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Identifying Emergency Department Patients With Chest Pain who are at Low Risk for Acute Coronary Syndromes

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Abstract

Though a minority of patients presenting to the emergency department with chest pain have acute coronary syndromes, identifying the patients who may be safely discharged and determining whether further testing is needed remains challenging. From the prehospital care setting to disposition and follow-up, this systematic review addresses the fundamentals of the emergency department evaluation of patients determined to be at low risk for acute coronary syndromes or adverse outcomes. Clinical risk scores are discussed, as well as the evidence and indications for confirmatory testing. The emerging role of new technologies, such as high-sensitivity troponin assays and advanced imaging techniques, are also presented.

CME Objectives

Upon completion of this article, you should be able to:

1. Identify major pitfalls that can lead to a missed diagnosis of acute coronary syndromes.
2. Effectively apply clinical risk scores for better risk stratification.
3. Identify patients who are at low risk of acute coronary syndromes and short-term major adverse cardiac outcome.
4. Apply a current, evidence-based strategy on the use of confirmatory testing following ED evaluation.

Prior to beginning this activity, see "Physician CME Information" on the back page.

Case Presentations

A 65-year-old man with a history of hypertension, diabetes, and prior myocardial infarction presents to the ED after he experienced a 20-minute episode of dull, aching, left-sided chest discomfort while doing yard work an hour ago. His wife tells you that he's been having similar episodes on and off for the past 2 weeks. He is pain-free on arrival, and his vital signs are unremarkable. His ECG, chest x-ray, and troponin are all normal. When you go back into the room to reassess him, he says he feels fine and asks if he can go home. You hesitate and wonder if it would be safe to send him home without further testing.

A 22-year-old college student presents with sharp, left-sided chest pain and shortness of breath. He recently returned from a spring break trip to Mexico and reports symptoms of an upper respiratory infection. He feels that his chest pain is worse when lying flat, and is concerned he's having a heart attack. His vital signs and physical examination are normal. He has no past medical history, no cardiac risk factors, and no family history of heart disease. His triage ECG is normal. ACS seems unlikely, but as you're thinking through your differential diagnosis, you wonder if you need to do any other tests to rule it out definitively.

A 46-year-old woman with end-stage renal disease, hypertension, diabetes, and tobacco use presents with dull, aching, substernal chest pain radiating to her arms and shortness of breath that began shortly after completing dialysis. She is hypertensive, but her vital signs are otherwise normal. She has soft, bibasilar inspiratory crackles on pulmonary examination. Her initial ECG shows nonspecific T-wave changes and left ventricular hypertrophy, but it is otherwise unremarkable. Her troponin is elevated at 0.098 ng/mL (conventional sensitive troponin I assay, reference range 0-0.04 ng/mL), but when you review her records, you see it is similar to baseline from previous testing. She is treated with aspirin and nitroglycerin, and her chest pain improves. On review of her records, you note that she had an unremarkable stress test (pharmacologic myocardial perfusion imaging) about 6 months ago. Your partner says, "Oh, she's here all the time with chest pain. There's never anything wrong with her." You wonder what other tests should be done, and how to interpret her elevated troponin.

Introduction

Every year in the United States, there are approximately 8 million emergency department (ED) visits for chest pain, but only 13% to 25% lead to a diagnosis of acute coronary syndromes (ACS).[1,2] ACS is a group of potentially life-threatening conditions comprised of ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation mycocardial infarction (NSTEMI), and unstable angina. For the evaluation of suspected ACS in the ED, consensus guidelines recommend obtaining electrocardiogram (ECG) and cardiac biomarker testing in addition to the basic history, physical examination, and chest radiography.[2-8] If these tests are unremarkable, guidelines then recommend further confirmatory testing. Despite the extensive testing typically performed for patients with chest pain from suspected ACS, a landmark study by Pope et al estimated that more than 2% of patients with ACS are mistakenly discharged from the ED, potentially leading to increased risk of harm.[9] Although this study is nearly 20 years old, more-recent research has shown similar miss rates, suggesting that the ED evaluation of chest pain for suspected ACS remains challenging despite advances in knowledge and technology.[10-12]

The term *low-risk patient* is inherently unclear and can mean different things among providers. In most literature, patients with chest pain who are described as being at low risk for ACS are those who: (1) are hemodynamically stable, (2) are without concerning features on history or examination, and (3) do not have immediate objective evidence of myocardial ischemia on initial ECGs and biomarker testing.[2] Current consensus guidelines further define the low-risk patient as one who has a < 1% risk of a major adverse cardiac event (MACE) or death at ≥ 30-days' follow-up.[3] For the purposes of this article, we define the low-risk patient more broadly as one who may be safely discharged home with little, if any, further testing. This issue of *Emergency Medicine Practice* reviews the current evidence regarding ED evaluation and risk stratification strategies for patients presenting with chest pain from suspected ACS.

Critical Appraisal of the Literature

There is a large body of research on the evaluation and management of undifferentiated chest pain in the ED. Narrowing this work to chest pain only from presumed ACS yielded 1145 articles (using the search terms *chest pain, acute coronary syndrome*, and *emergency department*). Among these, articles from the following categories were reviewed: *low risk* (169 articles), *risk stratification* (168 articles), *clinical decision rules* (35 articles), *stress testing* (91 articles), *cardiac imaging* (128 articles), and *disposition* (31 articles). The Cochrane Library was searched using the term *chest pain* (77 articles) and *acute coronary syndrome* (16 articles), but none were directly applicable to this topic. A National Guideline Clearinghouse search (www.guideline.gov) using the terms *low-risk, chest pain*, and *acute coronary syndrome* yielded 104 articles, 8 of which were applicable. Additional references were gathered by reviewing the bibliographies of selected articles generated from these searches.

Relevant guidelines and statements from various professional groups were reviewed. Guidelines and statements that have superseded older versions were emphasized.

Selected Abbreviations

ACI-TIPI	Acute Cardiac Ischemia Time-Intensive Predictive Instrument
ACS	Acute coronary syndromes
ADAPT	Two-hour Accelerated Diagnostic Protocol to Assess Patients with Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker
ASPECT	Asia-Pacific Evaluation of Chest Pain Trial
CAD	Coronary artery disease
CATCH	Cardiac CT in the Treatment of Acute Chest Pain Trial
CCTA	Coronary computed tomography angiography
CI	Confidence interval
CK-MB	Creatinine kinase-MB isoenzyme
CT	Computed tomography
ECG	Electrocardiogram
EDACS	Emergency Department Assessment of Chest Pain Score
GRACE	Global Registry of Acute Coronary Events
HEART	History, ECG, Age, Risk Factors, Troponin [Score]
MACE	Major adverse cardiac event
mSv	Millisievert
mV	Millivolt
NACPR	North American Chest Pain Rule
NPV	Negative predictive value
NSTEMI	Non-ST-segment elevation myocardial infarction
PROMISE	Prospective Multicenter Imaging Study for Evaluation of Chest Pain
PROSPECT	Prospective Randomized Outcome Trial Comparing Radionuclide Stress Myocardial Perfusion Imaging and ECG-gated CCTA
PURSUIT	Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy
STEMI	ST-segment elevation myocardial infarction
TIMI	Thrombolysis in Myocardial Infarction [Score]
TRO CT	Triple-rule-out computed tomography

Etiology and Pathophysiology

Myocardial ischemia results when myocardial oxygen supply and demand are mismatched. This mismatch activates free nerve endings of visceral afferent sympathetic and vagal fibers originating in the myocardium and causes substernal chest discomfort referred to as *angina*.[13] Sensory afferents of the C1-C2 (neck and jaw) and C5-C6 (upper arm) dermatomes often overlap these fibers, which can cause referred pain from these areas. There is also considerable overlap from sensory afferents of the vagus nerve, phrenic nerve, intercostal nerves, and others. This can give rise to atypical symptoms of myocardial ischemia (known as *anginal equivalents*), such as shortness of breath or nausea. Alternatively, activation of these pathways by irritation of the esophagus, pleura, or aorta can lead to anginal-type pain from noncardiac sources.[14]

True anginal chest pain (ie, chest pain from myocardial ischemia) is most commonly due to atherosclerotic obstructive coronary artery disease (CAD). Once an atherosclerotic plaque reaches ≥ 70% total vessel diameter, blood flow through the vessel becomes limited at times of increased myocardial oxygen demand, causing myocardial ischemia.[15] Plaque rupture or endothelial erosion can cause thrombosis within the vessel, causing vessel occlusion and myocardial infarction (type 1 myocardial infarction).[4] However, nonobstructive processes such as coronary microvascular disease, coronary artery vasospasm, aortic stenosis, left ventricular hypertrophy, shock, and anemia can also lead to myocardial ischemia and infarction (type 2 myocardial infarction).

Most confirmatory tests focus on the diagnosis of atherosclerotic CAD. Stress testing indirectly detects CAD by assessing for cardiac wall motion abnormalities and perfusion deficits that are typically caused by flow-limiting stenoses. Coronary computed tomography angiography (CCTA) is a newer imaging technique that directly visualizes CAD and can measure the degree of stenosis. CT imaging can also measure coronary arterial calcification, which is associated with underlying CAD (sensitivity and specificity of coronary artery calcification scanning for predicting clinically significant CAD is estimated at 97%-100% and 54%-63%, respectively).[16]

Differential Diagnosis

The differential diagnosis of chest pain can be divided broadly into ischemic cardiac causes, nonischemic cardiac causes, and noncardiac causes. **(See Table 1, page 4.)** In addition to ACS, the immediately life-threatening causes of chest pain that must be considered in every patient include pulmonary embolism, aortic dissection, tension pneumothorax, perforating peptic ulcer, and esophageal perforation (Boerhaave syndrome). The complete differential diagnosis also includes other potentially serious causes such as pericarditis, pneumonia, pancreatitis, and hepatobiliary disease.

Prehospital Care

Approximately 25% of patients presenting to the ED for evaluation of chest pain arrive by ambulance.[1] The ECG is perhaps the most important tool available to prehospital care providers, as it can greatly affect treatment and destination decisions. It is well established that trained prehospital providers can accurately identify STEMI without physician intervention, and that prehospital activation of the cardiac catheterization laboratory reduces door-to-balloon time and improves patient outcomes.[3,5] The American Heart Association guidelines support prehospital provider decision-making with regard to therapeutic interventions, destination selection, and prehospital catheterization laboratory activation. However, only approximately 30% of patients with ACS have STEMI,[6] and newer research is focusing on ECG parameters that are correlated with NSTEMI (eg, ischemia-induced repolarization dispersion), which could lead to earlier detection of ischemia.[17,18]

Point-of-care troponin assays may also be available to prehospital providers and can facilitate detection of cardiac ischemia prior to hospital arrival.[19] A recent randomized trial showed that use of prehospital point-of-care troponin resulted in earlier ED disposition.[20] However, point-of-care troponin assays are less sensitive and less reliable than in-hospital assays, and cannot be used to rule out ACS.[21]

Emergency Department Evaluation

No single component of the history, physical examination, or initial diagnostic testing can reliably exclude ACS, but various clinical risk scores incorporate this information to identify patients at low risk for ACS or serious short-term outcome.

History

A focused history should be obtained from all stable patients. Historical features of a patient's chest pain cannot reliably rule in or rule out ACS, but may be

Table 1. Differential Diagnosis of Chest Pain[2,14]

Origin of Pain	Organ System	Condition	Typical Features
Ischemic cardiac chest pain	Cardiac	Stable angina	Substernal aching, pressure, or burning; referred pain in the neck, jaw, or arms; triggered with exertion, improved with rest or nitroglycerin
		Unstable angina	Same as stable angina, but with a change in the pattern of pain (eg, episodes are more frequent, prolonged, severe, or occurring at rest)
		Acute myocardial infarction	Same as angina, but more severe and sustained
Nonischemic cardiac chest pain	Cardiac	Pericarditis	Sharp, sustained, pleuritic; worse when supine
		Myocarditis	Variable symptoms; may mimic angina or pericarditis
		Mitral valve prolapse	Sharp, stabbing; unchanged with activity; persistent and chronic
Noncardiac chest pain	Vascular	Aortic dissection	Intense, "tearing," sudden onset; variable location (type A often felt in chest, type B often felt in back)
	Pulmonary	Pulmonary embolism	Often pleuritic, sudden onset; associated with dyspnea
		Tension pneumothorax	Pleuritic, sudden in onset; associated with dyspnea, typically unilateral; increased risk in smokers and patients with Marfan syndrome
		Pneumonia	Pleuritic; typically unilateral; gradual onset
		Bronchospastic disease	Tightness, pleuritic; may be reproducible with palpation
		Pleuritis	Pleuritic, worse with forceful breathing (eg, coughing or sneezing); often associated with symptoms of autoimmune disease
	Gastrointestinal	Esophageal rupture (Boerhaave syndrome)	Severe retrosternal pain after vomiting; may be associated with subcutaneous emphysema
		Perforated peptic ulcer	Sudden, severe epigastric pain, gradually becoming generalized; peritoneal abdominal findings; may radiate to chest
		Gastroesophageal reflux disease	Burning retrosternal discomfort; postprandial; worse when supine, may mimic angina
		Esophageal dysmotility	Intermittent retrosternal chest pain; may mimic gastroesophageal reflux disease; associated with dysphagia
	Musculoskeletal	Costal inflammation	Anterior chest wall pain that is reproducible on palpation
	Hematologic	Acute chest syndrome (sickle cell disease)	Chest pain associated with tachypnea, fever, hypoxia, and infiltrate on chest x-ray
	Miscellaneous	Herpes zoster	Burning, throbbing pain in a dermatomal distribution; may be constant or intermittent; triggered by light touch (allodynia); pain may precede rash
		Panic disorder	Chest tightness associated with dyspnea and anxiety

associated with a higher or lower likelihood of ACS. A 2015 review that included 58 studies found that pain radiating to both arms, pain similar to prior ischemia, and a change in the pattern of pain over the past 24 hours were the most helpful historical features in predicting ACS. These features had a positive likelihood ratio (LR) ≥ 2.0 and a confidence interval (CI) excluding 1.0.[22] This review also found that pleuritic pain is less likely to be associated with ACS (positive LR, 0.35-0.61; CI excluding 1.0). Using the same criteria, a 2005 review found that chest pain that radiates to the shoulders or arms, pain that is associated with exertion, or pain associated with diaphoresis was most predictive of ACS. Conversely, pain described as pleuritic, positional, or reproducible with palpation (colloquially referred to as "the 3 Ps"); pain described as sharp or stabbing; or pain not associated with exertion was least predictive.[23] Women, the elderly, and diabetic patients are more likely to present with "atypical" symptoms of ACS (eg, pain outside of the chest, lack of pain, or symptoms such as nausea or dyspnea).[24,25]

Several landmark studies have shown that patients' age and gender and their description of symptoms are associated with the presence of clinically significant CAD.[26-28] However, these studies examined patients who had undergone invasive angiography, a population that differs from most patients presenting to the ED with chest pain. A more recent study of patients with chest pain who underwent noninvasive CCTA has suggested that these historical features greatly overestimate the actual prevalence of CAD.[29]

In general, classic cardiac risk factors (hypertension, hyperlipidemia, diabetes, smoking, and family history of CAD) are not independently predictive of ACS in patients presenting to the ED with chest pain;[30,31] however, these classic cardiac risk factors may be more useful in younger patients. A prospective analysis of nearly 11,000 patients found that among those aged < 40 years, the presence of zero risk factors had a negative LR of 0.17 for ACS (95% CI, 0.04-0.66), and the presence of 4 or more risk factors had a positive LR of 7.39 (95% CI, 3.09-17.67).[32]

Physical Examination

The physical examination in patients with chest pain is often normal, and abnormalities found on examination are often nonspecific for ACS. Hypotension, the presence of a new mitral regurgitation murmur, and the presence of a third heart sound all increase the likelihood of ACS.[6] Chest pain that is reproducible on palpation is perhaps the most useful finding in lowering the likelihood of ACS; a systematic review showed that this finding had a LR of 0.28 for ACS (95% CI, 0.14-0.54).[22] However, none of these features can be used to reliably rule in or rule out ACS. As such, the physical examination is perhaps more important for assessing overall hemodynamic function and the likelihood of alternative diagnoses of chest pain. For example, the examination findings of oxygen saturation < 95% or unilateral leg swelling are strongly associated with pulmonary embolism.[33] A prospective cohort study of 250 patients found that an aortic regurgitation murmur, pulse differential (absence of unilateral carotid or upper extremity pulse), or blood pressure differential > 20 mm Hg between the arms are independent predictors of thoracic aortic dissection. Focal neurologic signs may also suggest dissection, but were seen in only 13% of patients in this study.[34] A brief dermatologic examination may uncover vesicular lesions suggestive of herpes zoster.

Diagnostic Studies

Electrocardiogram

For patients with suspected ACS, an ECG should be obtained within 10 minutes of arrival.[2] For patients arriving by ambulance, compare the prehospital ECG to the initial ECG obtained in the ED. A small prospective study showed that 12.5% of prehospital ECGs had clinically significant abnormalities (ST elevation or depression, T-wave inversion, or arrhythmia) that were not seen on the initial ED ECG, leading to a change in physician management nearly two-thirds of the time.[35]

In the United States, 29% to 38% of patients with ACS present with STEMI.[36] STEMI is defined as new ST elevation at the J point of ≥ 1 mm (0.1 mV) in ≥ 2 contiguous leads. (Exception: some degree of ST elevation is considered normal in leads V_2-V_3; up to 1.5 mm in women, 2 mm in men aged ≥ 40 years, and 2.5 mm in men aged < 40 years.)[4] Significant ST elevation typically signifies transmural ischemia from acute coronary artery occlusion (type 1 myocardial infarction).[37] New horizontal or downsloping ST depression ≥ 0.5 mm (0.05 mV) and T-wave inversion ≥ 1 mm (0.1 mV) in ≥ 2 contiguous leads can also indicate myocardial ischemia, though this typically signifies subendocardial ischemia. A large retrospective review found these abnormalities in 22.9% and 14% of patients with NSTEMI, respectively.[38] T waves and other ECG features can vary from minute to minute in an ischemic event. **(See Figure 1, page 6)** Serial ECGs at 5- to 10-minute intervals are recommended if the initial ECG is nondiagnostic but the patient still has concerning symptoms.

Errors in ECG interpretation can lead to a missed diagnosis of ACS. Pope et al found that 11% of patients with missed ACS actually had subtle ST elevation of 1 to 2 mm.[9] Other factors, such as left bundle branch block, left ventricular hypertrophy, electrolyte abnormalities, or digoxin use may further confound ECG interpretation in patients with suspected ACS. The ECG also often shows nonspecific

abnormalities that may indicate an increased risk of adverse outcome. In a recent retrospective study of over 2300 patients, Knowlman et al found that even commonly seen nonspecific changes (such as isolated T-wave inversion in lead III or V_1) confer an increased likelihood of MACE at 30 days.[39] **(See Table 2.)** This knowledge is incorporated into some clinical risk scores, such as the HEART Score (history, ECG, age, risk factors, troponin).[40] For more information on the HEART Score, see the section "Early Risk Stratification and Clinical Risk Scores," page 7.

Ultimately, a normal ECG does confer a lower risk of ACS and MACE, but as with all components of the ED evaluation of chest pain, the ECG cannot be used alone to reliably rule out ACS. In a multicenter prospective study of nearly 400,000 patients with myocardial infarction, 7.9% had a normal initial ECG,[41] and in the study by Knowlman et al, 5% of patients with chest pain and a normal ECG had a MACE within 30 days.[39]

Biomarkers

Cardiac biomarkers are the most objective tests for myocardial injury available to the emergency clinician and should be obtained for all patients with suspected ACS. Troponin, a protein specific to myocardial cells, is the preferred biomarker; CK-MB and myoglobin are no longer recommended for ED use due to their decreased sensitivity and specificity for myocardial injury.[6] Two forms of troponin, cardiac troponin I and cardiac troponin T, are used by modern immunoassays to detect myocardial injury, and most guidelines make no distinction between the 2 forms.[42]

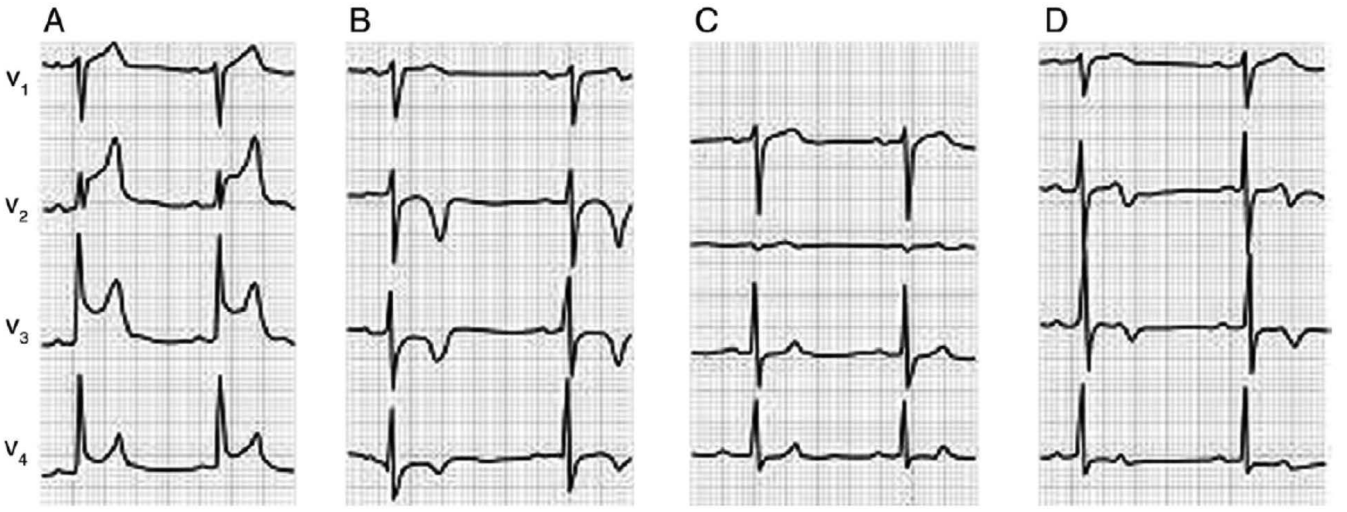
The timing of troponin testing in relation to the onset of symptoms is important. Observational data have shown that when using conventional sensitive assays, troponin is detectable within 3 hours of ED arrival in nearly all patients with myocardial injury, regardless of when symptoms began.[43,44] Therefore, most guidelines recommend that, if symptoms are suggestive of ACS but troponin is negative on

Table 2. Electrocardiographic Classification and Likelihood of 30-day Major Adverse Cardiac Event[39]

Electrocardiographic Classification	Positive LR for 30-day MACE
Normal	0.4
Nonspecific ST and/or T-wave changes	1.2
Abnormal, but not diagnostic of ischemia	1.2
Ischemia or prior infarction known to be old	2.6
Ischemia or prior infarction not known to be old	9.7
Consistent with acute myocardial infarction	15.8

Major adverse cardiac events include acute myocardial infarction, cardiovascular death, unstable angina, or revascularization.
Abbreviations: LR, likelihood ratio; MACE, major adverse cardiac event.

Figure 1. Serial Electrocardiograms in a Patient With Acute Left Anterior Descending Artery Occlusion



(A) Note initial ST elevation in V_1-V_4 during acute LAD artery occlusion. (B) Spontaneous reperfusion of the LAD causes deep T-wave inversions. (C) Reocclusion of the LAD now causes "pseudo-normalization" of T waves. (D) Spontaneous reperfusion again causes T-wave inversions.
Abbreviation: LAD, left anterior descending artery.
Reprinted from *Journal of Electrocardiology.* Volume 43, Issue 2. Kjell Nikus, Olle Pahlm, Galen Wagner, et al. Electrocardiographic classification of acute coronary syndromes: a review by a committee of the International Society for Holter and Non-Invasive Electrocardiology. Pages 91-103. Copyright 2010, with permission from Elsevier.

arrival, a second value should be obtained in 3 to 6 hours.[3,5] Newer high-sensitivity troponin assays (discussed further in the "Controversies and Cutting Edge" section, page 12) aim to shorten this time even further. A single negative troponin may be sufficient if symptoms began 6 to 8 hours prior, but caution should be used with this approach if the history is inexact, if the patient has a higher pretest probability of ACS, or when using older, less-sensitive troponin assays.[2,6] Nonetheless, negative troponin testing does not entirely rule out ACS, due to the possibility of unstable angina, which is a purely clinical diagnosis. Therefore, interpretation of troponin values should always be done in conjunction with clinical risk-stratification tools.

The sensitivity of troponin for ruling out myocardial infarction is excellent, but elevated troponin is not specific for myocardial infarction. One observational study of 615 patients with elevated troponin found that the overall positive predictive value for ACS was only 56%.[45] Other nonischemic conditions, including heart failure, pulmonary embolism, chronic kidney disease, and sepsis, can cause myocardial injury and elevated troponin.[46] To increase the specificity of elevated troponin for ACS, delta troponin measurements are recommended. The National Academy of Clinical Biochemistry recommends using a dynamic change of 20% or more to define myocardial infarction in patients with baseline elevations in troponin (level of evidence B).[47] Note that this change can be an increase or a decrease, in which increasing troponin signifies an evolving myocardial infarction, while decreasing troponin signifies a resolving myocardial infarction.

Early Risk Stratification and Clinical Risk Scores

Clinical risk scores are additional tools used for risk stratification of patients being evaluated for suspected ACS. The ideal clinical risk score for the ED would be one that could reliably and efficiently identify all patients who are at low risk for ACS or MACE and who can be safely discharged home. A variety of scores have been developed or adapted for this purpose. These are summarized in **Appendix 1, pages 14-15.**

The Thrombolysis in Myocardial Infarction (TIMI) Score and the HEART Score are perhaps the most useful scores for the ED evaluation of undifferentiated chest pain from suspected ACS, and they are described in further detail in **Table 3, page 8**. The term *low risk* is inherently unclear, but is used in all of the clinical risk scores described in following sections.[48] Risk must also be considered in terms of the outcome(s) and follow-up periods used to define it (eg, nonfatal myocardial infarction vs cardiac arrest, or 48 hours vs 30 days).

The TIMI Score

The TIMI Score was initially designed to predict 14-day mortality in patients with confirmed NSTEMI or unstable angina.[49] It has since been validated in several studies for use in the undifferentiated chest pain patient in the ED, but a meta-analysis of these validation studies showed that patients in the lowest-risk group (TIMI score = 0) still had a 30-day incidence of cardiac events of 1.8%, which may be unacceptably high.[50] The addition of serial biomarker measurements may increase the accuracy of the TIMI score. Two observational studies, ASPECT and ADAPT, used the TIMI Score and biomarkers (troponin I, CK-MB, and myoglobin in ASPECT; troponin I only in ADAPT) at 0 and 2 hours, and they showed sensitivity and negative predictive value (NPV) of 99.3% to 99.7% and 99.1% to 99.7%, respectively.[51,52]

Link to online MDCalc calculator for the TIMI Risk Score for UA/NSTEMI:

- www.mdcalc.com/timi-risk-score-ua-nstemi

The HEART Score

The HEART Score,[40] developed specifically for risk stratification of patients with undifferentiated chest pain, has been validated nationally and internationally and performs similarly to the TIMI Score, with low-risk patients having a 0.9% to 1.7% risk of MACE at 6-week follow-up.[53-55] As with TIMI, the addition of serial biomarker measurements may also increase accuracy; Mahler et al used the HEART Score with biomarkers (troponin I, CK-MB) at 0 hours and 4 to 6 hours and demonstrated a sensitivity and NPV of 100%.[56]

Link to online MDCalc calculator for the HEART Score:

- www.mdcalc.com/heart-score-major-cardiac-events)

The Vancouver Chest Pain Rule

The Vancouver Chest Pain Rule, also developed for risk stratification of patients with undifferentiated chest pain, showed a sensitivity of 98.8% and NPV of 99.0% for the detection of ACS in its derivation study.[57] However, the biomarker used in the derivation study was CK-MB, while the major validation studies have included different biomarkers. This has yielded substantial differences in sensitivity and NPV in subsequent validation studies: CK-MB, 95.1% and 98.6%, respectively;[58] conventional troponin, 98.8% and 98.1%;[59] high-sensitivity troponin, 91.0 to 99.1% and 94.4 to 98.6%.[59,60] This limits the generalizability of this clinical risk score.

Link to online MDCalc calculator for Vancouver Chest Pain Rule:

- www.mdcalc.com/vancouver-chest-pain-rule

The North American Chest Pain Rule

The North American Chest Pain Rule (NACPR) was developed using rigorous methodological standards and it identified 18% of patients as being suitable for early discharge with 100% sensitivity for excluding MACE at 30 days.[61] However, one validation study in a separate population found that the NACPR identified only 4.4% of patients as suitable for early discharge, raising concern that this rule, in practice, may not identify enough low-risk patients to be clinically useful.[62] Further prospective external validation of this rule is needed.

Summary

Unfortunately, there is no perfect clinical risk score. Many were derived without the use of contemporary biomarkers that are recommended by international consensus guidelines.[4] Study design, outcome measures, and performance on subsequent validation studies vary significantly.[75-77] These factors can make it difficult to compare clinical risk scores directly to one another or draw firm conclusions about their accuracy.

Chest Radiography

Chest radiography is recommended in the ED evaluation of patients for possible ACS.[2] However, the majority of chest x-rays performed in this population are normal. One prospective study of over 500 ED patients with nontraumatic chest pain found that > 90% of chest x-rays performed in this population were normal, though 2.1% had abnormalities requiring acute intervention, including pulmonary edema, consolidation, or large pleural effusions.[78]

Table 3. Summary of the TIMI Score and HEART Score[40,49-55]

TIMI Score			
Component		**Points**	**Scoring, % Risk of MACE, (Endpoint)**
Age ≥ 65 years		1	• Derivation study: TIMI 0-1 = 4.7% (14 days) • Meta-analysis: TIMI 0 = 1.8%, TIMI 1 = 4.0% (30 days) • ASPECT: TIMI 0 + negative biomarkers at 0-2 hours = 0.9% (30 days) • ADAPT: TIMI 0 + negative biomarkers at 0-2 hours = 0.25% (30 days)
≥ 3 risk factors (family history of CAD, HTN, HLD, diabetes, or tobacco use)		1	
Known CAD ≥ 50% stenosis		1	
Aspirin use in past 7 days		1	
Severe angina (≥ 2 episodes in past 24 hours)		1	
ECG ST deviation ≥ 0.5 mm (depression or elevation)		1	
Positive biomarker (derivation study used CK-MB and/or troponin)		1	
HEART Score			
Component	**Description**	**Points**	**Scoring, % Risk of MACE, (Endpoint)**
History	Highly suspicious for angina	2	Derivation study (423 ± 106 days) • 0-3 = low risk = 2.5% • 4-6 = moderate risk = 20.3% • ≥ 7 = high risk = 72.7% Validation studies (30 days - 6 weeks) • 0-3 = low risk = 0.9%-1.7% • 4-6 = moderate risk = 11.6%-16.6% • ≥ 7 = high risk = 43.1%-65.2%
	Moderately suspicious (anginal symptoms and nonspecific elements)	1	
	Slightly suspicious (nonspecific elements)	0	
ECG	Significant ST changes	2	
	Nonspecific repolarization disturbance (repolarization abnormalities without significant ST depression, bundle branch block, left ventricular hypertrophy, changes from digoxin, or unchanged known repolarization disturbances)	1	
	Normal	0	
Age	≥ 65 years	2	
	45-64 years	1	
	< 45 years	0	
Risk factors (diabetes, tobacco use, HTN, HLD, family history of CAD, obesity)	≥ 3 or history of coronary revascularization, MI, stroke, or peripheral arterial disease	2	
	1-2	1	
	0	0	
Troponin (conventional sensitive troponin I assay with cutoff 0.04 ng/mL)	≥ 3x normal limit	2	
	1-3x normal limit	1	
	≤ normal limit	0	

Abbreviations: ASPECT, Asia-Pacific Evaluation of Chest Pain Trial; ADAPT, Two-hour Accelerated Diagnostic Protocol to Assess Patients with Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker; CAD, coronary artery disease; CK-MB, creatine kinase MB-isoenzyme; ECG, electrocardiogram; HEART [Score], history, ECG, age, risk factors, troponin; HLD, hyperlipidemia; HTN, hypertension; MACE, major adverse cardiac event; MI, myocardial infarction; TIMI [Score], Thrombolysis in Myocardial Infarction.

Reducing the number of chest x-rays performed in this population could decrease radiation exposure and increase ED throughput, although attempts to validate a clinical decision rule designed for this purpose have been unsuccessful.[79]

Confirmatory Testing

The general purpose of confirmatory testing is to identify obstructive CAD (either by direct visualization or indirectly by inducing regional ischemia) that would benefit from further treatment. Confirmatory testing may take the form of exercise electrocardiography and/or various types of noninvasive imaging, including exercise or chemical myocardial perfusion imaging, rest or stress echocardiography, cardiac magnetic resonance imaging (MRI), and CCTA. The estimated diagnostic accuracy of these tests for detecting obstructive CAD are summarized in **Table 4.** Note that it is difficult to determine diagnostic accuracy precisely, due to variations in study design and reporting. Also, because most research on this topic is subject to verification bias (ie, patients who are referred for angiography likely had abnormal confirmatory testing), the true sensitivity is probably lower, and the true specificity is probably higher than what is actually reported.[80]

The rationale for performing confirmatory testing is based on well-established research showing that patients with abnormal tests are at higher risk of myocardial infarction and MACE.[82-85] Intuitively, for patients with undifferentiated chest pain, the most useful benefit of performing confirmatory testing after an unremarkable ED workup would be the identification of patients with unstable angina who may not have objective evidence of myocardial ischemia on the diagnostic studies described previously but are still at risk for MACE. However, the ability of confirmatory testing to achieve this is unclear. First, obstructive CAD identified on confirmatory testing is not necessarily the cause of the patient's chest pain. Second, the yield of most confirmatory tests in patients with normal ECGs and negative contemporary biomarkers is very low; observational studies have shown that stress testing in these patients is likely to be positive only 5% to 11% of the time,[86-89] though one study showed a yield of 19.6% in patients with TIMI scores ≥ 3.[90] Third, false-positive stress tests are common: of patients with abnormal stress tests who are then referred for invasive angiography, only about one-third are found to have clinically significant obstructive CAD.[83,91] False positives are likely even more common in patients with a low pretest probability of CAD.

Most importantly, several recent observational studies have suggested that confirmatory testing does not provide any incremental improvement in outcome in patients with chest pain and normal or nondiagnostic ECGs and negative biomarkers.[86,88-90,92,93] These findings are supported by a retrospective review of over 420,000 ED visits for chest pain; the cohort of patients who underwent confirmatory testing after an unremarkable workup had significantly higher rates of downstream cardiac catheterization and revascularization procedures, but no significant difference in incidence of myocardial infarction at 7-day and 180-day follow-up compared to the cohort who had no confirmatory testing.[94]

CCTA deserves further discussion because its use as a confirmatory test in ED chest pain patients is dramatically increasing; one review found a 434% increase in CCTA utilization in this population from 2006 to 2013.[95] A normal CCTA confers excellent prognosis, with pooled negative LR of MACE at median 20-month follow up of 0.008 (95% CI, 0.0004-0.17), according to one meta-analysis.[84] A later meta-analysis showed that CCTA generally decreases ED length of stay and cost compared to other methods of confirmatory testing.[96] However, this study also found that patients who underwent CCTA had a 2.1% higher rate of invasive coronary angiography and a 2% higher rate of revascularization (percutaneous coronary intervention or coronary artery bypass graft) than those who underwent other methods of confirmatory testing, but that there was no significant difference in frequency of MACE at follow-up.

Table 4. Estimated Diagnostic Accuracy of Confirmatory Testing for Detection of Coronary Artery Disease With ≥ 50% Stenosis[79]

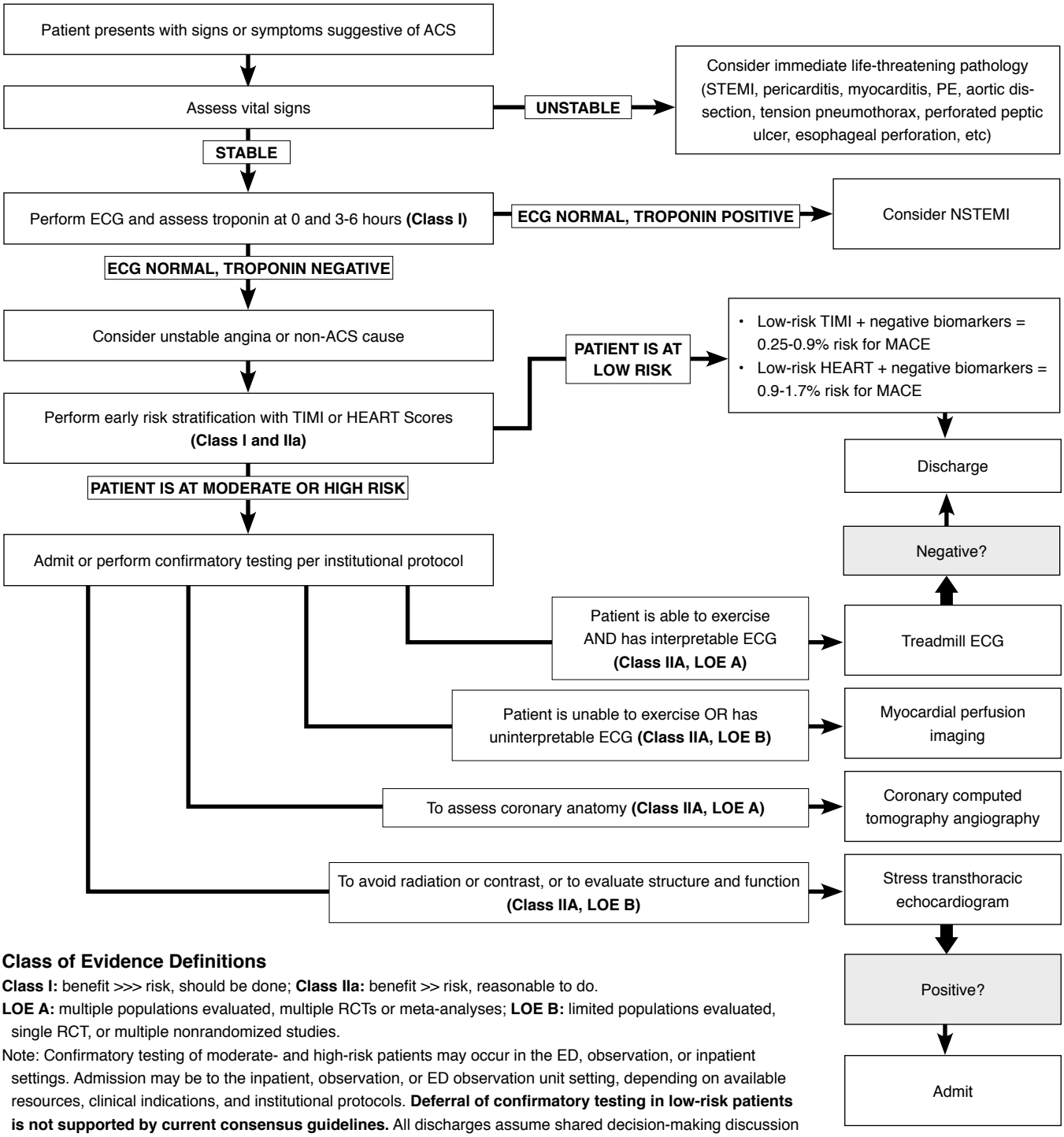
Test	Sensitivity (%)	Specificity (%)
Exercise ECG	61	70-77
MPI (exercise)	82-88	70-88
MPI (pharmacologic)	88-91	75-90
Echo (exercise)	70-85	77-89
Echo (pharmacologic)	85-90	79-90
Cardiac MRI	87-88	56-70
CCTA	93-97	80-90

Abbreviations: CCTA, coronary computed tomography angiography; echo, echocardiogram; ECG, electrocardiogram; MPI, myocardial perfusion imaging; MRI, magnetic resonance imaging.

Summary

Current consensus guidelines recommend that all patients with normal serial ECGs and negative biomarkers undergo confirmatory testing before discharge or within 72 hours.[2,6-8] However, it is becoming clearer that confirmatory testing adds little to no additional benefit for patients already at low risk of MACE, based on the diagnostic studies and risk-stratification protocols described previously, and can cause harm and increase cost by leading to unnecessary invasive testing and treatment.

Clinical Pathway for Emergency Department Testing of Patients With Signs or Symptoms of Acute Coronary Syndromes



Class of Evidence Definitions

Class I: benefit >>> risk, should be done; **Class IIa:** benefit >> risk, reasonable to do.

LOE A: multiple populations evaluated, multiple RCTs or meta-analyses; **LOE B:** limited populations evaluated, single RCT, or multiple nonrandomized studies.

Note: Confirmatory testing of moderate- and high-risk patients may occur in the ED, observation, or inpatient settings. Admission may be to the inpatient, observation, or ED observation unit setting, depending on available resources, clinical indications, and institutional protocols. **Deferral of confirmatory testing in low-risk patients is not supported by current consensus guidelines.** All discharges assume shared decision-making discussion of risks, benefits, alternatives, and return precautions, and that close outpatient follow-up can be arranged. This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

Abbreviations: ACS, acute coronary syndromes; ECG, electrocardiogram; HEART, History, ECG, Age, Risk Factors, Troponin [Score]; LOE, level of evidence; MACE, major adverse cardiac event; NSTEMI, non-ST-segment elevation myocardial infarction; PE, pulmonary embolism; RCT, randomized controlled trial; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction [Score].

Treatment

Patients with chest pain who are at low risk for ACS or MACE may be candidates for interventions related to primary prevention and lifestyle modification, though benefits specific to this population have not been studied.

Aspirin is beneficial for primary prevention of cardiovascular disease. A meta-analysis including 95,000 patients showed aspirin use was associated with a 12% proportional reduction in serious vascular events, including first myocardial infarction, though the benefits of its use must be balanced against the risk of bleeding.[97] 2016 United States Preventive Services Task Force guidelines recommend the initiation of 81 mg/day of aspirin in patients who are at ≥ 10% 10-year risk of cardiovascular disease (Grade B recommendation for patients aged 50-59 years, Grade C for patients aged 60-69 years, inconclusive evidence for patients aged < 50 or > 70 years).[98]

Initiation of antihypertensive treatment from the ED in at-risk populations is safe and effective in lowering mean blood pressure at short-term follow-up.[99] A 2013 American College of Emergency Physicians Clinical Policy supported the initiation of antihypertensive therapy in at-risk populations (eg, those with poor follow-up) with markedly elevated blood pressure in the ED, though this is a Level C consensus recommendation and the benefits of this practice are not evidence based.[100]

Special Populations

Chest Pain in Women

Several important differences must be considered during the evaluation of women with chest pain. First, compared with men of the same age, women have an overall lower prevalence of obstructive CAD and a higher likelihood of atypical symptoms, which can lead to delayed diagnosis and increased likelihood of being discharged with missed myocardial infarction.[9,101] Second, ECG criteria for detection of myocardial infarction are different in women. Minor J-point elevation in V_2-V_3 can be a normal variant in men and women, but a study of 1332 healthy volunteers established that the upper limit of normal in women is lower than that of men.[102] Third, exercise stress testing is less accurate in women; a meta-analysis including 4113 women found that the sensitivity of exercise electrocardiography and exercise myocardial perfusion imaging for the detection of CAD was 0.61 and 0.78, respectively, compared to 0.68 and 0.85 in similar meta-analyses of studies that included a majority of men.[103] Interestingly, of the clinical risk scores discussed previously, only PURSUIT includes gender in the model, but this score should not be used for ED patients with undifferentiated chest pain.

Younger Patients

The prevalence of ACS is < 2% in patients aged < 40 years,[32] but 4% to 8% of myocardial infarctions still occur in this age group.[104] Nonetheless, observational research has shown that, among patients in this age group with chest pain, those who have no known history of heart disease and no cardiac risk factors (hypertension, elevated cholesterol, tobacco use, diabetes, and family history of premature CAD) are at < 1% risk of ACS and MACE at 30 days[104] and 1 year.[105] Another observational study showed that even when cardiac risk factors are present, if the patient had a normal ECG and negative initial biomarker (either CK-MB or conventional troponin I), the risk of ACS or MACE at 30-day follow-up was 0.14%.[106] Not surprisingly, several retrospective observational studies have shown that confirmatory testing is very low-yield in this age group; out of 1650 stress tests performed in a total of 1993 patients, 20 were positive, of which only 4 were judged to be true-positive on angiography.[93,107-109]

Elderly Patients

The evaluation of the elderly patient with chest pain is especially challenging. Patients aged ≥ 75 years have increased incidence, prevalence, and severity of CAD and ACS.[36] Elderly patients often have atypical and nonspecific symptoms, the ECG is less accurate,[110] and elevated troponin is less specific for myocardial infarction.[111] Most clinical risk scores include age as an independent risk factor, decreasing their ability to identify low-risk patients who may be suitable for discharge.[112] Medical comorbidities or exercise limitations may limit the types of testing that can be performed, though if there are no obvious contraindications, confirmatory testing is generally safe to perform in the elderly.[2]

Patients With Known Coronary Artery Disease or Previous Cardiac Testing

Patients with known CAD who present with chest pain have a higher pretest probability of ACS; one systematic review found that prior CAD conferred a positive LR of 2.0 (95% CI, 1.4-2.6) for ACS in patients presenting with chest pain.[22] Pre-existing CAD can also make the ED evaluation more challenging. For example, the ECG may be more difficult to interpret due to baseline evidence of prior myocardial infarction, bundle branch block, conduction abnormalities, or arrhythmia.[113] Cardiac biomarkers may be chronically elevated from nonischemic conditions related to previous CAD (eg, congestive heart failure) and acute elevations may therefore be more difficult to detect and interpret.[46] Even if the ED evaluation is unrevealing, patients with known CAD may still be at intermediate or high risk for ACS or MACE based on the clinical risk scores described previously and may be more likely to require further

evaluation and risk stratification.[40,49,57,61] Certain confirmatory tests may not be possible; for example, pre-existing ECG abnormalities or exercise intolerance may preclude exercise electrocardiography, or extensive CAD or coronary artery calcification may decrease the accuracy of CCTA.[80] However, if the patient has no evidence of myocardial infarction and is hemodynamically stable, confirmatory testing is generally safe and is the next recommended step for risk stratification.[80,87] The initial confirmatory test of choice in patients with known CAD is often myocardial perfusion imaging, due to the reasons described previously, and because this modality can more accurately localize potential myocardial ischemia.[80]

The prognostic utility of previous cardiac testing in patients presenting with new chest pain is unclear. Annualized rates of myocardial infarction or cardiac death in outpatients who have had a negative stress test are 0.80% for exercise treadmill, 0.65% for exercise myocardial perfusion imaging, and 1.78% for pharmacologic myocardial perfusion imaging (the higher event rate in pharmacologic myocardial perfusion imaging is attributed to greater comorbidities in patients who are unable to exercise).[85] Patients with normal or nearly normal cardiac catheterizations have excellent long-term prognosis and very low risk of MACE at 5- and 10-year follow-up.[114,115]

Controversies and Cutting Edge

High-Sensitivity Troponin Testing

The ability of modern troponin assays to detect smaller and smaller levels of circulating troponin continues to improve. The United States Food and Drug Administration approved the first high-sensitivity troponin T assay for use in the United States in January 2017, though several other high-sensitivity assays have been used outside of the United States since 2009.[116] These high-sensitivity assays have been shown to lead to earlier diagnosis of myocardial infarction, potentially decreasing ED length of stay and time to disposition or definitive treatment.[117] They also increase the NPV of a normal troponin level, improving risk stratification and prognostication.[118-120]

However, as discussed previously, many conditions other than ACS can cause release of troponin, and high-sensitivity troponin assays are even less specific for ACS than their conventional counterparts. As noted before, delta troponin can increase specificity for ACS, though the optimal delta for high-sensitivity assays has not yet been defined. Tiny changes in troponin due to biologic or analytic variation become detectable with high-sensitivity assays, and may be higher than the 20% threshold used to define myocardial infarction with conventional sensitive assays in patients with an elevated baseline level.[121]

High-sensitivity troponins could reduce or even eliminate the diagnosis of unstable angina.[122] Unstable angina is distinguished from NSTEMI on the basis of normal cardiac biomarkers, so as high-sensitivity assays detect smaller levels of troponin that would otherwise be missed by conventional assays, this can increase the number of patients who are diagnosed with NSTEMI. Indeed, a prospective study of 1124 patients found that the introduction of high-sensitivity troponin led to a relative increase in the diagnosis of myocardial infarction (through new diagnoses of NSTEMI) by 22% and a corresponding relative decrease in the diagnosis of unstable angina by 19%.[123]

Triple-Rule-Out Computed Tomography

The "triple-rule-out" (TRO) CT combines CT angiography of the coronary arteries concurrently with the pulmonary arteries and aorta, thereby simultaneously evaluating for CAD, pulmonary embolism, and aortic dissection.[124] TRO CT typically requires additional contrast volumes and radiation exposure over dedicated CT imaging alone, with one study citing a mean difference of 38 mL and 4.84 mSv, respectively.[125] There may be incremental diagnostic yield to TRO CT over dedicated CT imaging alone,[126] but at present, there are no clearly defined populations of ED patients that benefit from TRO CT.

Disposition

Most patients presenting to the ED with chest pain who are hemodynamically stable, have normal or nondiagnostic serial ECGs, negative serial biomarkers, and are at low risk for MACE based on a validated clinical risk score can be safely discharged, and despite current consensus guideline recommendations, do not seem to benefit from additional confirmatory testing. Patients with an unremarkable ED evaluation but who are still at intermediate or high risk for ACS or MACE based on validated clinical risk scores are more likely to benefit from admission to an observation or inpatient setting for confirmatory testing and further risk stratification.

Many institutions are incorporating accelerated diagnostic protocols that aim to identify these low-risk patients in a safe and efficient manner. For example, the University of Maryland Medical System developed an evidence-based Accelerated Diagnostic Protocol in 2015 that uses conventional troponin assays, risk stratification using the HEART Score, and defined shared decision-making between the provider and patient.[127] Patients with a single negative troponin and a HEART Score of 0 to 3 may choose from 3 options for disposition: (1) discharge home with outpatient follow-up (< 2% risk of MACE at 4 weeks); (2) stay for repeat troponin at 3 hours and, if negative, discharge home with outpatient follow-up (< 1% risk of MACE at 4 weeks); or

(3) be placed in observation for further testing or treatment as indicated. This accelerated diagnostic protocol highlights a number of variables that may differ from other validated accelerated diagnostic protocols and between individual institutions and providers, but its core principles of focused testing with contemporary cardiac biomarkers, risk stratification with a validated clinical risk score, and shared decision-making between the provider and patient are crucial to every safe disposition.

Time- and Cost-Effective Strategies

- Conventional sensitive troponin assays can detect myocardial infarction within 3 hours in most patients; high-sensitivity assays aim to shorten this time even more, though with the disadvantage of decreased specificity.
- Most patients who are at low risk for ACS or MACE, as determined by a negative ED workup including serial biomarkers and risk stratification using a validated clinical risk score, do not benefit from confirmatory testing.
- Accelerated diagnostic protocols can shorten ED length of stay and decrease resource utilization.

Summary

By using a combination of the clinical history, physical examination, ECG, biomarkers, and validated clinical risk scores, many patients who present to the ED with chest pain can be efficiently and safely identified as having a low risk for ACS and MACE at short-term follow-up. Confirmatory testing likely adds little to no additional prognostic information in such patients and can lead to unnecessary invasive testing and harm; however, it is still recommended by current consensus guidelines and may be advised by local institutional protocols. The use of high-sensitivity troponin assays can improve the detection of myocardial infarction, but at the cost of decreased specificity.

Case Conclusions

Your first patient had a high pretest probability of ACS, given his age, history, comorbidities, and description of symptoms. His initial ECG was normal, but was repeated to detect transient ischemic changes. His initial troponin was negative, but it was obtained < 6 hours after the onset of symptoms, so it was repeated 3 hours after the initial sample was obtained. The patient's HEART score was 6 (2 points for highly suspicious symptoms, 2 points for age, and 2 points for prior history of myocardial infarction), placing him at moderate risk (12%-16.6%) for MACE within 6 weeks. Based on these factors, the patient was admitted to the observation unit and had a stress echocardiogram that was positive; consequently, he was sent for cardiac catheterization, where 2-vessel disease was identified, and the patient received 2 stents.

For the 22-year-old college student patient, he was already at very low risk for ACS or future MACE given his age, lack of cardiac risk factors or previous cardiac history, lack of family history of premature cardiac disease, the atypical nature of symptoms, and his normal ECG. If a troponin was obtained and was negative, this would, theoretically, lower his risk even further, and the TIMI or HEART clinical risk scores could also then be applied (both would show low risk). Consensus guidelines would recommend confirmatory testing after this evaluation, but this would likely add no benefit. However, given this patient's history, pulmonary embolism or pericarditis was higher on the differential diagnosis and further ED testing therefore focused on these conditions. Bedside ultrasound showed a small pericardial effusion, a diagnosis of viral pericarditis was made, and the patient was treated with colchicine and NSAIDs.

The patient with ESRD had risk factors for CAD and symptoms concerning for angina. The presence of inspiratory crackles on examination was nonspecific for ACS, but could have indicated volume overload or congestive heart failure, especially given her history of ESRD. Her ECG had nonspecific abnormalities that could indicate myocardial ischemia. Her troponin was elevated but at her baseline, suggesting chronic nonischemic myocardial injury rather than ACS; however, this patient should be presumed to have ACS until proven otherwise. The troponin was repeated at 3 hours, since a > 20% interval change would strongly suggest myocardial infarction. The patient's HEART score was 7 (2 points for highly suspicious symptoms, 1 point for nonspecific repolarization disturbances on ECG, 1 point for age, 1 point for risk factors, and 2 points for troponin ≥ 3x normal limit), placing her at high risk (50%-65%) for MACE within 6 weeks. Her negative recent stress test was reassuring, but the annual rate of myocardial infarction or cardiac death in all patients after a negative stress pharmacologic myocardial perfusion imaging is nearly 2%. The repeat troponin was unchanged; however, due to her high HEART score, she was admitted for cardiac catheterization, which showed 4-vessel disease that was not amenable to stents; consequently she underwent 4-vessel bypass surgery.

Appendix 1. Summary of Major Clinical Risk Scores (Derivation Studies Only) (Continued on page 15)

Score (Year Created, Country of Origin)	Purpose	Outcome	Endpoint	Biomarkers	Results for Lowest-Risk Group	Appropriate for Identification of Low-Risk Patients in the ED?	Recommended by AHA?[3]
Goldman[63] (1982, USA)	Detect MI, determine admission level of care (ICU vs non-ICU)	Acute MI, acute ischemic heart disease without infarction, or "other"	6-10 months	Serum aspartate aminotransferase, CK, CK-MB, LDH	1% risk of MI (2 patients, no deaths); 3% risk of acute ischemic heart disease without infarction (8 patients, 1 death)	No	No
ACI-TIPI[64] (1991, USA)	Estimate likelihood of cardiac ischemia and determine appropriate admission level of care (ICU vs non-ICU)	MI or acute cardiac ischemia at time of ED presentation	Data collected at 0 and 48 hours; also abstracted later from hospital records	CK was recorded but not included in final model	1.8% risk of MI; 3.8% risk of cardiac ischemia ("low risk" defined as < 10% risk of ACS)	No	No
TIMI[49] (2000, 10 countries) MDCalc link: www.mdcalc.com/timi-risk-score-ua-nstemi	Identify prognostic factors for patients with NSTEMI or UA; later adapted for use in undifferentiated chest pain	All-cause mortality, new or recurrent MI, severe recurrent ischemia requiring urgent revascularization	14 days	CK-MB and/or troponin	1.2% all-cause mortality; 2.3% new or recurrent MI; 1.2% urgent revascularization	Derivation study not appropriate; subsequent validation studies have adapted this rule for ED use[51,52,65,66]	Yes
PURSUIT[67] (2000, 28 countries)	Identify prognostic factors for patients with NSTEMI or UA	Death or nonfatal recurrent MI	30 days	CK-MB	0.6% risk of mortality; 8.2% risk of nonfatal recurrent MI	No	No
GRACE[68] (2003, 14 countries) MDCalc link: www.mdcalc.com/grace-acs-risk-mortality-calculator	Estimate risk of in-hospital mortality for patients with ACS (STEMI, NSTEMI, or UA)	All-cause mortality during hospitalization	Variable	CK-MB, CK, and/or troponin	< 0.2% risk of outcome	No	No

Abbreviations: ACI-TIPI, Acute Cardiac Ischemia Time-Insensitive Predictive Instrument; ACS, acute coronary syndromes; AHA, American Heart Association; CK, creatine kinase; CK-MB, creatine kinase-MB isoenzyme; ED, emergency department; GRACE, Global Registry of Acute Coronary Events; ICU, intensive care unit; LDH, lactate dehydrogenase; MI, myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; PURSUIT, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; UA, unstable angina; USA, United States of America.

Appendix 1. Summary of Major Clinical Risk Scores (Derivation Studies Only) (Continued from page 14)

Score (Year Created, Country of Origin)	Purpose	Outcome	Endpoint	Biomarkers	Results for Lowest-Risk Group	Appropriate for Identification of Low-Risk Patients in the ED?	Recommended by AHA?[3]
National Heart Foundation of Australia (2006, Australia)[69,70]	Identify prognostic factors for patients with NSTEMI or UA; later adapted for use in undifferentiated chest pain	ACS or MI at presentation, MACE (death, cardiac arrest, revascularization, cardiogenic shock, arrhythmia) at short-term follow-up	0, 7, and 30 days	Troponin I	1.6% risk of ACS or MI (1 patient with UA), no MACE at 7 or 30 days	Derivation study not appropriate; subsequent validation studies have adapted this rule for ED use[73,74]	No
Vancouver Chest Pain Rule[57,73] (2006, Canada) MDCalc link: www.mdcalc.com/vancouver-chest-pain-rule	Risk stratification of undifferentiated chest pain	MI (including death without other obvious cause) or definite UA	30 days	CK-MB, CK, and/or troponin I	1.2% risk of outcome (2 patients with UA)	Yes	Yes
HEART[40] (2008, Netherlands) MDCalc link: www.mdcalc.com/heart-score-major-cardiac-events	Risk stratification of undifferentiated chest pain	MI, PCI, CABG, and/or death	Variable (average 423 ± 106 days)	Troponin I	2.5% risk of outcome (1 patient with CABG)	Yes	Yes
North American Chest Pain Rule[61] (2012, Canada, USA)	Risk stratification of undifferentiated chest pain	MI, revascularization, and/or death of cardiac or unknown cause	30 days	Troponin T and I	0 outcomes in patients aged ≤ 40 years; 0.66% risk of outcome in patients aged > 40 years (1 patient with STEMI during stress test, 3 patients with PCI, but no MI or death)	Yes	Yes
Emergency Department Assessment of Chest Pain[74] (2014, Australia, New Zealand) MDCalc link: www.mdcalc.com/emergency-department-assessment-chest-pain-score-edacs	Risk stratification of undifferentiated chest pain	MACE (STEMI, NSTEMI, emergency revascularization, death from cardiac cause, ventricular arrhythmia, cardiac arrest, cardiogenic shock, high atrioventricular block)	30 days	Troponin	0.15% risk of outcome (3 patients)	Yes	No

Abbreviations: ACS, acute coronary syndromes; AHA, American Heart Association; ED, emergency department; CABG, coronary artery bypass graft; CK, creatine kinase; CK-MB, creatine kinase-MB isoenzyme; HEART [Score], history, ECG, age, risk factors, troponin; MACE, major adverse cardiac event; MI, myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PURSUIT, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina; USA, United States of America.

Risk Management Pitfalls in Managing Patients at Low Risk for Acute Coronary Syndromes

1. **"My patient was young and healthy, so I didn't suspect ACS."**
   Younger patients are at lower risk of ACS, but 4% to 8% of myocardial infarctions still occur in patients < 40 years old. While traditional cardiac risk factors are generally not useful in the management of undifferentiated chest pain, a high risk-factor burden is more predictive of ACS in younger patients. Validated clinical risk scores can identify very-low-risk patients in this age group with excellent accuracy.

2. **"Her symptoms didn't sound like angina, so ACS wasn't even in my differential diagnosis."**
   A patient's history cannot reliably exclude ACS. Atypical symptoms are often present and are more common in women, the elderly, and diabetics. Additional testing, especially in these population groups, should be considered to reliably rule out ACS.

3. **"The pain was reproducible on palpation, so I ruled out ACS."**
   Pain that is reproducible on palpation lowers the risk of ACS, but does not exclude it.

4. **"The ECG was normal, so I didn't think further testing was indicated."**
   A normal ECG lowers the risk of ACS but does not adequately exclude it, and nearly 8% of patients with myocardial infarction have a normal ECG. Misinterpretation of the ECG is also a factor associated with missed diagnosis of ACS. Accuracy is increased by obtaining serial ECGs.

5. **"His chest pain began 6 hours prior, so I thought 1 troponin would be sufficient."**
   Troponin will be detectable within 6 hours in nearly all patients with myocardial infarction. However, if the history is inexact, if the patient has a moderate to high pretest probability of ACS, or if the troponin assay is older or less-sensitive, additional samples should be considered.

6. **"The patient had negative serial troponins, so I thought that ruled out ACS."**
   Currently, unstable angina is a purely clinical diagnosis, and biomarkers will be negative in this condition. Negative biomarkers should be used in conjunction with validated clinical risk scores for optimal risk stratification.

7. **"He had chest pain and an elevated troponin, so I diagnosed him as having a myocardial infarction."**
   The specificity of troponin for myocardial infarction is less than its sensitivity, and troponin can be elevated in many other conditions that cause nonischemic myocardial injury (eg, heart failure, pulmonary embolism, chronic kidney disease, sepsis).

8. **"My patient had a TIMI score of 0, so I excluded ACS and discharged him without further testing."**
   A TIMI score of 0 confers a 1.8% risk of 30-day MACE, which may be unacceptably high. Using TIMI in conjunction with serial biomarkers improves its prognostic ability.

9. **"My patient had normal serial ECGs and negative serial troponins, so I told him that ACS was ruled out and he didn't need any further testing."**
   There is strong evidence to suggest that confirmatory testing does not add any incremental benefit in low-risk patients. However, this approach has not been tested in randomized trials, and is not yet endorsed by consensus guidelines. Furthermore, patients who are at intermediate or high risk of ACS or MACE as determined by a validated clinical risk score should undergo further testing, even with normal ECGs and negative troponins.

10. **"She had a negative stress test 6 months prior and the ECG was normal, so I thought it was safe to send her home without any further testing."**
    The annual event rate (myocardial infarction or cardiac death) is about 1% after any stress test. Any patient presenting to the ED with chest pain should be evaluated with ECG and biomarkers, and risk stratified using a validated clinical risk score, despite the recent negative stress test.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study is included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the author, are noted by an asterisk (*) next to the number of the reference.

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CME Questions

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1. Proven benefits of prehospital care to patients with possible ACS include all of the following EXCEPT:
a. Earlier identification of STEMI
b. Decreased time to reperfusion
c. Ability to rule out MI with prehospital point-of-care troponin assays
d. Selection of optimal treating hospital

2. Which historical feature most increases the likelihood of ACS?
a. Chest pain that is associated with exertion
b. Chest pain that is pleuritic
c. Chest pain that is described as "stabbing"
d. Chest pain that has been present for several hours

3. Which physical examination finding most decreases the likelihood of ACS?
a. Presence of a third heart sound
b. Hypotension
c. Pulmonary rales
d. Chest pain that is reproducible on palpation

4. Which ECG meets the criteria for STEMI?
a. J-point elevation of 0.2 mV in V_2-V_3 in a 30-year-old woman
b. J-point elevation of 0.15 mV in V_2-V_3 in a 50-year-old man
c. J-point elevation of 0.2 mV in V_2-V_3 in a 30-year-old man
d. J-point elevation of 0.05 mV in V_5-V_6 in any adult

5. Which clinical risk score was developed specifically for ED patients with undifferentiated chest pain?
a. ACI-TIPI b. TIMI
c. GRACE d. HEART

6. What has been shown to increase the accuracy of the TIMI score in the evaluation of undifferentiated chest pain?
a. Checking serial biomarkers
b. Checking serial ECGs
c. Checking CK-MB in addition to troponin
d. Performing exercise electrocardiography

7. Regarding younger patients and ACS, which of the following is TRUE?
a. Traditional cardiac risk factors are not helpful for risk stratification in this group.
b. Up to 8% of myocardial infarctions occur in patients aged < 40 years.
c. Confirmatory testing is beneficial in younger patients with an unremarkable ED workup.
d. Biomarkers should not be obtained for younger patients.

8. All of the following factors make the evaluation of suspected ACS in the elderly more challenging EXCEPT:
a. Elevated troponins are less specific for myocardial infarction in the elderly.
b. Atypical symptoms are more common in the elderly.
c. Most clinical risk scores incorporate age, making it more difficult to identify low-risk patients.
d. Confirmatory testing cannot be performed in the elderly.

9. Regarding high-sensitivity troponin assays, all of the following are true EXCEPT:
a. More patients are diagnosed with unstable angina and fewer patients are diagnosed with NSTEMI.
b. They can lead to shorter ED length of stay.
c. They can detect smaller circulating levels of troponin.
d. They have decreased specificity for myocardial infarction.

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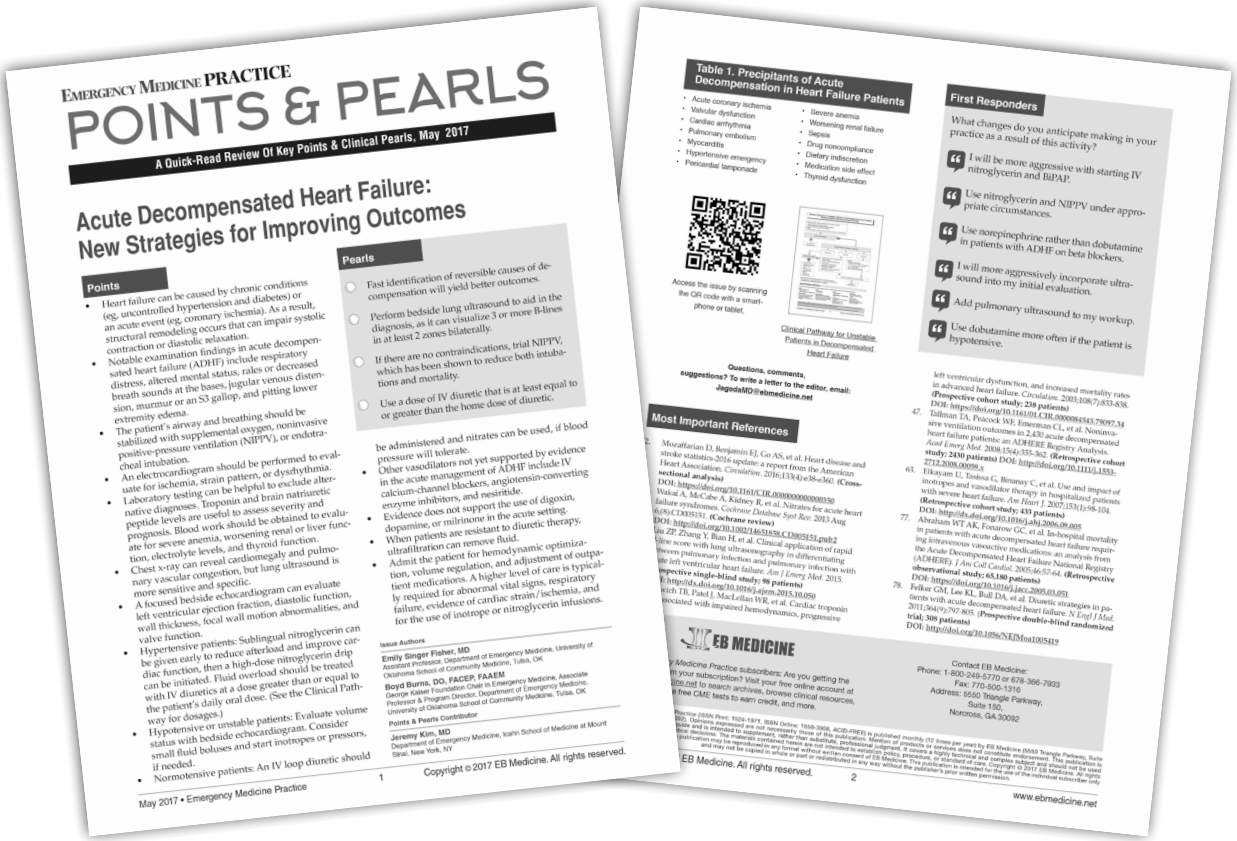

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