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## Testing of Low-Risk Patients Presenting to the Emergency Department With Chest Pain

### A Scientific Statement From the American Heart Association

Ezra A. Amsterdam, MD, Chair; J. Douglas Kirk, MD, Co-Chair; David A. Bluemke, MD, FAHA; Deborah Diercks, MD; Michael E. Farkouh, MD; J. Lee Garvey, MD; Michael C. Kontos, MD; James McCord, MD; Todd D. Miller, MD, FAHA; Anthony Morise, MD, FAHA; L. Kristin Newby, MD; Frederick L. Ruberg, MD; Kristine Anne Scordo, PhD, RN, ACNP-BC; Paul D. Thompson, MD, FAHA; on behalf of the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology, Council on Cardiovascular Nursing, and Interdisciplinary Council on Quality of Care and Outcomes Research

**Abstract**—The management of low-risk patients presenting to emergency departments is a common and challenging clinical problem entailing 8 million emergency department visits annually. Although a majority of these patients do not have a life-threatening condition, the clinician must distinguish between those who require urgent treatment of a serious problem and those with more benign entities who do not require admission. Inadvertent discharge of patients with acute coronary syndrome from the emergency department is associated with increased mortality and liability, whereas inappropriate admission of patients without serious disease is neither indicated nor cost-effective. Clinical judgment and basic clinical tools (history, physical examination, and electrocardiogram) remain primary in meeting this challenge and affording early identification of low-risk patients with chest pain. Additionally, established and newer diagnostic methods have extended clinicians' diagnostic capacity in this setting. Low-risk patients presenting with chest pain are increasingly managed in chest pain units in which accelerated diagnostic protocols are performed, comprising serial electrocardiograms and cardiac injury markers to exclude acute coronary syndrome. Patients with negative findings usually complete the accelerated diagnostic protocol with a confirmatory test to exclude ischemia. This is typically an exercise treadmill test or a cardiac imaging study if the exercise treadmill test is not applicable. Rest myocardial perfusion imaging has assumed an important role in this setting. Computed tomography coronary angiography has also shown promise in this setting. A negative accelerated diagnostic protocol evaluation allows discharge, whereas patients with positive findings are admitted. This approach has been found to be safe, accurate, and cost-effective in low-risk patients presenting with chest pain. (*Circulation*. 2010;122:1756-1776.)

**Key Words:** AHA Scientific Statements ■ acute care ■ angina ■ coronary disease ■ cost-effectiveness ■ diagnostic techniques and procedures ■ emergency department ■ prognosis ■ stress test ■ chest pain unit

There are >8 million visits to emergency departments (EDs) for chest pain or other symptoms consistent with myocardial ischemia annually in the United States, which makes this the second most frequent cause of ED encounters

in adults<sup>1</sup>; however, only a minority of these patients have a life-threatening condition. Therefore, the challenge to clinicians is rapid identification of those who require admission for urgent management and those with a benign cause who

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can be discharged directly from the ED. Failure to detect acute coronary syndrome (ACS) and inadvertent discharge of such patients from the ED may exceed 2%, with a risk-adjusted mortality ratio that is nearly 2-fold that of patients hospitalized for ACS, and it is also associated with substantial liability.<sup>2</sup> Fewer than 5% of patients presenting with chest pain have ST-segment-elevation myocardial infarction (MI),<sup>3,4</sup> and up to 25% have non-ST-segment-elevation ACS.<sup>5,6</sup> Thus, rapid, optimal therapy for patients with ACS must be balanced against recognition of patients with non-critical syndromes for whom hospitalization and extensive evaluation are unnecessary, expensive, potentially hazardous, and an ineffective use of limited resources.

To meet this challenge, an increasing array of diagnostic strategies and modalities have been applied, including chest pain units (CPUs), new cardiac biomarkers, risk scores, accelerated diagnostic protocols (ADPs), and non-invasive imaging of the myocardium and coronary arteries.<sup>7,8</sup> The utility of several of these methods for safe and accurate identification of patients with minimal risk of ACS is well established, and limited data with more recent approaches have shown promise. In this regard, it is emphasized that the primary goal of evaluation of these patients in the acute setting is accurate risk stratification and identification by exclusion of ACS and other serious conditions rather than detection of coronary artery disease (CAD). To achieve this goal, most strategies have used stress testing, with or without cardiac imaging, or rest myocardial scintigraphy, on the basis of the premise that a negative result markedly reduces the likelihood of ACS. The absence of obstructive CAD indicated by computed tomography coronary angiography (CTCA) has recently been used to confirm very low risk of ACS. However, with all of these methods, clinical judgment is essential for optimal interpretation and application.

The purpose of the present document is to provide current information on the appropriate application of these diagnostic tools in management of low-risk patients presenting with acute chest pain. This is a narrative review developed from evidence obtained by a comprehensive search of the English language medical literature and current guidelines during the past 3 decades. Specific areas targeted include clinical assessment, testing methods, special populations, and outcomes. Literature citations were limited to articles listed in Index Medicus. Of the numerous studies included, 5 were prospective randomized trials and the remainder were rigorous observational studies,<sup>9</sup> most of which included at least 100 patients with follow-up of  $\geq 30$  days. The few smaller studies were included for either their historical or methodological importance. This document was evaluated by 6 outside reviewers selected by the American Heart Association. The writing group represents a broad spectrum of investigators with experience and expertise pertaining to the multiple aspects of evaluation of low-risk patients presenting to the ED with chest pain. Management adheres to current guidelines where applicable and includes relevant information regard-

ing the specific issues in low-risk patients. An overview of the evaluation of these patients is depicted in the Figure,<sup>10</sup> in which this group is denoted by "Possible ACS."

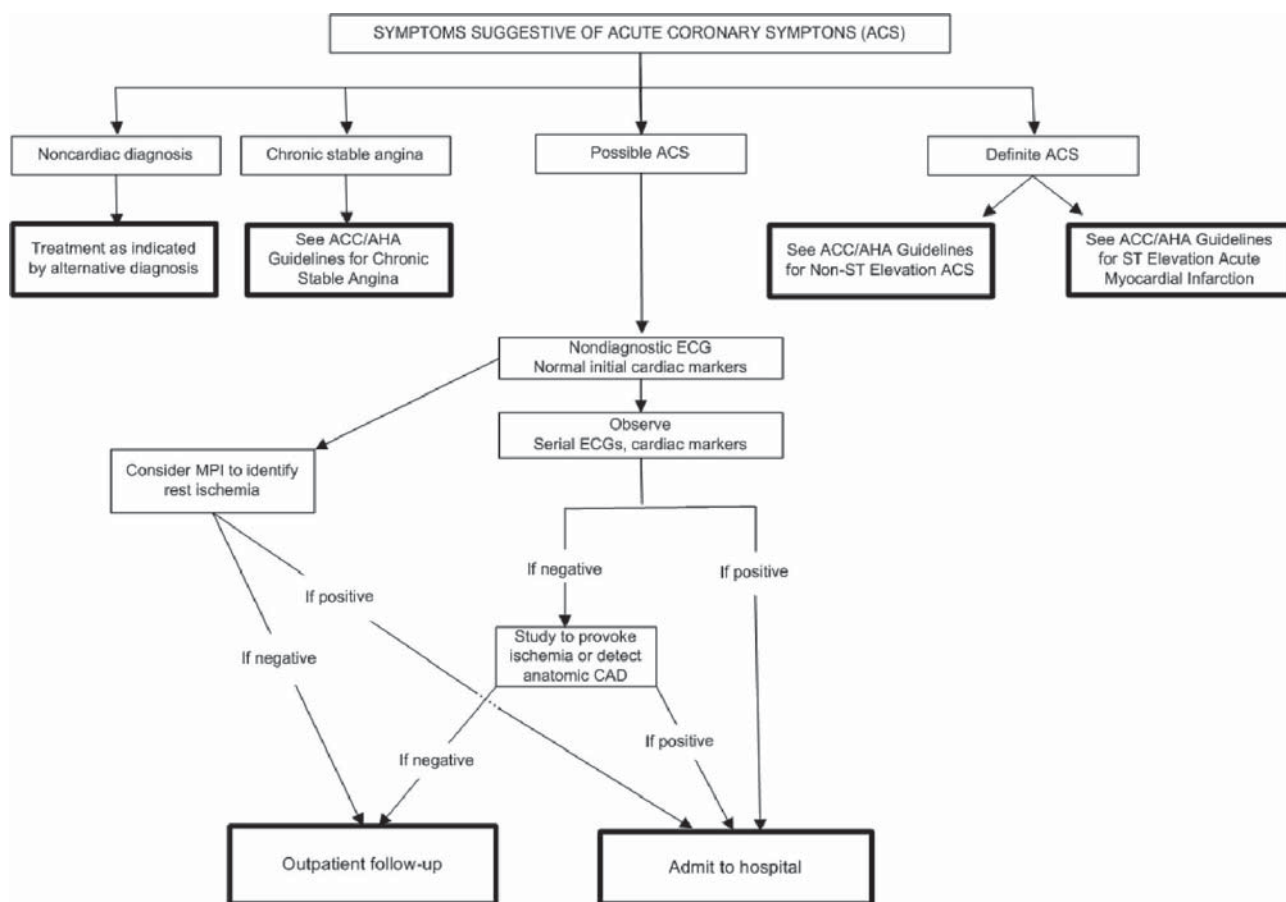
### Identification of Low Clinical Risk

Risk stratification begins with the initial approach to the patient, which provides important insight into the hazard for cardiovascular complications. It has been demonstrated that among patients presenting to the ED with chest pain, those with  $<5\%$  probability of MI can be identified from the presenting symptoms, past history, and electrocardiogram (ECG).<sup>4,11</sup> This approach was recently affirmed in a study of 2271 patients presenting to the ED with chest pain, in which a low-risk group with a 30-day major cardiovascular event rate (death, MI, stroke, or revascularization) of 2.5% could be recognized.<sup>4</sup> An important concept to emerge from these and similar observations is that although the cause of chest pain in these patients is frequently elusive, basic clinical tools provide powerful estimates of cardiac risk.<sup>5,12,13</sup> Concomitant with the rapid exclusion of important noncardiac causes of chest pain, risk stratification into categories defined by the American College of Cardiology/American Heart Association criteria should be performed as indicated by the history, physical examination, ECG, and cardiac injury markers (Table 1).<sup>14</sup> Low-risk patients for ACS are those with no hemodynamic derangements or arrhythmias, a normal or near-normal ECG, and negative initial cardiac injury markers, which correlate with low likelihood of ACS in Table 1.

On the basis of the initial clinical presentation, patients are considered for 1 of the following strategies: (1) Those with objective evidence of ACS or hemodynamic or electric instability are admitted for urgent therapy; (2) stable patients with no objective evidence of ischemia (normal or near-normal ECG and negative baseline cardiac injury markers) are considered low risk and can be admitted to an observation unit (CPU) for further evaluation by an ADP. The latter comprises serial ECGs and cardiac injury markers. In those in whom these studies are negative, a confirmatory test is performed by any of several methods, from exercise treadmill testing (ETT) to cardiac imaging, depending on the specific features of each patient. Negative results further minimize the probability of ACS, thereby optimizing the safety and rationale of discharging these patients. Those with positive ECGs or cardiac injury markers are diagnosed with ACS and admitted; patients with a positive confirmatory test are also admitted with an increased likelihood of ACS (Figure).

### Chest Pain Units

CPUs are predicated on the understanding that low risk is not no risk. These units provide an integrated approach to further stratification of low-risk patients by short-term observation with repeat ECGs and serial cardiac injury markers.<sup>5,15-18</sup> The units vary in form and may either occupy a designated area or function as "virtual" units, primarily comprising personnel and process.<sup>19</sup> They are usually directed by an emergency physician, but their successful implementation requires close



**Figure.** Evaluation of patients presenting with symptoms suggestive of ACS. ACC indicates American College of Cardiology; AHA, American Heart Association. Adapted from Braunwald et al,<sup>10</sup> with permission from Lippincott Williams & Wilkins. Copyright 2000, American Heart Association.

coordination between emergency physicians and cardiologists, as well as personnel from other departments (eg, hospitalist, radiology, nuclear medicine, and nursing). A recent report indicated that units certified by the Society of Chest Pain Centers had better adherence to Medicare and Medicaid core measures for treatment of acute MI than institutions without these certified units.<sup>20</sup> As of 2010, 560

CPUs had been certified by the Society of Chest Pain Centers.<sup>21</sup>

### Accelerated Diagnostic Protocols

CPUs are based on a protocol-driven process typically comprising an ADP. As previously described, this process uses serial ECGs and cardiac injury markers, usually

**Table 1. Likelihood That Signs and Symptoms Represent an ACS Secondary to CAD**

Feature	High Likelihood	Intermediate Likelihood	Low Likelihood
	Any of the following:	Absence of high-likelihood features and presence of any of the following:	Absence of high- or intermediate-likelihood features but may have:
History	Chest or left arm pain or discomfort as chief symptom reproducing prior documented angina Known history of CAD, including MI	Chest or left arm pain or discomfort as chief symptom Age >70 years Male sex Diabetes mellitus	Probable ischemic symptoms in absence of any of the intermediate likelihood characteristics Recent cocaine use
Examination	Transient MR murmur, hypotension, diaphoresis, pulmonary edema, or rales	Extracardiac vascular disease	Chest discomfort reproduced by palpation
ECG	New, or presumably new, transient ST-segment deviation ( $\geq 0.1$ mV) or T-wave inversion in multiple precordial leads	Fixed Q waves ST depression 0.05 to 0.1 mV or T-wave inversion > 0.1 mV	T-wave flattening or inversion <0.1 mV in leads with dominant R waves or normal ECG
Cardiac markers	Elevated cardiac TnI, TnT, or CK-MB	Normal	Normal

CAD indicates coronary artery disease; CK-MB, MB fraction of creatine kinase; MI, myocardial infarction; MR, mitral regurgitation; TnI, troponin I; and TnT, troponin T. Modified with permission from Anderson et al.<sup>14</sup>

**Table 2. Common Causes of Acute Chest Pain**

System	Syndrome	Clinical Description	Presenting Features
Cardiovascular	Stable angina	Retrosternal pressure, heaviness, burning; may radiate to arms, neck, jaw	Provoked by physical or emotional stress
	Unstable angina	Same as stable angina but usually more severe and prolonged	Occurs at rest or with minimal exertion
	Acute MI	Same as angina but usually more severe	Usually $\geq$ 30-min duration; associated symptoms include dyspnea, weakness, diaphoresis
	Aortic dissection	Sudden severe pain, may radiate to back	Commonly associated with hypertension or connective tissue disease
	Pericarditis	Pleuritic pain, worse in supine position	Fever, pericardial friction rub
Pulmonary	PE	Sudden onset of pain and dyspnea; pain may be pleuritic with pulmonary infarction	Dyspnea, tachypnea, tachycardia
	Pneumonia	May be associated with localized pleuritic pain	Cough, fever, crackles
	Spontaneous pneumothorax	Unilateral pleuritic pain associated with dyspnea	Sudden onset of symptoms
Gastrointestinal	Esophageal reflux	Burning retrosternal and epigastric discomfort	Aggravated by large meals and postprandial recumbency
	Peptic ulcer	Prolonged epigastric or retrosternal burning	Relieved by antacid or food
	Biliary disease	Right-upper-quadrant pain	Unprovoked or following meal
	Pancreatitis	Intense epigastric and retrosternal pain	Associated with alcoholism, elevated triglycerides
Musculoskeletal	Costochondritis	Fleeting localized pain, may be intense	May be reproducible by pressure to affected site
	Cervical disc disease	Sudden fleeting pain	May be reproduced by movement of neck
Psychological	Somatoform disorders; sudden fleeting pain; may be reproduced by movement of neck	Symptoms are atypical for any organ system	Symptoms may persist despite negative evaluations of multiple organ systems

Adapted from Table 49 by Cannon and Lee in *Braunwald's Heart Disease*.<sup>8</sup> Copyright 2008, Elsevier.

obtained over a 6- to 12-hour period.<sup>5,16,18,22</sup> A negative evaluation consistent with no evidence of MI or ischemia is followed by a confirmatory study to exclude inducible ischemia, the absence of which permits patient discharge. Although ETT is the most widely used confirmatory test in an ADP, this varies with the circumstances, as described below.

### Initial Assessment

Historical information in patients with chest pain is crucial in determining the cause of symptoms and risk stratification. Because myriad conditions can cause chest pain, a systematic approach to assessment of symptoms should be pursued. Table 2 lists the important differential diagnoses in patients with chest pain.<sup>8</sup> The history should include questions related to pain location, onset, character, radiation, alleviating and exacerbating factors, and time course; history of similar episodes; severity on a scale of 1 to 10; and associated symptoms, including diaphoresis, dyspnea, dizziness, palpitations, and nausea. Although they predict the long-term probability of a coronary event, cardiac risk factors are usually not helpful in identification of ACS in patients presenting with acute chest pain<sup>5,23,24</sup>; however, in patients <40 years of age, it was reported that a very high risk factor burden (4 to 5 risk factors) increased the

likelihood of ACS by >20-fold compared with the absence of any risk factors.<sup>24</sup>

### Symptoms

Myocardial ischemia usually produces chest discomfort that is diffuse and often radiates to the arm, neck, or jaw. Ischemic cardiac pain manifests by chest heaviness, pressure, tightness, squeezing, or burning and is often provoked by exertion, emotional stress, or temperature extremes. Because chest discomfort due to myocardial ischemia tends to be similar in location and quality during recurrent episodes, it is helpful diagnostically if the symptoms are consistent with prior episodes.

A high degree of suspicion and recognition of atypical presentations is important, because a significant number of patients present with "anginal equivalents" rather than chest pain. These symptoms include jaw, neck, or arm discomfort; dyspnea; nausea; vomiting; diaphoresis; and unexplained fatigue. These are seen more frequently in the elderly, women, and diabetic patients. Sharp, stabbing, or reproducible pain reduces but does not exclude the likelihood of ACS. Pleuritic chest pain is consistent with a pulmonary condition, musculoskeletal disease, or pericarditis. However, the Multi-center Chest Pain Study found that 22% of patients presenting with symptoms described as sharp or stabbing pain (13% with pleuritic pain and 7% with pain reproduced on palpation)



were eventually diagnosed with ACS.<sup>11</sup> The National Heart Attack Alert Program recommends that patients with any of the aforementioned presenting symptoms should be assessed immediately and referred for rapid evaluation.<sup>25</sup>

The pain of angina pectoris often occurs episodically, lasts from 2 to 10 minutes during physical exertion, and is relieved by rest. If symptoms persist for >10 minutes, MI, unstable angina, aortic dissection, or pulmonary embolism (PE) should be considered (Table 2). Pain that is abrupt in onset and worst at onset is often associated with pneumothorax, aortic dissection, or PE. Nontraumatic musculoskeletal pain usually manifests vaguely, and the circumstances that led to its onset may not be recalled. However, like MI, all these conditions can present atypically, which necessitates a high index of suspicion when patients with chest pain are evaluated.

Chest pain due to myocardial ischemia may be relieved by rest or sublingual nitroglycerin; however, relief with nitroglycerin should not be used as a diagnostic test for determining chest pain origin in the ED because it does not predict myocardial ischemia.<sup>26–28</sup> Postprandial chest discomfort is suggestive of gastroesophageal causes but can be a manifestation of severe CAD.<sup>29</sup> A combination of severe chest pain and diaphoresis or vomiting strongly suggests ACS, but aortic dissection and PE should also be considered. Other symptoms that support an ischemic origin of chest pain include dyspnea, particularly in the elderly, because dyspnea may predominate over chest pain,<sup>30</sup> in which case a pulmonary source should also be strongly considered. Rarely, palpitations may be the presenting symptom of cardiac arrhythmias in the setting of ACS or PE. Patients with PE, pneumonia, and severe bronchitis occasionally present with hemoptysis. In addition, fever and chills usually point to an infectious or inflammatory process such as pneumonia, pleurisy, or pericarditis.

### Physical Examination

The physical examination, although more specific than sensitive, can be useful to identify higher-risk patients. Signs of heart failure reflect left or right ventricular dysfunction. Bruits usually indicate peripheral arterial disease and increase the risk of concomitant CAD. The examination should also target potential noncardiac causes for the patient's symptoms, such as unequal extremity pulses (aortic dissection), prominent murmurs (endocarditis), friction rub (pericarditis), fever and abnormal lung sounds (pneumonia), or reproduction of chest pain with palpation of the chest wall (musculoskeletal disorders). A normal physical examination is present in the majority of uncomplicated cases of ACS and contributes to the initial impression of low clinical risk.

### Electrocardiogram

In addition to clinical status, the initial ECG is the most informative tool for early risk stratification, and it should be obtained within 10 minutes of ED presentation.<sup>31</sup> The ECG provides important diagnostic and prognostic information and is pivotal in the triage process. In patients presenting with a nonischemic ECG and no prior evidence of CAD, the frequency

of MI was 2%, and in those with a history of CAD, it was 4%.<sup>5</sup> Other data indicate that a normal or minimally abnormal ECG may be associated with non-ST-segment-elevation MI in 1% to 6% of patients and with unstable angina in 4%.<sup>32</sup> If the initial ECG is negative, repeat ECGs (eg, 5- to 10-minute intervals) have been recommended, because serial changes of ischemia or injury may evolve.<sup>31</sup> An alternative and more sensitive method than intermittent ECG recordings is continuous ST-segment monitoring. Its utility in indicating subclinical ischemia has been demonstrated during observation of high-risk patients presenting with chest pain, but the yield of this method in low-risk patients is minimal.<sup>33,34</sup>

ST elevation is closely associated with total or near-total coronary occlusion and indicates that the patient is a potential candidate for acute coronary reperfusion therapy. ST-segment depression ( $\geq 0.05$  mV) in the absence of left ventricular hypertrophy is associated with a marked increase in risk for MI, as well as subsequent ischemic complications.<sup>35–37</sup> Furthermore, adverse prognosis has been related directly to the degree of ST-segment depression.<sup>28</sup> However, even a near-normal ECG, indicated by <0.05 mm of ST-segment depression and absence of T-wave inversion, may be associated with increased risk in patients with a history of CAD.

Patients with minor, nonspecific T-wave changes in the absence of high-risk clinical features are at low risk, but marked and symmetrical T-wave inversion ( $\geq 0.20$  mV) is consistent with ACS.<sup>38</sup> The distinction between non-ST-segment-elevation MI and unstable angina in patients with the aforementioned ST-segment and T-wave alterations is based on cardiac injury marker evidence of myocardial necrosis. The presence or absence of ischemic ST-segment and T-wave changes during chest pain in ACS patients has been shown to increase both the positive and negative predictive value of the ECG for adverse events compared with the ECG recording in the absence of pain<sup>39</sup>; however, this has not been a consistent finding, particularly in patients with undifferentiated chest pain, such as those managed in a CPU.<sup>40</sup> Significant Q waves ( $\geq 0.03$  seconds in 2 contiguous leads) unaccompanied by acute ST-segment or T-wave alterations are consistent with prior MI, but in the absence of other high-risk clinical features, they place the patient only at intermediate risk.<sup>10,41</sup> Bundle-branch block and paced rhythm identify increased risk.<sup>10,12</sup>

Additional methods have been applied to increase the sensitivity of the ECG for detection of ischemia/injury. A true posterior MI, which is suggested by marked ST-segment depression, upright T waves, and tall R waves in leads V<sub>1</sub> through V<sub>4</sub>, can be confirmed by ST-segment elevation isolated to posterior leads V<sub>7</sub> through V<sub>9</sub>.<sup>42</sup> In patients with inferior ST-elevation MI, right-sided leads (V<sub>4</sub>R through V<sub>6</sub>R) may detect ST-segment elevation indicative of right ventricular infarction. Posterior and right-sided leads have been combined in an 18-lead format, which yielded an 8% increase in sensitivity for MI compared with the standard 12-lead ECG, although with a 7% decrease in specificity.<sup>43</sup> These additional leads have been studied only in small numbers of patients.

### Chest Roentgenogram

The chest roentgenogram is abnormal in 85% to 90% of patients with aortic dissection and may reveal mediastinal widening, enlarged cardiac silhouette due to pericardial effusion, left pleural effusion, or calcium sign ( $\geq 1.0$  cm displacement of intimal calcium from the soft tissue border of the aorta). In patients with PE, the chest roentgenogram may show focal lung oligemia, a peripheral wedge-shaped density above the diaphragm, or an enlarged descending right pulmonary artery, but more often than not, it is normal. Most patients with uncomplicated ACS have a normal chest roentgenogram. Other relevant entities evident on the chest roentgenogram include pneumonia, pneumothorax, and pneumomediastinum.

### Cardiac Biomarkers

Current guidelines recommend measurement of a cardiac injury marker (which should include a highly sensitive and specific cardiac troponin assay) in all patients with suspected myocardial ischemia.<sup>14,44,45</sup> In patients who present early (within 6 hours of symptom onset), measurement should be repeated 6 to 8 hours after occurrence of symptoms in those with initially negative results. Patients who arrive  $>8$  hours after symptom onset may only need a single measurement to exclude acute MI.<sup>14,44,45</sup> Attempts at reducing the time to accurate diagnosis include shorter sampling intervals, quantitation of serial changes (delta) over time, and use of a combination of injury markers such as creatine kinase-MB and myoglobin in addition to a cardiac troponin.<sup>46-51</sup> Initial reports of the latter approach suggested this strategy provided superior risk stratification compared with a single-marker approach<sup>48-51</sup>; however, these data reflect the use of early-generation troponin assays, which suffered from imprecision at the standard cutoff values for MI.

Contemporary troponin assays have improved sensitivity, specificity, and precision at lower levels.<sup>45,52,53</sup> When used serially to detect changes over short intervals, their sensitivity is higher than that of more traditional injury markers, which obviates the need for creatine kinase-MB or myoglobin measurement, even in patients with onset of symptoms shortly before presentation.<sup>54</sup> Current studies have confirmed that contemporary troponin assays can identify the majority of MIs within 3 hours of ED arrival.<sup>55,56</sup>

Although an elevated cardiac troponin level is indicative of myocardial necrosis, it does not specify the mechanism of injury. An abnormal value alone may not indicate MI, because there are numerous nonischemic causes of elevated cardiac troponin.<sup>57</sup> Confirmation of MI is based on evidence of myocardial necrosis afforded by the clinical setting and pattern of troponin values. Criteria include a rise or fall of cardiac troponin with at least 1 value above the 99th percentile of the upper reference limit and at least 1 of the following: Symptoms of cardiac ischemia, characteristic ECG alterations, or imaging evidence of a new regional wall-motion abnormality (RWMA).<sup>58</sup> Current recommendations are for a turnaround time of  $<60$  minutes for central laboratory reporting of cardiac injury marker data. If this cannot be achieved,

point-of-care methods should be considered; however, the latter are limited by lower accuracy than contemporary troponin assays.<sup>59</sup>

A variety of other biomarkers have been found to have independent value for predicting subsequent ischemic events, particularly mortality, in patients with ACS<sup>45,57</sup>; however, few of these newer biomarkers are commercially available, nor have they been validated in an undifferentiated population, such as patients presenting to the ED with chest pain. In most studies, the primary outcome has been long-term mortality, which is arguably less important than MI in the initial assessment of the ED patient. Currently, only 2 of these biomarkers, B-type natriuretic peptide (or N-terminal prohormone B-type natriuretic peptide) and high-sensitivity C-reactive protein, are available for routine use, and only B-type natriuretic peptide is typically used in the ED. The utility of B-type natriuretic peptide has been demonstrated in a number of investigations, and elevations of this marker provide powerful risk stratification across a broad spectrum of ACS patients.<sup>60-62</sup> However, B-type natriuretic peptide should not be considered a specific biomarker of ischemia, because abnormal values frequently occur in ED patients and are more likely to identify those who have systolic dysfunction related to heart failure rather than ACS.<sup>63,64</sup> High-sensitivity C-reactive protein has had value in predicting long-term cardiac events, but its role in the acute setting of ED patients presenting with chest pain is less well defined, and currently available data do not suggest it is important in this context.<sup>45,46,52</sup>

### Clinical Risk Scores

A useful approach to risk stratification has been the development of a variety of risk-scoring systems based on the history and initial clinical presentation. The simplest criteria rely on 1 set of cardiac injury markers, an ECG, and a history of CAD. If none of these are present or abnormal, the patient can be considered low risk, with a probability of MI  $<6\%$ .<sup>5</sup> More sophisticated risk-stratification schemes<sup>35,36,65</sup> have been developed in high-risk patients with ACS to indicate prognosis but are not intended to establish a diagnosis in a low-risk heterogeneous population of patients presenting with chest pain and no objective evidence of ACS. The Thrombolysis In Myocardial Infarction (TIMI) risk score is the most widely used score but has yielded mixed results when applied in low-risk patients.<sup>66</sup> Furthermore, even in patients with the lowest TIMI scores (eg, 0 to 1), additional risk stratification is required, because the event rate in this group was not negligible.<sup>67</sup>

The Global Registry of Acute Coronary Events (GRACE) scoring system has been reported to accurately predict risk in an undifferentiated chest pain population, but it is more complex than the TIMI score, and many of its variables are not available in patients who present to the ED.<sup>68</sup> Variables common to different scoring systems include indicators of hemodynamic status, clinical risk factors, and objective evidence of ACS. Favorable (low risk) scores allow consideration for CPU management. These scoring systems are recommended as guides for risk stratification and should be

applied as adjuncts to, not substitutes for, clinical judgment in the evaluation of patients presenting with chest pain.

### Confirmatory Test Selection in ADPs

ETT is the cornerstone of confirmatory testing in an ADP.<sup>15,16,17</sup> Its advantages include its relatively modest cost, availability, ease of performance, and important prognostic information. Criteria for this test are the patient's ability to exercise and a normal baseline ECG that allows interpretation of exercise-induced ST-segment alterations. If these conditions are not fulfilled, an imaging test (eg, myocardial perfusion imaging [MPI] or echocardiogram) is considered, with or without stress (pharmacological or exercise). In addition, coronary angiography (invasive or CTCA) has also been used. Again, the primary purpose of confirmatory testing as part of an ADP during CPU observation is to further minimize the likelihood of ACS to a level so low that discharge is safe. Of the multiple studies performed on test methods in low-risk patients, 5 were prospective, randomized, controlled trials. The latter assessed treadmill testing,<sup>69</sup> treadmill testing or myocardial perfusion scintigraphy,<sup>70</sup> myocardial perfusion scintigraphy,<sup>71</sup> conventional coronary angiography,<sup>72</sup> and CTCA.<sup>73</sup> The largest trial used acute rest MPI.<sup>71</sup> These studies will be considered in detail in their respective sections below.

### Exercise Treadmill Testing

#### Evolution of Concept

Extensive experience has confirmed the safety and rationale of incorporating ETT into current CPU protocols. In the decade after 1994, there was major evolution in the role of ETT in patients admitted for possible ACS. Initial recommendation that the test be withheld until patients were clinically stable for 48 hours<sup>74</sup> was followed by demonstration of its safety and efficacy, as noted in the 31st Bethesda Conference on Emergency Care in 1999, in which it was stated that "...early exercise testing as a key element has been associated with reduced hospital stay and lower costs."<sup>19</sup> A subsequent science advisory of the American Heart Association concluded that contemporary studies "confirmed the safety of symptom-limited treadmill exercise ECG testing after 8 to 12 hours of evaluation ... in patients identified as low to intermediate risk" by injury markers and ECGs.<sup>75</sup> This strategy was incorporated in the 2002 guidelines of the American College of Cardiology/American Heart Association for management of patients with non-ST-segment-elevation ACS, in whom ETT was recommended after 6 to 8 hours of evaluation that revealed no evidence of ischemia or injury at rest.<sup>10,41</sup> The current American College of Cardiology/American Heart Association guidelines for stress testing and for management of non-ST-segment-elevation ACS recommend that ETT without imaging should be performed as the initial test in low- to intermediate-risk patients who present with ischemic symptoms and can exercise, do not have significant baseline ECG changes that preclude interpretation ( $\geq 0.05$ -mV ST-segment depression, left ventricular hypertrophy with any repolarization abnormality), and are not taking digoxin.<sup>16,76</sup> Criteria for performing ETT in patients in

**Table 3. ETT: Patient Selection, Procedure, and End Points**

Patient selection criteria	
Able to exercise	
ECG: Normal or minor ST-T changes	
Hemodynamically stable, no arrhythmia	
Negative cardiac injury markers	
Procedure	
Bruce or modified Bruce protocol	
End points	
Symptom-limited	
Ischemia ( $\geq 0.10$ mV of horizontal ST depression or elevation)	
Decreased blood pressure ( $\geq 10$ mm Hg systolic) during exercise test	
Result	
Positive: $\geq 0.10$ mV of horizontal ST-segment depression*	
Negative: No exercise-induced abnormalities at 85% MPHR	
Nondiagnostic: $< 85\%$ MPHR with no ECG evidence of ischemia	
MPHR indicates maximum predicted heart rate.	
*Although most data on ED treadmill testing refer to ST-segment abnormalities, other important variables include functional capacity, Duke treadmill score, heart rate recovery, chronotropic incompetence, and ventricular arrhythmias.	

a CPU and end points of testing are shown in Table 3. The safety of the test is based on strict adherence to these criteria.

#### Utility of Exercise Testing in CPUs

This strategy has been validated by multiple studies that included approximately 3000 patients who underwent ETT after  $\leq 12$  hours of negative observation<sup>69,77-86</sup> (Table 4). No adverse effects of early ETT were reported. Another study of 400 patients who received ETT or stress imaging tests after a negative ADP showed similarly excellent prognostic findings.<sup>70</sup> Outcomes at 6 months did not differ from those of a control group of chest pain patients who were managed by usual hospital admission at a higher cost. During follow-up of 1 to 17 months in the aforementioned studies, there was only 1 reported cardiac death, and the incidence of nonfatal cardiac events, predominantly MI and revascularization, was 0% to 2%, which reflects a very high negative predictive value for subsequent cardiac events after ETT in CPU patients. The low positive predictive value for an ACS and its variability among studies (Table 4) is likely related to the differences in the study cohorts. Although the positive predictive value is low, the number of unnecessary admissions is reduced. Even more abbreviated ADPs were safely used in the past in selected low-risk patients with either no cardiac injury markers<sup>87</sup> or a single set of markers obtained before ETT.<sup>77,83</sup>

#### Exercise Test Protocol and End Points

The exercise protocol used has usually been the modified Bruce method; however, the standard Bruce protocol is reasonable in patients in whom adequate functional capacity is anticipated. In addition to the objective data afforded by the ETT, failure of the test to reproduce the chest pain that prompted the ED visit is important in markedly lowering the



**Table 4. Studies of ETT in ADPs\***

Reference	No. of Patients	Positive Tests, %†	Negative Predictive Value, %‡	Positive Predictive Value, %‡	Adverse Exercise Test Events
Tsakonis et al <sup>78</sup>	28	18	100		0
Kerns et al <sup>79</sup>	32	0	100		0
Gibler et al <sup>80</sup>	782	1	99	44	0
Gomez et al <sup>69</sup>	100	7	100	0	0
Zalenski et al <sup>81</sup>	224	8	98	16	0
Polanczyk et al <sup>82</sup>	276	24	98	15	0
Kirk et al <sup>83</sup>	212	13	100	57	0
Diercks et al <sup>84</sup>	747	3	99	37	0
Sarullo et al <sup>86</sup>	190	30	99	77	0
Amsterdam et al <sup>77</sup>	1000	13	89	33	0
Ramakrishna et al <sup>85</sup>	125	27	100	8	0

\*Includes studies in which results of exercise ECG tests could be distinguished from those of other forms of stress testing.

†Positive exercise ECG.

‡Based on clinical follow-up or further cardiac evaluation.

§Randomized controlled trial.

Adapted from Amsterdam et al.<sup>15</sup>

likelihood of ACS. The criteria for a positive test for ischemia are the standard indicators:  $\geq 0.10$  mV of horizontal or downsloping ST-segment depression or  $\geq 0.10$  mV of ST elevation. Although meta-analyses have demonstrated that the sensitivity of ETT to detect CAD is approximately 70% and its specificity is 75%,<sup>88</sup> the rationale of the test in this setting is to risk stratify patients to a very low probability of ACS and subsequent complications if the test is negative. Functional capacity, which has not been a widely applied measure in this setting, is a powerful prognostic indicator, and achievement of  $< 3$  metabolic equivalents (METs) is associated with increased risk, as are chronotropic incompetence, abnormal heart rate recovery, and a decrease in blood pressure during ETT.<sup>89</sup> Conversely, achievement of  $\geq 7$  METs on ETT without exercise-induced abnormalities is associated with a low likelihood of ACS and low risk for subsequent ischemic events. Risk stratification can be enhanced by the integration of multiple ETT variables into scores such as the Duke Treadmill Score.<sup>90</sup> Other exercise-induced alterations that indicate an abnormal response and the need for further evaluation include angina and arrhythmias. These findings are additional end points for the ETT (Table 3). To optimize the safety of exercise testing in this patient population, the test is stopped at the onset of minimal criteria of ischemia (0.10 mV of ST-segment shift), in contrast to patients performing elective, outpatient ETT. If patients do not reach 85% of age-predicted maximum heart rate and there is no ECG evidence of ischemia, the test is considered nondiagnostic, and further assessment, such as by stress imaging or angiography, is considered. The 85% criterion, although conventional, has not been validated. Moreover, it was found that in this patient population, a negative ETT with a peak heart rate of 80% of maximum predicted was associated with excellent short- and long-term prognosis of CPU patients.<sup>77</sup>

### Test Supervision

Although guidelines exist for supervision of ETT by noncardiologists and nonphysicians,<sup>88</sup> these guidelines do not cover

the topic of exercise testing in a CPU. Although there are numerous studies that support the safety of ETT performed by cardiologists in the ED<sup>15</sup> (Table 4), other reports describe the safety and accuracy of specially trained healthcare professionals in performing ETT in low-risk patients presenting with chest pain.<sup>76,82,84,88,91–93</sup> This capability could potentially obviate the need for direct supervision of ETT by cardiologists in low-risk populations. In this regard, there were no adverse effects of ETT performed by specially trained internists or emergency physicians in a CPU.<sup>77,92</sup> It has also been shown that these physicians not only safely supervised ETT but also accurately interpreted the findings.<sup>92</sup> Additionally, nurse-supervised dobutamine stress echocardiography (DSE) was shown to be safe and accurate in patients presenting to the ED with chest pain.<sup>94</sup>

Most of these studies were small and not randomized, and they were thus underpowered to detect any differences in adverse clinical outcomes in tests supervised by cardiologists and noncardiologists; however, on the basis of the available literature and in alignment with existing guidelines for stress testing,<sup>76,88</sup> it is reasonable for appropriately trained personnel, including emergency physicians, internists, and hospitalists, to perform ETT in the ED or CPU with cardiology consultation closely available. It could be anticipated that a system that uses trained noncardiologist healthcare professionals to perform ETT in CPUs would better align limited resources with overall healthcare needs and serve as a potentially cost-effective alternative for many facilities.<sup>95–97</sup>

### Cost-Effectiveness

The cost-effectiveness of ADPs that include ETT has been demonstrated in comparisons of this strategy with regular care that entails hospital admission of low-risk patients presenting with chest pain. Early evaluation of ETT in the ED demonstrated the potential for cost savings with this approach.<sup>79</sup> A subsequent study of 317 patients reported a cost saving of \$567 per patient managed by the rapid

**Table 5. Diagnostic Accuracy of Rest MPI in Patients With Acute Chest Pain and a Nonischemic ECG**

Reference	n	Radiopharmaceutical	Sensitivity, %	Specificity, %	NPV, %	Outcome
Varetto et al <sup>111</sup>	64	Tc-mibi	100	92	100	CAD
Hilton et al <sup>112</sup>	102	Tc-mibi	94	83	99	CAD/AMI
Tatum et al <sup>113</sup>	438	Tc-mibi	100	78	100	AMI
Kontos et al <sup>116</sup>	532	Tc-mibi	93	71	99	AMI
Heller et al <sup>115</sup>	357	Tc-tet	90	60	99	AMI
Kontos et al <sup>114</sup>	620	Tc-mibi	92	67	99	AMI
Udelson et al <sup>*71</sup>	1215	Tc-mibi	96	NR	99	AMI
Schaeffer et al <sup>117</sup>	479	Tc-mibi	77	92	99	ACS

NPV indicates negative predictive value; AMI, acute MI; Tc-mibi, <sup>99m</sup>Tc-sestamibi; Tc-tet, <sup>99m</sup>Tc-tetrofosmin; and NR, not reported.

\*Randomized controlled trial.

Adapted from Kontos and Tatum.<sup>107</sup>

protocol compared with usual care.<sup>81</sup> In a randomized controlled trial, a rapid protocol was associated with half the length of stay and \$624 less per patient compared with hospital admission.<sup>69</sup> A larger study of 424 patients demonstrated no difference in cardiac events at 6 months in those managed with an ADP or usual care, but the cost was 61% higher in the latter group.<sup>70</sup>

### Outpatient Stress Testing

Ideally, confirmatory testing would be available at all times to complete the CPU evaluation and enhance the safety of early discharge after a negative ADP. Furthermore, many patients will not return for outpatient testing because of issues such as noncompliance, lack of insurance, or logistical problems; however, availability 24 hours per day is not feasible in many institutions. An alternative strategy, recognized by American College of Cardiology/American Heart Association guidelines,<sup>10,41</sup> approves outpatient ETT in selected low-risk chest pain patients after a negative evaluation by serial ECGs and cardiac injury markers. The criteria for discharge before stress testing are (1) no further ischemic chest discomfort, (2) normal or nondiagnostic initial and follow-up ECG, and (3) normal cardiac injury marker measurements.

Although there are no randomized trials concerning this issue, observational data have found this strategy to be appropriate, with no adverse cardiac events during the interval between hospital discharge and outpatient ETT. In a prospective study, 92% of 979 patients presenting to the ED with chest pain who fulfilled criteria for low risk during a 6-hour ADP underwent outpatient ETT.<sup>98</sup> There were 3 nonfatal MIs but no deaths during follow-up. A previous report of 344 patients who had negative ECGs and cardiac injury markers over 12 hours and were discharged to outpatient ETT revealed 2 deaths (0.6%) and no other cardiac events during 60 days of follow-up.<sup>99</sup> A third study found no cardiac events in a subgroup of 157 patients who had outpatient ETT.<sup>100</sup> The short-term likelihood of a cardiac event in low-risk patients is very small and supports the rationale of outpatient stress testing when the preferred strategy of pre-discharge testing is unavailable. The safety and utility of outpatient ETT are predicated on performance of the test within 72 hours (24 hours is preferable), reliability of the

patient to follow up for the test, and close communication between the CPU physician and the patient's personal physician.

### Myocardial Imaging

The major stress imaging methods currently applied in CPUs in patients without evidence of ischemia/infarction are MPI and echocardiography. Both can be performed with exercise or pharmacological stress; MPI can also be used at rest to detect ischemia. The latter capability represents an important advance, because reduced regional myocardial perfusion at rest is the pathophysiological basis of ACS. By contrast, stress-induced ischemia reflects an inadequate increase in coronary blood flow in response to augmented myocardial oxygen demand, which may characterize both stable CAD and ACS. Both MPI and echocardiography are more accurate in detecting CAD than ETT. Moreover, these methods afford information on left ventricular function and the location and extent of ischemia. Although there is no known hazard of echocardiography, MPI is associated with significant radiation exposure. Sensitivity and specificity of stress MPI for obstructive CAD have been reported as 87% and 73%, respectively,<sup>101</sup> and for stress echocardiography, they are approximately 86% and 81%, respectively.<sup>102</sup> Although there are no randomized controlled trials of rest/stress imaging in the CPU setting, their utility has been well demonstrated in the outpatient setting, and the method has been extended successfully to the CPU.<sup>70</sup> Although this increased sensitivity is an advantage, it could also result in detection of CAD in the absence of ACS more frequently than with ETT, which would result in hospitalization of patients with stable disease. Furthermore, despite the disparity in sensitivity for detection of CAD, the negative predictive values for ACS of ETT and the stress imaging methods, on which discharge from the CPU depends, are comparable (Tables 4, 5, and 6); however, the versatility of the myocardial imaging methods for assessment of the substantial number of patients not suitable for ETT has afforded them a vital role in the evaluation of low-risk patients presenting with chest pain.<sup>103</sup>

The major reasons for selecting an imaging test (with or without stress) rather than ETT include patients' inability to

**Table 6. Predictive Accuracy of Stress Echocardiography in Patients Presenting to the ED With Chest Pain**

Reference	Test	No. of Patients	Follow-Up, mo	Positive Test, n	ACE With Positive Test, n	PPV, %	Negative Test, n	ACE With Negative Test, n	NPV, %
Geleijnse <sup>127</sup>	DSE	80	6	36	0 Death 0 MI 9 UA 10 Revasc	53	44	0 Death 1 MI 1 UA 2 Revasc	89
Bholasingh <sup>124</sup>	DSE	377	6	26	1 Death 2 MI 2 UA 3 Revasc	30	351	1 Death 0 MI 6 UA 7 Revasc	96
Nucifora <sup>125</sup>	DSE	107	2	20	0 Death 0 MI 1 Revasc	5	87	0 Death 4 MI 4 Revasc	100
Trippi <sup>94</sup>	DSE	137	3	7	1 MI 1 UA	29	130	0 Death 0 MI 0 Revasc	98

ACE indicates adverse cardiac event; PPV, positive predictive value; NPV, negative predictive value; UA, unstable angina; and Revasc, myocardial revascularization.

exercise and baseline ECG alterations. Stress imaging can be performed with treadmill exercise or a pharmacological agent such as dobutamine<sup>102</sup>; alternatively, the coronary vasodilators dipyridamole, adenosine, and regadenoson<sup>104</sup> are commonly used during MPI. Dobutamine increases myocardial oxygen demand, and the vasodilators detect CAD by inducing a maldistribution of coronary perfusion through preferential vasodilation of normal coronary arteries. For MPI in patients admitted to a CPU, exercise or pharmacological stress with thallous chloride Tl 201 (<sup>201</sup>Tl) has been used and has yielded excellent sensitivity and negative predictive value for detection of CAD and prediction of cardiac events<sup>70,85,101,105,106</sup>; however, this method has largely been supplanted by the use of technetium 99m butilfenin (<sup>99m</sup>Tc) radiopharmaceuticals (<sup>99m</sup>Tc sestamibi and <sup>99m</sup>Tc tetrofosmin) for acute rest imaging with single-photon emission computed tomography (SPECT).<sup>107</sup> Tc 99m is taken up by the myocardium and distributed in proportion to tissue perfusion, and unlike <sup>201</sup>Tl, its redistribution is negligible. Thus, even with delayed imaging, it reflects myocardial perfusion at the time of injection. This method also obviates the need for acute stress testing in many patients.<sup>107</sup>

Iodine 123-betamethyl-*p*-iodophenyl-pentadecanoic acid is a methyl branched-chain fatty acid undergoing investigation as a marker of myocardial ischemia. It is not readily metabolized, and its retention by normal cardiac cells affords excellent myocardial images.<sup>108</sup> An advantage of this method is its reduced myocardial uptake long after resolution of ischemic symptoms.

Stress echocardiography also provides risk stratification beyond that of the basic clinical indicators, and results are available immediately. In addition to its noninvasive methodology, echocardiography poses no risk from radiation exposure. It can also provide structural and functional data, as well as findings that suggest nonischemic causes for patients' symptoms, including PE, valvular heart disease, cardiomyopathies, and pericardial disease.<sup>109</sup>

### Acute Rest MPI

This strategy, which uses 1 of the 2 <sup>99m</sup>Tc radiopharmaceuticals, relies on patients' rest symptoms to serve as the "stress" portion of the study. A perfusion defect indicates acute ischemia, acute infarction, or old infarction. Patients can be injected in the ED while experiencing symptoms, with delayed imaging after stabilization. The images obtained subsequently provide a "snapshot" of myocardial perfusion at the time of injection. Normal perfusion is associated with very low clinical risk, which allows patients to be discharged with further outpatient rest/stress MPI if indicated to detect underlying CAD.<sup>107</sup> In addition, simultaneous assessment of wall motion is obtained, which enables the differentiation of perfusion defects that result from artifacts or soft tissue attenuation from those that occur as a result of ischemia.<sup>110</sup> Left ventricular ejection fraction is also acquired, which provides quantitative determination of systolic function. Rest MPI has a class 1 indication in current guidelines for evaluation of patients with chest pain and a nonischemic ECG.<sup>103</sup>

Multiple studies have demonstrated that rest MPI can accurately identify low- and high-risk patients (Table 5).<sup>71,111–116</sup> In addition, rest MPI significantly increases both diagnostic and prognostic information beyond that of the ECG and clinical variables. These advantages were confirmed in a prospective multicenter trial of 2475 patients who presented to the ED with chest pain and nonischemic ECGs.<sup>71</sup> Patients were randomized to receive usual care with or without the addition of rest MPI. Sensitivity of the 2 strategies was similar (96% and 97%, respectively), but patients in the MPI arm had a significantly lower hospitalization rate, which translated into an estimated savings of \$70 per patient. Other studies also indicate the potential cost-effectiveness of rest MPI related to a decrease in the number of patients requiring admission.<sup>112</sup> By more appropriate selection of diagnostic procedures, the rate of coronary angiography in low-risk patients can also be reduced.<sup>112,115</sup> One center has developed a protocol that

categorizes all chest pain patients into 1 of 5 risk strata based on the probability of ACS derived from clinical and ECG variables.<sup>113</sup> Patients considered at low to moderate risk for ACS (eg, absence of ischemic ECG changes or history of CAD) undergo further risk stratification by rest MPI. Rest MPI also can be used as an alternative to admission in patients presenting with cocaine-associated chest pain. In a study of 216 consecutive patients with chest pain after recent cocaine use who underwent rest MPI, only 5 (2.3%) had abnormal studies, including 2 with acute MI.<sup>114</sup>

Acute rest MPI has several limitations. As noted previously, a perfusion defect can indicate a new or old MI, which can be distinguished by cardiac injury markers. To differentiate prior infarction from acute ischemia, repeat imaging during a pain-free state is performed. Resolution of a perfusion defect indicates that the initial defect was secondary to acute ischemia; if the defect persists, prior MI is more likely. Additionally, small areas of ischemic myocardium (3% to 5% of the left ventricle) may not be detected. Therefore, optimal use is typically in conjunction with at least 1 set of cardiac injury markers that offer complementary information to MPI. Furthermore, by quantifying the ischemic area, rest MPI may be a more optimal means of assessing ischemic risk than cardiac injury markers alone. The availability of imaging during all hours is a potential logistical issue; however, in a study in which patients presenting between 12 AM and 6 AM were injected with <sup>99m</sup>Tc sestamibi during that interval, there was no difference in diagnostic accuracy between delayed and immediate imaging.<sup>117</sup>

### Positron Emission Tomography

Similar to technetium-based single-photon emission computed tomography studies, positron emission tomography (PET) assesses myocardial perfusion after chemical stress by injection of a tracer (typically rubidium 82 or nitrogen 13 ammonia). PET offers certain advantages over single-photon emission computed tomography, including greater spatial resolution, higher sensitivity, and more reliable attenuation correction, albeit at a higher cost.<sup>118</sup> Furthermore, coregistration of PET images with computed tomography (PET-CT) can further improve test performance. Despite this potential, data regarding PET or PET-CT for the assessment of patients in the ED are few, most likely because of cost and the limited availability of accessible imaging systems.

### Echocardiography

#### Rest Echocardiography

RWMAs induced by ischemia are detected by echocardiography almost immediately after their onset, preceding ECG alterations and symptoms.<sup>119</sup> Therefore, echocardiography has been used for diagnosis and risk assessment in patients presenting to the ED with symptoms that suggest ACS. In high-risk populations, such as those with ST-segment elevation, rest echocardiography is comparable to invasive ventriculography in detecting RWMA.<sup>120</sup> Factors that determine the diagnostic accuracy of rest echocardiography to detect MI include infarct size, timing of the study in relation to symptoms, echocardiography protocols, and technology. Furthermore, detection of an RWMA requires involvement of

>20% of transmural myocardial thickness.<sup>121</sup> These factors account for the wide variability in negative (57% to 98%) and positive (31% to 100%) predictive values of rest echocardiography for MI at presentation in 9 studies of 955 patients.<sup>109</sup> Similarly, 2 studies with >900 patients in each study reported sensitivities of 99%<sup>122</sup> and 48%<sup>80</sup> for detection of MI by rest echocardiography. A more recent study in patients admitted with symptoms suggestive of ACS revealed a negative predictive value of 97% but a positive predictive value of only 24%.<sup>123</sup> These latter results are comparable to those of ETT in a similar patient population (Table 4). Although a normal rest echocardiogram in patients admitted to a CPU, like a normal ECG, is an indicator of low clinical risk, it may be insufficiently sensitive for detection of subtle RWMAs that may reflect ischemia in patients with unstable angina in whom cardiac markers are also negative.<sup>121</sup> Moreover, the age of an RWMA cannot be determined by echocardiography. Other echocardiography methods have been used to further evaluate patients presenting to the ED with chest pain. Regional myocardial perfusion has been assessed by intravenous injection of an echocardiography contrast agent that is taken up by the myocardium in proportion to regional coronary blood flow, thereby affording echocardiographic depiction of areas of inadequate perfusion.<sup>109</sup> There are limited data on this method in patients presenting to the ED with chest pain.<sup>122</sup>

#### Stress Echocardiography

Stress echocardiography has enhanced the diagnostic capability of echocardiography by detecting inducible wall-motion abnormalities as a reflection of significant CAD (>50% stenosis) in patients with normal resting wall motion. Although stress echocardiography can be performed by exercise, an alternative method in CPU patients is DSE.

DSE has demonstrated generally excellent negative predictive value for obstructive CAD in CPU patients and has also provided important prognostic information regarding early and late cardiac events<sup>94,124–126</sup> (Table 6). The negative predictive value of DSE in 351 patients was 96% at 6-month follow-up<sup>124</sup>; there were no cardiac events after 2 months in 87 patients with negative DSE<sup>125</sup>; and in 80 low-risk patients, the negative predictive value of DSE was 91% at 6 months.<sup>127</sup> DSE has also been performed by an innovative approach in which specially trained nurses and sonographers administered the test and transmitted the data by telemedicine to cardiologists for interpretation.<sup>94</sup> Continued use of this method has been shown to be safe and accurate in >700 patients, among whom only 3.1% of tests resulted in arrhythmias or RWMAs, all of which resolved without intervention.<sup>128</sup> However, acute MI occurred with DSE in the elective outpatient setting when higher doses of dobutamine were given than are used in current practice.<sup>129</sup>

### Coronary Artery Imaging

#### Coronary Calcium Score

Based on its close association with atherosclerosis, coronary artery calcification is considered a marker of CAD. It can be detected and quantified by either electron beam computed tomography or multidetector computed tomography. The



coronary artery calcium (CAC) score is a quantitative index of the extent of calcification, has been used as an estimate of coronary plaque burden and confers independent risk. Population studies have demonstrated that a high CAC score is associated with increased risk for coronary events and, conversely, zero CAC indicates very low risk.<sup>129a</sup> In patients presenting to the ED with undifferentiated chest pain, a zero CAC score has been associated with a negative predictive value approaching 100% for early adverse events in studies of 100 to >1000 patients<sup>129b–129f</sup>; this prognostic value was maintained on follow-up of >4 years.<sup>129c</sup> Although the sensitivity of the CAC score for cardiac events is high, its positive predictive value is unsatisfactory and often entails additional evaluation. Further, not all coronary plaques contain calcium. Calcification does not identify obstructive CAD, and increasing CAC is associated with advancing age and male sex.<sup>129a</sup> The emergence of CTCA has now redirected the focus of imaging in ED patients from risk stratification with CAC to direct visualization of coronary artery narrowing and plaque identification.

### Computed Tomography Coronary Angiography

Unlike ETT, MPI, and echocardiography, CTCA provides anatomic rather than functional information regarding coronary patency and produces a noninvasive coronary angiogram. Application of computed tomography to coronary artery imaging is now feasible with the advent of 64-slice multidetector (or multislice) computed tomography scanners, although even current systems are suboptimal, requiring slow heart rates (and frequently a  $\beta$ -blocking agent) for optimal image resolution.<sup>130</sup> The acquisition of scan data is synchronized (or gated) to the surface ECG and collected over a 10- to 20-second period during subject breath holding while contrast is injected ( $\approx 80$  mL). Current systems afford clear visualization of the major coronary arteries and branch vessels, with spatial resolution that approaches but is still inferior to that of conventional angiography.

Although it is noninvasive, there are risks associated with CTCA, including allergy to iodinated contrast medium and the hazard of ionizing radiation. The average radiation dose of a 64-slice CTCA varies widely depending on sex and body size but is approximately equivalent to 250 to 500 chest roentgenograms, which is only slightly greater than rest-stress <sup>99m</sup>Tc MPI.<sup>131</sup> The effective dose to breast and lung tissue is roughly 3-fold higher, however, which increases the estimated lifetime attributable risk of malignancies to these tissues, particularly in younger female patients.<sup>132</sup>

Limited studies have explored the utility of CTCA in low-risk populations such as those who present to the ED with chest pain of questionable origin, to determine the utility of the method in triage of this population. In a series of 103 patients presenting to the ED with chest pain, CTCA revealed normal vessels or nonobstructive CAD (negative predictive value 100%), and none of the patients discharged from the ED had a major adverse cardiovascular event at 5 months.<sup>133</sup> A larger single-center study of 368 patients yielded similar results, with a sensitivity of 100% and a negative predictive value of 100% for ACS after 6 months of follow-up.<sup>134</sup> A

report of nearly 600 ED patients (TIMI risk score 0 to 2) likewise demonstrated a negative predictive value of 100% for adverse events within 30 days. However, the low prevalence of disease in this study limits its generalizability as only 7 patients in the cohort were found to have CAD; no patients had death or MI.<sup>134a</sup> Other smaller studies of CTCA in the ED setting are consistent with these short-term findings.<sup>73,135–137</sup> Furthermore, normal or nonobstructive CTCA was associated with no deaths or MIs after 15 months<sup>135</sup> and 3 years of observation.<sup>137</sup> Compared with standard care, CTCA has been reported to decrease time to diagnosis (15.0 versus 3.4 hours), the number of repeat evaluations for chest pain, and cost.<sup>73</sup> In contrast to these salutary results, the positive predictive value of the method is more limited than the negative predictive value, which can lead to unnecessary invasive angiography in a significant number of patients.

CTCA may provide a more comprehensive examination of patients with chest pain<sup>138</sup> and specifically exclude other life-threatening causes such as PE and aortic dissection, comprising what has been termed colloquially the “triple rule-out.” Although feasible, such scans are technically more challenging, require larger volumes of contrast and more radiation, require a longer scan time (increased breath holding), and can result in incomplete imaging of 1 of the 3 target organs.<sup>139</sup> However, recent small-scale studies have suggested that the overall image quality for such all-encompassing scans is comparable to that of dedicated coronary, aortic, or pulmonary angiographic studies.<sup>140,141</sup>

CTCA has several limitations. Between 25% and 50% of patients presenting to the ED with chest pain may not be candidates for this technique because of obesity, contrast allergy, intolerance to  $\beta$ -blockade, arrhythmia, renal insufficiency, or history of CAD.<sup>134,136</sup> A significant minority will have suboptimal coronary artery visualization, coronary calcium that obscures vessels (eg, elderly patients), or moderate stenosis, which typically requires further noninvasive evaluation.<sup>136</sup> Because of concerns about long-term cancer risk, CTCA should be used with utmost caution in younger, particularly female, patients, and only when other test methods that do not use ionizing radiation are unavailable. However, it has been reported recently from a 15-institution collaborative study of CTCA that the radiation dose could be reduced substantially (53%) with no significant effect on image quality.<sup>142</sup> Newer CTCA systems, not yet tested in CPU settings, permit data acquisition without  $\beta$ -blockade and/or with very short breath holding.

CTCA has the potential for major clinical utility in the triage of selected low-risk patients presenting to the ED with chest pain because of its very high negative predictive value. Obstructive CAD can be excluded reliably in many patients, and available data support the safety and feasibility of ED discharge after a normal or nonobstructive CTCA. Larger, multicenter studies are required before this technology can be considered widely applicable. In this regard, the ROMICAT II (Rule Out Myocardial Infarction using Computer Assisted Tomography) trial, a multicenter, randomized study of the utility of CTCA in the ED setting, has been funded by the National Heart, Lung, and Blood Institute.<sup>143</sup>

### Magnetic Resonance Imaging

In contrast to CTCA, there is a paucity of data regarding the utility of cardiac magnetic resonance imaging in the triage of acute chest pain patients. Sensitivity and specificity for identification of CAD in patients presenting with chest pain have been reported as 96% and 83%, respectively, with adenosine stress perfusion and late gadolinium enhancement.<sup>144</sup> In a prospective study of 161 patients, sensitivity and specificity for identification of ACS were 84% and 85%, respectively.<sup>145</sup> The addition of T2-weighted imaging to assess myocardial edema increased the detection of ACS to 93%.<sup>146</sup> No short- or long-term outcome data were presented with any of these studies, which precludes conclusions on postdischarge risk; however, these data suggest a potential role for cardiac magnetic resonance imaging in the acute chest pain setting for noninvasive identification of ACS.

### Special Populations

The inclusion of certain subgroups in ADPs, such as patients with known CAD, diabetic patients, the elderly, women, young patients, and those with chest pain associated with stimulant use, may raise additional concerns. Some of these groups have been considered intermediate risk, whereas others are at very low risk. The distinction between low and intermediate risk is blurred because they exist on a continuum. However, the presence of any of the following suggests intermediate risk: Prior history of CAD, ECG with ST-segment depression 0.05 to <0.10 mV and/or flat or inverted T waves <0.20 mV deep, diabetes mellitus, chronic kidney disease, and advanced age. Because of the presence of the foregoing factors, more intermediate-risk patients will be evaluated by imaging studies than those in the low-risk group in whom ETT is typically applicable. However, the utility of ETT has been demonstrated in a large proportion of intermediate-risk patients who are clinically stable and can exercise, including those with a history of CAD, diabetes, and advanced age.

### Patients With CAD

Although the likelihood of ACS in patients with a history of CAD is higher than in most admitted to a CPU, their suitability for risk stratification primarily should be related to the immediate risk of ACS based on symptoms, ECG, and initial cardiac injury markers. Clinical judgment is crucial in these patients, but a history of CAD should not exclude a patient from CPU evaluation. Selected patients who initially were stratified as low risk have successfully undergone CPU assessment. In a report of 100 patients with previously documented CAD who presented with chest pain and underwent CPU evaluation, >70% had negative ETTs, two thirds of the total group were discharged directly from the CPU, and there were no adverse cardiac events during 6 months of follow-up.<sup>147</sup> Other studies have included patients with CAD with similar results.<sup>18,77</sup>

### Diabetic Patients

Patients with diabetes mellitus constitute a group at high risk for CAD and can present a challenge to conventional ETT because of limitations related to comorbidities such as obesity, peripheral arterial disease, and baseline ECG alterations; however, limited

data indicate that judicious patient selection has been associated with safe and accurate evaluation by ETT.<sup>77</sup> The utility of rest MPI in the ED was demonstrated in a subset of 341 diabetic patients with symptoms of cardiac ischemia.<sup>148</sup> Although the diabetic cohort had a higher rate of hospitalization and confirmed ACS, MPI was equally effective in reducing unnecessary admissions in diabetic and nondiabetic patients. Thus, carefully selected diabetic patients can undergo a standard ETT as part of an ADP. For those not suitable for ETT, myocardial imaging is appropriate.

### Elderly Patients

The expanding elderly population poses an increasing challenge for risk stratification. There is an increased probability of CAD in this group, as well as comorbidities and baseline ECG alterations that may limit the utility of ETT; however, ETT was successful in ADPs that included men and women older than 80 years<sup>77</sup> and 90 years.<sup>113</sup> In this group of patients, it is often appropriate to use an exercise protocol with a reduced intensity, such as the modified Bruce protocol, or a diagnostic test with high sensitivity that does not require exercise, ie, pharmacological stress imaging.<sup>149</sup> In the outpatient setting, exercise and pharmacological stress imaging add incremental prognostic value to clinical information,<sup>150,151</sup> and these tests should be considered in the CPU.

### Influence of Medications

An important consideration in patients with CAD is their presentation while taking antianginal medications. Both  $\beta$ -blockers and nondihydropyridine calcium channel blockers reduce exertional heart rate and blood pressure and may thereby limit the utility of ETT by decreasing myocardial oxygen demand. Evaluation of this problem in 176 patients who were admitted to a CPU while receiving chronic  $\beta$ -blocker and/or calcium channel blocker therapy revealed that in patients taking either of these drugs, the rate of nondiagnostic ETT was twice that in the group not taking them<sup>152</sup>; however, the majority of patients taking these drugs (61%) had a diagnostic ETT, which confirms the utility of exercise testing in these patients. Furthermore, adequate functional capacity ( $\geq 5$  METs) with no exercise-induced abnormalities in patients taking these drugs is consistent with low clinical risk. Thus, use of these medications should not preclude ETT in the evaluation of patients in a CPU. In cases in which it is anticipated that exercise testing will not be valid because of low resting heart rate, vasodilator stress MPI should be considered.

### Women

Baseline ECG alterations, labile ST-segment changes, breast artifact, lower exercise capacity, and false-positive test results pose additional challenges in women<sup>153</sup>; however, if the baseline ECG is normal and exercise capacity by history is adequate, the test should be ETT.<sup>88</sup> Furthermore, the Duke treadmill score provides accurate diagnostic and prognostic estimates in women and should be considered, especially to help identify false-positive ETTs.<sup>154</sup> Imaging techniques in the outpatient setting have also been established as safe and accurate in women. Stress

MPI in women was associated with a negative predictive value of 99% for MI,<sup>155</sup> and similar results were shown with negative stress echocardiography.<sup>156</sup>

### Cocaine and Methamphetamine

The incidence of MI in patients with chest pain after cocaine use has been reported as 0.7% to 6.0%.<sup>157,158</sup> The utility of an ADP in this group was investigated prospectively to determine the safety of a 6- to 12-hour period of observation that included serial ECGs and cardiac injury markers in 302 patients without initial evidence of MI who either tested positive for or acknowledged recent cocaine use.<sup>159</sup> During the ADP, there were no deaths, and 4 patients had nonfatal MIs. Half of the group underwent ETT before discharge, and only 4 results (3%) were positive (2 true-positives). There were no differences in outcomes in those with or without ETT before discharge. Long-term follow-up revealed a 1-year cardiac event rate of <1%.<sup>160</sup> Others have applied this approach to both cocaine and methamphetamine use. A retrospective review of 2871 low- to intermediate-risk patients in a CPU identified 401 (14%) who tested positive for methamphetamine or cocaine use.<sup>161</sup> There was no difference in the prevalence of cardiac chest pain in those with (17%) and without (13%) stimulant use, and management was accomplished safely. Recent recommendations indicate that management of patients with cocaine-associated chest pain by an ADP is safe and cost-effective.<sup>162</sup> ETT is optional, and its consideration should be based on the likelihood of underlying CAD. It is also reasonable to also apply these recommendations to patients with methamphetamine-related chest pain.

### Young Patients

In young patients with low CAD risk and no illicit drug use, the probability of ACS is minimal.<sup>163</sup> The utility of ETT in these patients has been a concern because of its low positive predictive value. Although data in CPU patients <40 years old are limited, a normal ETT in this group has a very high negative predictive value.<sup>77</sup> Furthermore, although a majority of the positive results are false, this problem is mitigated by the limited number of positive tests. In this regard, it has been shown recently that ETT in 220 CPU patients <40 years old resulted in only 6 positive tests, none of which were confirmed as true positives.<sup>164</sup> ETT in this very-low-risk population should include consideration of cost versus the low likelihood of detecting ACS; however, several reports indicate that a very-high-risk profile in young patients, such as those with metabolic syndrome<sup>165</sup> and multiple risk factors,<sup>24</sup> conveys an increased likelihood of ACS.

### Follow-Up of Patients With Negative CPU Evaluations

These patients usually have a noncardiac cause of their symptoms and often require further evaluation.<sup>5</sup> Identification of the origin and management of symptoms can diminish diagnostic uncertainty, prevent unnecessary returns to the ED, and improve quality of life.

Common causes of noncardiac chest pain are multiple (Table 1) in patients with negative CPU evaluations. In up to

40% of these patients, panic attack<sup>166</sup> or somatoform disorders may be the causative factors.<sup>19</sup> These episodes frequently have been unrecognized by physicians during the acute attack and on follow-up. Other patients with nonischemic chest pain may sense physiological stimuli as discomfort or pain in the chest.<sup>167</sup> To assuage persistent patient concerns even after an extensive negative noninvasive evaluation, coronary angiography to exclude CAD and alleviate concern may be considered in some patients, which suggests a potential role for CTCA.

### Recidivism in CPU Patients

Repeat visits to the CPU in patients with negative evaluations are frequent and have included 21% to 26% of patients.<sup>72,82</sup> They require not only attention to possible psychological issues but also careful reexamination for previously undetected cardiac or other disease. Furthermore, in patients with recurrent CPU admissions, repeat ETT has limited value, and an imaging study with or without stress is more appropriate. Ultimately, as noted above, coronary angiography (invasive or CTCA) may be indicated.

There has been 1 prospective randomized trial that compared early ETT to early coronary angiography in 123 low-risk patients presenting with chest pain to determine whether a negative invasive approach reduced repeat ED visits.<sup>72</sup> Coronary angiography detected CAD more frequently than ETT (19% versus 7%, respectively). Although more patients in the former group proceeded to revascularization, there was no difference in cardiac events at 1-year follow-up; however, angiography lowered recidivism to the ED for chest pain compared with the noninvasive strategy (10% versus 30% of patients, respectively). Because of the low risk of these patients, the small but definite risk of complications from invasive evaluation, and the utility of noninvasive tests, coronary angiography cannot be considered a first step in the assessment of this group, but there may be a role for CTCA in selected patients.

A frequent concern pertaining to patients with repeated negative CPU visits is the interval over which negative testing remains valid. Although there are no studies of this question, commonly referred to as the "warranty period" of a normal test in CPU patients, data from outpatient studies may be relevant. In stable outpatients with and without a history CAD, it was found that a normal stress MPI was associated with an overall cardiac event rate of 1.1% (0.6% per year) during a nearly 2-year follow-up, but the event rate was 1.4% to 1.8% in the highest-risk subgroups.<sup>168</sup> Predictors of events included a history of CAD, increased age, and diabetes. A recent report of serial coronary angiography in electively evaluated outpatients revealed that luminal diameter in angiographically normal arteries decreased by <3% per year. Loss of luminal diameter in arteries with minor irregularities progressed at 6% per year. However, plaque rupture typically occurs at the site of non-flow-limiting lesions, so these estimates of progression of disease are not absolute indicators of risk for ACS.<sup>169</sup>

For patients admitted to a CPU, clinical features plus alteration in symptoms and the details of prior testing are important considerations in selection of further testing. Depending on these factors, it is reasonable to proceed to a more definitive test than performed previously to improve risk stratification.

## Disclosures

## Writing Group Disclosures

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\*Modest.

†Significant.



## Reviewer Disclosures

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# Correction

In the article by Amsterdam et al, “Testing of Low-Risk Patients Presenting to the Emergency Department With Chest Pain: A Scientific Statement From the American Heart Association,” which published ahead of print on July 26, 2010, and appears in the October 26, 2010, issue of the journal (*Circulation*. 2010;122;1756–1776), several corrections were needed.

1. On page 4, Table 1 has been replaced in its entirety. The original table appeared as:

**Table 1. Likelihood That Signs and Symptoms Indicate ACS Secondary to CAD**

Feature	High Likelihood (Any of the Following)	Intermediate Likelihood (Absence of High-Likelihood Features and Presence of Any of the Following)	Low Likelihood (Absence of High- or Intermediate-Likelihood Features but May Have Any of the Following)
History	<ul style="list-style-type: none"> <li>● Accelerating tempo of ischemic symptoms in preceding 48 h</li> </ul>	<ul style="list-style-type: none"> <li>● Prior MI, peripheral or cerebrovascular disease, or CABG; prior aspirin use</li> </ul>	
Character of pain	<ul style="list-style-type: none"> <li>● Prolonged ongoing (&gt;20 min) rest pain</li> </ul>	<ul style="list-style-type: none"> <li>● Prolonged (&gt;20 min) rest angina, now resolved, with moderate or high likelihood of CAD</li> <li>● Rest angina (&lt;20 min) or relieved with rest or sublingual NTG</li> </ul>	<ul style="list-style-type: none"> <li>● New-onset or progressive Canadian Cardiovascular System Class III or IV angina the past 2 weeks without prolonged (&gt;20 min) rest pain but with moderate or high likelihood of CAD</li> </ul>
Clinical findings	<ul style="list-style-type: none"> <li>● Pulmonary edema, most likely due to ischemia</li> <li>● New or worsening mitral regurgitation murmur</li> <li>● S<sub>3</sub> or new/worsening rales</li> <li>● Hypotension, bradycardia, tachycardia</li> <li>● Age &gt;75 y</li> </ul>	<ul style="list-style-type: none"> <li>● Age &gt;70 y</li> </ul>	
ECG	<ul style="list-style-type: none"> <li>● Angina at rest with transient ST-segment changes &gt;0.05 mV</li> <li>● Bundle-branch block, new or presumed new</li> <li>● Sustained ventricular tachycardia</li> </ul>	<ul style="list-style-type: none"> <li>● T-wave inversions &gt;0.2 mV</li> <li>● Pathological Q waves</li> </ul>	<ul style="list-style-type: none"> <li>● Normal or unchanged ECG during an episode of chest discomfort</li> </ul>
Cardiac markers	<ul style="list-style-type: none"> <li>● Elevated troponin</li> </ul>	<ul style="list-style-type: none"> <li>● Normal troponin</li> </ul>	<ul style="list-style-type: none"> <li>● Normal troponin</li> </ul>

CABG indicates coronary artery bypass graft surgery; NTG, nitroglycerin.

Adapted from Braunwald et al,<sup>10</sup> with permission from Lippincott Williams & Wilkins. Copyright 2000, American Heart Association.

The updated table appears in the current version of the online article.

2. On page 4, column 1, paragraph 2, line 5 reads “(PE) should be considered (Table 1).” It has been updated to read “(PE) should be considered (Table 2).”
3. On page 12, column 1, before the heading “Computed Tomography,” the heading “Coronary Artery Imaging,” the subheading “Coronary Calcium Score,” and a new paragraph were added. The heading “Computed Tomography Coronary Angiography” was changed to a subheading. The text before the “Computed Tomography Coronary Angiography” subheading now reads:

## “Coronary Artery Imaging

### Coronary Calcium Score

Based on its close association with atherosclerosis, coronary artery calcification is considered a marker of CAD. It can be detected and quantified by either electron beam computed tomography or multidetector computed tomography. The coronary artery calcium (CAC) score is a quantitative index of the extent of calcification, has been used as an estimate of coronary plaque burden and confers independent risk. Population studies have demonstrated that a high CAC score is associated with increased risk for coronary events and, conversely, zero CAC indicates very low risk.<sup>129a</sup> In patients presenting to the ED with undifferentiated chest pain, a zero CAC score has been associated with a negative predictive value approaching 100% for early adverse events in studies of 100 to >1000 patients<sup>129b–129f</sup>; this prognostic value was maintained on follow-up of >4 years.<sup>129c</sup> Although the sensitivity of the CAC score for cardiac events is high, its positive predictive value is unsatisfactory and often entails additional evaluation. Further, not all coronary plaques contain calcium. Calcification does not identify obstructive CAD, and increasing CAC is associated with advancing age and male sex.<sup>129a</sup> The emergence of CTCA has now redirected the focus of imaging in ED patients from risk stratification with CAC to direct visualization of coronary artery narrowing and plaque identification.

### Computed Tomography Coronary Angiography”

4. On page 12, column 1, the last paragraph, the 11th line, new text has been added so that it now reads: Coronary Calcium Score “...value of 100% for ACS after 6 months of follow-up.<sup>134</sup> A report of nearly 600 ED patients (TIMI risk score 0 to 2) likewise demonstrated a negative predictive value of 100% for adverse events within 30 days. However, the low prevalence of disease in this study limits its generalizability as only 7 patients in the cohort were found to have CAD; no patients had death or MI.<sup>134a</sup> Other smaller studies of CTCA...”
5. On page 12, column 2, the heading “Magnetic Resonance Imaging” has been changed to a subheading.
6. On page 20, in the References, references 129a through 129f and 134a were added.

These corrections have been made to the current online version of the article, which is available at <http://circ.ahajournals.org/cgi/reprint/CIR.0b013e3181ec61df>.

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