The Rational Clinical Examination

Does This Patient With Chest Pain Have Acute Coronary Syndrome?
The Rational Clinical Examination Systematic Review

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IMPORTANCE About 10% of patients with acute chest pain are ultimately diagnosed with acute coronary syndrome (ACS). Early, accurate estimation of the probability of ACS in these patients using the clinical examination could prevent many hospital admissions among low-risk patients and ensure that high-risk patients are promptly treated.

OBJECTIVE To review systematically the accuracy of the initial history, physical examination, electrocardiogram, and risk scores incorporating these elements with the first cardiac-specific troponin.

STUDY SELECTION MEDLINE and EMBASE were searched (January 1, 1995-July 31, 2015), along with reference lists from retrieved articles, to identify prospective studies of diagnostic test accuracy among patients admitted to the emergency department with symptoms suggesting ACS.

DATA EXTRACTION AND SYNTHESIS We identified 2992 unique articles; 58 met inclusion criteria.

MAIN OUTCOMES AND MEASURES Sensitivity, specificity, and likelihood ratio (LR) of findings for the diagnosis of ACS. The reference standard for ACS was either a final hospital diagnosis of ACS or occurrence of a cardiovascular event within 6 weeks.

RESULTS The clinical findings and risk factors most suggestive of ACS were prior abnormal stress test (specificity, 96%; LR, 3.1 [95% CI, 2.0-4.7]), peripheral arterial disease (specificity, 97%; LR, 2.7 [95% CI, 1.5-4.8]), and pain radiation to both arms (specificity, 96%; LR, 2.6 [95% CI, 1.8-3.7]). The most useful electrocardiogram findings were ST-segment depression (specificity, 95%; LR, 5.3 [95% CI, 2.1-8.6]) and any evidence of ischemia (specificity, 91%; LR, 3.6 [95% CI,1.6-5.7]). Both the History, Electrocardiogram, Age, Risk Factors, Troponin (HEART) and Thrombolysis in Myocardial Infarction (TIMI) risk scores performed well in diagnosing ACS: LR, 13 (95% CI, 7.0-24) for the high-risk range of the HEART score (7-10) and LR, 6.8 (95% CI, 5.2-8.9) for the high-risk range of the TIMI score (5-7). The most useful for identifying patients less likely to have ACS were the low-risk range HEART score (0-3) (LR, 0.20 [95% CI, 0.13-0.30]), low-risk range TIMI score (0-1) (LR, 0.31 [95% CI, 0.23-0.43]), or low to intermediate risk designation by the Heart Foundation of Australia and Cardiac Society of Australia and New Zealand risk algorithm (LR, 0.24 [95% CI, 0.19-0.31]).

CONCLUSIONS AND RELEVANCE Among patients with suspected ACS presenting to emergency departments, the initial history, physical examination, and electrocardiogram alone did not confirm or exclude the diagnosis of ACS. Instead, the HEART or TIMI risk scores, which incorporate the first cardiac troponin, provided more diagnostic information.

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Clinical Scenario

Case 1

A 42-year-old, previously healthy woman presents to the emergency department with 45 minutes of crushing substernal chest pain. On arrival to the emergency department, the pain is completely relieved by nitroglycerin, the electrocardiogram (ECG) is unremarkable, and initial troponin level is 0.01 ng/mL (reference range, 0.00-0.08 ng/mL).

Case 2

A 74-year-old man with a myocardial infarction 3 years prior presents to the emergency department with several days of intermittent burning retrosternal chest pain. The ECG shows Q waves in leads II, III, and aVF that were present on his last ECG 3 months prior; there are no new ischemic changes. His initial troponin level is 0.14 ng/mL (reference range, 0.00-0.08 ng/mL).

Are these patients having acute coronary syndrome (ACS)?

Background

Why Is This an Important Question to Answer With a Clinical Evaluation?

More than 8 million patients present to US emergency departments each year with acute chest pain,[1] though as few as 10% will ultimately be diagnosed with acute coronary syndrome (ACS), a clinical diagnosis encompassing ST-segment elevation myocardial infarction (STEMI), non–STEMI (NSTEMI), and unstable angina. Many more patients undergo prolonged emergency department observation or hospital admission to rule out ACS,[2] followed by stress testing or cardiac catheterization. In part because so many patients are observed or admitted, the percentage of patients with ACS discharged home during the initial emergency department visit is low. In 1 study that included 10 689 patients, 2.2% of those presenting with acute chest pain and ultimately diagnosed with ACS were mistakenly discharged from the emergency department, though the mortality risk ratio was similar for those with ACS mistakenly discharged to home vs those admitted (risk ratio, 1.4 [95% CI, 0.4-4.1]; absolute risk, 7.7% mortality for those discharged vs 5.7% for those admitted).[3] There are no firm guidelines for what rate of missed ACS is acceptable in practice, and the threshold is likely to differ among emergency department providers and hospitals. A recent, multinational survey of 1029 emergency department physicians found that a majority desired a miss rate less than 1%.[4] Several studies demonstrated that clinical impression alone is not sufficiently sensitive to exclude ACS or significant coronary artery disease at this threshold.[5,6]

Clinical Classification and Case Definitions

Physicians seek to categorize patients presenting with symptoms concerning for myocardial ischemia into 1 of 3 groups: STEMI, non–ST-segment elevation ACS (NSTE-ACS, which includes NSTEMI and unstable angina), and noncardiac chest pain.

A prior systematic review in this series examined the performance of history, physical examination, and ECG in determining the presence or absence of myocardial infarction.[7] Subsequently, more studies addressed the performance of elements of the history, physical examination, and ECG in distinguishing between ACS and noncardiac chest pain.

Because STEMI can be excluded by ECG and occurs in less than 25% of patients presenting with symptoms concerning for ischemia, the key distinction in the majority of patients is between NSTE-ACS and noncardiac chest pain.[8] Determining the appropriate diagnostic category is imperative to subsequent management decisions; therefore, professional societies have published recommendations to aid clinicians in evaluating patients with suspected ACS.[1,9] The recommendations propose an initial ECG within 10 minutes of presentation, clinical examination, and baseline cardiac troponin testing followed by serial ECGs and cardiac troponin evaluation over an 8- to 23-hour observation period. Patients with NSTE-ACS require admission to a monitored bed, coronary care unit, or intensive care unit, with immediate administration of guidelines-directed medical therapy, including antiplatelet and antithrombotic therapy.[9,10] Patients with noncardiac chest pain may be discharged home or undergo a period of observation.

Myocardial infarction is defined as at least 1 elevation in cardiac troponin above the 99th percentile reference limit of the assay with a typical rise or fall, along with either symptoms of ischemia, ECG changes consistent with ischemia, imaging evidence of loss of viable myocardium, or detection of an intracoronary thrombus.[11] By contrast, ACS (encompassing both myocardial infarction and unstable angina) has no such consensus definition and remains a clinical diagnosis without a clear reference standard, though some groups have proposed a standardized definition for research purposes.[12] Despite increasing sensitivity of cardiac troponin assays, there still exist cases of biomarker-negative ACS (ie, unstable angina).[13] For the purposes of diagnostic studies, some investigators use discharge diagnosis or have a panel adjudicate final diagnosis based on clinical history and hospital course. However, the majority of investigators have chosen a reference standard based on follow-up, with ACS defined as the incidence of a clinical end point (such as cardiovascular death, myocardial infarction, coronary revascularization, or medically managed significant coronary artery disease [CAD]) within a certain timeframe after the initial presentation. Both reference standards introduce verification bias (in which the result of a screening test influences whether or not the reference standard test is performed) and incorporation bias (in which the result of the screening test is a component of the reference standard).

When clinical end points are used as the reference standard, patients with risk factors or symptoms will more likely undergo further testing, which in turn makes them more likely to undergo revascularization or be diagnosed with obstructive CAD, thereby reaching a clinical end point. This verification bias results in an overestimation of sensitivity so that the negative likelihood ratio (LR−) is less useful than it appears for identifying patients without ACS, while specificity is underestimated so that the positive likelihood ratio (LR+) is actually better than it appears. When the discharge diagnosis or adjudicated final diagnosis is used as the reference standard, the index test may be used directly in determining the reference standard, which creates incorporation bias. Incorporation bias means that both the LR+ and LR− appear more useful than they actually are.

We estimated the pretest probability for ACS among all patients presenting to the emergency department in whom the diagnosis of ACS is suspected, without regard for age, sex, or other traditional cardiac risk factors. The ECG and often the cardiac troponin level are available at the time of the clinician's first evaluation. We focused on features of the history, physical examination, and ECG that increase or decrease the estimated likelihood of ACS. We also systematically reviewed decision aids that incorporate elements of the history, physical examination, and ECG on initial emergency department presentation combined with initial cardiac troponin results.

Methods

Search Strategy and Study Selection

We performed English-language searches in MEDLINE and EMBASE from January 1, 1995 (the beginning of the cardiac troponin era) to July 31, 2015, using the following Medical Subject Headings (MeSH) terms and search strategy: *physical examination* or *medical history taking* or *professional competence* or *sensitivity and specificity* or *reproducibility of results* or *observer variation* or *diagnostic tests, routine* or *decision support techniques* or *Bayes theorem* or *risk assessment* or *electrocardiography* and *chest pain* and *emergency service, hospital*. For our EMBASE search, we replaced the MeSH terms with the appropriate Emtree terms. We also searched for key words related to each MeSH term in the title and abstract. After identifying articles, we reviewed references from appropriate articles to identify additional references for this systematic review.

Titles and abstracts for all articles were screened independently and in duplicate by the primary author (A.C.F.) and 1 additional author (J.A.R. or S.A.G.). If either author identified the article as potentially appropriate for inclusion, the full text of the article was reviewed in detail and data were extracted independently and in duplicate. If data sufficient for generation of a 2 × 2 table could be extracted, the methods of the article were reviewed in further detail by 2 authors independently, and methodological quality and eligibility were determined.

Inclusion Criteria

For the accuracy of elements of the history, physical examination, ECG, or decision aids that consider those elements plus cardiac troponin level on presentation, we included studies that met the following criteria: (1) patients presenting to an emergency department with suspected ACS; (2) test (history, physical examination, ECG, or decision aid combining those elements plus cardiac troponin level on presentation), described in adequate detail; and (3) outcome (either final hospital discharge diagnosis of ACS [either as determined by the treating physician or by systematic central adjudication by reviewers using a prespecified definition of ACS] or clinical cardiac events [encompassing at least cardiovascular death, myocardial infarction, and revascularization] through 14 days to 6 weeks after presentation).

Exclusion Criteria

We excluded studies testing decision aids or accelerated diagnostic protocols that required serial ECGs or troponin measurements, as these tools cannot be used at the time of the initial emergency department assessment, and as such are not helpful in determining a patient's probability of ACS at the time of the clinician's first evaluation of the patient with chest discomfort. As the focus of this review was initial examination of the undifferentiated patient with potential NSTE-ACS (NSTEMI or unstable angina), studies enrolling only patients after assignment to emergency department observation units were excluded because these patients represent preselected low-risk populations. We also excluded studies that selected for only intermediate- or high-risk patients, studies that did not include a cardiac event during the index presentation as a major adverse cardiac event, and studies with an end point of myocardial infarction rather than all ACS. Studies evaluating index tests that incorporated high-sensitivity troponin were excluded, as this test is not yet available in the United States. We included only articles published in peer-reviewed literature, and did not seek unpublished data. For each included article, we evaluated the Rational Clinical Examination level of evidence (eAppendix 1 in the Supplement),[14] and evaluated bias with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) Criteria, a meta-analytic system devised specifically for diagnostic studies (eAppendix 2 in the Supplement).[15] Studies with a Rational Clinical Examination quality level of 3 through 5 were excluded.

Clinical Prediction Rules

The Thrombolysis in Myocardial Infarction (TIMI) risk score was initially derived as a prognostic rule to predict 14-day outcomes in a clinical trial population of patients with ACS.[16] It uses 7 variables (1 of these variables is a composite of traditional risk factors), each scored as present or absent to give a score of 0 through 7. The History, ECG, Age, Risk Factors, Troponin (HEART) risk score; the Heart Foundation of Australia and Cardiac Society of Australia and New Zealand (HFA/CSANZ) rule; and the Agency for Healthcare Policy and Research (AHCPR) rule were derived a priori based on expert opinion, and have been tested exclusively in populations of patients with undifferentiated suspected ACS. Like the TIMI score, the HEART score incorporates elements of history, presentation ECG, and presentation cardiac troponin results.[17-23] Unlike the TIMI risk score, each of its 5 elements is scored from 0 through 2, to give a total score of 0 through 10. The HFA/CSANZ and AHCPR algorithms provide a list of high- and intermediate-risk features. If none are present, patients are at low risk.

The Global Registry of Acute Coronary Events (GRACE) risk score was derived by multivariable modeling in an international observational study of patients with confirmed ACS to predict in-hospital and 6-month death or recurrent myocardial infarction. Like the TIMI risk score, the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) score was derived from a clinical trial of patients with ACS as a prognostic tool.[24] The Emergency Department Assessment of Chest Pain Score (EDACS) was designed to be incorporated (along with baseline and 2-hour troponin results) into an accelerated diagnostic protocol to rapidly exclude ACS in patients presenting to the emergency department with chest pain. It incorporates age, sex, risk factors, and various chest pain characteristics.[25]

Features of the TIMI risk score, the HEART risk score, the HFA/CSANZ rule, and the AHCPR rule are summarized in the **Box**.

Box. Clinical Decision Rules Used in Diagnosing Acute Coronary Syndrome (ACS)

TIMI Risk Score[16]

Assesses for the presence of 7 variables to give a score from 0 through 7: age ≥65 years; 3 or more cardiac risk factors; known CAD; aspirin use; ≥2 episodes of angina in the preceding 24 hours; ST-segment elevation or depression ≥0.5 mm; and elevation in cardiac biomarkers

HEART Risk Score[22]

Scores 5 categories on a scale of 0 through 2 to give a score from 0 through 10:

- History: 0 points for history incompatible with ACS, 1 point for a history potentially compatible with ACS, 2 points for a history strongly suggestive of ACS
- ECG: 0 points for a normal ECG, 1 point for an ECG with nonspecific repolarization abnormalities, 2 points for an ECG with ST depression or transient ST elevation
- Age: 0 points for <45 years, 1 point for 45-65 years, 2 points for >65 years
- Risk factors: 0 points for no risk factors, 1 point for 1-2 risk factors, 2 points for ≥3 risk factors or known CAD
- Troponin level: 0 points for normal troponin level, 1 point for troponin level of 1-3 × upper limit of normal, 2 points for troponin level of >3 × upper limit of normal

HFA/CSANZ Rule[76]

Scores patients as low, intermediate, or high risk based on clinical parameters:

- High risk: either prolonged chest discomfort; ST depression, transient ST elevation, or T-wave inversion on ECG; hemodynamic compromise; sustained ventricular tachycardia; left ventricular systolic dysfunction; percutaneous coronary intervention within 6 months or any prior coronary artery bypass grafting; diabetes or chronic kidney disease with typical symptoms; any positive cardiac biomarker
- Intermediate risk: not meeting high-risk criteria and either age >65 years, known CAD, non–high-risk ECG, 2 or more cardiac risk factors, diabetes or chronic kidney disease with atypical symptoms, or prior aspirin use
- Low risk: not meeting high- or low-risk criteria

AHCPR Rule[1]

Scores patients as low, intermediate, or high risk based on clinical parameters:

- High risk: either reproduction of prior anginal pain, known CAD, hemodynamic instability or pulmonary edema, ST-segment deviation or T-wave inversion, or elevated cardiac biomarkers
- Intermediate risk: not meeting high-risk criteria and either chest pain or left arm pain as chief symptom, age >70 years, male sex, diabetes mellitus, known noncardiac vascular disease, ECG with Q waves or nonspecific ST-segment changes
- Low risk: not meting criteria for high or intermediate risk

Analysis

We calculated the sensitivity, specificity, and LRs from the abstracted data. Summary data for dichotomous findings are reported as a range when a finding was evaluated in 2 studies, univariate random effects summary measures when the finding was evaluated in 3 studies using Comprehensive Meta-Analysis (Biostat), version 2.2046, and bivariate random effects summary measures for findings evaluated in 4 or more studies using SAS (SAS Institute), version 9.2. The summary prevalence of disease was calculated as a random effects estimate from the included studies, and the point estimate was combined with the LRs to calculate the predictive values.

Heterogeneity was assessed for the LRs for findings assessed in at least 3 studies. The heterogeneity for these studies is displayed through both the CI and I^2 statistic. The I^2 statistic describes the percentage of total variation across studies that is due to heterogeneity rather than chance. Heterogeneity is qualitatively considered as low, moderate, or high corresponding to I^2 values of 25%, 50%, and 75%, respectively.[26] Publication bias was assessed by 3 methods: Begg and Mazumdar rank correlation, Egger regression intercept, and the trim and fill procedure.[27]

For meta-analysis of risk scores, studies were included only if they provided data for each risk score stratum. With multiple thresholds on an ordinal scale, the sensitivity and specificity terms lack definition. Thus, we calculated a random-effects summary LR at each threshold for the risk scores. Studies that reported data for ranges of risk scores were excluded from the summary measures, though their data are presented as part of the systematic review.

Of 195 symptoms, signs, risk factors, ECG findings, and integrated algorithms evaluated, 164 of these (84%) were compared with a reference standard of cardiac events at follow-up rather than discharge diagnosis of ACS, but the sample sizes were too small for meaningful comparisons of findings based on the reference standard.

Results

Of 2992 unique articles; 58 articles met our inclusion criteria and were included in the systematic review (eFigure in the Supplement) as Rational Clinical Examination level 1 through 2 studies (eTable 1 in the Supplement).[17-23,25,28-74] For each variable evaluated, data were extracted from 1 to 12 studies; the total number of studies providing data for each variable, and the total number of patients enrolled in those studies are presented in Tables 1 through 4. Risk of bias for each included study is shown in eTable 2 in the Supplement. All studies enrolled either consecutive patients presenting to the emergency department with chest pain or chest pain during prespecified hours of the day. Twenty studies compared elements of the history or presentation ECG with a reference standard of final diagnosis of centrally or locally adjudicated ACS; the remainder used a reference standard of 14-day to 6-week cardiac events. The between-clinician reliability was moderate to good for risk factors (κ>0.60) and ECG (κ>0.55), but for chest pain quality, location, radiation, and associated symptoms, reliability was fair (κ range, 0.29-0.37) (eAppendix 3 in the Supplement).

Pretest Probability of ACS in All Patients Presenting to the Emergency Department With Suspected ACS

Rates of final ACS diagnosis ranged from 5% to 42% (median, 14% [interquartile range, 10%-20%]).The estimated incidence of ACS in the 28 studies that evaluated a risk score was 13% (95% CI, 11%-16%), I^2 = 99%. There was no publication bias based on

Table 1. Performance of Cardiac Risk Factors in Diagnosing Acute Coronary Syndrome[a]

Test	No. Studies	No. Patients	% (95% CI) Sensitivity	% (95% CI) Specificity	LR+ (95% CI)	I^2, %	LR− (95% CI)	I^2, %	%[b] PPV	%[b] NPV
Abnormal prior stress[c,61]	1	1777	12 (8-16)	96 (95-97)	3.1 (2.0-4.7)		0.92 (0.88-0.96)		32	12
Peripheral arterial disease[21,23,49]	3	6034	7.5 (2-11)	97 (95-99)	2.7 (1.5-4.8)	0	0.96 (0.94-0.98)	64	29	13
Prior CAD[37,40,49,57,60]	5	6396	41 (13-69)	79 (60-98)	2.0 (1.4-2.6)	87	0.75 (0.56-0.93)	96	23	10
Prior myocardial infarction[d]	9	10 491	28 (21-36)	82 (78-86)	1.6 (1.4-1.7)	42	0.88 (0.81-0.93)	81	19	12
Diabetes[e]	9	10 237	26 (21-32)	82 (77-85)	1.4 (1.3-1.6)	4	0.90 (0.86-0.94)	45	17	12
Cerebrovascular disease[21,23,49,70]	4	6682	10 (8-13)	93 (91-94)	1.4 (1.1-1.8)	18	0.97 (0.94-0.99)	14	17	13
Men[f]	12	21 113	66 (62-76)	50 (44-51)	1.3 (1.2-1.3)	65	0.70 (0.64-0.77)	39	16	9
Hyperlipidemia[g]	10	10 288	42 (31-55)	67 (56-79)	1.3 (1.1-1.5)	70	0.85 (0.77-0.93)	69	16	11
Hypertension[h]	11	10 931	59 (53-66)	52 (44-60)	1.2 (1.1-1.3)	51	0.78 (0.72-0.85)	29	15	10
Any tobacco use[i]	9	7 381	38 (28-47)	65 (55-75)	1.1 (0.9-1.3)	75	0.96 (0.85-1.1)	77	14	13
Family history of CAD[21,23,40,49,51,54,58]	7	8 717	37 (26-47)	64 (58-71)	1.0 (0.9-1.2)	54	0.99 (0.91-1.1)	65	13	13
Obesity[21,41,60]	3	4887	40 (26-55)	68 (48-84)	1.0 (0.9-1.2)	45	0.99 (0.88-1.1)	44	13	13
Prior CABG[23,31,58,70]	4	5902	9.1 (6-14)	91 (87-94)	0.97 (0.5-2.1)	77	1.00 (0.92-1.1)	77	13	13

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; LR+, positive likelihood ratio; LR−, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

[a] See eTable 4 in the Supplement for results from individual studies.

[b] PPV and NPV calculated assuming an acute coronary syndrome rate of 13%. The included studies had an acute coronary syndrome rate of 13% (95% CI, 11%-16%).

[c] When the summary measure was from less than 3 studies, the I^2 was not calculated.

[d] References 21, 23, 37, 49, 54, 58, 60, 70.

[e] References 21, 23, 31, 40, 49, 51, 58, 62, 70.

[f] References 21, 23, 31, 40, 47, 49, 51, 54, 58, 60, 62, 70.

[g] References 21, 23, 40, 49, 51, 54, 58, 60, 62, 70.

[h] References 21, 23, 31, 40, 49, 51, 54, 58, 60, 62, 70.

[i] References 21, 31, 40, 49, 51, 54, 58, 60, 62.

prevalence as evident through inspection of the funnel plot and 3 assessments for publication bias (Begg and Mazumdar, $P = .75$; Egger regression intercept, $P = .89$; trim and fill procedure, no studies trimmed). These data are consistent with a recent report from the Centers for Disease Control and Prevention, which indicated that 13% of emergency department visits for chest pain resulted in a diagnosis of ACS in 2007-2008.[75]

Accuracy of the Clinical Examination in Diagnosing ACS

Clinical impression. One well-performed study including 458 patients examined the diagnostic accuracy of overall clinical impression in the diagnosis of ACS.[72] Before they saw initial serum troponin and ECG results but after taking a full history, resident and attending physicians were asked to estimate the probability that a patient presenting with chest discomfort had ACS on a 5-point Likert scale. A choice of "definite" ACS had a diagnostic LR of 4.0 (95% CI, 2.5-6.6); "probable" ACS, 1.8 (95% CI, 1.3-2.4); "could be" ACS, 0.66 (95% CI, 0.46-0.96); "probably not" ACS, 0.20 (95% CI, 0.09-0.44); and "definitely not" ACS, 0.36 (95% CI, 0.05-2.8).

Risk factors. Family history of CAD, history of tobacco use, and obesity were not strong predictors of an ACS diagnosis (**Table 1**). Findings suggesting ACS (LR+≥2.0 and CI that excluded 1.0) were history of abnormal prior stress test (specificity, 96%; LR, 3.1 [95% CI, 2.0-4.7]) and peripheral arterial disease (specificity, 97%; LR, 2.7 [95% CI, 1.5-4.8]). For identifying patients less likely to have ACS, no risk factor when absent conferred an LR of 0.5 or lower.

Symptoms. Findings with an LR+ of 2.0 or higher and a CI that excluded 1.0 (**Table 2**) were pain radiation to both arms (specificity, 96%; LR, 2.6 [95% CI, 1.8-3.7]), pain similar to prior ischemia (specificity, 79%; LR, 2.2 [95% CI, 2.0-2.6]), and change in pain pattern over the prior 24 hours (specificity, 86%; LR, 2.0 [95% CI, 1.6-2.4]). Response to nitroglycerin was unhelpful; both improvement and lack of improvement had LRs approaching 1.0. Pleuritic pain had an LR range of 0.35 to 0.61.

Physical examination. Only 2 well-conducted studies, each enrolling more than 600 patients, tested the performance of physical examination findings in diagnosing ACS. Hypotension (**Table 3**) was the strongest clinical sign (LR, 3.9 [95% CI, 0.98-15]), though the CI was broad and did not exclude 1.0. Of all risk factors, symptoms, and signs, pain reproduced by palpation lowered the likelihood of ACS most (LR, 0.28 [95% CI, 0.14-0.54]).

ECG. In all studies,* ECGs were interpreted by physicians rather than computer algorithms (**Table 4**), but the extent of clinical information available to them generally was not described. Many studies evaluated an ischemic ECG vs a nonischemic ECG. Though there was some variability in how individual studies defined an ischemic ECG, an ischemic ECG had considerable specificity in diagnosing ACS (specificity, 91%; sensitivity, 32%; LR+, 3.6 [95% CI, 1.6-5.7]). ST-segment depression further enhanced specificity with a corresponding decrease in sensitivity (specificity, 95%; sensitivity, 25%; LR+, 5.3 [95% CI, 2.1-8.6]).

*References 17, 20-23, 31, 37, 39, 44, 45, 49, 62, 67, 68, 70

Table 2. Performance of Chest Pain Characteristics in Diagnosing Acute Coronary Syndrome[a]

	No.		% (95% CI)						%[c]	
Test	Studies	Patients	Sensitivity	Specificity	LR+ (95% CI)	I^2, %[b]	LR− (95% CI)	I^2, %[b]	PPV	NPV
Radiation to both arms[49]	1	2718	11 (8.3-15)	96 (95-96)	2.6 (1.8-3.7)		0.93 (0.89-0.96)		28	12
Pain similar to prior ischemia[49]	1	2718	47 (42-53)	79 (77-80)	2.2 (2.0-2.6)		0.67 (0.60-0.74)		25	9
Change in pattern over prior 24 h[49]	1	2718	27 (23-32)	86 (85-88)	2.0 (1.6-2.5)		0.84 (0.79-0.90)		23	11
"Typical" chest pain[d,47,49,54,60,62,71]	6	14 584	66 (58-74)	66 (49-83)	1.9 (0.94-2.9)	98	0.52 (0.35-0.69)	95	22	7
Worse with exertion[e,49,73]	2	5049	38-53	73-777	1.5-1.8		0.66-0.83		18-21	9-11
Radiation to neck or jaw[37,49,60]	3	4018	24 (15-36)	84 (76-90)	1.5 (1.3-1.8)	0	0.91 (0.87-0.95)	7.2	18	12
Recent episode of similar pain[73]	1	2331	55 (50-60)	56 (54-59)	1.3 (1.1-1.4)		0.80 (0.71-0.90)		16	11
Radiation to left arm[37,47,49]	3	13 613	40 (28-54)	69 (61-76)	1.3 (1.2-1.4)	0	0.88 (0.81-0.96)	69	16	12
Radiation to right arm[49]	1	2718	5.4 (3.4-8.3)	96 (95-97)	1.3 (0.78-2.1)		0.99 (0.96-1.0)		16	13
Associated diaphoresis[e,49,60]	2	3249	24-28	79-82	1.3-1.4		0.91-0.93		16-17	12-12
Associated dyspnea[49,60,62]	3	3648	45 (42-49)	61 (59-63)	1.2 (1.1-1.3)	0	0.89 (0.82-0.96)	0	15	12
Abrupt onset[49]	1	2718	76 (71-80)	32 (30-34)	1.1 (1.0-1.2)		0.75 (0.61-0.91)		14	10
Any improvement with nitroglycerin[40,66,73]	3	3218	71 (23-95)	35 (44-86)	1.1 (0.93-1.3)	86	0.90 (0.85-0.96)	0	14	12
"Typical" radiation[e,f,54,62]	2	560	25-32	69-96	1.0-5.7		0.78-0.98		13-46	10-13
Burning pain[e,49,60]	2	3249	12-16	84-92	1.0-1.4		0.97-1.0		13-17	13-13
Associated nausea/vomiting[e,49,60]	2	3249	21-22	77-80	0.92-1.1		0.98-1.0		12-14	13-13
Associated palpitations[60]	1	3487	6.0 (3.5-10)	91 (88-94)	0.71 (0.37-1.3)		1.0 (0.98-1.1)		10	13
Associated syncope[73]	1	2331	9.0 (6.4-12)	84 (82-85)	0.55 (0.39-0.76)		1.1 (1.1-1.1)		8	14
Pleuritic pain[e,37,49]	2	3487	18-36	78-93	0.35-0.61		1.1-1.2		6.6-8.4	14-15

Abbreviations: LR+, positive likelihood ratio; LR−, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

[a] See eTable 5 in the Supplement for results from individual studies.

[b] When the summary measure was from less than 3 studies, the I^2 was not calculated.

[c] PPV and NPV calculated assuming an acute coronary syndrome rate of 13%. The included studies had an acute coronary syndrome rate of 13% (95% CI, 11%-16%).

[d] "Typical" chest pain was defined by the individual studies, or when studies described pressure-like chest pain.

[e] When index tests were evaluated in 2 studies, data was reported from both studies as a range.

[f] "Typical" radiation was defined by the individual studies.

Table 3. Performance of Physical Examination Elements in Diagnosing Acute Coronary Syndrome[a]

	No.		% (95% CI)				%[b]	
Test	Studies	Patients	Sensitivity	Specificity	LR+ (95% CI)	LR− (95% CI)	PPV	NPV
Hypotension (SBP<100)[31]	1	634	3.1 (1.2-7.9)	99 (98-100)	3.9 (0.98-15)	0.98 (0.95-1.0)	37	13
Lung rales[31]	1	634	9.2 (5.3-16)	95 (93-97)	2.0 (1.0-4.0)	0.95 (0.90-1.0)	23	12
Tachypnea[31]	1	634	10 (5.9-16)	95 (92-96)	1.9 (0.99-3.5)	0.95 (0.89-1.0)	22	12
Tachycardia (heart rate>120)[31]	1	619	3.2 (0.86-7.9)	98 (96-99)	1.3 (0.42-3.94)	0.99 (0.96-1.0)	16	13
Pain reproduced on palpation[37]	1	839	5.5 (2.5-10)	80 (77-84)	0.28 (0.14-0.54)	1.2 (1.0-1.2)	4.0	15

Abbreviations: LR+, positive likelihood ratio; LR−, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; SBP, systolic blood pressure.

[a] See eTable 6 in the Supplement for results from individual studies.

[b] PPV and NPV calculated assuming an acute coronary syndrome rate of 13%. The included studies had an acute coronary syndrome rate of 13% (95% CI, 11%-16%).

Clinical prediction rules. Multiple studies examined the performance of clinical prediction rules incorporating history, ECG, and initial cardiac troponin result (**Table 5**). The scales fell into natural likelihood groupings of high (likelihood of ACS greatly increases with an LR much higher than 2), intermediate (likelihood of ACS is >1.0 and approximates 2.0), indeterminate (likelihood of ACS approximates 1.0), and low (ACS much less likely with an LR much lower than 0.5).

Table 4. Performance of the ECG in Diagnosing Acute Coronary Syndrome[a]

Test	No. Studies	No. Patients	% (95% CI) Sensitivity	% (95% CI) Specificity	LR+ (95% CI)	I^2, %	LR− (95% CI)	I^2, %	%[b] PPV	%[b] NPV
ST depression[17,21-23,49,62,70]	7	9589	25 (16-34)	95 (92-99)	5.3 (2.1-8.6)	89	0.79 (0.71-0.87)	84	44	11
Ischemic ECG[c]	7	16 559	32 (24-40)	91 (85-97)	3.6 (1.6-5.7)	97	0.74 (0.68-0.81)	87	35	10
T wave inversion[49,62,70]	3	3765	24 (15-38)	87 (69-95)	1.8 (1.3-2.7)	77	0.89 (0.86-0.93)	0	21	12

Abbreviations: ECG, electrocardiogram; LR+, positive likelihood ratio; LR−, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

[a] See eTable 7 in the Supplement for the results from individual studies.

[b] PPV and NPV calculated assuming an acute coronary syndrome rate of 13%. The included studies had an acute coronary syndrome rate of 13% (95% CI, 11%-16%).

[c] References 17, 31, 38, 39, 45, 49, 67, 68. Ischemic ECG defined as any T wave inversion, ST depression, Q waves.

Table 5. Performance of Clinical Decision Tools in Diagnosing Acute Coronary Syndrome[a]

Risk Level	Threshold	LR (95% CI)[b]	% I^2	Predictive Value[c]
High				
HEART score[18,20,21,23]	7-10	13 (7.0-24)	89	66
TIMI score[d]	5-7	6.8 (5.2-8.9)	56	50
Intermediate				
HEART score[18,20,21,23]	5-6	2.4 (1.6-3.6)	96	26
TIMI score[d]	3-4	2.4 (2.1-2.7)	77	26
HFA/CSANZ rule[38,58,63]	High risk	2.8 (2.6-3.0)	0	29
Indeterminate				
HEART score[18,20,21,23]	4	0.79 (0.53-1.2)	88	11
TIMI score[d]	2	0.94 (0.85-1.0)	23	12
Low				
HEART score[18,20,21,23]	0-3	0.20 (0.13-0.30)	78	2.9
TIMI score[d]	0-1	0.31 (0.23-0.43)	96	4.4
HFA/CSANZ rule[38,58,63]	Low to intermediate risk	0.24 (0.19-0.31)	10	3.5

Abbreviations: HEART, History, Electrocardiogram, Age, Risk Factors, Troponin; HFA/CSANZ, The Heart Foundation of Australia and Cardiac Society of Australia and New Zealand; LR, likelihood ratio; TIMI, Thrombolysis in Myocardial Infarction.

[a] See Box for acronyms definition; see eTable 8 in the Supplement for the results from individual studies.

[b] Summary LR from studies that report original data at each threshold without combining across clinical decision rule thresholds.

[c] Predictive value calculated assuming an acute coronary syndrome rate of 13%. The included studies had an acute coronary syndrome rate of 13% (95% CI, 11%-16%).

[d] References 20, 28, 29, 32-34, 36, 38, 39, 46, 49, 52, 55, 56, 58, 62, 65.

The TIMI risk score has been evaluated in several studies enrolling unselected patients presenting to the emergency department with acute chest pain.† Compared with individual components of the history, it has excellent accuracy for ACS; patients with a TIMI score of 5 or higher have a summary LR for ACS of 6.8 (95% CI, 5.2-8.9) (Table 5); whereas patients with a TIMI score of 0 through 1 have an LR of 0.31 (95% CI, 0.23-0.43). A modified TIMI risk score, which assigns 5 points for an ischemic ECG or elevated cardiac troponin level on presentation performs similarly to the original version in diagnosing ACS.[32,34,50,57]

The diagnostic performance of the HEART score is similar to the TIMI risk score among high-likelihood patients (HEART score range of 7-10), for whom the LR for the diagnosis of ACS was 13 (95% CI, 7.0-24) (Table 5), and in low-likelihood patients (HEART score range of 0-3), for whom the LR was 0.20 (95% CI, 0.13-0.30).[17-23]

After combining patients that the HFA/CSANZ algorithm classified as either low or intermediate risk, the HFA/CSANZ rule had similar accuracy to the TIMI and HEART risk scores for identifying low-risk patients (LR, 0.24 [95% CI, 0.19-0.31] in patients identified as low or intermediate risk), but did not identify a high-risk group (LR, 2.8 [95% CI, 2.6-3.0]) (Table 5).[38,53,58,63,76]

†References 17, 20, 29, 32-34, 36, 39, 46, 50, 52, 55-57, 62, 64, 65, 69

The AHCPR algorithm, which was first published before the troponin era, is less accurate.[43,49] In the 1 study of AHCPR that reported at all 3 strata (low, intermediate, and high), low-risk patients had an LR for ACS diagnosis of 0.36, and high-risk patients had an LR for ACS diagnosis of 1.8.[43]

In addition to these widely studied clinical prediction rules, other rules combining history, ECG, and cardiac troponin have been evaluated, but either in single studies or in a way that resists meta-analysis. Four large, high-quality studies evaluated the accuracy of the GRACE risk score for ACS diagnosis[17,38,55,56]; however, each divided patients into groups using different GRACE score cutoffs. In each study, the GRACE score was compared with the TIMI risk score, and its accuracy was comparable.

In the era before the advent of serum troponin assays and percutaneous coronary intervention, Goldman et al[77] developed a score to predict the likelihood of in-hospital complications among pa-

tients presenting to the emergency department with chest pain. This score was recently evaluated in 1 small, but high-quality, study involving 256 patients, and it demonstrated poor predictive accuracy (sensitivity, 69%; specificity, 47%).[33] The PURSUIT score was evaluated in 1 large, high-quality diagnostic study that compared its performance with the TIMI and GRACE risk scores, and it was found to be slightly less accurate than these risk scores.[55] The EDACS has been evaluated in 1 large, high-quality study enrolling 2 separate cohorts of patients: 1 cohort for derivation and 1 cohort for validation. Using the investigators' cutoff of less than 16 to define low risk, the EDACS was highly sensitive, with an LR− of 0.03 (95% CI, 0.01-0.10; sensitivity, 98%) in the validation cohort, but lacked specificity (LR+, 2.4 [95% CI, 2.2-2.6]; specificity, 58%).[25]

Discussion

In this systematic review, we identified 58 high-quality studies focusing on the accuracy or precision of elements of the history, physical examination, and ECG for ACS diagnosis, as well as the accuracy of clinical prediction tools incorporating these elements along with cardiac troponin level. We found that the accuracy of risk factors and symptoms was generally poor, and that any individual element was unlikely to be helpful in making an ACS diagnosis. Moreover, even those risk factors and symptoms that performed better tended to be more specific than sensitive, and most parameters had poor sensitivity. Overall clinical impression, incorporating all elements of the history and physical examination performed better, but the best diagnostic tests were clinical prediction tools (eg, TIMI score, HEART score, and HFA/CSANZ rule) that incorporated historical elements along with the initial ECG and cardiac troponin results.

In the era of contemporary, sensitive measurements of cardiac troponin, a diagnosis of myocardial necrosis can often be made within 1 to 3 hours of a patient's arrival in the emergency department based on laboratory results alone,[78,79] and the coming era of high-sensitivity troponin assays will only increase the sensitivity of this laboratory parameter.[80-82] However, a cardiac troponin level may be above the 99th percentile in a number of clinical conditions; thus, it is not specific for the diagnosis of myocardial infarction, and interpretation of the result depends on serial testing and the clinical context.[82] Risk scores can be effective because they synthesize the clinical context, ECG, and cardiac troponin into a quantitative assessment of pretest probability. However, effective use of these composite risk scores requires the clinician to determine each component independent of the others.

Study Limitations

Patients receiving an ACS diagnosis in the included studies represented were heterogeneous. The use of revascularization, in particular, to support the diagnosis of ACS at presentation has limitations; chiefly, that revascularization is limited to patients who undergo angiography and reflects an anatomic diagnosis of CAD rather than identifying unstable coronary plaque. It is likely that, in each study in which revascularization was included as a component of the ACS end point, among patients for whom the diagnosis of ACS was supported purely by revascularization, there was a subset that had true acute coronary artery thrombosis at presentation and a subset that underwent revascularization for stable atherosclerotic coronary disease. This limitation may have been partially overcome by pursuing an analysis limited to studies employing rigorously defined and centrally adjudicated ACS diagnosis as their reference standard; however, only 4 studies representing 2930 patients across 26 index tests used centrally adjudicated ACS as their reference standard, and no index test was evaluated in more than 2 studies that used this standard. This would considerably limit the statistical rigor of such an approach.

Regardless, the heterogeneous nature of ACS diagnosis in these studies and the inclusion of revascularization in studies utilizing a composite end point as their reference standard reflects the reality of clinical practice. Patients ultimately diagnosed with ACS do represent a spectrum of pathophysiologic processes. To the emergency department physician seeing the patient with potential ACS, the relevant question is whether the patient will benefit from inpatient treatment of ACS (particularly with anticoagulation, antiplatelet therapy, and cardiac catheterization) or can be sent home with a diagnosis of noncardiac chest pain.

The heterogeneous nature of patients receiving an ACS diagnosis is further reflected in the considerable heterogeneity for many of the index tests evaluated. Beyond the different reference standards employed, the studies defined index tests differently and enrolled different patient populations, further increasing heterogeneity between the studies. For these reasons, significant heterogeneity is extremely common in meta-analyses of diagnostic tests.[83] Nevertheless, the CIs for many of the index tests are narrow enough to inform clinical practice because the goal of the emergency department evaluation is to broadly categorize patients into low, medium, and high likelihood of ACS.

A second limitation of this systematic review is verification and incorporation biases in the included studies. ACS is a clinical diagnosis, and information related to the history, ECG, and cardiac troponin level at presentation is necessarily incorporated into the final diagnosis. Even in studies that use a hard end point like 30-day cardiovascular death, myocardial infarction, or revascularization, patients with more traditional cardiac risk factors, ECG abnormalities, or troponin elevation are more likely to undergo further diagnostic testing that will lead to revascularization. A diagnostic study could overcome this limitation by standardizing a diagnostic pathway such that all patients in the study undergo identical diagnostic testing, including some form of an evaluation for ischemia followed by cardiac catheterization. However, such a study would be impractical and potentially expose patients without ACS to unnecessary diagnostic procedures that have associated risks but no benefit.

Third, though many studies met our inclusion criteria, the studies assessed a wide array of index tests, such that only a minority of the included studies contributed data for any given test. For example, chest pain radiation to both arms and history of a prior abnormal stress test were both strong predictors of ACS, but both were evaluated in only a single study. All physical examination findings were also evaluated in only 1 study. This limits our ability to combine data across studies to reduce bias from any single study. Readers should note instances in which the accuracy of an index test is supported by only 1 or 2 studies, as the evidence in support of the accuracy of these tests may be less robust than for tests evaluated in a larger number of studies. However, all studies included in the meta-analysis were of high quality, and most were large; as a result, no index test included in this meta-analysis has been assessed in

fewer than 560 rigorously evaluated patients. Moreover, the TIMI and HEART risk scores, which we found to have the best diagnostic performance for ACS, were evaluated in 16 and 4 high-quality studies, respectively, that enrolled more than 30 000 and 13 000 patients. The HFA/CSANZ rule has not been as widely studied and does not stratify patients into as many levels of probability.

In addition, our study is limited by our decision to exclude studies incorporating high-sensitivity troponin. We excluded these studies because high-sensitivity troponin is not yet available in the United States, and because we wanted to avoid the inherent confusion caused by discussing risk models incorporating high-sensitivity and standard troponin assays. Moreover, though high-sensitivity troponin has been evaluated in a number of high-quality studies evaluating the utility of serial measurements of cardiac biomarkers for the exclusion of ACS, to our knowledge, it has not been evaluated as a component of risk models incorporating a single cardiac biomarker measured on presentation, which was the focus of this review.

Finally, we do not know how the assessment of chest pain history that is part of the prediction rules is affected by knowledge of the ECG and troponin level. In current emergency clinical practice, these tests are often obtained before the clinician evaluates the patient. However, independence of the items in the scores requires that the chest pain history not be influenced by the results of the ECG and troponin level.

Bottom Line

The cardiac troponin level and ECG in the context of symptoms suggestive of an underlying ischemic etiology should be the focus for assessment, rather than individual risk factors, symptoms, and signs in isolation. Using 1 of the available clinical prediction tools at the initial evaluation gives the highest likelihood of correctly identifying or excluding ACS. Physicians should use the results of the prediction tools when deciding whether or not to forgo serial evaluation and testing. A rational approach to the patient with suspected ACS would be to use the HEART or TIMI risk score combined with a hospital's background prevalence of ACS to determine the initial prestress test probability of ACS. Using the average pretest probability of 13%, the probability of ACS decreased to 2.9% (95% CI, 1.9%-4.3%) for a HEART score of 0 through 3 and to 4.4% (95% CI, 3.3%-6.0%) for a TIMI score of 0 through 1. Thus, these risk scores alone may not be adequate to lower the probability sufficiently to achieve a miss rate lower than 1%, as desired by a majority of emergency department physicians. A lower probability can be obtained only for patients with a lower pretest probability or with serial evaluation. Several accelerated diagnostic protocols involving serial cardiac troponin measurements in low-risk patients accurately rule out ACS without stress testing; the clinical variables and risk scores identified in this analysis will help clinicians identify low-risk patients for inclusion in these accelerated diagnostic protocols.[18,39,67,84,85]

Scenario Resolution

For each patient, we assume a pretest probability of 13%.

Case 1

The patient, despite a story consistent with typical angina, has a HEART risk score of 2. A HEART risk score of 2 has an LR for the diagnosis of ACS of 0.2, and the posttest probability is 3%. Relief of her pain with nitroglycerin is unhelpful for diagnosing or ruling out ACS. She could be considered for an accelerated diagnostic protocol with early discharge if a second cardiac troponin is negative.

Case 2

The patient has known CAD and is elderly. His ECG does not show dynamic changes, and troponin elevation is mild. With a HEART score of 6, he is at intermediate risk (LR, 2.4), yielding a posttest probability of 26%. He should be admitted and treated for ACS.

ARTICLE INFORMATION

Author Contributions: Drs Fanaroff and Simel had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Fanaroff, Simel, Newby.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Fanaroff, Rymer, Simel.
Critical revision of the manuscript for important intellectual content: Rymer, Goldstein, Simel, Newby.
Statistical analysis: Fanaroff, Rymer, Goldstein, Simel.
Administrative, technical, or material support: Rymer, Goldstein.
Study supervision: Simel, Newby.

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