  - 56–60 (add 8 points)
  - 61–65 (add 10 points)
  - 66–70 (add 12 points)
  - 71–75 (add 14 points)
  - 76–80 (add 16 points)
  - 81–85 (add 18 points)
  - 86+ (add 20 points)
- Known coronary artery disease (previous myocardial infarction, coronary bypass surgery or percutaneous coronary intervention) *or* ≥3 cardiac risk factors (hypertension, hyperlipidemia, diabetes mellitus, smoking in past 90 d, or family history of premature coronary artery disease in first-degree relative age <55 y) in patients aged 18–50 y old (add 4 points)
- Male sex (add 6 points)
- Typical symptoms
  - Diaphoresis (add 3 points)
  - Pain radiating to arm, shoulder, neck, or jaw (add 5 points)
- Atypical symptoms
  - Pain with inspiration (subtract 4 points)
  - Pain reproduced by palpation (subtract 6 points)

For EDACS accelerated diagnostic protocol (EDACS-ADP) classification, patients with any of the following were considered non-low-risk: (1) EDACS score ≥16, (2) new ischemic ECG, (3) positive troponin (>99th percentile) or (4) presence of crescendo angina (pain that is recurrent and worsening, lasts at least 5–10 minutes, and occurs at rest or with minimal exertion).

Table 2. HEART Score

- History (standardized as the net number of high-risk minus low-risk symptoms)*
  - ≥2 net symptoms (highly suspicious, 2 points)
  - 0–1 net symptoms (moderately suspicious, 1 point)
  - <0 net symptoms (slightly suspicious, 0 points)
- ECG findings (E)
  - New ischemic changes (ST-segment depressions ≥0.05 mV in 2 contiguous leads or T-wave inversions ≥1 mV; 2 points)
  - Repolarization abnormalities, bundle branch blocks, paced rhythms, nonspecific T wave or ST-changes, or evidence of prior infarction (1 point)
  - Normal (0 points)
- Age (y)
  - ≥65 (2 points)
  - 45–64 (1 point)
  - <45 (0 points)
- Risk factors (hypercholesterolemia, hypertension, diabetes mellitus, smoking in past 90 d, family history of premature coronary artery disease in first-degree relative aged <55 y, body mass index ≥30)
  - 3 risk factors *or* known atherosclerotic disease (coronary revascularization, stroke, myocardial infarction, peripheral artery disease; 2 points)
  - 1–2 risk factors (1 point)
  - 0 risk factors (0 points)
- Troponin
  - Less than or equal to the 99th percentile of normal limit (0 points)
  - 1 to 3 times the 99th percentile normal of limit (1 point)
  - >3 times the 99th percentile of normal limit (2 points)

For HEART (History, Electrocardiogram, Age, Risk Factors, and Troponin) Score pathway classification, patients with any of the following were considered non-low-risk: (1) HEART score ≥4, (2) new ischemic ECG, (3) positive troponin (>99th percentile), or (4) a history of coronary artery disease (note that this last criterion was *not* used for Risk Stratification–Acute Coronary Syndrome scoring).

*High-risk symptoms=exertional chest pain or dyspnea; pain radiating to arm, shoulder, neck or jaw; diaphoresis; nausea or vomiting; Low-risk symptoms=pain worse with inspiration; pain reproduced by palpation; sharp or stabbing pain.

testing in 2 hours intervals[27] was recommended unless 1 of 2 criteria was met: (1) serial troponin values were unchanged or decreasing over a minimum 2-hour interval, with the last troponin being measured at least 4.5 hours from pain onset, or (2) a troponin value below the level of quantitation (LOQ) was obtained at least 3 hours (if both EDACS and HEART indicated low risk) or 4.5 hours (all others) from pain onset. The 4.5-hour cut-off represents the midpoint of the guideline recommended 3- to 6-hour window from pain onset for troponin testing, while a 3-hour cut-off was reserved for those at very low risk.[6] Both cut-offs were further justified based on a plateau in diagnostic performance of fourth-generation troponin assays within 2 to 4 hours from chest pain onset.[28] Once no further serum troponin measurements were recommended, and after physicians entered their gestalt for ACS, an estimate of 60-day MACE risk was provided along with recommendations for disposition (Figure 1).

Outcomes

The primary outcome was 60-day MACE, defined as the composite outcome of acute myocardial infarction, cardiac arrest, cardiogenic shock, all-cause mortality or coronary revascularization (surgical or percutaneous) within 60 days of the index encounter. Acute myocardial infarction, cardiac arrest, or cardiogenic shock was considered to have occurred if a corresponding *International Classification of Diseases, Tenth Revision* (*ICD-10*) code was the first or second diagnosis listed at an inpatient or ED encounter within the integrated health system, or was used in a coded claim for services provided at facilities outside of the integrated health system (any coding position). For coronary revascularization, any corresponding *ICD-10* procedure or Current Procedural Terminology code during a hospitalization within or outside of the integrated health system was counted. All-cause mortality was determined using a composite death database comprising KPNC mortality records, California Department of Public Health Vital Records, and Social Security Death Index data. A list of *ICD-10* and Current Procedural Terminology codes used are available in Data S2.

The secondary outcome was 60-day MACE excluding percutaneous or surgical coronary revascularizations (MACE-CR). This outcome was used because of a lack of reliable methodology, specifically following an ED visit,[29] to categorize coronary revascularization procedures as either elective or nonelective based on diagnostic and/or billing codes, and because inclusion of elective coronary revascularization procedures is inconsistent with consensus agreements on appropriate MACE end points.[30] Thus, the primary outcome represents a conservative MACE estimate, whereas the true MACE incidence lies somewhere between MACE and MACE-CR.

Data Analysis

For the purpose of comparative analysis of RISTRA-ACS, we assessed performance of the algorithm as both a rule-out and a graded-risk stratification approach. For the former, we compared the very-low-risk RISTRA designation (<0.5% predicted 60-day MACE risk) against several alternative rule-out strategies: (1) HEART score <4, (2) HEART pathway low risk, (3) EDACS-ADP low risk, (4) physician gestalt for ACS of ≤2%, and (5) troponin below the LOQ. We chose physician gestalt of ≤2% a priori as a cut point based on an estimated 1% to 2% MACE risk for a HEART score <4.[31] Using the LOQ as the troponin-only rule-out threshold was based on literature demonstrating that the LOQ for the AccuTnI+3 is a strong discriminator of MACE risk in several study settings,[21,32] being consistent with observations of increased cardiovascular risk among patients with high-sensitivity troponin values in the upper range of normal.[33,34] In addition, because RISTRA-ACS used a combination of troponin below the LOQ, HEART pathway, and EDACS-ADP,

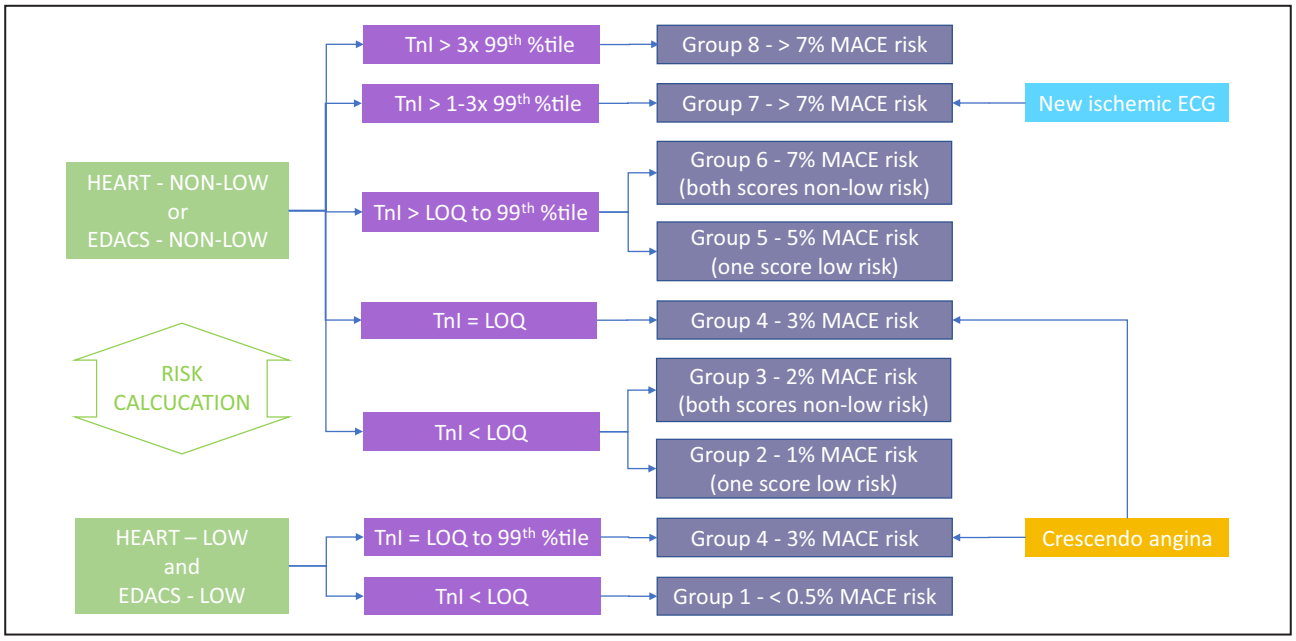

Figure 1. RISTRA-ACS algorithm.
Upon data entry into the electronic clinical decision support interface (RISTRA), risk estimation begins with calculation of both the HEART score and the EDACS (green boxes). Subsequent risk adjustment is based on the peak troponin value (purple boxes) obtained at least 3 hours from symptom onset (if both HEART and EDACS scores indicate low risk) or at least 4.5 hours from pain onset (if either HEART or EDACS scores indicate non-low risk). A minimum risk override was implemented in the presence of crescendo angina (yellow box, minimal risk 3%) or new ischemic ECG changes (>7% risk), with higher risk assignment allowed if criteria were present. Risk estimates were presented to the clinician following completion of data entry and troponin testing completion, indicated by either a stable or decreasing troponin value on repeated measures at least 2 hours apart *or* a single measure below the LOQ at or beyond the above specified time from pain onset. EDACS indicates Emergency Department Assessment of Chest Pain Score; HEART, History, Electrocardiogram, Age, Risk Factors, Troponin; LOQ, limit of quantitation; MACE, major adverse cardiac event at 60 days; RISTRA-ACS, Risk Stratification–Acute Coronary Syndrome; and TnI, troponin I.

direct comparisons to these individual components was of interest. The relative performance among rule-out approaches was assessed using standard test characteristics (sensitivity, specificity, likelihood ratios, and predictive values) and decision curve analysis (see below). Our a priori hypothesis was that RISTRA-ACS would achieve a NPV >99.5%, inclusive of 95% CIs, when used as a rule-out approach.

For graded-risk strategies, we compared 3 approaches with RISTRA-ACS: (1) HEART score, (2) physician gestalt for ACS, and (3) troponin-only strata (peak troponin within 6 hours of ED arrival using 4 strata of <LOQ, LOQ to 99th percentile, 1 to 3 times the 99th percentile, or >3 times the 99th percentile). The choice of the LOQ as a cut point is explained above, while the use of the 99th percentile and 3 times the 99th percentile were chosen to mirror troponin categorization by both the HEART score and RISTRA-ACS.[35] Performance was assessed by discrimination (area under the receiver operating characteristic curve [AU-ROC]), calibration (calibration plots and the Hosmer-Lemeshow test), and accuracy (scaled Brier score).[36] The scaled Brier score is a normalized variant of the Brier score in which the scaled Brier=1−(Brier score)/(maximum possible Brier score). A higher Brier score indicates a less informative model, and the maximum Brier score represents a completely uninformative model in which prediction accuracy is purely driven by the disease prevalence. Thus, a scaled Brier score indicates accuracy of a given model relative to a fully uninformative model. Of note, the direction of the scaled Brier is inverted relative to the standard Brier score (ie, a higher scaled Brier score indicates better accuracy). To assess calibration, we split the data set equally into testing and validation sets to compare predicted risks (testing) against observed risks (validation) and constructed corresponding calibration plots. We also reported the Hosmer-Lemeshow test statistic, with values <0.05 indicating poor calibration, though it has been noted that this statistic should not be interpreted in isolation.[37] Ninety-five percent CIs for the AU-ROC curve and scaled Brier score were calculated using bootstrapped estimates from 2000 replicates. We defined a difference between AU-ROCs to be significant if the *P* value for the difference was <0.05, and the difference between scaled Brier scores to be significant if there was no overlap of 95% CIs.

To assess clinical utility and reclassification among the various rule-out and graded-risk approaches, we used decision curve analysis. Decision curves plot the net benefit for a given risk stratification strategy across a range of risk thresholds, allowing comparison of relative net benefit between strategies at varying degrees of risk tolerance, and are generally preferred to alternative reclassification statistics (eg, the net reclassification index) as being less subject to bias and misinterpretation.[38–40] Details regarding calculation of net benefit and decision curve analysis presentation are available in Data S3.[41,42] All data analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

There were 17 249 uses of RISTRA-ACS eCDS among 1 603 448 total ED encounters during the study period, of which 13 192 met study inclusion criteria as outlined in Figure 2. The median age was 58 years, 44% were male patients, 23% were diabetic, and 13% had a known history of coronary artery disease (Table 3). A single troponin test was sent in 55% and 85% were discharged home directly from the ED. Overall, 3.7% had a 60-day MACE and 3.3% had a 60-day MACE-CR. In comparison, among patients without RISTRA-ACS eCDS use who were potentially study eligible, the proportion with 60-day MACE was higher; 5.5% among those with an ED diagnosis of chest pain (n=47 078, Table S1) and 7.8% among those with a chief complaint of chest pain or discomfort (n=69 894, Table S2, groups not mutually exclusive).

Test characteristics of rule-out approaches for 60-day MACE and 60-day MACE-CR are presented in Table 4. RISTRA-ACS, HEART pathway, and physician gestalt for ACS had the highest sensitivities for 60-day MACE (range 96.7%–97.6%), with RISTRA-ACS and HEART pathway demonstrating the lowest negative likelihood ratios (0.06, 95% CI, 0.03–0.10 and 0.07, 95% CI, 0.04–0.11, respectively). Accordingly both RISTRA-ACS and the HEART

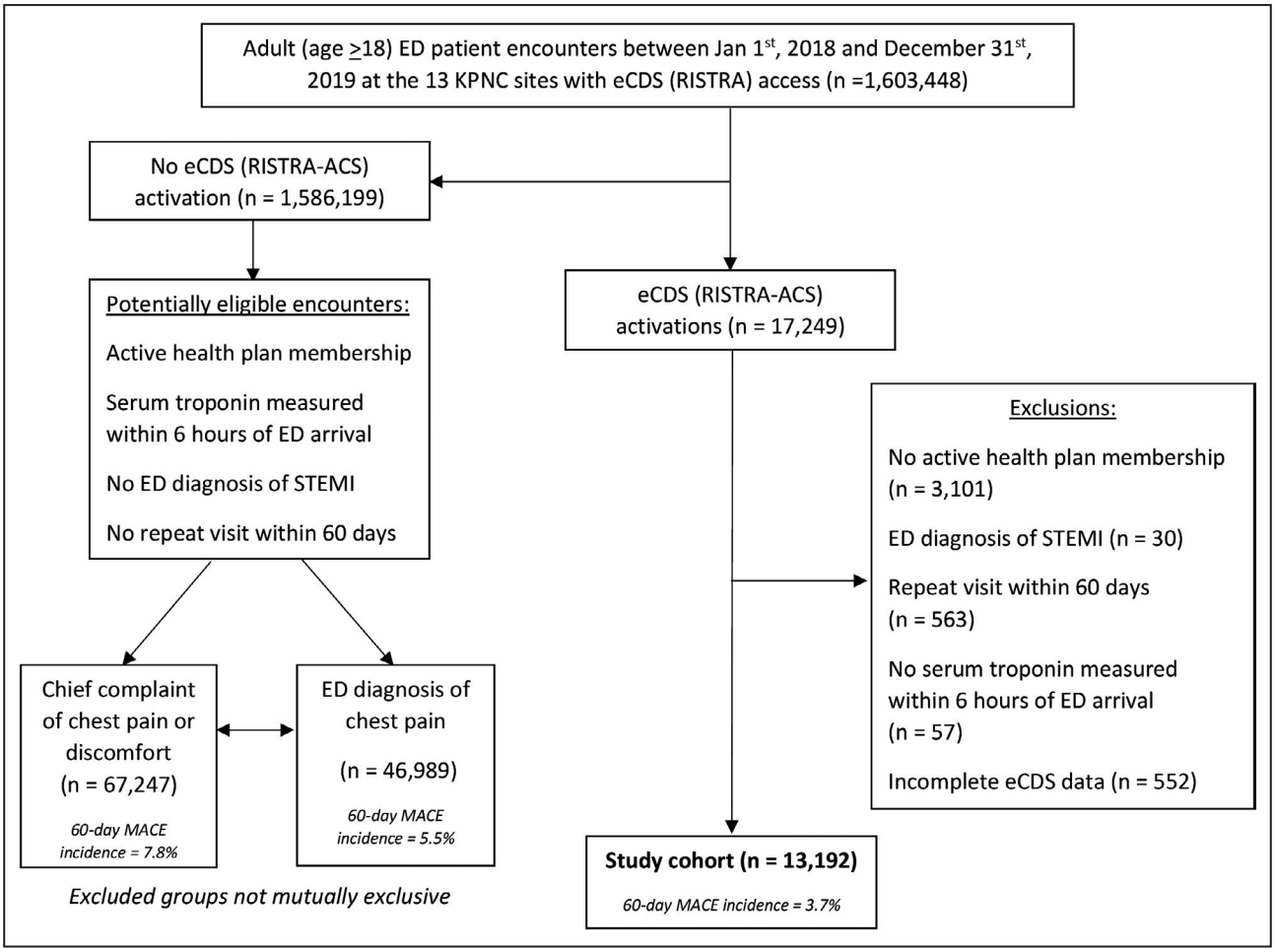

Figure 2. Study cohort flow chart.
eCDS indicates electronic clinical decision support; ED, emergency department; KPNC, Kaiser Permanente Northern California; MACE, major adverse cardiac event; RISTRA-ACS, Risk Stratification–Acute Coronary Syndrome; and STEMI, ST-segment–elevation myocardial infarction.

Table 3. Study Cohort Characteristics

	N=13 192
Chief complaint	
Chest pain or chest discomfort, %	85
Risk factors	
Age, y, median (IQR)	58 (47–69)
Male sex, %	44
Hypertension, %	48
Hypercholesteremia, %	47
Diabetes mellitus, %	23
CAD, %	13
Coronary revascularization, %	8
Myocardial infarction, %	9
Stroke or TIA, %	6
Peripheral artery disease, %	2
Smoker, %	9
Family history premature CAD in first-degree relative, %	6
Obesity, %	42
Presenting symptoms	
Diaphoresis, %	6
Radiation to arm/jaw/neck/shoulder, %	17
Pain on palpation, %	10
Pain on inspiration, %	10
Exertional symptoms, %	12
Atypical sharp/stabbing pain, %	22
Nausea or vomiting, %	22
Crescendo angina, %	5
ECG interpretation	
Normal, %	63
Nondiagnostic, %	33
New ischemic changes, %	4
Peak troponin within 6 h of ED arrival	
< LOQ, %	88
LOQ to 99th percentile, %	7
1–3 times 99th percentile, %	2
>3 times 99th percentile, %	2
Risk scores	
HEART score, median (IQR)	4 (3–5)
Low risk by HEART pathway, %	47
EDACS score, median (IQR)	11 (7–16)
Low risk by EDACS-ADP, %	67
ED disposition	
Admission, %	4
Observation, %	11
Discharge, %	85
60-d outcomes	
MACE, %	3.7
MACE-CR, %	3.3
Any coronary revascularization, %	1.8
All-cause mortality, %	0.4

CAD indicates coronary artery disease; EDACS, Emergency Department Assessment of Chest Pain Score; EDACS-ADP, Emergency Department Assessment of Chest Pain Score Accelerated Diagnostic Protocol; HEART, History, Electrocardiogram, Age, Risk Factors, Troponin; IQR, interquartile range; LOQ, limit of quantitation; MACE, major adverse cardiac event at 60 days; MACE-CR, major adverse cardiac event at 60 days excluding coronary revascularization; RISTRA-ACS, Risk Stratification–Acute Coronary Syndrome; and TIA, transient ischemic attack.

pathway had NPVs for 60-day MACE with CIs >99.5% (99.8%, 95% CI, 99.6%–99.9% and 99.7%, 95% CI, 99.6%–99.9%, respectively) and were thus accurately representative of the very low 60-day MACE risk designation (<0.5%) by RISTRA-ACS. Results were similar for MACE-CR.

Comparative evaluation of the graded-risk approaches is presented in Table 5. As compared with the HEART score, troponin-only strata, and physician gestalt for ACS, RISTRA-ACS demonstrated the highest discrimination for 60-day MACE with an AU-ROC of 0.92 (95% CI, 0.91–0.94, $P<0.0001$ for difference in AU-ROC compared with all others). ROC curves for 60-day MACE and MACE-CR are presented in Figures S1 and S2, respectively. Calibration plots for 60-day MACE and MACE-CR indicated good calibration for RISTRA-ACS and troponin strata but unstable calibration for HEART score and physician gestalt (Figures 3 and 4, respectively). Calibration was likewise acceptable for all approaches by the Hosmer-Lemeshow test except for the HEART score. The highest accuracy, as assessed by the scaled Brier score, was shared by RISTRA-ACS and troponin strata. Findings were similar for MACE-CR.

Decision curves are presented in Figure 5 (MACE outcomes for rule-out strategies), Figure 6 (MACE outcomes for graded-risk strategies), Figure 7 (MACE-CR outcomes for rule-out strategies), and Figure 8 (MACE-CR outcomes for graded-risk strategies). The preferred approach varied by risk threshold and disease prevalence. For example, in terms of highest net benefit, at the observed 3.7% prevalence of 60-day MACE a "test all" strategy was dominant below a 0.3% risk threshold, either RISTRA-ACS or HEART pathway dominated for risk thresholds between 0.3% and 1.2%, EDACS-ADP was dominant for risk thresholds between 1.3% and 1.5%, and a troponin-only (below LOQ) strategy dominated for risk thresholds >1.5%. These risk thresholds shifted rightward at an assumed MACE prevalence of 10%: a "test all" strategy was dominant below a risk threshold of 0.7% while RISTRA-ACS or HEART pathway

Table 4. Comparative Performance of "Rule-Out" Risk Stratification Strategies for Emergency Department Patients With Chest Pain and Concern for Acute Coronary Syndrome (n=13 192)

	Troponin < LOQ	EDACS-ADP	HEART Score	HEART Pathway	RISTRA-ACS	Physician Gestalt
Low-risk classification, n (%)	11 686 (89)	8786 (67)	6265 (47)	6194 (47)	5444 (41)	2332 (18)
Primary outcome: 60-d MACE						
True positives (n=492)	396	442	434	476	480	478
Sensitivity	80.5 (76.7–84.0)	89.8 (86.8–92.4)	88.2 (85.0–91.0)	96.7 (94.8–98.1)	97.6 (95.8–98.7)	97.2 (95.3–98.4)
True negatives (n=12 700)	11 590	8736	6207	6099	5432	2318
Specificity	91.3 (90.7–91.8)	68.8 (68.0–69.6)	48.9 (48.0–49.8)	48.0 (47.2–48.9)	42.8 (41.9–43.6)	18.3 (17.6–18.9)
Positive likelihood ratio	9.2 (8.6–9.9)	2.9 (2.8–3.0)	1.7 (1.7–1.8)	1.9 (1.8–1.9)	1.7 (1.7–1.7)	1.2 (1.2–1.2)
Negative likelihood ratio	0.21 (0.18–0.26)	0.15 (0.11–0.19)	0.24 (0.19–0.31)	0.07 (0.04–0.11)	0.06 (0.03–0.10)	0.16 (0.09–0.26)
Positive predictive value	26.3 (24.1–28.6)	10.0 (9.2–11.0)	6.3 (5.7–6.9)	6.7 (6.2–7.3)	6.2 (5.7–6.8)	4.4 (4.0–4.8)
Negative predictive value	99.2 (99.0–99.3)	99.4 (99.3–99.6)	99.1 (98.8–99.3)	99.7 (99.6–99.9)	99.8 (99.6–99.9)	99.4 (99.0–99.7)
Secondary outcome: 60-d MACE-CR						
True positives (n=430)	378	398	377	417	422	418
Sensitivity	88.0 (84.5–90.8)	92.6 (89.7–94.9)	87.7 (84.2–90.6)	97.0 (94.9–98.4)	98.1 (96.4–99.2)	97.2 (95.2–98.6)
True negatives (n=12 762)	11 634	8754	6212	6102	5436	2320
Specificity	91.1 (90.7–91.6)	68.6 (67.8–69.4)	48.4 (47.6–49.3)	47.8 (46.9–48.7)	42.6 (41.7–43.7)	18.2 (17.5–18.9)
Positive likelihood ratio	10.0 (9.3–11.0)	3.0 (2.8–3.1)	1.7 (1.6–1.8)	1.9 (1.8–1.9)	1.7 (1.7–1.7)	1.2 (1.2–1.2)
Negative likelihood ratio	0.13 (0.10–0.17)	0.11 (0.08–0.15)	0.25 (0.20–0.33)	0.06 (0.04–0.11)	0.04 (0.02–0.09)	0.15 (0.09–0.27)
Positive predictive value	25.1 (22.9–27.3)	9.0 (8.2–9.9)	5.4 (4.9–6.0)	5.9 (5.4–6.5)	5.4 (5.0–6.0)	3.8 (3.5–4.2)
Negative predictive value	99.6 (99.4–99.7)	99.6 (99.5–99.8)	99.2 (98.9–99.4)	99.8 (99.6–99.9)	99.9 (99.7–99.9)	99.5 (99.1–99.7)

Strategies are ranked from left to right by decreasing proportion of low-risk classification. EDACS-ADP indicates Emergency Department Assessment of Chest Pain Score Accelerated Diagnostic Protocol; LOQ, limit of quantitation; MACE, major adverse cardiac event; and MACE-CR, major adverse cardiac event excluding coronary revascularization.

dominated for risk thresholds of 0.7% upwards and through 2.0%. For graded-risk strategies, RISTRA-ACS or troponin-only strata had the highest net benefit through risk thresholds of 10%. Findings were similar for MACE-CR.

DISCUSSION

There were 3 key findings from this study. First, both RISTRA-ACS and the HEART pathway had the highest NPV and lowest negative likelihood ratios, yielding the highest net benefit within a broad range of acceptable low-risk thresholds. This finding also reinforces a recent prospective study by Stopyra et al in showing a higher NPV of the HEART pathway over EDACS-ADP.[18] Second, RISTRA-ACS and troponin-only strata approaches had the highest discrimination and accuracy among graded-risk strategies, reinforcing the strong correlation between absolute troponin levels and cardiovascular risk and, accordingly, the weakness of an underweighted treatment of troponin in the HEART score (as reflected in its suboptimal calibration). Third, the novel RISTRA-ACS algorithm was successfully validated as being able to combine rule-out and graded-risk strategies to achieve risk stratification performance that was equivalent or superior to comparators. Two lesser findings were the suboptimal performance of unstructured physician gestalt as compared with structured risk scores and the overall safety of a time-from-pain-onset approach to troponin testing. Our discussion will focus on how these observations might guide clinical practice and future research.

To start, given literature suggesting a testing threshold of 2% risk for suspected ACS and recent clinical guidelines endorsing a 1% to 2% acceptable MACE miss rate for ED patients with chest pain, the value of discriminating among patients with a collective incidence of downstream MACE <2% using graded-risk approaches deserves clarification.[10,43] At issue is the fact that calculations around testing thresholds are sensitive to evolving assumptions surrounding absolute risks and benefits. To this point, we previously revisited the 2% risk testing threshold for ACS calculated by Kline et al[43] in 2005 using the same equation by Pauker et al[44] but with updated estimations of test performance, risks, and benefits. Using these updated assumptions, we arrived at significantly lower testing thresholds, ranging between 0.7% and 0.9% risk.[21] We also extrapolated cost-effective analyses of diagnostic strategies for suspected ACS by Goodacre et al[45] to estimate a cost of 150 000 US dollars per quality-adjusted life year gained when using computed tomographic coronary angiography at a testing threshold of 0.7% risk. Accordingly, we would contend that the subgroup of patients with risks confidently below

Table 5. Comparative Performance of Graded-Risk Stratification Strategies for Emergency Department Patients With Chest Pain and Concern for Acute Coronary Syndrome (n=13 192)

	Physician Gestalt*	HEART Score†	Troponin Group‡	RISTRA-ACS Group§
Median (IQR)	10 (4–20)	4 (3–5)	1 (1–1)	2 (1–4)
Primary outcome: 60-d MACE				
AU-ROC (95% CI)	0.85 (0.83–0.87)	0.88 (0.86–0.89)	0.89 (0.87–0.89)	0.92 (0.91–0.94)
P value for change in AU-ROC (compared with next lowest)	NA	*P*=0.014	*P*=0.35	*P*<0.001
Scaled Brier score (95% CI)	30 (26–34)	26 (22–30)	45 (40–49)	42 (38–46)
Hosmer-Lemeshow test	0.84	<0.01	0.67	0.53
Secondary outcome: 60-d MACE-CR				
AU-ROC (95% CI)	0.86 (0.84–0.88)	0.89 (0.87–0.90)	0.93 (0.91–0.94)	0.94 (0.93–0.96)
P value for change in AU-ROC (compared with next lowest)	NA	*P*=0.018	*P*<0.001	*P*<0.001
Scaled Brier score (95% CI)	31 (26–35)	28 (23–32)	50 (45–54)	47 (42–51)
Hosmer-Lemeshow test	0.64	<0.01	0.43	0.44

Comparison between incremental risk strategies using measures of discrimination (AU-ROC), calibration (Hosmer-Lemeshow test), and overall performance (scaled Brier score, 95% CIs are derived based on 2000 bootstrap replicates). Strategies are ranked from left to right by increasing AU-ROC (95% CIs are derived based on 2000 bootstrap replicates). Hosmer-Lemeshow test: we split the cohort randomly into 2 samples—a developmental sample and validation sample. We fit the model using the developmental sample, then test the calibration of the model by performing the goodness-of-fit on the validation sample. AU-ROC indicates area under receiver operating characteristic curve; HEART, History, Electrocardiogram, Age, Risk Factors, Troponin; IQR, interquartile range; MACE, major adverse cardiac event; MACE-CR, major adverse cardiac event excluding coronary revascularization; NA, not applicable; and RISTRA-ACS, Risk Stratification–Acute Coronary Syndrome.

*Unstructured physician estimate of acute coronary syndrome risk, range 1% to 100%.

†Range 0 to 10, see Table 1.

‡Peak troponin within 6 hours of emergency department arrival (4 groups): less than level of quantitation (group 1), level of quantitation to 99th percentile (group 2), 1 to 3 times 99th percentile (group 3), >3 times the 99th percentile (group 4).

§Eight groups, see Figure 1.

these testing thresholds (eg, low-risk HEART pathway or very-low-risk RISTRA-ACS designations) should be given a "no further testing" recommendation.

At the same time, whether patients in the higher end of the low-risk range (ie, 1%–2% risk) benefit from further downstream testing is both speculative and contentious. Several studies examining outcomes following objective cardiac testing among undifferentiated ED patients with chest pain have demonstrated increases in coronary revascularizations but no notable impact on the incidence of near-term MACE-CR.[46–48] Accordingly many have questioned this practice, as well as whether coronary revascularization should be included as part of a composite MACE outcome metric for ED decision-making.[49] However, long-term studies have found small reductions in myocardial infarction and mortality several years following randomization to computed tomographic coronary angiography in both ED patients with chest pain and outpatients with stable angina.[50,51] Thus, while guidelines emphasizing urgent (ie, within 72 hours) objective cardiac testing for low-risk ED patients with chest pain have rightly been questioned, there is arguably still a role for discrete risk stratification among low-risk patients to better identify which ED patients might benefit from directed outpatient follow-up.[52,53] In this context, a graded-risk strategy such as RISTRA-ACS that incorporates both troponin strata (and specifically differentiation between low- and high-normal-range troponin values) and structured clinical risk scores is appealing as a means of effectively discriminating between the "no further testing" and "nonurgent testing" low-risk subgroups.

Another notable finding of this study concerns the performance of unstructured physician gestalt for ACS. Most studies of physician gestalt for ACS in the ED have measured gestalt before any testing and found suboptimal predictive performance.[12,13,54] In this study, physician gestalt was measured after troponin and ECG testing and, when using a gestalt cut-off of 2% risk or less, demonstrated a sensitivity on par with the HEART pathway and RISTRA-ACS. However, because of the lower specificity of physician gestalt, the NPV and negative likelihood ratio were inferior as compared with structured risk scores. We are aware of only 1 other study that assessed physician gestalt following ECG and troponin testing that similarly resulted in high sensitivity (98%) and low specificity (17%) for 30-day ACS.[55] The low specificity seen in these studies reflects a general tendency of ED physicians to overestimate risk.[12] Accordingly when assessed as a graded-risk strategy, physician gestalt demonstrated lower overall discrimination as compared with the HEART score, troponin strata, or RISTRA-ACS. However, it does appear that unstructured pretest physician gestalt can at least improve risk prediction among intermediate-risk patients with nondiagnostic troponin and ECG results.[56] Whether posttest gestalt can be integrated

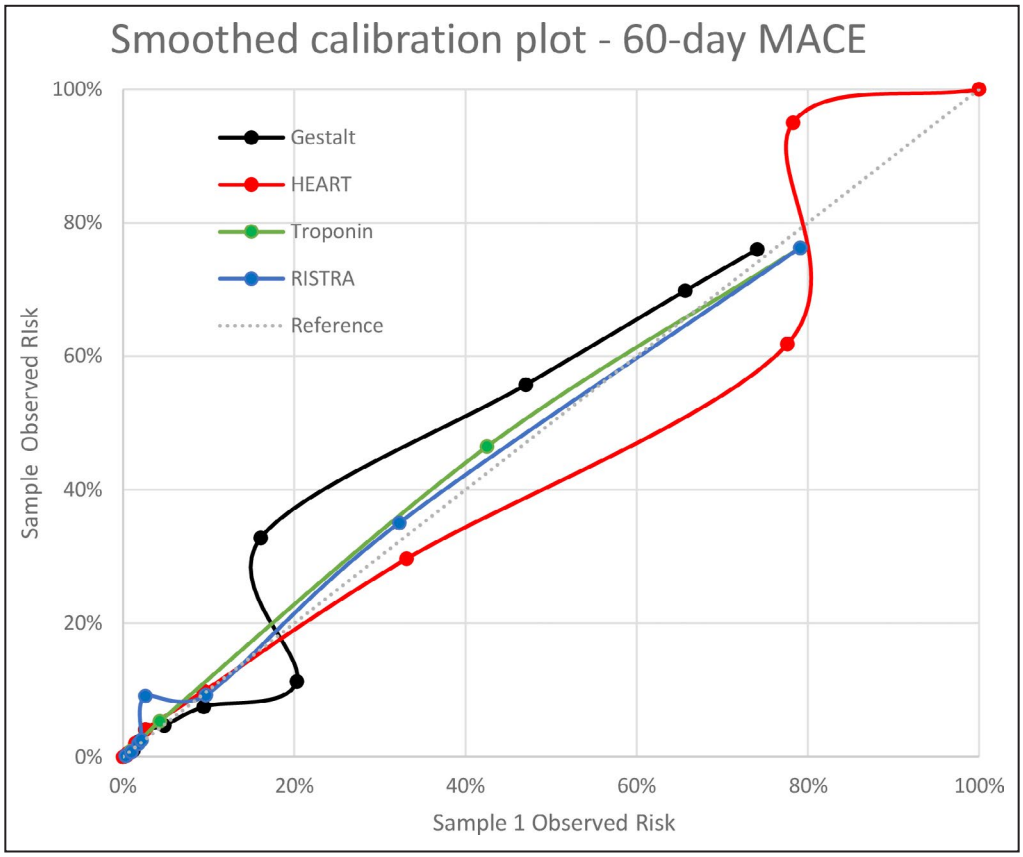

Figure 3. Smoothed calibration plot comparing graded-risk approaches for the primary outcome of 60-day MACE.
Approaches are: (1) physician gestalt (Gestalt), (2) HEART score (HEART), (3) troponin strata (Troponin), and (4) RISTRA-ACS (RISTRA). Calibration was determined using a random split of the study cohort into equal portions to generate sample 1 (testing data set) and sample 2 (validation data set). HEART indicates History, Electrocardiogram, Age, Risk Factors, Troponin; MACE, major adverse cardiac events; and RISTRA-ACS, Risk Stratification–Acute Coronary Syndrome.

with other incremental risk approaches is deserving of future study.

Finally, regarding the safety of a time-from-pain-onset approach to troponin testing for ED patients with chest pain, use of RISTRA-ACS enabled >50% of patients to receive accurate risk stratification using only a single troponin measurement. This contrasts with the fixed troponin measurements at 0 and 2 or 3 hours required by EDACS-ADP and HEART pathway, respectively. While these standardized 0 and 2- or 3-hour approaches to troponin testing have been promoted as less confusing and error prone,[11] calculation of the HEART score using a representative troponin drawn at least 3 hours from symptom onset has likewise been shown to be a safe and reliable approach.[57] Thus, our data further demonstrate the safety (and potential for improved ED throughput) using a time-from-pain-onset approach to troponin testing, specifically when aided by eCDS. It should be emphasized, however, that we added a layer of safety by requiring serial troponin testing at 2-hour intervals for any values at or above the LOQ until values either exceeded the 99th percentile or had plateaued or decreased.[21,27,32,58,59]

Limitations

Patients enrolled in this study had a lower incidence of MACE (3.7%) in comparison to other prospective ED studies of patients with suspected ACS in the United States that reported MACE incidences in the 8% to 12% range.[26,42] We believe this is because clinicians were less likely to use eCDS when faced with overt evidence of ACS, in which the perceived benefit is low, as opposed to cases of clinical uncertainty.[60] This is evidenced by the proportion of enrolled patients who were found to have serum troponin levels above the 99th percentile (4%), which was less than half that of nonenrolled patients with chief complaints of chest pain (9%) but closer to nonenrolled patients with ED diagnoses of chest pain (6%). As such, enrolled patients appear more representative of a patient population with undiagnosed chest pain.[9,61] While a lower outcome incidence does raise concern for spectrum

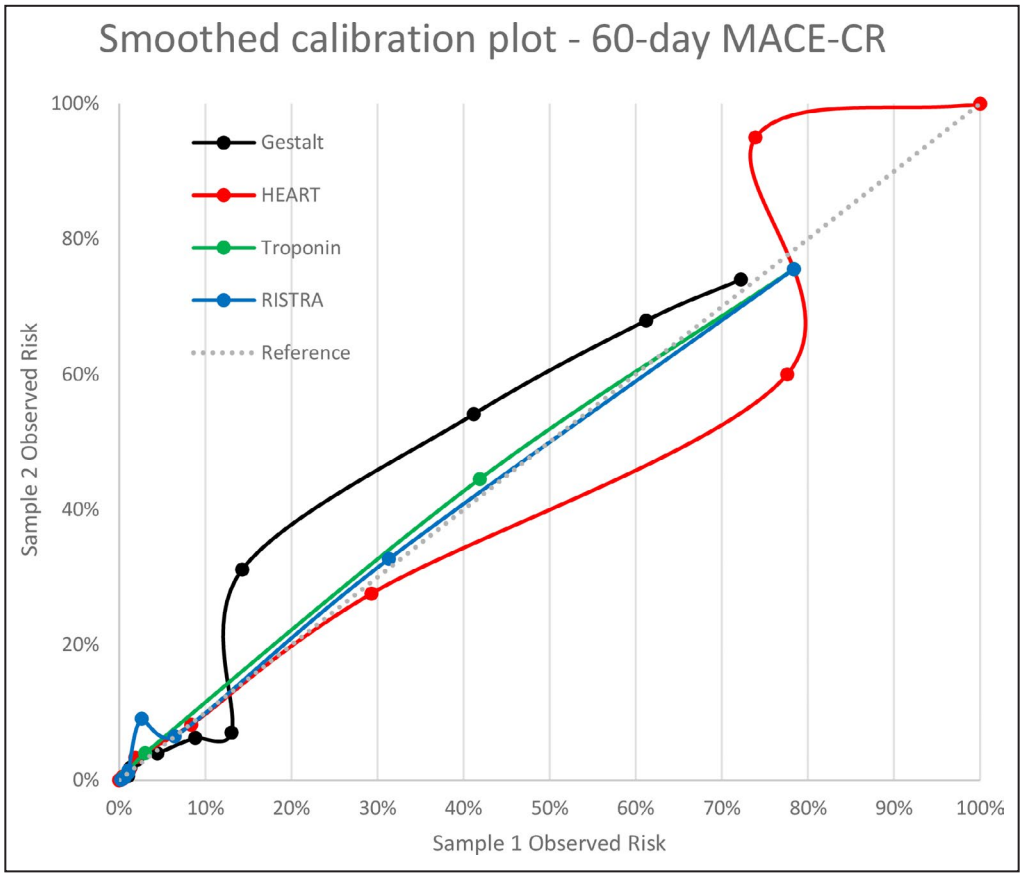

Figure 4. Smoothed calibration plot comparing graded-risk approaches for the secondary outcome of 60-day MACE-CR.
Approaches are: (1) physician gestalt for acute coronary syndrome (Gestalt), (2) HEART score (HEART), (3) troponin strata (Troponin), and (4) RISTRA-ACS (RISTRA). Calibration was determined using a random split of the study cohort into equal portions to generate sample 1 (testing data set) and sample 2 (validation data set). HEART indicates History, Electrocardiogram, Age, Risk Factors, Troponin; MACE-CR, major adverse cardiac events minus coronary revascularization; and RISTRA-ACS, Risk Stratification–Acute Coronary Syndrome.

effect in diagnostic test characteristics, sensitivity and specificity for the established rule-out approaches (HEART score, HEART pathway, and EDACS-ADP) are consistent with those reported in external validation studies.[15,26,62,63] Thus the findings and conclusions are likely applicable across similar practice settings for the clinical scenario in question (equipoise for possible ACS), though external validation is warranted, especially given that this study was restricted to insured patients within an integrated health system.

There were also several deviations within RISTRA-ACS from typical tabulations of the underlying risk scores. We used a standardized method for determining the History subscore of the HEART score, a variation on how the History subscore is typically calculated in practice (the latter being largely based on gestalt). While this may appear to limit generalizability of the findings, it is consistent with the approach taken in the largest implementation study of the HEART pathway in the United States.[26] Considering the relatively low interrater reliability of the history component of the HEART score,[64] an automated standardized approach is arguably preferable.[26] Likewise the overall automated score calculation approach in RISTRA-ACS avoids calculation errors, which have been shown to occur in up to 15% of HEART score determinations.[65] RISTRA-ACS also did not consider a history of coronary artery disease as an independent non-low-risk criterion, consistent with the original HEART pathway randomized controlled trial[16] but in contrast to the later implementation study,[26] in part because of concern for overutilization as compared with standard practice at study sites. Finally, the original EDACS-ADP included a "red flag" non-low-risk criterion of "an unstable presentation consisting of abnormal vital signs or pain that is ongoing or in a crescendo pattern."[15] We only included the "crescendo pattern" part of this criterion because of an unclear definition of "abnormal vital signs" and

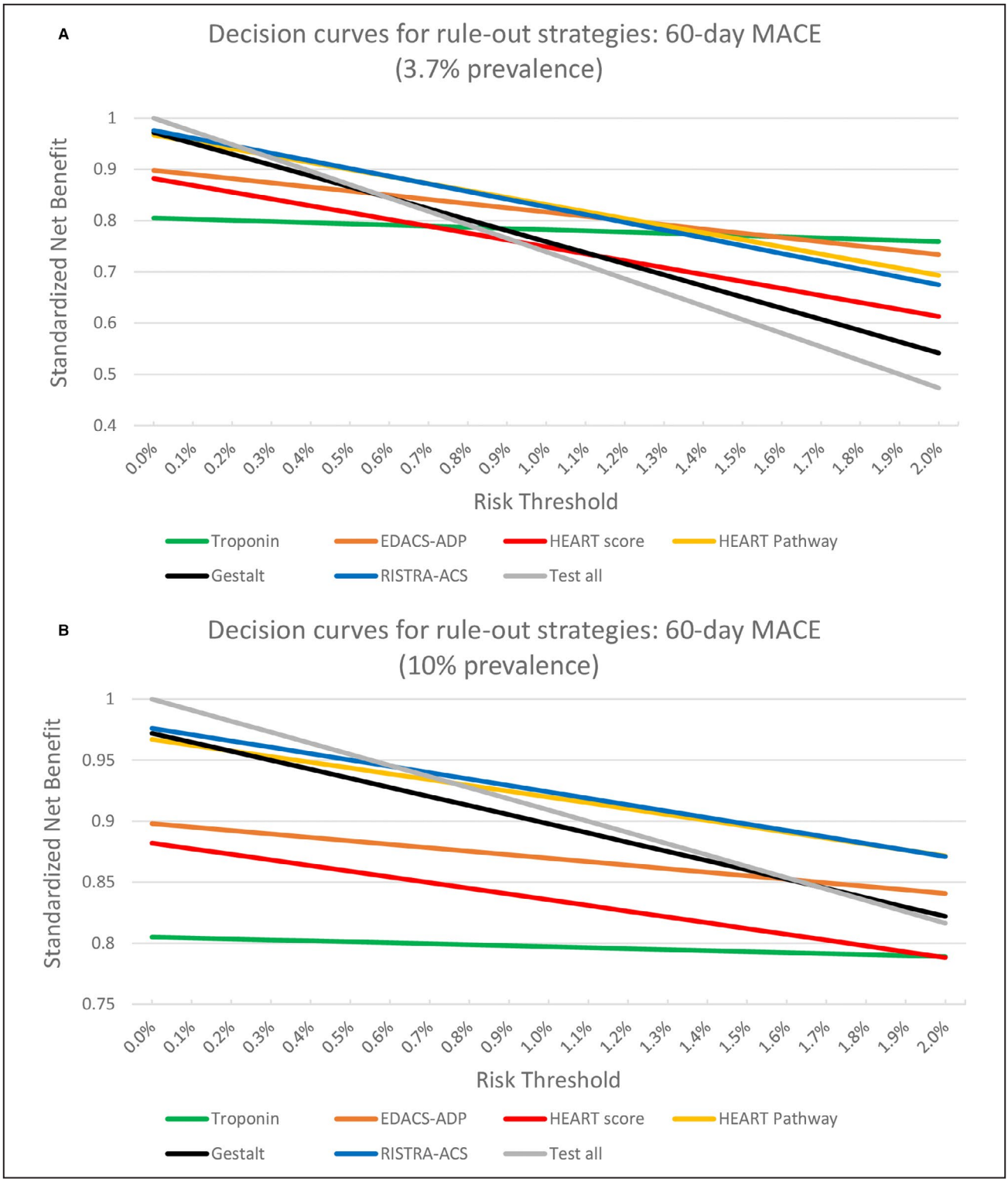

Figure 5. Decision curves for rule-out approaches and 60-day MACE at (A) the observed MACE prevalence of 3.7% and (B) a theoretical MACE prevalence of 10%.
The horizontal axis is restricted to risk thresholds between 0% and 2% to represent a range of low-risk definitions. Approaches are: (1) troponin below the level of quantitation (Troponin), (2) Emergency Department Assessment of Chest Pain Score Accelerated Diagnostic Protocol (EDACS-ADP low risk), (3) HEART score <4 (HEART score), (4) HEART Pathway low risk (HEART Pathway), (5) physician gestalt for acute coronary syndrome ≤2% (Gestalt), and (6) very-low-risk categorization by RISTRA-ACS (RISTRA-ACS). The "test all" line represents an approach in which all patients undergo further testing (ie, a strategy with 100% sensitivity and 0% specificity). HEART indicates History, Electrocardiogram, Age, Risk Factors, Troponin; MACE, major adverse cardiac events and RISTRA-ACS, Risk Stratification–Acute Coronary Syndrome.

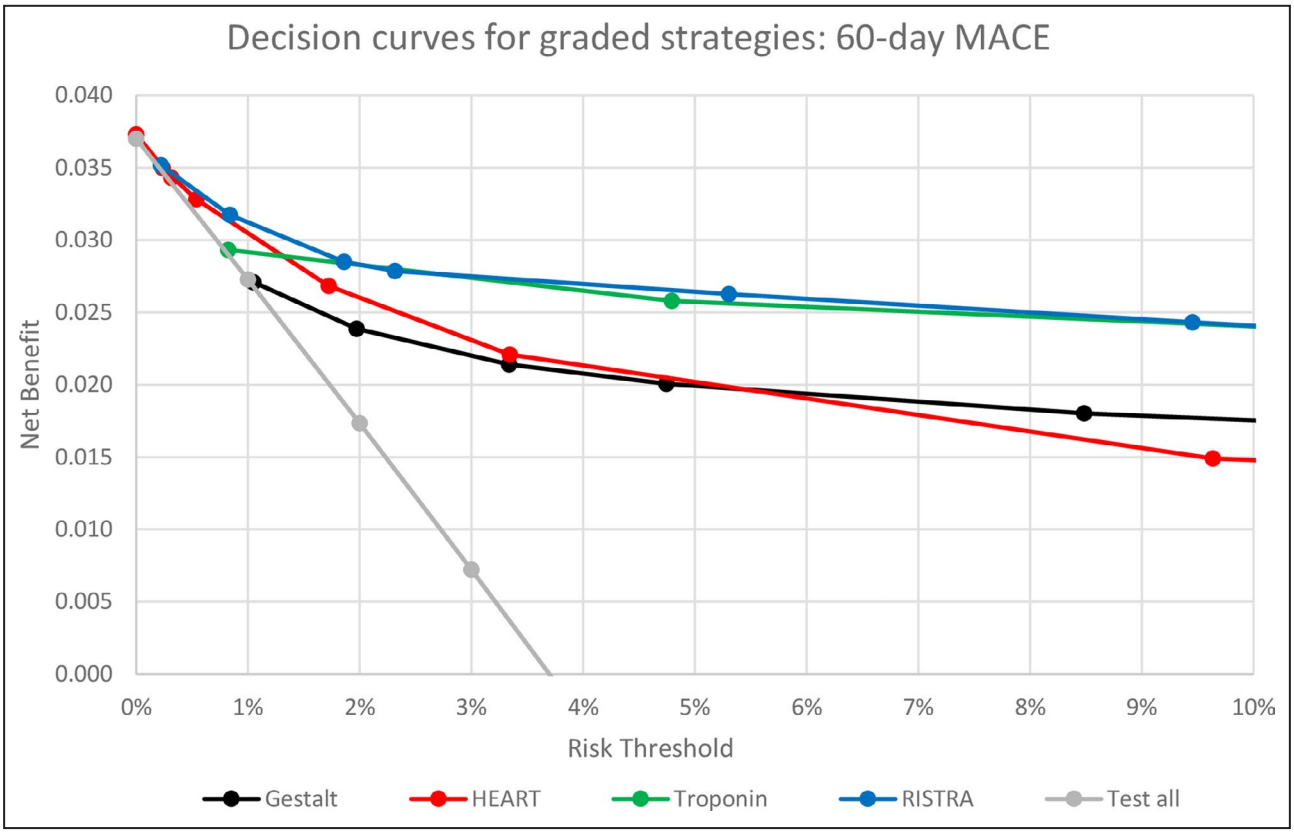

Figure 6. Decision curves for graded-risk approaches and the primary outcome of 60-day MACE.
The horizontal axis is restricted to risk thresholds between 0% and 10% to represent a range of low-to-moderate-risk definitions. Approaches are: (1) physician gestalt for acute coronary syndrome (Gestalt), (2) HEART score (HEART), (3) troponin strata (Troponin), and (4) RISTRA-ACS (RISTRA). The "test all" line represents an approach in which all patients undergo further testing (ie, a strategy with 100% sensitivity and 0% specificity). HEART indicates History, Electrocardiogram, Age, Risk Factors, Troponin; MACE, major adverse cardiac events; and RISTRA-ACS, Risk Stratification–Acute Coronary Syndrome.

the dubious positive predictive value of "pain that is ongoing" in the setting of negative troponins and nonischemic ECGs.[14,66]

The outcomes in this study were determined electronically based on diagnosis and procedural coding as opposed to prospective follow-up, raising the potential for both underestimation and overestimation of MACE. For the former, by restricting the study cohort to patients with continuous health plan membership during the follow-up period, we were able to obtain a full accounting of healthcare encounters both within and outside of the integrated system. Given the need for hospitalization following MACE, it is highly unlikely that a correct diagnosis would be omitted, especially with routine oversight of inpatient encounters by medical coding specialists. Likewise, it is difficult to imagine that patients would seek exclusive out-of-pocket care for these problems. Accordingly, the bigger issue may be overestimation of MACE because of the inclusion of any coronary revascularization or myocardial infarction event. While the impact of including any coronary revascularization is addressed by the secondary outcome of MACE-CR, we did not attempt to distinguish between the various subclassifications of myocardial infarction, with type 1 (myocardial infarction caused by acute coronary thromboembolic phenomena) being most pertinent to the study aims.[67] However, considering that the morbidity associated with non-type-1 myocardial infarction is nontrivial, we feel it is preferable to allow for liberal estimates in ensuring the safety of risk stratification protocols, especially given entities such as "myocardial infarction with nonobstructive coronary arteries," which highlight that the true causes of myocardial infarction are not always clear.[67,68]

Finally, since RISTRA recorded and/or reported elements of multiple strategies (eg, binary classification by both the HEART pathway and EDACS-ADP, physician gestalt, absolute troponin values, and RISTRA-ACS risk estimate) it is unclear what, if any, risk prediction data physicians used in arriving at their disposition decisions. Ultimately there are wide variations in hospital admission and objective cardiac testing surrounding ED chest pain,[3,4] but no clear evidence that this

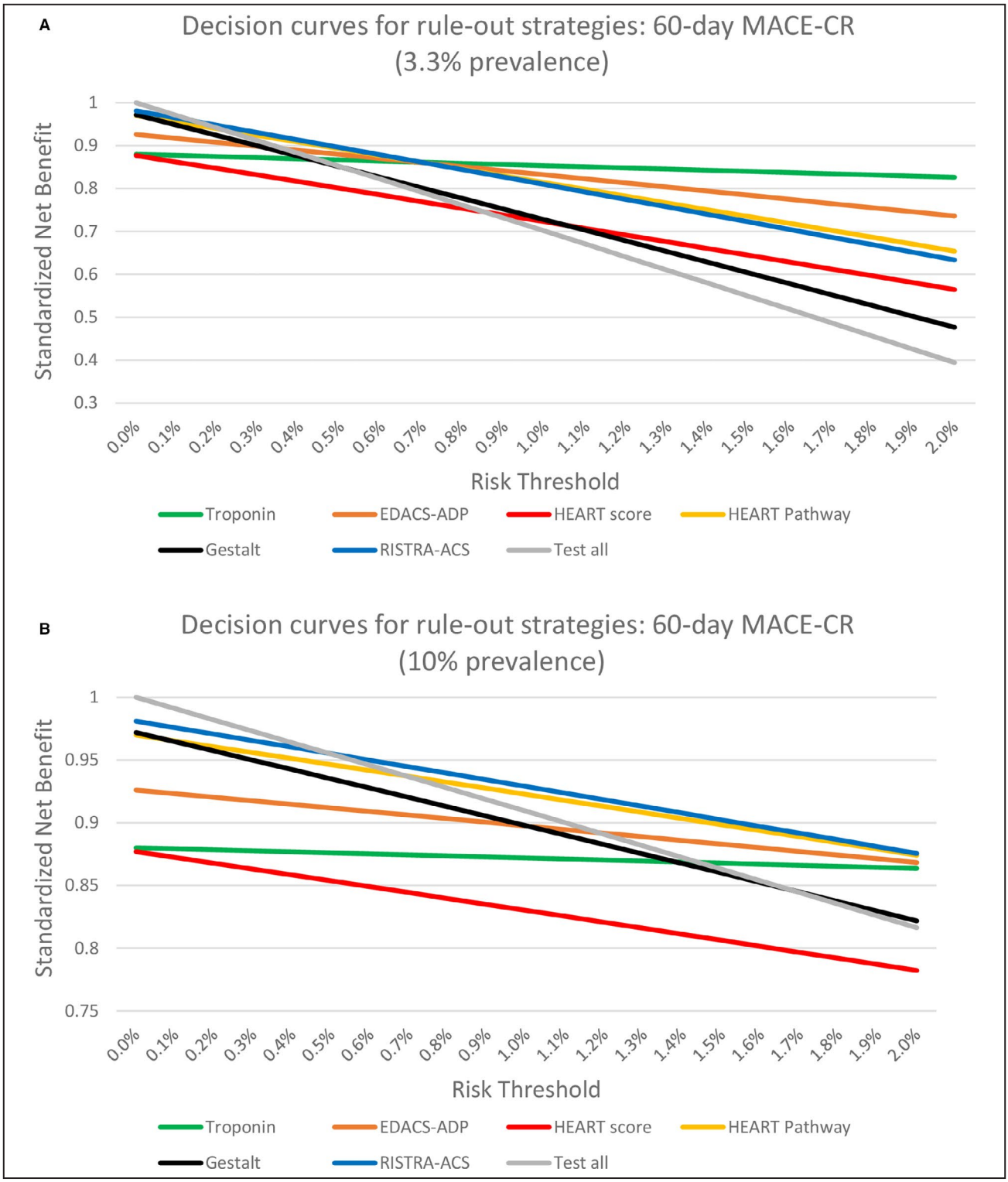

Figure 7. Decision curves for rule-out approaches and 60-day MACE-CR at (A) the observed MACE-CR prevalence of 3.3% and (B) a theoretical MACE-CR prevalence of 10%.

The horizontal axis is restricted to risk thresholds between 0% and 2% to represent a range of low-risk definitions. Approaches are: (1) troponin below the level of quantitation (Troponin), (2) Emergency Department Assessment of Chest Pain Score Accelerated Diagnostic Protocol (EDACS-ADP low risk), (3) HEART score <4 (HEART score), (4) HEART Pathway low risk (HEART Pathway), (5) physician gestalt for acute coronary syndrome ≤2% (Gestalt) and (6) very-low-risk categorization by RISTRA-ACS (RISTRA-ACS). The "test all" line represents an approach in which all patients undergo further testing (ie, a strategy with 100% sensitivity and 0% specificity). HEART indicates History, Electrocardiogram, Age, Risk Factors, Troponin; MACE-CR, major adverse cardiac events without revascularization; and RISTRA-ACS, Risk Stratification–Acute Coronary Syndrome.

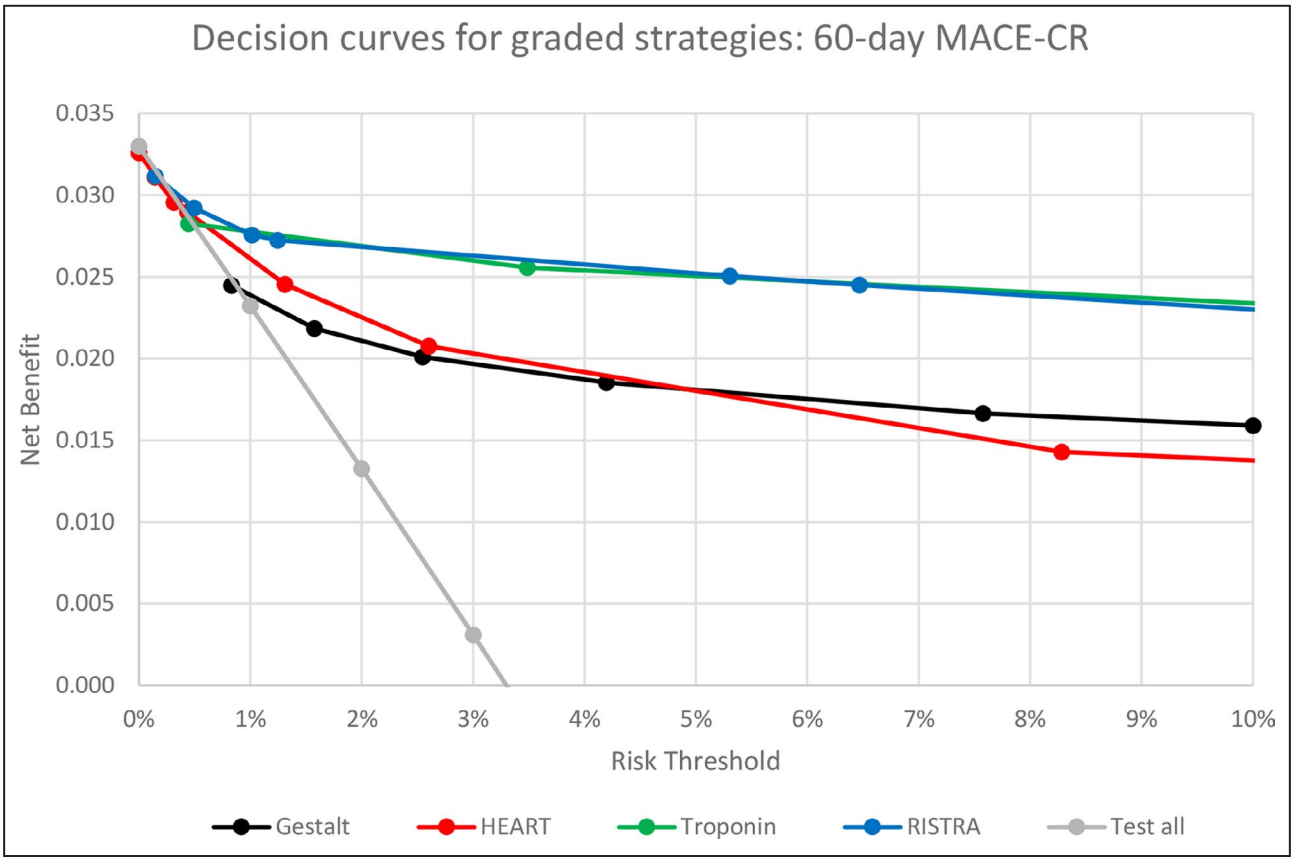

Figure 8. Decision curves for graded-risk approaches and the secondary outcome of 60-day MACE-CR.
The horizontal axis is restricted to risk thresholds between 0% and 10% to represent a range of low-to-moderate-risk definitions. Approaches are: (1) physician gestalt for acute coronary syndrome (Gestalt), (2) HEART score (HEART), (3) troponin strata (Troponin), and (4) RISTRA-ACS (RISTRA). The "test all" line represents an approach in which all patients undergo further testing (ie, a strategy with 100% sensitivity and 0% specificity). HEART indicates History, Electrocardiogram, Age, Risk Factors, Troponin; MACE-CR, major adverse cardiac events without revascularization; and RISTRA-ACS, Risk Stratification–Acute Coronary Syndrome.

variation impacts near-term outcomes for the majority of patients.[69,70] Thus we believe the risk of bias in this data set towards any given strategy is low.

CONCLUSIONS

In comparing several risk stratification strategies for ED patients with chest pain with suspected ACS, including a novel algorithm (RISTRA-ACS), we found that either the HEART pathway and RISTRA-ACS had the best rule-out performance, while RISTRA-ACS was the best overall performing graded-risk approach. While requiring further validation, RISTRA-ACS is attractive as a single-risk stratification strategy that can differentiate between several lower levels of risk, allowing clinicians to better determine the urgency and/or need for further workup following initial evaluation in the ED.

ARTICLE INFORMATION

Received November 6, 2020; accepted February 22, 2021.

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Acknowledgments

We would like to thank the emergency medicine physicians of The Permanente Medical Group for diligently providing prospective data for this study. The Kaiser Permanente CREST Network Investigators are inclusive of all authors listed herein.

Sources of Funding

This project is supported by The Permanente Medical Group (TPMG) Delivery Science Research Program.

Disclosures

None.

Supplementary Material

Datas S1–S3
Tables S1–S2
Figures S1–S2

REFERENCES

1. Owens PL, Barrett ML, Gibson TB, Andrews RM, Weinick RM, Mutter RL. Emergency department care in the United States: a profile of national data sources. *Ann Emerg Med*. 2010;56:150–165. DOI: 10.1016/j.annemergmed.2009.11.022.
2. Hsia RY, Hale Z, Tabas JA. A national study of the prevalence of life-threatening diagnoses in patients with chest pain. *JAMA Intern Med*. 2016;176:1029–1032. DOI: 10.1001/jamainternmed.2016.2498.
3. Venkatesh AK, Dai Y, Ross JS, Schuur JD, Capp R, Krumholz HM. Variation in US hospital emergency department admission rates by clinical condition. *Med Care*. 2015;53:237–244. DOI: 10.1097/MLR.0000000000000261.
4. Sabbatini AK, Nallamothu BK, Kocher KE. Reducing variation in hospital admissions from the emergency department for low-mortality conditions may produce savings. *Health Aff (Millwood)*. 2014;33:1655–1663. DOI: 10.1377/hlthaff.2013.1318.
5. Amsterdam EA, Kirk JD, Bluemke DA, Diercks D, Farkouh ME, Garvey JL, Kontos MC, McCord J, Miller TD, Morise A, et al. Testing of low-risk patients presenting to the emergency department with chest pain: a scientific statement from the American Heart Association. *Circulation*. 2010;122:1756–1776. DOI: 10.1161/CIR.0b013e3181ec61df.
6. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *Circulation*. 2014;130:2354–2394. DOI: 10.1161/CIR.0000000000000133.
7. Napoli AM, Arrighi JA, Siket MS, Gibbs FJ. Physician discretion is safe and may lower stress test utilization in emergency department chest pain unit patients. *Crit Pathw Cardiol*. 2012;11:26–31. DOI: 10.1097/HPC.0b013e3182457bee.
8. Aldous S, Richards AM, Cullen L, Pickering JW, Than M. The incremental value of stress testing in patients with acute chest pain beyond serial cardiac troponin testing. *Emerg Med J*. 2016;33:319–324. DOI: 10.1136/emermed-2015-204823.
9. Hermann LK, Newman DH, Pleasant WA, Rojanasarntikul D, Lakoff D, Goldberg SA, Duvall WL, Henzlova MJ. Yield of routine provocative cardiac testing among patients in an emergency department-based chest pain unit. *JAMA Intern Med*. 2013;173:1128–1133. DOI: 10.1001/jamainternmed.2013.850.
10. American College of Emergency Physicians Clinical Policies Subcommittee on Suspected Non STEACS, Tomaszewski CA, Nestler D, Shah KH, Sudhir A, Brown MD. 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:e65–e106. DOI: 10.1016/j.annemergmed.2018.07.045.
11. Hollander JE, Than M, Mueller C. State-of-the-art evaluation of emergency department patients presenting with potential acute coronary syndromes. *Circulation*. 2016;134:547–564. DOI: 10.1161/CIRCULATIONAHA.116.021886.
12. Kline JA, Stubblefield WB. Clinician gestalt estimate of pretest probability for acute coronary syndrome and pulmonary embolism in patients with chest pain and dyspnea. *Ann Emerg Med*. 2014;63:275–280. DOI: 10.1016/j.annemergmed.2013.08.023.
13. Body R, Cook G, Burrows G, Carley S, Lewis PS. Can emergency physicians 'rule in' and 'rule out' acute myocardial infarction with clinical judgement? *Emerg Med J*. 2014;31:872–876. DOI: 10.1136/emermed-2014-203832.
14. Than M, Flaws D, Sanders S, Doust J, Glasziou P, Kline J, Aldous S, Troughton R, Reid C, Parsonage WA, et al. Development and validation of the emergency department assessment of chest pain score and 2 h accelerated diagnostic protocol. *Emerg Med Australas*. 2014;26:34–44. DOI: 10.1111/1742-6723.12164.
15. Than MP, Pickering JW, Aldous SJ, Cullen L, Frampton CM, Peacock WF, Jaffe AS, Goodacre SW, Richards AM, Ardagh MW, et al. Effectiveness of EDACS versus ADAPT accelerated diagnostic pathways for chest pain: a pragmatic randomized controlled trial embedded within practice. *Ann Emerg Med*. 2016;68:93–102.e101. DOI: 10.1016/j.annemergmed.2016.01.001.
16. Mahler SA, Riley RF, Hiestand BC, Russell GB, Hoekstra JW, Lefebvre CW, Nicks BA, Cline DM, Askew KL, Elliott SB, et al. The HEART Pathway randomized trial: identifying emergency department patients with acute chest pain for early discharge. *Circ Cardiovasc Qual Outcomes*. 2015;8:195–203. DOI: 10.1161/CIRCOUTCOMES.114.001384.
17. Greenslade JH, Carlton EW, Van Hise C, Cho E, Hawkins T, Parsonage WA, Tate J, Ungerer J, Cullen L. Diagnostic accuracy of a new high-sensitivity troponin i assay and five accelerated diagnostic pathways for ruling out acute myocardial infarction and acute coronary syndrome. *Ann Emerg Med*. 2018;71:439–451.e433. DOI: 10.1016/j.annemergmed.2017.10.030.
18. Stopyra J, Snavely AC, Hiestand B, Wells BJ, Lenoir KM, Herrington D, Hendley N, Ashburn NP, Miller CD, Mahler SA. Comparison of accelerated diagnostic pathways for acute chest pain risk stratification. *Heart*. 2020;106:977–984. DOI: 10.1136/heartjnl-2019-316426.
19. Mark DG, Huang J, Kennedy CJ, Vinson DR, Ballard DW, Reed ME; Kaiser Permanente CNI. 60-day major adverse cardiac events in emergency department patients with non-low modified heart scores. *Am J Emerg Med*. 2020;38:2760.e5–2760.e8. DOI: 10.1016/j.ajem.2020.05.081.
20. Baugh CW, Greenberg JO, Mahler SA, Kosowsky JM, Schuur JD, Parmar S, Ciociolo GR Jr, Carr CW, Ghazinouri R, Scirica BM. Implementation of a risk stratification and management pathway for acute chest pain in the emergency department. *Crit Pathw Cardiol*. 2016;15:131–137. DOI: 10.1097/HPC.0000000000000095.
21. Mark DG, Huang J, Chettipally U, Kene MV, Anderson ML, Hess EP, Ballard DW, Vinson DR, Reed ME; Kaiser Permanente CNI. Performance of coronary risk scores among patients with chest pain in the emergency department. *J Am Coll Cardiol*. 2018;71:606–616. DOI: 10.1016/j.jacc.2017.11.064.
22. Vinson DR, Mark DG, Chettipally UK, Huang J, Rauchwerger AS, Reed ME, Lin JS, Kene MV, Wang DH, Sax DR, et al. Increasing safe outpatient management of emergency department patients with pulmonary embolism: a controlled pragmatic trial. *Ann Intern Med*. 2018;169:855–865. DOI: 10.7326/M18-1206.
23. Ekstrom HL, Kharbanda EO, Ballard DW, Vinson DR, Vazquez-Benitez G, Chettipally UK, Dehmer SP, Kunisetty G, Sharma R, Rauchwerger AS, et al. Development of a clinical decision support system for pediatric abdominal pain in emergency department settings across two health systems within the HCSRN. *EGEMS (Wash DC)*. 2019;7:15. DOI: 10.5334/egems.282.
24. Simon LE, Rauchwerger AS, Chettipally UK, Babakhanian L, Vinson DR, Warton EM, Reed ME, Kharbanda AB, Kharbanda EO, Ballard DW. Text message alerts to emergency physicians identifying potential study candidates increase clinical trial enrollment. *J Am Med Inform Assoc*. 2019;26:1360–1363. DOI: 10.1093/jamia/ocz118.
25. Venge P, Lagerqvist B, Diderholm E, Lindahl B, Wallentin L. Clinical performance of three cardiac troponin assays in patients with unstable coronary artery disease (a FRISC II substudy). *Am J Cardiol*. 2002;89:1035–1041. DOI: 10.1016/S0002-9149(02)02271-3.
26. Mahler SA, Lenoir KM, Wells BJ, Burke GL, Duncan PW, Case LD, Herrington DM, Diaz-Garelli J-F, Futrell WM, Hiestand BC, et al. Safely identifying emergency department patients with acute chest pain for early discharge. *Circulation*. 2018;138:2456–2468. DOI: 10.1161/CIRCULATIONAHA.118.036528.
27. Storrow AB, Christenson RH, Nowak RM, Diercks DB, Singer AJ, Wu AHB, Kulstad E, LoVecchio F, Fromm C, Headden G, et al. Diagnostic performance of cardiac troponin I for early rule-in and rule-out of acute myocardial infarction: results of a prospective multicenter trial. *Clin Biochem*. 2015;48:254–259. DOI: 10.1016/j.clinbiochem.2014.08.018.
28. Keller T, Zeller T, Ojeda F, Tzikas S, Lillpopp L, Sinning C, Wild P, Genth-Zotz S, Warnholtz A, Giannitsis E, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. *JAMA*. 2011;306:2684–2693. DOI: 10.1001/jama.2011.1896.
29. Derington CG, Heath LJ, Kao DP, Delate T. Validation of algorithms to identify elective percutaneous coronary interventions in

administrative databases. *PLoS One*. 2020;15:e0231100. DOI: 10.1371/journal.pone.0231100.
30. Cullen L, Than M, Brown AF, Richards M, Parsonage W, Flaws D, Hollander JE, Christenson RH, Kline JA, Goodacre S, et al. Comprehensive standardized data definitions for acute coronary syndrome research in emergency departments in Australasia. *Emerg Med Australas*. 2010;22:35–55. DOI: 10.1111/j.1742-6723.2010.01256.x.
31. Van Den Berg P, Body R. The HEART score for early rule out of acute coronary syndromes in the emergency department: a systematic review and meta-analysis. *Eur Heart J Acute Cardiovasc Care*. 2018;7:111–119. DOI: 10.1177/2048872617710788.
32. Storrow AB, Nowak RM, Diercks DB, Singer AJ, Wu AHB, Kulstad E, LoVecchio F, Fromm C, Headden G, Potis T, et al. Absolute and relative changes (delta) in troponin I for early diagnosis of myocardial infarction: results of a prospective multicenter trial. *Clin Biochem*. 2015;48:260–267. DOI: 10.1016/j.clinbiochem.2014.09.012.
33. Willeit P, Welsh P, Evans JDW, Tschiderer L, Boachie C, Jukema JW, Ford I, Trompet S, Stott DJ, Kearney PM, et al. High-sensitivity cardiac troponin concentration and risk of first-ever cardiovascular outcomes in 154,052 participants. *J Am Coll Cardiol*. 2017;70:558–568. DOI: 10.1016/j.jacc.2017.05.062.
34. Roos A, Bandstein N, Lundback M, Hammarsten O, Ljung R, Holzmann MJ. Stable high-sensitivity cardiac troponin T levels and outcomes in patients with chest pain. *J Am Coll Cardiol*. 2017;70:2226–2236. DOI: 10.1016/j.jacc.2017.08.064.
35. Backus BE, Six AJ, Kelder JC, Bosschaert M, Mast EG, Mosterd A, Veldkamp RF, Wardeh AJ, Tio R, Braam R, et al. A prospective validation of the HEART score for chest pain patients at the emergency department. *Int J Cardiol*. 2013;168:2153–2158. DOI: 10.1016/j.ijcard.2013.01.255.
36. Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, Pencina MJ, Kattan MW. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology*. 2010;21:128–138. DOI: 10.1097/EDE.0b013e3181c30fb2.
37. Van Calster B, McLernon DJ, van Smeden M, Wynants L, Steyerberg EW; Topic Group 'Evaluating diagnostic t, prediction models' of the Si. Calibration: the Achilles heel of predictive analytics. *BMC Med*. 2019;17:230. DOI: 10.1186/s12916-019-1466-7.
38. Vickers AJ, Van Calster B, Steyerberg EW. Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests. *BMJ*. 2016;352:i6. DOI: 10.1136/bmj.i6.
39. Kerr KF, Wang Z, Janes H, McClelland RL, Psaty BM, Pepe MS. Net reclassification indices for evaluating risk prediction instruments: a critical review. *Epidemiology*. 2014;25:114–121. DOI: 10.1097/EDE.0000000000000018.
40. Pepe MS, Fan J, Feng Z, Gerds T, Hilden J. The net reclassification index (NRI): a misleading measure of prediction improvement even with independent test data sets. *Stat Biosci*. 2015;7:282–295. DOI: 10.1007/s12561-014-9118-0.
41. Kerr KF, Brown MD, Zhu K, Janes H. Assessing the clinical impact of risk prediction models with decision curves: guidance for correct interpretation and appropriate use. *J Clin Oncol*. 2016;34:2534–2540. DOI: 10.1200/JCO.2015.65.5654.
42. Hess EP, Brison RJ, Perry JJ, Calder LA, Thiruganasambandamoorthy V, Agarwal D, Sadosty AT, Silvilotti MLA, Jaffe AS, Montori VM, et al. Development of a clinical prediction rule for 30-day cardiac events in emergency department patients with chest pain and possible acute coronary syndrome. *Ann Emerg Med*. 2012;59:115–125.e111. DOI: 10.1016/j.annemergmed.2011.07.026.
43. Kline JA, Johnson CL, Pollack CV Jr, Diercks DB, Hollander JE, Newgard CD, Garvey JL. Pretest probability assessment derived from attribute matching. *BMC Med Inform Decis Mak*. 2005;5:26. DOI: 10.1186/1472-6947-5-26.
44. Pauker SG, Kassirer JP. The threshold approach to clinical decision making. *N Engl J Med*. 1980;302:1109–1117. DOI: 10.1056/NEJM198005153022003.
45. Goodacre S, Thokala P, Carroll C, Stevens JW, Leaviss J, Al Khalaf M, Collinson P, Morris F, Evans P, Wang J. Systematic review, meta-analysis and economic modelling of diagnostic strategies for suspected acute coronary syndrome. *Health Technol Assess*. 2013;17:v–vi, 1–188. DOI: 10.3310/hta17010.
46. Reinhardt SW, Lin CJ, Novak E, Brown DL. Noninvasive cardiac testing vs clinical evaluation alone in acute chest pain: a secondary analysis of the ROMICAT-II randomized clinical trial. *JAMA Intern Med*. 2018;178:212–219. DOI: 10.1001/jamainternmed.2017.7360.
47. Kawatkar AA, Sharp AL, Baecker AS, Natsui S, Redberg RF, Lee M-S, Ferencik M, Wu Y-L, Shen E, Zheng C, et al. Early noninvasive cardiac testing after emergency department evaluation for suspected acute coronary syndrome. *JAMA Intern Med*. 2020;180:1621. DOI: 10.1001/jamainternmed.2020.4325.
48. Hulten E, Pickett C, Bittencourt MS, Villines TC, Petrillo S, Di Carli MF, Blankstein R. Outcomes after coronary computed tomography angiography in the emergency department: a systematic review and meta-analysis of randomized, controlled trials. *J Am Coll Cardiol*. 2013;61:880–892. DOI: 10.1016/j.jacc.2012.11.061.
49. Weinstock MB, Finnerty NM, Pallaci M. Time to move on: redefining chest pain outcomes. *J Am Heart Assoc*. 2019;8:e012542. DOI: 10.1161/JAHA.119.012542.
50. Goehler A, Mayrhofer T, Pursnani A, Ferencik M, Lumish HS, Barth C, Karády J, Chow B, Truong QA, Udelson JE, et al. Long-term health outcomes and cost-effectiveness of coronary CT angiography in patients with suspicion for acute coronary syndrome. *J Cardiovasc Comput Tomogr*. 2020;14:44–54. DOI: 10.1016/j.jcct.2019.06.008.
51. Scot-Heart Investigators, Newby DE, Adamson PD, Berry C, Boon NA, Dweck MR, Flather M, Forbes J, Hunter A, Lewis S, MacLean S, et al. Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med*. 2018;379:924–933. DOI: 10.1056/NEJMoa1805971.
52. Atzema CL, Maclagan LC. The transition of care between emergency department and primary care: a scoping study. *Acad Emerg Med*. 2017;24:201–215. DOI: 10.1111/acem.13125.
53. Chang AM, Hollander JE. For low-risk patients with suspected acute coronary syndrome, should urgent (72-hours) non-invasive cardiac testing be performed after biomarker exclusion of acute myocardial infarction. *Ann Emerg Med*. 2018;71:464–465. DOI: 10.1016/j.annemergmed.2017.08.048.
54. Oliver G, Reynard C, Morris N, Body R. Can emergency physician gestalt "rule in" or "rule out" acute coronary syndrome: validation in a multicenter prospective diagnostic cohort study. *Acad Emerg Med*. 2020;27:24–30. DOI: 10.1111/acem.13836.
55. Mahler SA, Miller CD, Hollander JE, Nagurney JT, Birkhahn R, Singer AJ, Shapiro NI, Glynn T, Nowak R, Safdar B, et al. Identifying patients for early discharge: performance of decision rules among patients with acute chest pain. *Int J Cardiol*. 2013;168:795–802. DOI: 10.1016/j.ijcard.2012.10.010.
56. Nestelberger T, Boeddinghaus J, Wussler D, Twerenbold R, Badertscher P, Wildi K, Miró Ò, López B, Martin-Sanchez FJ, Muzyk P, et al. Predicting major adverse events in patients with acute myocardial infarction. *J Am Coll Cardiol*. 2019;74:842–854. DOI: 10.1016/j.jacc.2019.06.025.
57. Ras M, Reitsma JB, Hoes AW, Six AJ, Poldervaart JM. Value of repeated troponin measurements to improve the safety of the HEART score for chest pain patients at the emergency department. *Crit Pathw Cardiol*. 2020;19:62–68. DOI: 10.1097/HPC.0000000000000213.
58. Cullen L, Parsonage WA, Greenslade J, Lamanna A, Hammett CJ, Than M, Tate J, Kalinowski L, Ungerer JPJ, Chu K, et al. Delta troponin for the early diagnosis of AMI in emergency patients with chest pain. *Int J Cardiol*. 2013;168:2602–2608. DOI: 10.1016/j.ijcard.2013.03.044.
59. Cullen L, Greenslade J, Than M, Tate J, Ungerer JPJ, Pretorius C, Hammett CJ, Lamanna A, Chu K, Brown AFT, et al. Performance of risk stratification for acute coronary syndrome with two-hour sensitive troponin assay results. *Heart Lung Circ*. 2014;23:428–434. DOI: 10.1016/j.hlc.2013.11.003.
60. Liberati EG, Ruggiero F, Galuppo L, Gorli M, González-Lorenzo M, Maraldi M, Ruggieri P, Polo Friz H, Scaratti G, Kwag KH, et al. What hinders the uptake of computerized decision support systems in hospitals? A qualitative study and framework for implementation. *Implement Sci*. 2017;12:113. DOI: 10.1186/s13012-017-0644-2.
61. Pope JH, Aufderheide TP, Ruthazer R, Woolard RH, Feldman JA, Beshansky JR, Griffith JL, Selker HP. Missed diagnoses of acute cardiac ischemia in the emergency department. *N Engl J Med*. 2000;342:1163–1170. DOI: 10.1056/NEJM200004203421603.
62. Mulherin SA, Miller WC. Spectrum bias or spectrum effect? Subgroup variation in diagnostic test evaluation. *Ann Intern Med*. 2002;137:598–602. DOI: 10.7326/0003-4819-137-7-200210010-00011.
63. Poldervaart JM, Reitsma JB, Backus BE, Koffijberg H, Veldkamp RF, Ten Haaf ME, Appelman Y, Mannaerts HFJ, van Dantzig J-M, van den Heuvel M, et al. Effect of using the HEART score in patients with chest pain in the emergency department: a stepped-wedge, cluster randomized trial. *Ann Intern Med*. 2017;166:689–697. DOI: 10.7326/M16-1600.

64. Gershon CA, Yagapen AN, Lin A, Yanez D, Sun BC. Inter-rater reliability of the heart score. *Acad Emerg Med*. 2019;26:552–555. DOI: 10.1111/acem.13665.
65. Ras M, Reitsma JB, Hoes AW, Six AJ, Poldervaart JM. Secondary analysis of frequency, circumstances and consequences of calculation errors of the HEART (history, ecg, age, risk factors and troponin) score at the emergency departments of nine hospitals in the netherlands. *BMJ Open*. 2017;7:e017259. DOI: 10.1136/bmjopen-2017-017259.
66. Swap CJ, Nagurney JT. Value and limitations of chest pain history in the evaluation of patients with suspected acute coronary syndromes. *JAMA*. 2005;294:2623–2629. DOI: 10.1001/jama.294.20.2623.
67. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology /American College of Cardiology/American Heart Association /World Heart Federation Task Force for the Universal Definition of Myocardial I. Fourth universal definition of myocardial infarction (2018). *Circulation*. 2018;138:e618–e651. DOI: 10.1161/CIR.0000000000000617.
68. Gaggin HK, Liu Y, Lyass A, van Kimmenade RRJ, Motiwala SR, Kelly NP, Mallick A, Gandhi PU, Ibrahim NE, Simon ML, et al. Incident type 2 myocardial infarction in a cohort of patients undergoing coronary or peripheral arterial angiography. *Circulation*. 2017;135:116–127. DOI: 10.1161/CIRCULATIONAHA.116.023052.
69. Sandhu AT, Heidenreich PA, Bhattacharya J, Bundorf MK. Cardiovascular testing and clinical outcomes in emergency department patients with chest pain. *JAMA Intern Med*. 2017;177:1175–1182. DOI: 10.1001/jamainternmed.2017.2432.
70. Natsui S, Sun BC, Shen E, Redberg RF, Ferencik M, Lee M-S, Musigdilok V, Wu Y-L, Zheng C, Kawatkar AA, et al. Higher emergency physician chest pain hospitalization rates do not lead to improved patient outcomes. *Circ Cardiovasc Qual Outcomes*. 2021;14:e006297. DOI: 10.1161/CIRCOUTCOMES.119.006297.

Supplemental Material

Data S1.

Supplemental Methods

Prospective data collection

RISTRA-ACS imported relevant structured data from the EHR (e.g. past medical history), which was modified and/or validated by the clinician, followed by user input of subjective elements from the clinical history. These included the timing of pain onset and the presence or absence of following symptoms: 1) pain on inspiration, 2) sharp or stabbing pain, 3) nausea or vomiting, 4) exertional symptoms, 6) radiation of pain to arm, shoulder, neck or jaw 7) diaphoresis 8) pain reproduced by palpation and 9) crescendo angina (pain which is recurrent and worsening, lasts at least 5-10 minutes, and occurs at rest or with minimal exertion). As in recent studies of the HEART pathway, the history component of the HEART score (range 0 to 2 points) was determined in a standardized fashion by considering the net balance of any "high risk" symptoms (e.g. pain radiating to the arm) against any "low risk" symptoms (e.g. pain reproduced with inspiration).[26] Physicians also provided a structured ECG interpretation as either 1) normal, 2) abnormal/non-diagnostic (defined as any repolarization abnormalities, bundle branch blocks, paced rhythms, old or non-specific T wave or ST-segment changes, or evidence of prior infarction) or 3) new ischemic change (new ST-segment depressions of at least 0.05 mV in 2 contiguous leads or T-wave inversions > 1 mV in depth). Finally, prior to receiving eCDS risk estimates (but after ECG interpretation and recommended troponin testing had been completed) physicians provided their overall gestalt for ACS on an ordinal scale ranging from 1% to 100% using a visual slider bar.

Data S2.

International Classification of Disease, 10th edition (ICD-10) and Current Procedural Terminology (CPT) codes for major adverse cardiac event (MACE) and coronary revascularization outcomes.

MACE outcome	ICD-10 code
Acute myocardial infarction	I21.0x, I21.1x, I21.2x, I21.3x, I21.4x, I21.9
Cardiac arrest	I49.0x, I46.x
Cardiogenic shock	R57.0, R57.9

Coronary revascularization outcome	ICD-10 procedure coding system	CPT code
Percutaneous coronary intervention*	0270xx, 0271xx, 2072xx, 0273xx	92920-92934, 92937, 92938, 92941, 92943, 92944, 92973
Coronary artery bypass grafting	0210xx	33510-33516, 33533-33536

* CPT codes from AHRQ QI™ ICD-10-CM/PCS Specification version 2018

Data S3.

Calculation of net benefit and presentation of decision curve analysis

The calculation of net benefit was as follows:

if disease prevalence = d and risk threshold = r,

Net benefit = Sensitivity x d – (1-specificity) x (1-d) x r/(1-r)

or

Net benefit = (true positives/total patients) – (false positives/total patients) x r/(1-r)

So, for example, a risk score with a very high sensitivity but lower specificity may have a higher net benefit if a low risk threshold is employed (e.g. < 0.5%), whereas an approach with a slightly lower sensitivity but higher specificity may have a higher net benefit at a higher risk threshold (e.g. 2%). Since the ranking of net benefit can also vary depending on disease prevalence, we performed a sensitivity analysis of the rule-out approaches using a MACE prevalence of 10% to better represent a typical MACE prevalence among ED chest pain patients in the United States, assuming negligible spectrum effect in test characteristics.[26, 42] For comparative purposes we also standardized the reported units of net benefit by normalizing to disease prevalence.[41] In accordance with decision curve analysis reporting guidance, a default strategy in which all patients undergo further testing and/or treatment ("test all") is also illustrated for comparison.[38]

Table S1. **Characteristics of potentially eligible non-enrolled patients with an ED diagnosis of chest pain.**

		N = 46,989
Risk factors	Age (median, IQR)	59 (47-72)
	Male (%)	44
	Hypertension (%)	52
	Hypercholesteremia (%)	50
	Diabetes (%)	26
	CAD (%)	21
	Coronary revascularization (%)	14
	Myocardial infarction (%)	15
	Stroke or TIA (%)	9
	Peripheral artery disease (%)	3
	Smoker (%)	9
	Family history premature CAD (%)	5
	Obesity (%)	41
Peak troponin within 6 hours of ED arrival	< LOQ (%)	79
	LOQ to 99th percentile (%)	14
	> 99th percentile (%)	6
ED disposition	Admission (%)	6
	Observation (%)	20
	Discharge (%)	73
60-day outcomes	MACE (%)	5.5
	MACE-CR (%)	4.7
	Coronary revascularization (%)	2.2
	All-cause mortality (%)	1.0

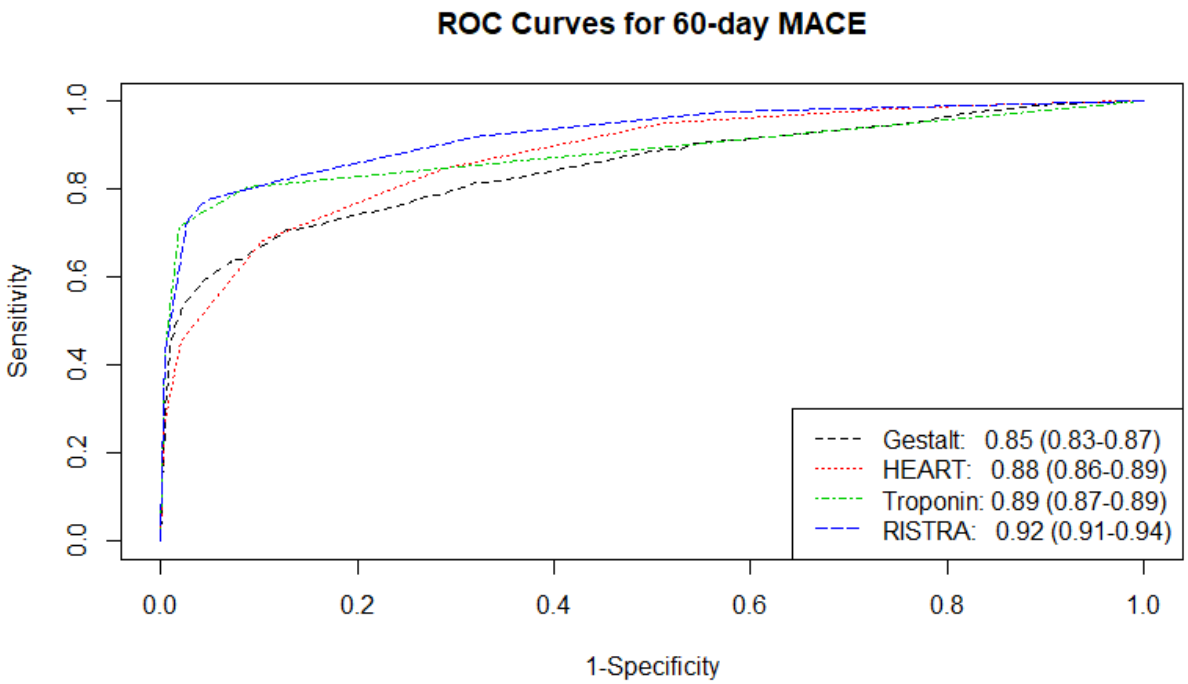
CAD = coronary artery disease; LOQ = limit of quantification; MACE = major adverse cardiac event at 60-days; MACE-CR = major adverse cardiac event at 60-days excluding coronary revascularization; TIA = transient ischemic attack.

Table S2. Characteristics of potentially eligible non-enrolled patients with a chief complaint of chest pain or chest discomfort.

		N = 67,247
Risk factors	Age (median, IQR)	60 (47-72)
	Male (%)	45
	Hypertension (%)	52
	Hypercholesteremia (%)	50
	Diabetes (%)	26
	CAD (%)	20
	Coronary revascularization (%)	13
	Myocardial infarction (%)	15
	Stroke or TIA (%)	9
	Peripheral artery disease (%)	4
	Smoker (%)	9
	Family history premature CAD (%)	5
	Obesity (%)	41
Peak troponin within 6 hours of ED arrival	< LOQ (%)	76
	LOQ to 99th percentile (%)	15
	> 99th percentile (%)	9
ED disposition	Admission (%)	11
	Observation (%)	17
	Discharge (%)	71
60-day outcomes	MACE (%)	7.8
	MACE-CR (%)	7.2
	Coronary revascularization (%)	2.9
	All-cause mortality (%)	1.5

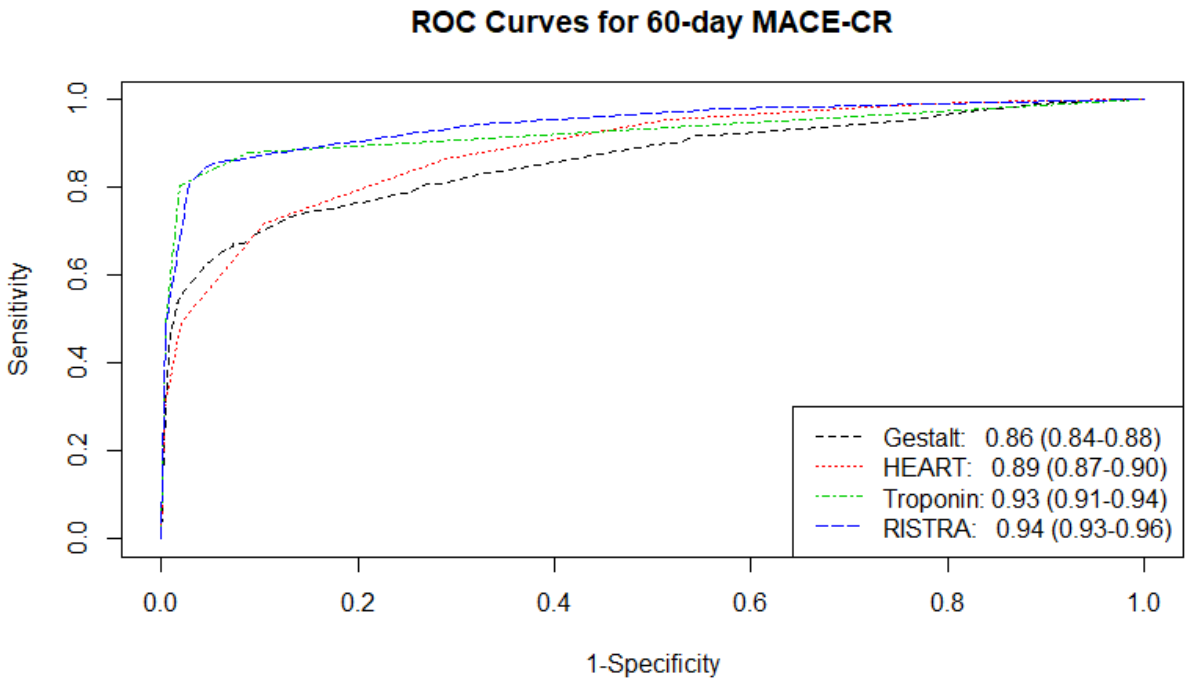
CAD = coronary artery disease; LOQ = limit of quantification; MACE = major adverse cardiac event at 60-days; MACE-CR = major adverse cardiac event at 60-days excluding coronary revascularization; TIA = transient ischemic attack.

Figure S1. Receiver operating characteristic (ROC) curves using graded risk stratification approaches for the primary outcome of 60-day major adverse cardiac events (MACE).



Approaches are: 1) physician gestalt for acute coronary syndrome (Gestalt), 2) HEART score (HEART), 3) troponin strata (Troponin) and 4) RISTRA-ACS (RISTRA). Area under the ROC for each strategy is shown in the legend with accompanying 95% confidence intervals.

Figure S2. Receiver operating characteristic (ROC) curves using graded risk stratification approaches for the secondary outcome of 60-day major adverse cardiac events excluding coronary revascularization (MACE-CR).



Approaches are: 1) physician gestalt for acute coronary syndrome (Gestalt), 2) HEART score (HEART), 3) troponin strata (Troponin) and 4) RISTRA-ACS (RISTRA). Area under the ROC for each strategy is shown in the legend with accompanying 95% confidence intervals.