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

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Study objective: This diagnostic accuracy study describes the performance of 5 accelerated chest pain pathways, calculated with the new Beckman's Access high-sensitivity troponin I assay.

Methods: High-sensitivity troponin I was measured with presentation and 2-hour blood samples in 1,811 patients who presented to an emergency department (ED) in Australia. Patients were classified as being at low risk according to 5 rules: modified accelerated diagnostic protocol to assess patients with chest pain symptoms using troponin as the only biomarker (m-ADAPT), the Emergency Department Assessment of Chest Pain Score (EDACS) pathway, the History, ECG, Age, Risk Factors, and Troponin (HEART) pathway, the No Objective Testing Rule, and the new Vancouver Chest Pain Rule. Endpoints were 30-day acute myocardial infarction and acute coronary syndrome. Measures of diagnostic accuracy for each rule were calculated.

Results: Data included 96 patients (5.3%) with acute myocardial infarction and 139 (7.7%) with acute coronary syndrome. The new Vancouver Chest Pain Rule and No Objective Testing Rule had high sensitivity for acute myocardial infarction (100%; 95% confidence interval [CI] 96.2% to 100% for both) and acute coronary syndrome (98.6% [95% CI 94.9% to 99.8%] and 99.3% [95% CI 96.1% to 100%]). The m-ADAPT, EDACS, and HEART pathways also yielded high sensitivity for acute myocardial infarction (96.9% [95% CI 91.1% to 99.4%] for m-ADAPT and 97.9% [95% CI 92.7% to 99.7%] for EDACS and HEART), but lower sensitivity for acute coronary syndrome ($\leq$95.0% for all). The m-ADAPT, EDACS, and HEART rules classified more patients as being at low risk (64.3%, 62.5%, and 49.8%, respectively) than the new Vancouver Chest Pain Rule and No Objective Testing Rule (28.2% and 34.5%, respectively).

Conclusion: In this cohort with a low prevalence of acute myocardial infarction and acute coronary syndrome, using the Beckman's Access high-sensitivity troponin I assay with the new Vancouver Chest Pain Rule or No Objective Testing Rule enabled approximately one third of patients to be safely discharged after 2-hour risk stratification with no further testing. The EDACS, m-ADAPT, or HEART pathway enabled half of ED patients to be rapidly referred for objective testing. [Ann Emerg Med. 2018;71:439-451.]

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INTRODUCTION

Background

More than 5.5 million people present to emergency departments (EDs) each year with chest pain and only 13% receive a diagnosis of acute coronary syndrome.[1] The assessment of such patients uses clinical history, ECGs, and serial cardiac troponin levels to rule out acute myocardial infarction.[2,3] Further objective testing is then used to rule out unstable angina pectoris. This process involves considerable time and represents significant economic burden to the health care system.[4] Research on efficient and safe approaches to rule out acute coronary syndrome is required.

Importance

Two major approaches have been proposed for accelerating the assessment of chest pain patients. The first is to use algorithms incorporating high-sensitivity cardiac troponin results on presentation or up to 2 hours after

Editor's Capsule Summary

What is already known on this topic

Accelerated diagnostic pathways are intended to expedite the emergency department disposition for patients evaluated for suspected acute coronary syndrome.

What question this study addressed

The study uses existing data sets to answer which accelerated diagnostic pathway performs best when used in conjunction with a new high-sensitivity troponin assay.

What this study adds to our knowledge

In a cohort of 1,811 patients with a low prevalence of acute myocardial infarction and acute coronary syndrome, this study reports that the accelerated diagnostic pathways had similar sensitivity for their intended classifications. The new Vancouver Chest Pain Rule and No Objective Testing Rule had the fewest false-negative results but were also substantially less specific.

How this is relevant to clinical practice

Although these results require independent confirmation, adding high-sensitivity troponins to existing diagnostic pathways may improve resource use in chest pain evaluations.

presentation.[5-8] High-sensitivity cardiac troponin assays provide improved ability to detect and quantify cardiac troponin compared with older troponin assays, leading to improved sensitivity for earlier acute myocardial infarction diagnosis.[9] However, there is wide variability in assay characteristics between manufacturers,[10] and each assay requires separate assessment of clinical performance.[3] Newly released assays, such as the Beckman Coulter Access high-sensitivity troponin I (Access hs-TnI) assay, require clinical validation before being included in existing chest pain assessment strategies. Furthermore, despite improvements in troponin assays, early troponin testing alone does not identify all patients at short-term risk for major adverse cardiac events or those with unstable angina pectoris.[11]

These issues have led to a second approach to the rapid assessment for acute coronary syndrome, the use of accelerated diagnostic pathways, which incorporate clinical information with troponin results to safely rule out acute myocardial infarction and acute coronary syndrome in ED patients. A variety of accelerated diagnostic pathways have been developed, including the History, ECG, Age, Risk Factors, and Troponin (HEART) pathway,[12] the modified accelerated diagnostic protocol to assess patients with chest pain symptoms using troponin as the only biomarker (m-ADAPT),[13] the Emergency Department Assessment of Chest Pain Score (EDACS) pathway,[14] the new Vancouver Chest Pain Rule,[15] and the No Objective Testing Rule.[16]

Such rules have high sensitivity for identifying cardiac events,[13-18] but they require validation when a new troponin assay is used. Furthermore, each score was developed for a slightly different purpose and their validation should use an endpoint that reflects this purpose. m-ADAPT and EDACS were developed to rapidly rule out acute myocardial infarction. Early objective testing is then recommended to identify the broader group of patients with unstable angina pectoris. Thus, successful validation of the m-ADAPT and EDACS rules requires that they identify a very high proportion of patients with acute myocardial infarction, with the identification of the broader cohort with acute coronary syndrome (including patients with unstable angina pectoris) being of lower importance. In contrast, the HEART, new Vancouver Chest Pain Rule, and No Objective Testing Rule were developed to identify a cohort of chest pain patients who could be discharged from the ED with no further cardiac testing. Relaxing the requirement for further testing means that the success of such rules depends on their ability to identify all patients with acute myocardial infarction and unstable angina pectoris (ie, all acute coronary syndromes). Otherwise, the identification and provision of appropriate medical treatment for patients with unstable angina pectoris may not occur.

Goals of This Investigation

This study evaluated 5 accelerated diagnostic pathways for the assessment of patients with symptoms suggestive of acute coronary syndrome: the HEART pathway, m-ADAPT, the EDACS pathway, the new Vancouver Chest Pain Rule, and the No Objective Testing Rule. The aim of this study was to evaluate the diagnostic performance of each of these scores when calculated with the new Access hs-TnI assay taken at 0 and 2 hours after presentation. In assessing diagnostic accuracy, we sought to use an endpoint that reflects the purpose for which each score was developed. The m-ADAPT and EDACS pathways were developed to rapidly rule out acute myocardial infarction, thereby allowing rapid referral for objective testing. As such, it is hypothesized (hypothesis 1) that m-ADAPT and EDACS will have high sensitivity ($\geq$99%) for acute myocardial infarction. In contrast, the HEART pathway, new Vancouver Chest Pain Rule, and No Objective Testing Rule were developed to

identify patients who could be discharged with no further objective testing. Their utility requires that they identify a high proportion of acute coronary syndrome patients. As such, it is hypothesized (hypothesis 2) that HEART, the new Vancouver Chest Pain Rule, and the No Objective Testing Rule will have high sensitivity (≥99%) for acute coronary syndrome.

The assessment of the accelerated diagnostic pathways used the entire cohort of patients and a single 99th percentile cutoff for the Access hs-TnI assay. However, the inclusion of sex-specific high-sensitivity troponin I cut points was also explored, given increasing interest in the use of such cut points.[19] Furthermore, a comparison of patients who presented early (≤2 hours) or late (>2 hours) after chest pain onset was examined, with international guidelines noting that some clinical decision rules may not be valid for early presenters.[3]

MATERIALS AND METHODS

Study Design and Setting

This study used data from 2 studies that were conducted to develop and validate accelerated chest pain protocols in the ED. The 2 studies were conducted within a tertiary hospital in Australia, and results of the primary studies have been previously reported.[20,21] The first cohort included 986 patients from the Australian cohort of the ADAPT study, a prospective observational study of adult patients presenting to the ED between November 2008 and February 2011.[20] The second was the cohort from the Improved Assessment of Chest Pain Trial, an intervention trial including 1,366 adult patients between February 2011 and March 2014.[21] The study protocols were approved by the Human Ethics and Research Committee and complied with the Declaration of Helsinki. The validation of clinical decision rules for the assessment of acute coronary syndrome was included as part of the protocol for both studies. Data from these 2 cohorts were used because they both had the same inclusion and exclusion criteria, were conducted within the same hospital, had the same procedures for data collection, had all necessary variables collected, and had available data for the Access hs-TnI. The New Zealand cohort of the ADAPT study was not included because it did not have Access hs-TnI data available.

Selection of Participants

For both studies, eligible patients were recruited during working hours (8 AM to 5 PM) if they were aged 18 years or older, had greater than or equal to 5 minutes of chest pain consistent with acute coronary syndrome, and were undergoing investigation for potential acute coronary syndrome. Pain consistent with acute coronary syndrome was defined with the American Heart Association definitions, including acute chest, epigastric, neck, jaw, or arm pain, or discomfort or pressure without a clear noncardiac source.[22] Patients were excluded if they had a clear alternative cause for the suspected symptoms other than acute coronary syndrome, they were unable or unwilling to provide informed consent, recruitment was considered inappropriate (eg, palliative treatment), they were pregnant, they had been recruited to the study within the past 45 days, they were transferred from another hospital, or they could not be contacted after discharge (eg, homeless). Patients were also excluded from the current study if they met the criteria for ST-segment elevation myocardial infarction (STEMI) on presentation. Such patients are urgently referred for revascularization and do not undergo investigation for acute coronary syndrome in the ED. Research nurses screened and enrolled consecutive eligible patients during working hours.

All patients in the first study (the observational study) were managed according to standard care, which included ECG and cardiac troponin I measurements at presentation, followed by troponin measurements 6 hours later (93.4% of all patients). A subset of patients in the second study (the interventional study) was deemed suitable for an accelerated assessment process in which presentation and 2-hour troponin tests were used rather than presentation and 6-hour tests. Such patients included those for whom the clinician was comfortable with accelerated testing and for whom the following features were absent: repetitive or ongoing chest pain despite initial treatment, ECG changes, hemodynamic compromise, syncope, previous percutaneous coronary intervention, or coronary artery bypass graft. All patients not eligible for accelerated testing underwent standard care, including presentation and 6-hour biomarkers.

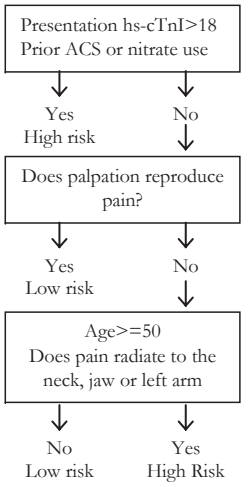
Data Collection and Processing

Research nurses collected data from patients, using standardized reporting guidelines.[23] Baseline characteristics, medical history, risk factors, and current medications were gathered directly from the patient. If the patient was unsure about an answer, a "no" response was recorded unless he or she was receiving a medication for these conditions.

ECGs and troponin samples were taken on presentation and 2 hours later. Blood samples were centrifuged and stored at –80°C (-112°F). These blood samples were later analyzed in a blinded fashion, using the Access hs-TnI assay. This assay has an overall 99th percentile of 17.5 ng/L and a limit of detection of 2.3 ng/L. Sex-specific 99th

Table 1. Details for the m-ADAPT, HEART, EDACS, and new Vancouver Chest Pain Rule scores.

Risk Score	m-ADAPT	HEART Pathway	EDACS	New Vancouver	NOT
Purpose of score	Identify patients at low risk of 30-day AMI, emergency revascularization, ventricular arrhythmia, high-level AV block, or cardiac death	Identify patients at low risk of 30-day all-cause mortality, AMI, or revascularization.	Identify patients at low risk of 30-day AMI, emergency revascularization, ventricular arrhythmia, high-level AV block, or cardiac death	Identify patients at low risk of 30-day AMI or UAP	Identify patients at low risk of 30-day AMI, cardiac death, emergency or urgent revascularization, or UAP
Recommendation for low-risk patients	Safe for early inpatient objective testing or discharge for outpatient objective testing	Discharge after 3 h with no further objective testing	Safe for early inpatient objective testing or discharge for outpatient objective testing	Discharge after 2 h with no further objective testing	Discharge after 2 h with no further objective testing
Definition of low risk	TIMI score $\leq$1 Troponin $\leq$99th percentile at 0 and 2 h No new ischemia on presentation ECG	HEART score $\leq$3 Troponin $\leq$99th percentile at 0 and 3 h	EDACS score $<$16 Troponin $\leq$99th percentile at 0 and 2 h No new ischemia on presentation ECG	As per new Vancouver	NOT rule=0 Troponin $\leq$99th percentile at 0 and 2 h No new ischemia on presentation ECG
Prevalence of primary endpoint in derivation study	MACE: 247/1,635 (15.1%)	ACS: 222/1,005 (22%)	MACE: 305/1,974 (15.5%)	ACS: Cohort 1: 165/763 (21.6%) Cohort 2: 119/906 (13.1%)	ACS: 565/3,188 (17.7%) in the entire cohort and 126/2,396 (5.3%) in patients with normal ECG and troponin

Details of risk score	1 point or each of: Age ≥65 y ≥3 risk factors (hypertension, dyslipidemia, family history of CAD, diabetes, or current smoking) Aspirin use within the last 7 days Severe angina within the past 24 h Significant coronary stenosis (>50%) ECG indicative of new ischemia High-sensitivity troponin >99th percentile on presentation	History Slightly suspicious (atypical pain only) (0 pts) Moderately suspicious (typical and atypical features) (1 pt) Highly suspicious (typical pain only) (2 pts) Patients were categorized as having typical pain if they presented with chest pain that they described as dull, heavy, crushing, pressure, or tight. Patients were categorized as having atypical pain if they presented without chest pain or pain that was described as sharp, burning, stabbing, or indigestionlike. ECG Normal (0 pts) Nonspecific changes, including prolonged PR, QRS, QTc intervals, bundle branch blocks, or left ventricular hypertrophy with strain (1 pt) Changes consistent with ACS (including ST-segment elevation at the J point in 2 or more contiguous leads, with the cutoff points ≥0.2 mV in lead V1, V2, or V3 or ≥0.1 mV in other leads; new ST-segment elevation with left bundle branch block; ST-segment depression of ≥0.5 mm (0.05 mV) in 2 or more contiguous leads (includes reciprocal changes); T-wave inversion of ≥1 mm (0.1 mV) including inverted T waves that are not indicative of acute MI; or Q waves ≥30 ms in duration) (2 pts) Age <45 y (0 pts); 45–65 y (1 pt); >65 y (2 pts) Risk factors 0 (0 pts) 1–2 (1 pt) ≥3 or history of atherosclerotic disease (2 pts) Troponin (initial) Negative (0 pts); 1–3 times normal limit (1 pt); >3 times normal limit (2 pts)	Age 18–45 y (2 pts); 46–50 y (4 pts); 51–55 y (6 pts); 56–60 y (8 pts); 61–65 y (10 pts); 66–70 y (12 pts); 71–75 y (14 pts); 76–80 y (16 pts); 81–85 y (18 pts); ≥86 y (20 pts) In patients aged 18–50 y, known CAD or ≥3 risk factors: (4 pts) Diaphoresis (3 pts) Pain radiates to arm, neck, or jaw (5 pts) Pain occurs or worsened with inspiration (pleuritic in nature) (–4 pts) Pain reproduced by palpation (–6 pts) Male sex (6 pts)		1 point for each of: Age ≥50 y ≥3 risk factors (hypertension, dyslipidemia, family history of CAD, diabetes, or current smoking) Previous MI or CAD

New Vancouver, New Vancouver Chest Pain Rule; *NOT*, No Objective Testing Rule; *AMI*, acute myocardial infarction; *UAP*, unstable angina pectoris; *AV*, atrioventricular; *MACE*, major adverse cardiac events; *ACS*, acute coronary syndrome; *CAD*, coronary artery disease.

m-ADAPT is a modified version of the ADAPT protocol for use with high-sensitivity troponin assays. As per ADAPT, this protocol uses TIMI score, ECG, and troponin level. A higher TIMI cutoff (≤1 rather than <1) is applied when used with a high-sensitivity troponin assay.

percentiles are 11.6 ng/L for women and 19.8 ng/L for men. All values were rounded to the nearest whole number in accordance with the practice of local laboratories, and an overall 99th percentile of 18 ng/L was used in this study. Sex-specific cut points were rounded to 12 for women and 20 for men.

Individuals were retrospectively classified as being at low risk or not according to the m-ADAPT, EDACS, HEART, new Vancouver Chest Pain Rule, and No Objective Testing Rule score pathways (Table 1). Such classification was performed blinded to the patient outcome. Data for computation of each of these protocols were collected as part of the original study, with the exception of the HEART pathway. For HEART, the history and ECG components were retrospectively calculated with definitions outlined in a previous validation study.[24] Furthermore, the HEART pathway uses 3-hour troponin tests, which were not available for this study. Tests taken 2 hours after the first troponin test were instead used because previous research has shown that these tests yield the same diagnostic accuracy as 3-hour tests.[25]

Thirty days after initial attendance, trained research nurses conducted telephone follow-up and medical record review. Information was obtained from the patient and from hospital databases about whether there had been any cardiac events, cardiac investigations, or contact with any health care provider during the 30-day period. All follow-up information was verified through contact with the health care provider, and original copies of medical records and cardiac investigation results were obtained. Relevant investigations included exercise stress testing, stress echocardiography, myocardial perfusion scanning, coronary computed tomography (CT) angiography, or coronary angiography. There was no loss to follow-up; information on all patients was obtained through direct patient contact, contact with the general practitioner, or hospital databases.

Outcome Measures

Several outcomes were included in the current study. The first was 30-day acute myocardial infarction. Patients met the criteria for acute myocardial infarction during their initial hospital presentation if they died of a cardiac cause or received a diagnosis of non–ST-segment myocardial infarction (NSTEMI), STEMI, or emergency revascularization during admission or within the 30-day period after presentation to the ED (Table E1, available online at http://www.annemergmed.com). The second outcome was 30-day acute coronary syndrome. Patients were deemed to meet the criteria for acute coronary syndrome if they died of a cardiac cause or received a diagnosis of STEMI, NSTEMI, emergency revascularization, unplanned revascularization, or unstable angina pectoris during admission or within the 30-day period after presentation. The diagnostic accuracy of all of the scores was calculated for both acute myocardial infarction and acute coronary syndrome. However, as per hypothesis 1, 30-day acute myocardial infarction is the primary endpoint for validating the m-ADAPT and EDACS scores. As per hypothesis 2, 30-day acute coronary syndrome is the primary endpoint when validating the HEART, new Vancouver Chest Pain Rule, and No Objective Testing Rule.

Local cardiologists assigned endpoints in this study using ECGs, troponin results, investigations, and information from the patient, and information from the medical record about whether there had been death, cardiac events, or cardiac investigations during or after discharge. A second cardiologist conducted a blind review of all patients who received a cardiovascular endpoint and 10% of cases with a noncardiovascular endpoint. In cases of disagreement, endpoints were agreed by consensus between the 2 cardiologists and an emergency physician. Although cardiologists had access to the patient's medical record to provide necessary information for assigning endpoints, they were not provided with details about whether the patient was at low risk or not according to any of the decision rules.

The troponin value used to adjudicate patient outcomes was the Beckman Coulter second-generation AccuTnI assay. This assay differs from the high-sensitivity assay used for calculation of the index tests. It is a contemporary sensitive assay (not a high-sensitivity cardiac troponin assay) with a limit of detection 0.01 μg/L, 99th percentile of 0.04 μg/L, and imprecision at the 99th percentile of 14%. In the observational study, presentation and 6-hour troponin levels were used for endpoint adjudication. In the intervention study, all available troponin levels were used. For both studies, a cardiac troponin I level above the 99th percentile of a normal health reference population (>0.04 μg/L) was used as the clinical cutoff in accordance with international guidelines.[2,26] Cardiologists were blinded to the Access hs-TnI data when conducting endpoint adjudication.

Primary Data Analysis

Data were analyzed with Stata (version 14; StataCorp, College Station, TX). Baseline characteristics of the sample were reported. The diagnostic accuracy of the 5 rules for 30-day acute myocardial infarction and 30-day acute coronary syndrome was assessed with sensitivity, specificity, positive predictive value, and negative predictive value.

A number of sensitivity analyses were also conducted. First, to examine whether time to presentation influenced the accuracy of the algorithms, the performance of each of the pathways was calculated for early and late presenters. Early presentation was defined as less than or equal to 2 hours, in line with previous research.[27] Second, sensitivity, specificity, positive predictive value, and negative predictive value for each of the pathways was assessed with sex-specific cut points rather than an overall high-sensitivity troponin I cut point.

RESULTS

Characteristics of Study Subjects

Data were available for 1,811 patients (Figure 1); 96 (5.3%) received a diagnosis of acute myocardial infarction during 30 days, and 139 (7.7%) received a diagnosis of 30-day acute coronary syndrome. Baseline characteristics of the population are provided in Table 2. The cohort was younger and had a lower prevalence of acute myocardial infarction or acute coronary syndrome than patients in the validation studies for each of the pathways.[12-16]

There were 1,660 patients (91.7%) with a presentation Access hs-TnI level below the 99th percentile. Twenty-three of these patients had a 30-day acute myocardial infarction, resulting in sensitivity of 76.0% (95% confidence interval [CI] 66.3% to 84.2%). Thirty patients had an elevated troponin level 2 hours later, leaving 1,630 patients (90.0%) with presentation and 2-hour troponin values below the 99th percentile. Ten of the 1,630 patients received a diagnosis of 30-day acute myocardial infarction, resulting in sensitivity of 89.6% (95% CI 81.7% to 94.9%).

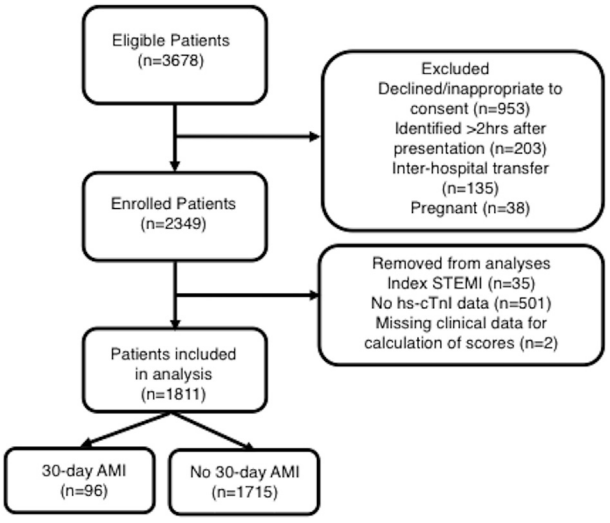


Figure 1. Patient flow.

Table 2. Baseline characteristics of the sample.

Characteristic	Total Cohort (n=1,811)
Mean age (SD), y	52.9 (13.9)
Male sex, No. (%)	1,086 (60.0)
Median time to presentation (IQR), h	3.7 (1.5–15.6)
Cardiovascular history, No. (%)	
Myocardial infarction	254 (14.0)
Angioplasty	156 (8.6)
Coronary artery bypass graft	93 (5.1)
Stroke	104 (5.7)
Congestive heart failure	48 (2.7)
Risk factors, No. (%)	
Hypertension	795 (43.9)
Dyslipidemia	758 (41.9)
Diabetes	231 (12.8)
Family history of CAD (<65 y)	738 (40.8)
Current or recent smoking	509 (28.1)

IQR, Interquartile range.

For 30-day acute myocardial infarction, there were 3 false-negative cases with the m-ADAPT pathway (sensitivity 96.9%; 95% CI 91.1% to 99.4%), 2 false-negative cases with either the EDACS or HEART pathways (sensitivity 97.9%; 95% CI 92.7% to 99.7%), and no false-negative cases with either the new Vancouver Chest Pain Rule or No Objective Testing Rule (sensitivity 100%; 95% CI 96.2% to 100%) (Figure 2 and Figure E1, available online at http://www.annemergmed.com). Sensitivity was similar for all accelerated diagnostic pathways. Details of missed cases are provided in Table E2, available online at http://www.annemergmed.com.

There were 10 false-negative cases for 30-day acute coronary syndrome with m-ADAPT (sensitivity 92.8%; 95% CI 87.2% to 96.5%), 11 with the EDACS pathway (sensitivity 92.1%; 95% CI 86.3% to 96.0%), 7 with the HEART pathway (sensitivity 95.0%; 95% CI 89.9% to 98.0%), 2 for the new Vancouver Chest Pain Rule (sensitivity 98.6%; 95% CI 94.9% to 99.8%), and 1 for the No Objective Testing Rule (sensitivity 99.3%; 95% CI 96.1% to 100%) (Figure 3 and Figure E2, available online at http://www.annemergmed.com). Details of missed unstable angina pectoris cases are provided in Table E3, available online at http://www.annemergmed.com.

A high proportion of patients were classified as being at low risk after incorporation of Access hs-TnI into the m-ADAPT protocol (1,165; 64.3%; 95% CI 62.1% to 66.5%), the EDACS pathway (1,132; 62.5%; 95% CI 60.2% to 64.7%), and the HEART pathway (902; 49.8%; 95% CI 47.5% to 52.1%). The new Vancouver Chest Pain Rule and the No Objective Testing Rule

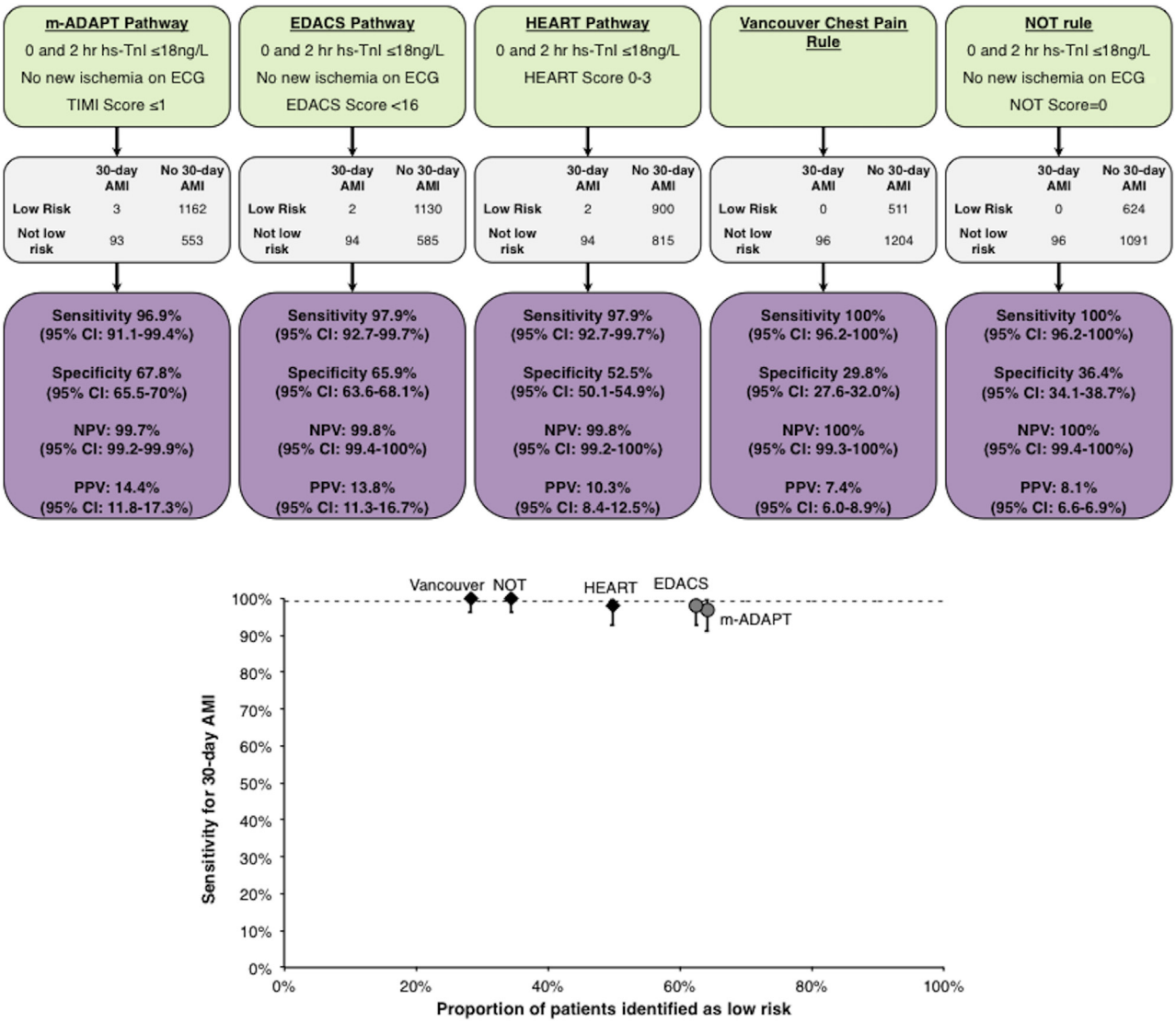


Figure 2. Sensitivity and proportion ruled out for 30-day acute myocardial infarction. Black diamonds on the graph represent clinical decision rules that were designed to identify patients who could be discharged with no further assessment. Gray squares on the graph indicate clinical pathways that identified patients who could rapidly be referred for objective testing. Dotted line represents 99% sensitivity, the figure deemed acceptable to emergency clinicians. *NPV,* Negative predictive value; *PPV,* positive predictive value.

identified only 511 patients (28.2%; 95% CI 26.2% to 30.4%) and 624 patients (34.5%; 95% CI 32.3% to 36.7%), respectively, as being at low risk.

Sensitivity Analyses

Sensitivity analyses are provided in Table 3. The scores performed similarly for early and late presenters. The use of sex-specific cut points had minimal effect on the results. There was one additional missed case of acute myocardial infarction for the EDACS score if sex-specific cut points were used. This was a man who received a diagnosis of NSTEMI and had a maximum high-sensitivity troponin I value of 19 ng/L.

LIMITATIONS

Potential limitations of the study merit consideration. First, clinical decision rules in this study were retrospectively calculated with data collected as part of a separate study. Future research should incorporate prospective calculation of the rules to provide a validation that reflects the realities of the clinical environment and to ensure that variables are defined as per the original rule.

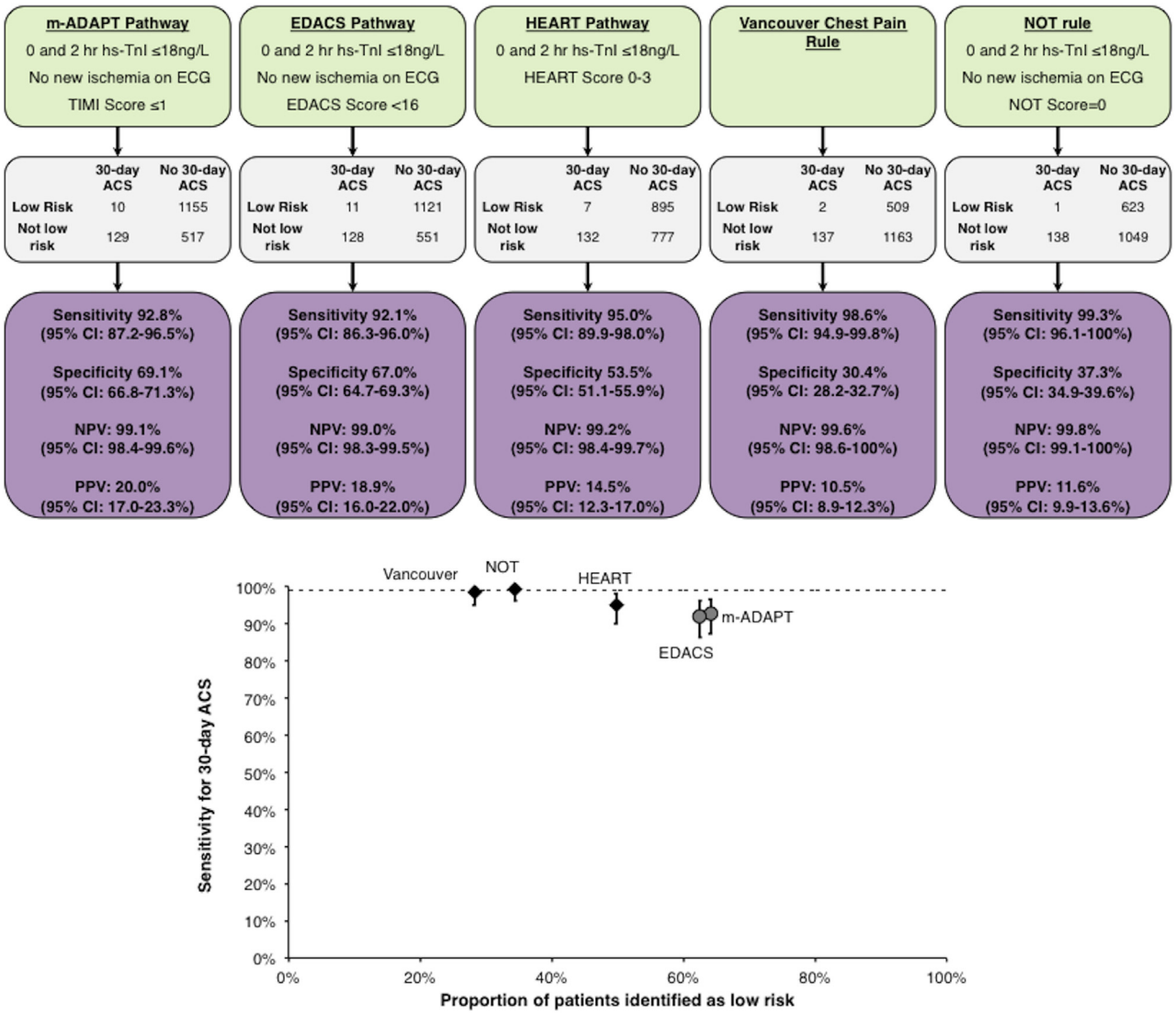


Figure 3. Sensitivity and proportion ruled out for 30-day acute coronary syndrome. Black diamonds on the graph represent clinical decision rules that were designed to identify patients who could be discharged with no further assessment. Gray squares on the graph indicate clinical pathways that identified patients who could rapidly be referred for objective testing. Dotted line represents 99% sensitivity, the figure deemed acceptable to emergency clinicians.

The HEART pathway was not calculated as originally outlined. In particular, the history component of this score was calculated with a definition outlined in a previous article[24] rather than using the clinician's subjective assessment performed at the admission. This may have changed the proportion of patients deemed to be at low risk and could have reduced the diagnostic accuracy for this score.

Second, the m-ADAPT, No Objective Testing Rule, and EDACS pathways were developed with the Brisbane and New Zealand cohort of the ADAPT study. Some of the participants (716) in this current article were from the Brisbane cohort of the ADAPT study. The overlap of participants in this study and the derivation studies may mean that the diagnostic accuracy for these rules is higher than it would be if a new external validation cohort were used.

Third, patients were recruited between 8 AM and 5 PM, introducing the potential for selection bias. However, our previous research reported that individuals presenting outside of work hours did not differ from those recruited within work hours in terms of demographics, risk factors, medical history, or diagnosis.[28]

Fourth, the prevalence of acute myocardial infarction and acute coronary syndrome in this study was low. This may influence the generalizability of the results.

Table 3. Sensitivity, specificity, and negative predictive value for sensitivity analyses.

Statistic	Sensitivity (95% CI)	NPV (95% CI)	Specificity (95% CI)	PPV (95% CI)
30-day AMI				
Early presenters (≤2 h), n=620, with 27 cases of AMI				
m-ADAPT	92.6 (75.7–99.1)	99.5 (98.3–99.9)	72.7 (68.9–76.2)	13.4 (8.8–19.1)
EDACS	100 (87.2–100)	100 (99.1–100)	66.9 (63.0–70.7)	12.1 (8.1–17.1)
HEART pathway	92.6 (75.7–99.1)	99.4 (97.8–99.9)	54.6 (50.5–58.7)	8.5 (5.6–12.3)
New Vancouver	100 (87.2–100)	100 (97.9–100)	29.2 (25.5–33.0)	6.0 (4.0–8.7)
NOT rule	100 (87.2–100)	100 (98.3–100)	37.3 (33.4–41.3)	6.83 (4.5–9.7)
Late presenters (>2 h), n=1,187, with 69 cases of AMI				
m-ADAPT	98.6 (92.2–100)	99.9 (99.2–100)	65.4 (62.5–68.2)	14.9 (11.8–18.6)
EDACS	97.1 (89.9–99.6)	99.7 (99.0–100)	65.5 (62.6–68.3)	14.8 (11.6–18.4)
HEART pathway	100 (94.8–100)	100 (99.4–100)	51.1 (48.5–54.5)	11.3 (8.9–14.1)
New Vancouver	100 (94.8–100)	100 (98.9–100)	30.2 (27.6–33.0)	8.1 (6.4–10.2)
NOT rule	100 (94.8–100)	100 (99.1–100)	36.0 (33.2–38.9)	8.8 (6.9–11.0)
Using sex-specific cut points (>12 ng/L for women and >20 ng/L for men)				
m-ADAPT	96.9 (91.1–99.4)	99.7 (99.2–99.9)	67.5 (65.2–69.7)	14.3 (11.7–17.2)
EDACS	96.9 (91.1–99.4)	99.6 (99.2–99.9)	65.5 (63.2–67.7)	13.6 (11.1–16.4)
HEART pathway	97.9 (92.7–99.7)	99.8 (99.2–100)	52.4 (50.0–54.8)	10.3 (8.4–12.5)
New Vancouver	100 (96.2–100)	100 (99.3–100)	29.7 (27.6–32.0)	7.4 (6.0–8.9)
NOT rule	100 (96.2–100)	100 (99.4–100)	36.3 (34.0–38.6)	8.1 (6.6–9.8)
30-day ACS				
Early presenters (≤2 h), n=620, with 39 cases of ACS				
m-ADAPT	89.7 (75.8–97.1)	99.1 (97.7–99.7)	73.8 (70.1–77.4)	18.7 (13.4–25.1)
EDACS	97.4 (86.5–99.9)	99.7 (98.6–100)	68.2 (64.2–71.9)	17.0 (12.3–22.6)
HEART pathway	94.9 (82.7–99.4)	99.4 (97.8–99.9)	55.8 (51.6–59.9)	12.6 (9.0–16.9)
New Vancouver	100 (91.0–100)	100 (97.9–100)	29.8 (26.1–33.7)	8.7 (6.3–11.7)
NOT rule	100 (91.0–100)	100 (98.3–100)	38.0 (34.1–42.1)	9.8 (7.0–13.1)
Late presenters (>2 h), n=1,187, with 100 cases of ACS				
m-ADAPT	94.0 (87.4–97.8)	99.2 (98.2–99.7)	66.8 (63.9–69.6)	20.7 (17.0–24.7)
EDACS	90.0 (82.4–95.1)	98.6 (97.5–99.3)	66.6 (63.7–69.4)	19.9 (16.3–23.8)
HEART pathway	95.0 (88.7–98.4)	99.1 (98.0–99.7)	52.5 (49.5–55.5)	15.5 (12.8–18.7)
New Vancouver	98 (93.0–99.8)	99.4 (97.9–99.9)	30.9 (28.2–33.8)	11.5 (9.5–13.9)
NOT rule	99.0 (94.6–100)	99.8 (98.6–100)	37.0 (34.1–39.9)	12.6 (10.4–15.2)
Using sex-specific cut points (>12 ng/L for women and >20 ng/L for men)				
m-ADAPT	92.8 (87.2–96.5)	99.1 (98.4–99.6)	68.8 (66.6–71.1)	19.8 (16.8–23.1)
EDACS	91.4 (85.4–95.5)	98.9 (98.1–99.4)	66.6 (64.3–68.9)	18.5 (15.7–21.7)
HEART pathway	95.0 (89.9–98.0)	99.2 (98.4–99.7)	53.5 (51.0–55.9)	14.5 (12.3–17.0)
New Vancouver	98.6 (94.9–99.8)	99.6 (98.6–100)	30.4 (28.2–32.7)	10.5 (8.9–12.3)
NOT rule	99.3 (96.1–100)	99.8 (99.1–100)	37.1 (34.8–39.5)	11.6 (9.8–13.6)

There were missing data on time to presentation for 4 patients.

Fifth, this study focused on achieving a sensitivity acceptable to emergency clinicians. Individual patients will have different beliefs about acceptable risk, and these should be considered.

DISCUSSION

This study evaluated the use of the Access hs-TnI assay (taken at 0 and 2 hours) within 5 established accelerated diagnostic pathways for the assessment of patients with symptoms suggestive of acute coronary syndrome. The study evaluated each of the scores against an endpoint that matched their stated aim, and as such, provides clinicians with guidance about the circumstances under which a particular score should be used. The use of the Access hs-TnI assay with either the new Vancouver Chest Pain Rule or the No Objective Testing Rule resulted in a combination strategy that could safely rule out 30-day acute coronary syndrome in 25% to 30% of patients. As such, these scores would be well suited within a health care system in which patients are discharged from the ED with no follow-up or for systems seeking to safely reduce ongoing patient testing. The use of the Access hs-TnI assay within the EDACS, m-ADAPT, or HEART rule pathways enabled double the number of patients (50% to 60%) to be classified as low risk, but did not achieve a sensitivity for either acute myocardial infarction alone or acute coronary syndrome that would be acceptable to clinicians (>99%). These rules may be used in a health care setting where the

ED is focused on rapid rule-out of acute myocardial infarction and where patients are then referred for outpatient cardiology review, outpatient objective testing, or inpatient objective testing.

Three of the rules examined in this study were designed to identify low-risk patients who could be discharged with no further testing: the new Vancouver Chest Pain Rule, the No Objective Testing Rule, and the HEART pathway. In the current study, inclusion of the Access hs-TnI assay within the new Vancouver Chest Pain Rule and No Objective Testing Rule identified a cohort of patients who had a near-zero risk for both acute myocardial infarction and acute coronary syndrome, thus supporting their use for early and safe rule-out of acute coronary syndrome. This finding is backed by the limited body of research validating the No Objective Testing Rule[29] and new Vancouver Chest Pain Rule.[30,31] However, contradictory findings for the new Vancouver Chest Pain Rule do exist, with one study from Singapore finding that the rule had only moderate sensitivity (78.1%) for acute myocardial infarction.[32] The explanation for this lower sensitivity is not clear, but may be attributable to differences in the troponin assay used (high-sensitivity troponin I versus high-sensitivity troponin T) or to the fact that the pain characteristics incorporated within the new Vancouver Chest Pain Rule are likely to have differential utility across cultures.[33]

The HEART pathway also has been used to identify low-risk patients who can be discharged with no further testing. In the current study, we found mixed support for the use of the HEART pathway to safely discharge patients. The HEART pathway had moderately high sensitivity for acute myocardial infarction and identified twice as many low-risk patients as the new Vancouver Chest Pain Rule or No Objective Testing Rule. This is in line with a previous study comparing the No Objective Testing Rule and HEART pathways.[29] However, the HEART pathway achieved lower sensitivity for acute coronary syndrome (95%) compared with the Vancouver Chest Pain Rule and No Objective Testing Rule. Furthermore, although sensitivity for acute myocardial infarction did not significantly differ across the 3 rules, the HEART pathway failed to achieve the 99% sensitivity for acute myocardial infarction that is deemed acceptable to clinicians.[34] Thus, it is unclear whether this rule would gain acceptance as a safe rule-out strategy with no further follow-up. Indeed, the sensitivity for acute myocardial infarction in this study aligns with that observed in a number of previous validations of the HEART pathway,[17,31] and a recent randomized trial reported that physicians were hesitant to refrain from admission and further diagnostic tests for low-risk HEART patients.[17] Nonetheless, high sensitivity for acute myocardial infarction, in combination with high proportions of patients identified as being at low risk, may make the HEART score a useful tool for rapidly identifying patients without acute myocardial infarction who could be discharged for further outpatient assessment.

The final 2 rules examined in this study (m-ADAPT and EDACS) were both designed as rapid diagnostic tools to enable early inpatient objective testing or discharge for outpatient objective testing. Our study supported the use of these tools for the accelerated assessment of acute myocardial infarction. The m-ADAPT and EDACS pathways calculated with the Access hs-TnI assay classified approximately two thirds of patients as low risk and achieved a moderately high sensitivity for acute myocardial infarction and acute coronary syndrome. This finding is consistent with results of previous research, with several studies finding that the m-ADAPT[31,35] and EDACS pathways[36,37] identified a high proportion of patients with major adverse cardiac events. In contrast, evaluation of these scores on a cohort in the United States found that neither the EDACS[38] nor the ADAPT[39] protocol performed as effectively when evaluated on US cohorts. Both studies incorporated only a small number of patients with major adverse cardiac events (17 for the EDACS evaluation and 31 for the ADAPT study) and further validations using larger US cohorts are required to confirm these results.

Each high-sensitivity troponin assay has different analytic characteristics and requires separate assessment of clinical performance. When the 99th percentile is used, the Access hs-TnI assay had sensitivity of 89.6% at 2 hours. This is similar to figures reported for an Australasian cohort using the Abbott high-sensitivity troponin I assay[13] and the Roche troponin T assay.[35] This sensitivity is too low for diagnosis of acute myocardial infarction and highlights the importance of incorporating troponin values into a clinical decision rule if early rule-out is required. Alternative strategies, such as the use of the limit of detection,[40,41] or the incorporation of early ECG and low-level troponins with Δ troponins,[5,7] also have shown potential using existing high-sensitivity cardiac troponin assays but require further assessment before use with the Beckman's assay.

In summary, in this cohort with a low prevalence of acute myocardial infarction and acute coronary syndrome, the use of the Access hs-TnI assay with either the new Vancouver Chest Pain Rule or the No Objective Testing Rule enabled approximately one third of patients to be safely discharged after 2-hour risk stratification with no further testing. The use of this assay within the EDACS, m-ADAPT, or HEART

rule pathways enabled more than half of ED patients to be rapidly referred for objective testing.

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Table E1. Definitions for endpoint adjudication.

Acute myocardial infarction	Diagnosis of acute myocardial infarction was made according to international guidelines and based on evidence of myocardial necrosis with evidence of ischemia (at least one of ECG changes or imaging results, including exercise tolerance testing, myocardial perfusion scan, stress echocardiography, CT coronary angiography, or coronary angiography during catheterization). Necrosis was diagnosed according to an increase or decrease of cardiac troponin concentration over at least 6 hours, with at least one value above the 99th percentile of the normal reference range, at a level of assay imprecision near 10%. If the troponin level was greater than the reference range but no increase or decrease was recorded, other causes of elevated troponin level were considered. If no alternative cause for the troponin-level increase was apparent and if the clinical presentation was suggestive of acute coronary syndrome, an adjudicated diagnosis of acute myocardial infarction was made. Acute myocardial infarction was classified as STEMI when there was new (or presumably new if no previous ECG result was available) ST-segment elevation on the ECG. Acute myocardial infarction was classified as NSTEMI when there was no new ST-segment elevation on ECG.
Unstable angina pectoris	Diagnosis of unstable angina pectoris was based on ischemic symptoms, ECG changes, and objective investigations (exercise stress testing, stress echocardiography, CT coronary angiography, myocardial perfusion scan, or angiography), with normal biomarker levels. This definition included patients with new symptoms or a changing symptom pattern (ie, from stable to unstable angina). Patients with equivocal ECG changes but clear positive changes on exercise tolerance testing or imaging evidence of critical coronary stenosis also were classified as having unstable angina pectoris.
Emergency revascularization	Emergency revascularization was defined as percutaneous coronary intervention or coronary artery bypass grafting in a symptomatic patient, in which the clinical status included either ischemic dysfunction (ongoing ischemia despite maximal medical therapy, acute evolving myocardial ischemia within 24 h before intervention, or pulmonary edema requiring intubation) or mechanical dysfunction (shock with or without circulatory support).
Unplanned revascularization	Unplanned revascularization included percutaneous coronary intervention or coronary artery bypass grafting that did not meet the emergency criteria above but was required during the same hospitalization to minimize chance of further clinical deterioration. Elective revascularization, or those procedures that could be deferred without increased risk of compromised cardiovascular outcome, was not included in the endpoint.

Table E2. Details about missed NSTEMI cases.

Pathway Missed	Sex	Age, Years	Time to Present, Hours	Outcome	Objective Testing	hs-cTnI at 0 and 2 Hours, ng/L*	cTnI at 0, 2, and 6 Hours, ng/L†	Risk Factors
EDACS	Female	65	8.4	Index UAP NSTEMI 1 day later	Angiogram	2 and 3	10, 10, 10	Family history, Htn, dyslipidemia
ADAPT	Male	51	3.4	NSTEMI	Angiogram (to PCI)	12 and 17	20, 50, 60	Family history, dyslipidemia, smoker, BMI >30 kg/m^2
ADAPT and HEART	Male	63	1.7	NSTEMI	Angiogram (to PCI)	3 and 5	90, 90, 100	Nil
ADAPT and HEART	Male	57	0.5	NSTEMI	Angiogram (to PCI)	2 and 10	10, 20, 120	Family history, BMI >30 kg/m^2
EDACS	Male	54	4.5	NSTEMI	Angiogram (to PCI)	8 and 17	ND, 50, 330	Htn, dyslipidemia, smoker, BMI >30 kg/m^2

hs-cTnI, Beckman's high-sensitivity troponin I assay; *cTnI*, Beckman's sensitive troponin I assay; *Htn*, hypertension; *PCI*, percutaneous coronary intervention; *BMI*, body mass index; *ND*, not done.
*99th percentile=18 ng/L.
†99th percentile=40 ng/L.

Table E3. Details about missed unstable angina cases.

Pathway Missed	Sex	Age, Years	Time to Present, Hours	Outcome	Objective Testing	hs-cTnI at 0 and 2 Hours, ng/L*	cTnI at 0, 2, and 6 Hours, ng/L†	Risk Factors
ADAPT	Male	63	3.9	UAP	Angiogram	6 and 6	10, 20, 20	Htn, dyslipidemia, BMI >30 kg/m^2
EDACS and HEART	Male	52	5.3	UAP	Angiogram	3 and 3	10, 20, 10	Previous angina, family history, Htn, dyslipidemia, BMI>30
EDACS	Female	63	3.1	UAP	Angiogram	6 and 7	20, 20, 20	Family history, Htn, dyslipidemia, BMI >30 kg/m^2
EDACS	Female	63	2.4	UAP	Angiogram	4 and 3	10, 20, 10	Family history, Htn, dyslipidemia, current smoker, BMI >30 kg/m^2
ADAPT, EDACS, and new Vancouver	Female	61	3	UAP	Angiogram (to PCI)	4 and 3	10, 10, 10	Diabetes, Htn
ADAPT, EDACS, and HEART	Female	63	22.4	UAP	Angiogram (to elective PCI)	4 and 3	10, 10, 10	Family history, smoker
EDACS and ADAPT	Female	54	0.9	UAP	Angiogram	2 and 2	10, 10, 10	Family history, Htn, dyslipidemia, smoker
All rules	Male	49	2.1	UAP	EST and MPS	2 and 1	10, 10, ND	BMI >30 kg/m^2
HEART	Male	48	17	UAP	Angiogram (to PCI)	2 and 3	10, 10, 10	Diabetes, smoker, BMI >30 kg/m^2
EDACS	Male	55	2.8	UAP	Angiogram (to PCI)	3 and 4	10, 10, 10	Previous MI, diabetes, family history, Htn, dyslipidemia
ADAPT	Male	45	0.8	UAP	Angiogram	3 and 3	10, 10, ND	Family history, Htn, dyslipidemia, smoker
ADAPT, EDACS, and HEART	Male	53	3.5	UAP	Angiogram (to PCI)	2 and 3	10, 10, 20	Family history, dyslipidemia

EST, Exercise stress test; *MPS*, myocardial perfusion scan.
*99th percentile=18 ng/L.
†99th percentile=40 ng/L.

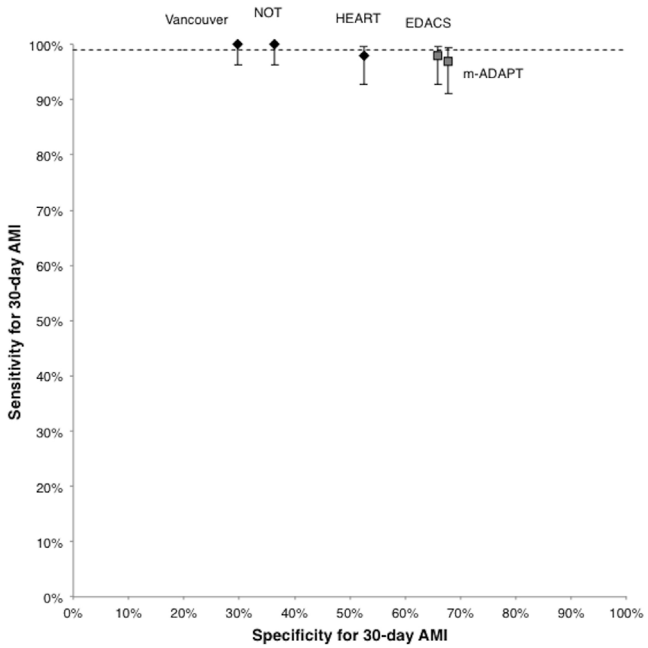

Figure E1. Sensitivity and specificity ruled out for 30-day acute myocardial infarction. Black diamonds represent clinical decision rules that were designed to identify patients who could be discharged with no further assessment. Gray squares indicate clinical pathways that identified patients who could rapidly be referred for objective testing. Dotted line represents 99% sensitivity, the figure deemed acceptable to emergency clinicians.

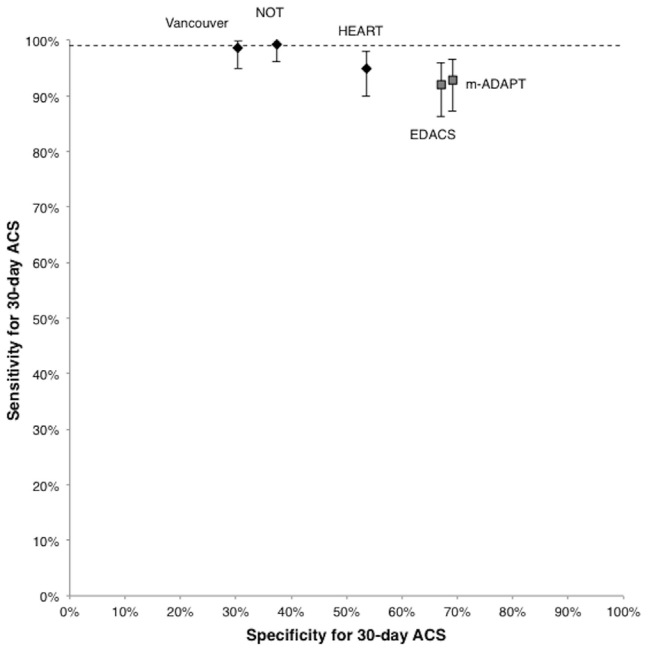

Figure E2. Sensitivity and specificity ruled out for 30-day acute coronary syndrome. Black diamonds represent clinical decision rules that were designed to identify patients who could be discharged with no further assessment. Gray squares indicate clinical pathways that identified patients who could rapidly be referred for objective testing. Dotted line represents 99% sensitivity, the figure deemed acceptable to emergency clinicians.