



## Diagnosis of acute cardiac ischemia

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Acute myocardial infarction (AMI) is the leading cause of death in the United States; as many as 1.1 million patients per year have myocardial infarctions [1], about half of these patients present to emergency departments (EDs). In addition, nearly twice as many patients present to EDs with unstable angina pectoris (UAP). Only 25% of patients who present to the ED with symptoms that suggest acute cardiac ischemia (ACI) will have a confirmed diagnosis of the same [2]. The missed diagnosis rate for AMI and UAP in this setting is about 2% each [3]. Physicians have the task of identifying, treating, and hospitalizing (in the appropriate unit) those patients with true ACI to avoid filling hospital telemetry, step-down units, and coronary care units (CCUs) with the large majority of patients who do not have ACI.

For many years, the diagnosis of ACI was more prognostic than therapeutic. Over the past three decades, physicians' diagnostic and triage decisions for patients with suspected cardiac ischemia have reflected two tendencies. First, as the number of acute interventions for treating dysrhythmias and preventing or limiting the size of AMI has grown, clinicians have tended to admit all patients with even a low suspicion of acute ischemia. Clinicians therefore have generally admitted nearly all (92%–98%) patients presenting with AMI [4–9], and nearly 90% of those presenting with ACI (ie, including those with AMI and those with UAP) [4,7,10]. The conscious strategy of maintaining a high diagnostic sensitivity (ie, that any error be toward overdiagnosis) has the intended effect: the diagnosis is generally missed in 2% of patients with AMI who seek attention in an ED [3]. High diagnostic sensitivity has been achieved at the cost of admitting many patients who do not have ACI (low diagnostic specificity). Only 18% to 42% (typically about 30%) of the 1.5 million patients admitted

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annually to CCUs [11] actually experience AMI [4,12–16], and only 50% to 60% have ACI [4,7,10,12].

Investigating the causes, progression, and treatment of ACI continues to be a national research priority, and this research continues to produce substantial progress in prevention, diagnosis, and treatment of ACI, and advances in understanding its molecular and cellular aspects. Over the past decade, there has been a virtual revolution in physicians' understanding of both the pathophysiology and the management of coronary artery disease (CAD) [17]. The conversion of a stable atherosclerotic lesion into a ruptured plaque with thrombosis has provided a unifying hypothesis for the etiology of acute coronary syndromes. From this thesis, physicians' understanding of ACI has evolved. Thus, UAP (ie, rest angina, new-onset angina, and increasing angina) and AMI are now well appreciated as parts of a "continuum" of myocardial ischemia. The overarching diagnosis of ACI has provided a framework for understanding the pathogenesis, clinical features, treatment, and outcome of patients across the spectrum of myocardial ischemia. For ED triage, the diagnosis of ACI better identifies patients for CCU or telemetry/step-down unit admission than does the diagnosis of AMI alone. This is partly because of the difficulty in differentiating unstable angina from infarction, and partly by intent, because it helps to reverse ischemia and prevent frank infarction. For patients with ACI and prolonged chest pain, but without infarction, the medium- and long-term mortality may be as poor or worse than for those who actually have AMI [3,18]. In clinical medicine, much research has been focused on the early diagnosis and treatment of ACI. This research has shown that early diagnosis and treatment of UAP is beneficial and may prevent AMI.

For clinical reasons, to promote the optimal use of a limited resource and to reduce unnecessary expenditure, research has focused on improving physicians' diagnostic and triage accuracy. There remains a need, however, for improved methods of diagnosis that can reduce unnecessary hospitalization for patients incorrectly presumed to have acute ischemia, without increasing the number of patients with acute ischemia who are sent home inappropriately [19]. To this end, and as mandated by Congress, in 1991, the National Heart, Lung, and Blood Institute of the National Institutes of Health instituted the National Heart Attack Alert Program (NHAAP) to focus on issues related to the rapid recognition and response to patients with symptoms and signs of ACI in emergency settings and published reports in 1997 and 2001 on technologies for identifying ACI in such settings [20,21].

This article discusses the state of the art in the diagnosis of ACI in the emergency setting by reviewing the roles of clinical features, standard electrocardiogram (ECG) analysis, and technological adjuncts available to supplement clinical judgement when evaluating patients with suspected ACI, one of emergency medicine's high-risk presentations. Some methodologic pitfalls inherent in this type of research are considered first.

## **Methodologic issues**

Consideration of the specific methods used in studies of patients with ACI is vital when critically reviewing studies of the diagnosis and triage of ED patients with suspected ACI. The key methodologic issues for applicability of study results are as follows:

- Representative patient sample seen in actual practice
- Prevalence of ischemic heart disease in study population
- Broad patient inclusion criteria, not just chest pain but anginal equivalents
- Study setting includes a range of settings
- Diagnostic endpoint includes unstable angina and acute infarction
- Completeness of follow-up
- Follow-up data appropriate and significant
- Validation of findings in generalized clinical trials

Central to any study is whether the patient sample studied is representative of ED patients seen in actual practice. Also, the positive predictive value (ie, the proportion of patients who actually have ACI among all those with a positive test or attribute) of a symptom, sign, or test result depends on the prevalence of ischemic heart disease in the study population [22]. Thus, the proportion of patients with false-positive results will be higher (and positive predictive value lower) in a population with a low prevalence of ischemia (all ED patients) compared with a population with a high prevalence (CCU patients). Even studies carried out in EDs may not be comparable when ACI prevalence is significantly different. Inclusion criteria can limit studies of ED patients if, for example, only patients with chest pain are studied [23–25], compared with the use of broad entry criteria including multiple symptoms that could be anginal equivalents, such as any chest discomfort, epigastric pain, arm pain, shortness of breath, dizziness, or palpitations [26]. Study setting (eg, urban versus rural, or teaching versus community hospital) can also affect the applicability of any findings to various practice settings.

Aside from the study sample, other methodologic issues warrant attention, including the appropriateness of the measured diagnostic endpoint. Some past ED studies have focused on identifying or predicting only AMI, but identifying UAP is also important for monitoring and early therapy, especially because approximately 9% of patients admitted with new-onset or UAP progress to infarction [27,28]. Completeness of follow-up also must be considered. Studies with substantial numbers of patients lost to follow-up may have ascertainment bias, especially when the participation rate among eligible patients is not high. Also important is the type of follow-up data collection: for example, the occurrence of AMI will be underestimated if follow-up evaluation does not include biomarker determination results.

Finally, validation of the findings of clinical studies is critical, especially for prediction rules and diagnostic aids; findings may be center or data

dependent. The ideal validation study is a prospective trial of a finding's or prediction rule's effects on patient care in diverse settings [29].

## **Clinical presentation**

### *Chest discomfort*

Chest pain or chest discomfort is one of the most common and complex symptoms for which patients seek emergency medical care. Published reports suggest that up to 7% of visits to the ED involve complaints relating to chest discomfort [30]. The complaint of chest discomfort encompasses a wide variety of conditions, which range from insignificant to high risk in terms of threat to the patient's life and include, but are not limited to, acute cardiac ischemia (AMI and UAP), thromboembolic disease (pulmonary embolism), aortic dissection, pneumothorax, pneumonia, myocarditis, and pericarditis. Chest discomfort may be perceived as pain or as sensations such as tightness, pressure, or indigestion, or as discomfort most noticeable for its radiation to an adjacent area of the body. Elderly patients or patients with diabetes may have altered ability to specifically localize discomfort. Individuals and cultural groups vary in their expression of pain and ability to communicate with health professionals, so that presentation may range from merely bothersome to cataclysmic for conditions that seem nearly equivalent when objective criteria are matched. The level of discomfort does not necessarily correlate with the severity of illness, making identification of potentially life-threatening conditions very difficult in certain patients. Because of the serious nature of many conditions presenting with chest discomfort and the potential for significant reduction in morbidity and mortality with early diagnosis and treatment, clinical policies have been developed to guide clinicians with their initial evaluation of chest discomfort, emphasizing prompt triage, assessment, and initiation of therapy [31]. These clinical policies are not reviewed here other than those that apply to ACI.

It is sometimes difficult to distinguish cardiac from noncardiac chest discomfort, even though chest pain is the hallmark of ACI. Physicians should take the time to elicit the exact character of the sensation (ie, without prompting the patient, if possible) and any pattern of radiation (if present). Typically, the chest discomfort of acute ischemia has a deep visceral character, preventing the patient from localizing the discomfort to a specific region of the chest. It is often described as a pressure-like heavy weight on the chest, a tightness, a constriction about the throat, and/or an aching sensation, not affected by respiration, position, or movement, that comes on gradually, reaches its maximum intensity over a period of 2 to 3 minutes, and lasts for minutes or longer rather than seconds. Pope et al's [2] study of 10,689 ED patients with suspected ACI found that the 76% of patients presenting with the complaint of chest pain or discomfort (including arm,

jaw, or equivalent discomfort) had a 29% incidence of ACI at final diagnosis (10% AMI, 19% UAP). In 69% of patients, chest pain or discomfort was the chief complaint, and this group had a 31% incidence of ACI (10% AMI, 21% UAP). In 21% of patients, chest pain or discomfort was the only complaint, and this group had a 32% incidence of ACI (9% AMI, 23% UAP). Furthermore, the same study showed that chest pain or discomfort, as chief complaint or presenting symptom, was more frequently associated with a final diagnosis of ACI (88% ACI versus 62% non-ACI; 92% ACI versus 71% non-ACI, respectively;  $P = 0.001$ ). Sharp, stabbing, or positional pain is less likely to represent ischemia [32], but does not exclude it: Lee et al [33] found that among ED patients with sharp or stabbing pain, 22% had acute ischemia (5% AMI, 17% UAP). Among those with partially pleuritic pain, 13% had acute ischemia (6% AMI, 7% UAP), and among the group with fully pleuritic pain, none were shown to have acute ischemia. Notably, 7% of the patients whose pain was fully reproduced by palpation nonetheless had acute ischemia (5% AMI, 2% UAP), and 24% of patients with pain partially reproduced with palpation had ischemia (6% AMI, 18% UAP).

Combinations of variables improved discrimination in these patients [23]. In patients with sharp or stabbing pain that was also pleuritic, positional, or reproducible by palpation, 3% had UAP and none had AMI. Furthermore, if these same patients had no history of ischemic heart disease, none had acute ischemia. The “partially” and “fully” groups were subjective and small in number.

The exact location of chest pain is not significantly different in patients with or without AMI [34], but chest pain that radiates to the arms or neck does increase the likelihood of AMI [35–37]. Sawe [34] reported on patients admitted with AMI; 71% had pain radiation to arms and/or necks. Pain radiated in 39% of patients admitted without AMI. Consistent with the classic description, 33% of patients who proved to have infarction had radiation to both arms, 29% to the left arm only, and 2% to the right arm only.

Some investigators believe that a significant number of patients with cardiac ischemia can present with abdominal pain as their chief complaint [23,25]. Pope et al's [2] series of ED patients found that 14% of study patients had this complaint; this group had a 15% incidence of ACI at final diagnosis (6% AMI, 9% UAP), but less than 1% of patients complained of abdominal pain as their chief or only complaint and these patients had a 4% incidence of ACI (2% AMI, 2% UAP). In the same study, abdominal pain as a chief complaint or presenting symptom was associated with a higher incidence of a non-ACI final diagnosis (0.6% non-ACI versus 0.1% ACI, 16% non-ACI versus 9% ACI, respectively;  $P = 0.001$ – $0.002$ ). Esophageal reflux and motility disorders are common masqueraders of ACI. In a study of all patients discharged from a CCU with undetermined causes of chest pain, over half had esophageal dysfunction [38]. When these patients' presenting complaints were compared with those of patients without ACI,

those with esophageal disorders were more likely to complain of a lump in their throat, acid taste, overfullness after eating, a hacking cough, and chest pain that caused awaking at night. They were less likely to report effort-related chest pain, a history of nitroglycerin use, or reliable chest pain relief with its use.

### *Anginal pain equivalents*

Dyspnea, present in approximately one third of patients with infarction in some series [23,36,39], is the most important anginal pain equivalent. In their multicenter ED trial, Pope et al [2] found that 16% of patients with suspected ACI presented with a chief complaint of shortness of breath and had an 11% incidence of ACI at final diagnosis (6% AMI, 5% UAP); in 8%, this was the only complaint, with a 10% incidence of ACI (5% AMI, 5% UAP). A final diagnosis of ACI was not more frequent in patients with a presenting symptom of shortness of breath (56% ACI versus 56% non-ACI;  $P = 0.5$ ). As a chief complaint, shortness of breath was more commonly associated with a final diagnosis of non-ACI (18% non-ACI versus 7% ACI;  $P = 0.001$ ), possibly reflecting a high prevalence of patients with lung disease in the study population. Because 4% to 14% of AMI patients [23,25,26] and 5% of UAP patients present only with sudden difficulty breathing [2], ACI should be considered as a cause of unexplained shortness of breath.

Both diaphoresis and vomiting, when associated with chest pain, increase the likelihood of infarction [16,29,36]. Diaphoresis occurs in 20% to 50% of patients with AMI [35,40]. One study showed that the presence of nausea without vomiting did not discriminate, but vomiting was significantly more frequent in patients who “ruled in” [36]. Pope et al [2] found nausea in 28% of patients with suspected ACI: patients with nausea as a presenting symptom had a 26% incidence of ACI at final diagnosis (10% AMI, 16% UAP); patients with nausea or vomiting as their chief complaint (2%) had a 15% incidence of ACI (11% AMI, 4% UAP); and less than 1% of patients had nausea or vomiting as their only symptom. The same study found vomiting present in 10% of patients: patients with vomiting as a presenting symptom had a 23% incidence of ACI (13% AMI, 10% UAP); patients with vomiting as the chief or only complaint had an incidence of ACI of less than 1%. Furthermore, the authors showed that a chief complaint of nausea or vomiting was more frequently associated with a final diagnosis of non-ACI (0.5% non-ACI versus 0.3% ACI;  $P = 0.15$ ), yet a presenting complaint of nausea was more commonly associated with a final diagnosis of ACI (30% ACI versus 27% non-ACI;  $P = 0.004$ ); a presenting complaint of vomiting did not show this association (10% ACI versus 10% non-ACI;  $P = 0.7$ ). In a CCU study, 43% of patients with Q-wave infarction but only 4% of patients with non-Q-wave infarctions or prolonged angina had vomiting [41].

So-called “soft” clinical features, such as fatigue, weakness, malaise, dizziness, and “clouding of the mind,” are surprisingly frequent, occurring in 11% to 40% of patients with AMI [29,34,36,39]. Prodromal symptoms (those occurring in the preceding days or weeks) are also frequent: 40% of patients report unusual fatigue or weakness, 20% to 39% report dyspnea, 14% to 20% report “emotional changes,” 20% have a change in appearance (eg, “looked pale”), and 8% to 10% experience dizziness [23,39]. Pope et al’s [2] study found that 28% of patients with suspected ACI presented to the ED with dizziness and had a 16% incidence of ACI (5% AMI, 11% UAP); in 5% of study patients, dizziness was their primary complaint, with a 4% incidence of ACI (2% AMI, 2% UAP); and in 1% of patients it was their only symptom (2% AMI, 0% UAP). In the same study, dizziness or fainting as a chief complaint were more commonly associated with a final diagnosis of non-ACI (7% non-ACI versus 1% ACI,  $P = 0.001$ ). Similarly, dizziness or fainting as presenting symptoms were more frequently associated with final diagnoses of non-ACI (31% non-ACI versus 19% ACI, and 8% non-ACI versus 2% ACI, respectively;  $P = 0.001$ ). ECG evaluation is helpful in low-prevalence patients with these vague complaints.

### *Atypical presentations*

Few studies address what proportion of ED patients with ACI present with atypical symptoms, a group for whom the diagnostic/triage decision is often most problematic. Among hospitalized patients with AMI, 13% to 26% had no chest pain or had chief complaints other than chest pain (eg, dyspnea, extreme fatigue, abdominal discomfort, nausea, or syncope) [23,25]. Pope et al’s [2] ED study of 10,689 patients presenting with a wide range of clinical symptoms found that 31% of patients with suspected ACI presented without chest pain, with a 26% incidence of ACI at final diagnosis (18% AMI, 8% UAP), and had chief complaints other than chest pain (eg, shortness of breath, abdominal pain, nausea, vomiting, dizziness, or fainting).

Among ED patients, no single atypical symptom is of overwhelming diagnostic importance, although combinations of symptoms can identify high-risk patients who should be admitted regardless of ECG findings. Pope et al [2] ranked atypical presenting symptoms in decreasing order of association with ACI at final diagnosis as follows: nausea (26%), shortness of breath (24%), vomiting (23%), dizziness (16%), abdominal pain (15%), and fainting (65%).

Data from community-based epidemiologic studies [24,42–44] suggest that 25% to 30% of all Q-wave infarctions go clinically unrecognized: half were truly silent, and half were associated with atypical symptoms in retrospect [24,43]. Because Q waves often resolve (in the Framingham Study, 10% of patients discharged after anterior infarction and 25% of those discharged after inferior infarction lost their Q waves within 2 years), the true incidence was underestimated [45].

The rate of erroneous discharge from the ED of patients with AMI may be a marker for atypical cases, but these studies were limited by inclusion criteria, small numbers, and lack of complete follow-up. Rates of 2% [5,46] and as high as 8% [8] have been reported. In the Pope et al [3] ED series, patients with suspected ACI reported rates of erroneous discharge of 2% (2.1% AMI, 2.3% UAP). Significantly, the early mortality rate (30-day) for these “missed” AMIs may be as high as 10% to 33% [3,5,8].

Finally, in their study of a large ED study of patients with UAP, Pope et al [3] found that 2.3% were not hospitalized. Over three fourths of the patients were evaluated by an attending physician, and more than one fourth by a consulting cardiologist. Although there was disagreement over the interpretation of 16% of the ECGs on subsequent review by an experienced cardiologist, this was not believed to be clinically significant in any of the cases. Given that most of the patients who were not hospitalized had Canadian Cardiovascular Society class 3 angina with new symptoms or symptoms that changed within 3 days before presentation, inaccuracies in the clinician’s assessment of the dynamic nature of anginal symptoms may have contributed to the failure to hospitalize patients with UAP.

### **Medical history**

In addition to the presenting clinical features, the presence of a CAD risk factor traditionally has been considered diagnostically helpful in the ED setting. Pope et al’s [2] ED series showed an association between patients with a history of diabetes mellitus (31% ACI versus 18% non-ACI;  $P = 0.001$ ), myocardial infarction (45% ACI versus 20% non-ACI;  $P = 0.001$ ), or angina pectoris (63% ACI versus 29% non-ACI;  $P = 0.001$ ) and a final diagnosis of ACI; however, these findings require careful interpretation. From the Framingham Study, it is well known that the risk for developing ischemic heart disease is increased over decades by the following factors: male gender, advancing age, a smoking habit, hypertension, hypercholesterolemia, glucose intolerance, ECG abnormalities, a type A personality, a sedentary lifestyle, and a family history of early CAD [23,47,48]. Clinicians customarily assess these factors when providing preventive care, because they predict the incidence of future coronary disease. Coronary risk factors were established to provide an estimate of risk over years, however. Thus, the Framingham Study showed that hypertension increases the risk of ischemic heart disease twofold over 4 years [24], but only a very small portion of this risk applies to the few hours of the ED patient’s acute illness. A patient’s report of coronary risk factors is also subject to biases and inaccuracies. This history is presumably less reliable than the methods used to assign risk in longitudinal studies.

Indeed, in a multicenter study, Jayes et al [49] found that most of the classic coronary risk factors have little predictive value for ACI when used

in the ED setting. Except for diabetes and a positive family history in men (none in women), no coronary risk factor significantly increased the likelihood that a patient had acute ischemia. Diabetes and family history each confer only about a twofold relative risk for acute ischemia in men, whereas chest discomfort, ST-segment abnormalities, and T-wave abnormalities confer relative risks of approximately twelve-, nine-, and fivefold, respectively. Because these results run counter to the prevailing clinical wisdom, it is possible that physicians who give risk-factor history great weight may inappropriately diagnose/triage ED patients, an issue that deserves further attention and investigation.

Finally, a past history of medication use for coronary disease increases the likelihood that the current chest pain is ACI. In the Boston City Hospital and the multicenter predictive instrument trials, a history of nitroglycerin use was found to be one of the most powerful predictors of ACI [7]. Nonetheless, nitrates can cause dramatic relief of chest pain from esophageal spasms [50] and thus the details of the history must be noted carefully.

### **Physical examination**

The physical examination is generally not very helpful in diagnosing ACI when compared with the value of historical data and ECG findings, except when it points to an alternate process. Clinicians must not be lulled into a sense of security by chest pain that is partially or fully reproduced by palpation, however, because 11% of these patients may have AMI or UAP [26]. Pope et al [2] found the pulse rate to be lower in patients with a final diagnosis of ACI versus those with a final diagnosis of non-ACI ( $P = 0.02$ ), but this difference was not considered clinically significant.

Pulse rate observation in isolation appeared to be generally not helpful in ACI identification. First, the patient's pulse rate could be slowed by the presence of  $\beta$ -blockers as part of a prior treatment regime or by coincident vagal stimulation from ACI (ie, reflex bradycardia and vasodepressor effects associated with inferoposterior wall ACI) or diagnostic/therapeutic procedures in the ED (eg, phlebotomy, intravenous access). Second, the patient's pulse may be increased by adrenergic excess from the anxiety of a visit to the ED, in addition to the adrenergic excess (eg, tachycardia and increased peripheral vascular resistance) associated with possible ongoing ACI.

In Pope et al's [2] series of ED patients, median first and highest systolic blood pressure (SBP) was higher in patients with a final diagnosis of ACI, which suggested that the adrenergic excess associated with ACI might be greater than that associated with non-ACI diagnoses. To use this hypothesis as a predictive factor, however, clinicians must have some idea of their patient's baseline blood pressure, which is not the case in most ED evaluations. Thus, the usefulness of this observation may be limited.

In the same series [2], in addition to the effect of adrenergic release during acute ischemia, the higher initial and highest pulse pressures found in patients with a final diagnosis of ACI may also reflect the lower compliance of the ischemic left ventricle. In addition, excess pulse blood pressure (the extent to which a patient's pulse pressure exceeded 40 mm Hg for patients with an SBP of >120 mm Hg) places patients who are candidates for thrombolytic therapy at increased risk of thrombolysis-related intracranial hemorrhage [29].

Pope et al [2] discovered that median first, median highest, and median lowest SBPs of patients with AMI, who subsequently were classified as Killip class 4 (cardiogenic shock), were above the threshold of this classification (SBP  $\leq$  90 mm Hg) for these three blood pressure observations. This suggests that the adrenergic excess associated with ACI may be greater than that associated with non-ACI diagnoses. More important, although the number of such patients in this analysis was relatively small, it did suggest that patients with ACI can present with apparently "normal" blood pressures and can go on to develop cardiogenic shock.

Observations of abnormal vital signs and certain combinations of these are critically important in clinical outcome prediction. The reported probability of infarction decreases with a normal respiratory rate [36] and increases with diaphoresis [16], but other signs mainly help identify high-risk patients with infarction [51]. In the predictive instrument for AMI mortality proposed by Selker et al [52], blood pressure, pulse, and their interaction figured prominently in three of the six clinical variables used to develop the prediction instrument.

Pope et al [2] reported that rales (of any degree), but not S3 gallops, were more frequently seen in patients with a final diagnosis of ACI. This finding is not surprising, as several clinical syndromes of pump failure can complicate ACI. The authors' failure to find association between an S3 gallop rhythm and ACI at final diagnosis is surprising, but it may have to do with a failure to document this finding consistently in the medical record on the part of the ED physicians at study sites.

## **Electrocardiogram**

### *Standard 12-lead ECG*

A complete summary of evidence related to the diagnostic utility of the standard ECG was recently published [20,21], and this background is not repeated here. The NHAAP's Working Group on Evaluation of Technologies for Identifying ACI [21], however, found that most studies evaluated the accuracy of the technologies and only a few evaluated the clinical impact of routine use. Further, the group concluded that although the standard ECG is a safe, readily available, and inexpensive technology with a relatively high sensitivity for AMI, it is not highly sensitive or specific

for ACI. The ECG remains an integral part of the evaluation of patients with chest pain, however, and the Working Group recommended that it remain the standard of care for evaluating patients with chest pain in the ED.

The ECG provides essential information when the diagnosis is not obvious by symptoms alone [53], despite one study noting that the results of the ECG infrequently changed triage decision based on initial clinical impressions [54]. The generally dominant weights given to ECG variables in mathematical models for predicting ACI substantiate this impression [4,7,10,15,16]. Moreover, the initial ECG is increasingly important in intrahospital triage because of its value in predicting complications of AMI [55–57].

The fundamental limitations in the standard ECG are as follows:

- Single brief sample
- Lack of perfect detection
- Baseline patterns
- Interpretation
- Clinical context
- Imperfect sensitivity and specificity

First, the ECG is a single brief sample of the whole picture of the changing supply-and-demand characteristics of unstable ischemic syndromes. If a patient with UAP is temporarily pain-free when the ECG is obtained, the resulting tracing may poorly represent the patient's ischemic myocardium.

Second, 12-lead ECG is limited by its lack of perfect detection [58]. Small areas of ischemia or infarction may not be detected; conventional leads do not examine satisfactorily the right ventricle [59] or posterior basal or lateral walls well (eg, AMIs in the distribution of the circumflex artery) [60,61].

Third, some ECG baseline patterns make interpretation difficult or impossible, including prior Q waves, early repolarization variant, left ventricular hypertrophy, bundle branch block, and dysrhythmias [62]. Lee et al [5] demonstrated that when the current ECG shows ischemic findings, availability of a prior comparison ECG improved triage.

Fourth, ECG waveforms are frequently difficult to interpret, causing disagreement among readers, so-called "missed ischemia." In a study of AMI patients sent home, ECGs tended to show ischemia or infarction not known to be old, with 23% of the missed diagnoses from misread ECGs [8]. Jayes et al [49] compared ED physician readings of ECGs with formal interpretations by expert electrocardiographers and calculated sensitivities of 0.59 and 0.64 and specificities of 0.86 and 0.83 for ST-segment and T-wave abnormalities, respectively. Both McCarthy et al [18] and a review of litigation in missed AMI cases [63] emphasized this factor of incorrect ECG interpretation. In the largest study to date of ACI in the ED, Pope et al [3]

found that although the rate of missed diagnoses of ACI (2.1% AMI, 2.3% UAP) was low, there was a small but important incidence of failure by the ED clinician to detect ST-segment elevations of 1 to 2 mm in the ECGs of patients with myocardial infarction (11%). Correct ECG interpretation by ED physicians is now doubly important because of the need to use interventions such as thrombolytic agents and percutaneous coronary angioplasty appropriately in ACI.

Fifth, the implications of the ECG findings must be interpreted in their clinical context, a process done intuitively by clinicians and formally stated in Bayesian analysis. When symptoms alone strongly suggest ischemia, a normal or minimally abnormal ECG does not substantially decrease the probability of ischemia. Conversely, when the presentation is inconsistent with acute ischemia, an abnormal ECG, unless diagnostic abnormalities are present, only modestly increases the likelihood of ischemia. Bayes' rule states that the ECG has the greatest impact when symptoms are equivocal [64]. This is illustrated by Table 1, which shows the probability of acute ischemia for combinations of history and ECG findings among 2801 patients admitted to the ED [11,65]; these data formed the basis for the Acute Ischemic Heart Disease Predictive Instrument [7].

Finally, the ECG suffers from imperfect sensitivity and specificity for ACI. When interpreted according to liberal criteria for myocardial infarction (ie, ECGs that show any of the following as positive for AMI: nonspecific ST-segment or T-wave changes abnormal but not diagnostic of ischemia; ischemia, strain, or infarction, but changes known to be old; ischemia or strain not known to be old; and probable AMI), the ECG operates with relatively high (but not perfect) sensitivity (99%) for AMI, at the cost of low specificity (23%; positive predictive value, 21%; negative predictive value, 99%). Conversely, when interpreted according to stringent criteria for AMI (only ECGs that show probable AMI), sensitivity (61%) drops; specificity equals 95%; positive predictive value, 73%; negative predictive value, 92%.

Despite its usefulness, the ECG is insufficiently sensitive to diagnose ACI consistently. The ECG should not be relied on to make the diagnosis but rather should be included with history and physical examination characteristics to identify patients who appear to have a high risk for ACI (ie, a supplement to, rather than a substitute for, physician judgement). In "rule-out AMI" patients, a negative ECG carries an improved short-term prognosis [55,66–69]. Providing the interpreter with old tracings would intuitively seem to be of value because baseline abnormalities make current evaluation difficult, yet Rubenstein and Greenfield's [70] study of 236 patients presenting to EDs with the complaint of chest pain found that only a small proportion might have benefited from having a previous baseline ECG available (5% might have avoided unnecessary admission). Furthermore, there was no patient for whom a baseline ECG would have aided in avoiding an inappropriate discharge. ECG sampling should be periodic, not

Table 1  
The original ACI predictive instrument's probabilities of acute ischemia for ED patients

Question: chest pain or pressure or left arm pain?	ECG abnormalities, % <sup>a</sup>					
	ST0T0	ST-T0	ST0↑↓	ST↑↓T0	ST-↑↑↓	ST↑↓T↑↓
Answer: yes, chief complaint						
History						
No heart attack <i>and</i> no NTG use	19	35	42	54	62	70
<i>Either</i> heart attack <i>or</i> NTG use ( <i>not both</i> )	27	46	53	64	73	85
<i>Both</i> heart attack <i>and</i> NTG use	37	58	65	75	80	90
Answer: yes, but not chief complaint						
History						
No heart attack <i>and</i> no NTG use	10	21	26	36	45	64
<i>Either</i> heart attack <i>or</i> NTG use ( <i>not both</i> )	16	29	36	48	56	74
<i>Both</i> heart attack <i>and</i> NTG use	22	40	47	59	67	82
Answer: no						
History						
No heart attack <i>and</i> no NTG use	4	9	12	17	23	39
<i>Either</i> heart attack <i>or</i> NTG use ( <i>not both</i> )	6	14	17	25	32	51
<i>Both</i> heart attack <i>and</i> NTG use	10	20	25	35	43	62

Directions: To determine a given patient's probability of acute ischemia, start by answering the questions at the top of the chart about the presence of chest pain and whether it is the chief complaint. This will lead to one of the three large boxes of probability values. Under the History heading are questions regarding history of heart attack or NTG use. Choose the row that corresponds to the patient's report of none, one, or both of these historical features. Then, to find the specific probability value, move across the appropriate row to the column corresponding to the ECG ST-segment and T-wave changes for the given patient. For example, for a patient with a chief complaint of chest pain, no history of heart attack or nitroglycerine use, and 1 mm or ST-segment depression and T-wave inversion, the probability of true ACI would be 78%. Note: Specific definitions of clinical features (questions) for original ACI predictive instrument are modified for use in this chart.

<sup>a</sup> Must be in two leads, excluding aVR.

*Abbreviations:* ACI, acute cardiac ischemia; NTG, nitroglycerin; ST-, ST-segment "straightening", ST↑↓, ST segment elevated at least 1 mm or depressed at least 1 mm; T↑↓, T wave "hyperacute" (>50% of R wave) or inverted at least 1 mm; ST0/T0, above-specified changes absent.

From McCarthy BD, Wong JB, Selker HP. Detecting acute cardiac ischemia in the emergency department: a review of the literature. *J Gen Intern Med* 1990;5:365–73.

just static. The pitfalls of not ordering ECGs in younger, atypical patients and of misinterpretation should be anticipated. Finally, clinicians should not be reluctant to obtain a second opinion, by fax transmission if necessary, for difficult tracings.

*ST-segment and T-wave abnormalities*

ST-segment and T-wave abnormalities are the sine quo non of ECG diagnosis of ACI. Numerous studies have found that 65% to 85% of CCU patients with ST-segment elevation alone have had an infarction [58,68,71]. Other investigators found that if both Q waves and ST-segment elevation were present, 82% to 94% of patients actually sustained AMI [58]. ST-segment elevation can occur in the absence of ischemia, however (eg, “early repolarization” variant, pericarditis, left ventricular hypertrophy, and previous infarction, even in the absence of a ventricular aneurysm) [72]. Conversely, Pope et al [2] reported that a large percentage of patients with ACI (20% AMI, 37% UAP) can present with initial normal ECGs.

Pope et al’s [2] study of ED patients with suspected ACI found that ST-segment elevation of either 1 to 2 mm or more than 2 mm was more frequently associated with a final diagnosis of ACI (9% ACI versus 7% non-ACI, and 5% ACI versus 1% non-ACI, respectively;  $P = 0.001$ ). A full 30% of patients with ST-segment elevation of 1 mm or greater had a final diagnosis of AMI. In addition, in a study of missed diagnosis of ACI in the ED, Pope et al [3] found a small but important incidence of failure by the ED clinician to detect ST-segment elevations of 1 to 2 mm in the ECGs of patients with AMI (11%). This incidence represents an important and potentially preventable contribution to the failure to admit such patients.

ST-segment depression usually indicates subendocardial ischemia. If these abnormalities are new, persistent, and marked, the likelihood of AMI increases. Approximately 50% to 67% of patients admitted with new or presumed-new isolated ST-segment depression have infarctions [59,71]; even more patients have probable ischemia. Pope et al [3] found that all degrees of ST-segment depression (0.5, 1, 1–2, and 2+ mm) were more commonly associated with a final diagnosis of ACI (12% ACI versus 7% non-ACI, 8% ACI versus 3% non-ACI, and 2% ACI versus 0% non-ACI, respectively;  $P = 0.001$ ). Of patients with ST-segment depression of at least 0.5 mm or greater, 19% had a final diagnosis of AMI. ST-segment depression may occur in nonischemic settings as well, including patients who are hyperventilating, those taking digitalis, those with hypokalemia, and those with left ventricular strain (without voltage criteria) [72].

Inverted T waves may reflect acute ischemia. One study showed that isolated T-wave inversion occurred in 10% of CCU admissions, 22% of who had AMI [73]. T-wave changes may reflect prior myocardial damage or left ventricular strain [72]. Pope et al [2] found that certain T-wave patterns (inverted 1–5 mm, inverted 5+ mm, or elevated) were more frequently associated with a final diagnosis of ACI (32% ACI versus 17% non-ACI, 1% ACI versus 0% non-ACI, and 4% ACI versus 1% non-ACI, respectively;  $P = 0.001$ ). Flattened T waves did not have the same association with a final diagnosis of ACI (18% ACI versus 20% non-ACI;  $P = 0.001$ ).

Furthermore, 39% of patients with inverted T waves of at least 1 mm or greater had a final diagnosis of AMI.

### *Q waves*

Q waves are diagnostic of myocardial infarction, but what is the age of the Q wave? In the Multicenter Investigation of Limitation of Infarct Size (MILIS) study of admitted CCU patients, isolated new or presumed-new inferior or anterior Q waves were associated with acute infarction in 51% and 77% of patients, respectively [58]. Other findings of the MILIS study are important: 12% of healthy young men have inferior Q waves [72–74]; pathologic Q waves can be from a previously unrecognized infarction and can mask new same-territory ischemia; Q waves alone do not identify ACI and are rarely the sole manifestation of AMI (6% in the MILIS study); and, finally, infarction can occur in the absence of Q waves [75,76]. Pope et al [2] showed that Q waves were more commonly associated with a final diagnosis of ACI (25% ACI versus 11% non-ACI;  $P = 0.001$ ) and that 29% of patients with Q waves present on their ECGs had a final diagnosis of AMI.

### *Nondiagnostic ECG patterns*

Nondiagnostic ST-segment and T-wave abnormalities may be defined as follows: ST-segment elevation or depression in two contiguous leads of less than 1 mm (0.1 mV), no new T-wave inversion in two contiguous leads, absence of significant Q waves (> 1 mm deep and 0.3-second duration) in two contiguous leads, no second- or third-degree heart block, and absence of a new conduction abnormality (eg, bundle branch block). These are the most difficult abnormalities to interpret and can result in overdiagnosis (no comparison ECG available) and underdiagnosis (baseline abnormality obscuration of ischemia) [77]. Lee et al [33] found that patients who are admitted to the ED with chest pain and nondiagnostic ECG abnormalities had a low risk of AMI but a significant risk of ACI. Pope et al [3] found that 53% of ED patients with a missed diagnosis of AMI had normal or nondiagnostic ECGs, as did 62% of patients with a missed diagnosis of UAP.

### *Normal ECG*

Among ED patients with normal ECGs (ie, lacking Q waves, primary ST-segment and T-wave abnormalities, and criteria for nondiagnostic abnormalities), 1% [33] to 6% [77] have been found to have AMI. Among admitted patients with normal ECGs, 6% to 21% had AMI [12,73,76–78]. Of patients discharged home with a normal ECG, only 1% had acute infarction [77]. Patients with a normal ECG and a suggestive clinical presentation still have a significant risk of ACI, especially if the ECG was obtained when the patient was pain free. A truly normal ECG in a patient unlikely to have acute ischemia, however, provides strong evidence against ACI [33].

In Pope et al's [2] series, patients with normal ST-segment and T waves and no Q waves more commonly had a final diagnosis of non-AMI, yet 20% of these patients had AMI and 37% had UAP at final diagnosis.

### *Prehospital 12-lead ECG*

The NHAAP Working Group on Evaluation of Technologies for Identifying AMI [21] found that the diagnostic accuracy of prehospital ECG for AMI and AMI is similar to that of the standard 12-lead ECG, which is the standard of care in the management of patients suspected of having AMI (Tables 2 and 3). The accumulation of evidence is substantial in both the total sample size and quality, and the data have been gathered from patient populations with few exclusion criteria. The evidence shows that obtaining a prehospital ECG does not prolong time in the field or delay transport to the ED. In addition, prehospital ECG-guided thrombolytic therapy can be administered 45 minutes to 1 hour earlier than hospital-based thrombolytics. Prehospital thrombolysis has a modest but significant impact on early mortality (6% reduction in the risk of death). Short-term, beneficial effects of thrombolysis on left ventricular ejection fraction have not been reported in randomized trials. The long-term survival benefits of prehospital thrombolysis remain uncertain. Although prehospital ECG has promise, the Working Group [21] stated that its best use would be in areas with long emergency medical service transportation times and perhaps in conjunction with prehospital thrombolytic therapy. Its routine use was not recommended.

### *Continuous ECG/serial ECG*

The Working Group found that two studies evaluated the test performance of continuous/serial 12-lead ECG in the ED, but there was no clinical impact study (Tables 2 and 3) [21]. One study, by Gibler et al [79], included a large retrospective population of 1010 patients participating in a 9-hour protocol. The serial ECG consisted of a 20-second interval between readings. The second study included patients from a veterans' hospital in which two ECGs were taken 4 hours apart [80]. The prevalences of AMI in these studies were very different (4% and 40%, respectively), given the low-risk populations. The sensitivity for AMI was low (21% and 25%, respectively) and the specificity was high (92% and 99%, respectively). With the limitations and the varied sources of data, a conclusion about the utility of this technology cannot be drawn.

### *Nonstandard lead ECG*

The data on the diagnostic performance of nonstandard lead ECG from the four studies reported vary too much to draw any conclusion [21]. The

studies used 15, 18, 22, and 24 leads and were conducted with selected patients for admission (Tables 2 and 3). The prevalence is reflective of this selective population: it ranged between 22% and 65% for AMI. There are no clinical impact studies on nonstandard ECGs.

### *Exercise stress ECG*

The data on the diagnostic performance of exercise stress testing to detect ACI in the ED are limited to two studies [81,82] (Tables 2 and 3). The overall data include a small sample size of a low-risk population. Although the diagnostic performance is encouraging, it would be premature to draw conclusions regarding this technology until additional high-quality studies are conducted.

There are also limited data on the clinical impact of exercise testing for ACI. Two studies [83,84] had no cardiac events and included very small sample sizes, 28 and 35 patients, respectively. Even with the addition of a third study [81], these three investigations comprised a total of only 272 subjects and are of low methodologic quality; the clinical impact of this technology is therefore unclear.

## **Biochemical markers of myocardial necrosis**

### *Creatine kinase, single and serial measurements*

There is much evidence for using creatine kinase (CK) as a single test administered at presentation to patients in the ED (Tables 2 and 3) [21]. The evidence suggests that the sensitivity of a single CK reading for AMI is low (36%) and specificity is modest (88%). Limited evidence suggests that the sensitivity of the test depends on the duration of the patient's symptoms; sensitivity increases with longer symptom duration. Test performance across studies did not appear to vary by type of hospital, inclusion criteria, AMI prevalence, or test threshold.

Only two studies have evaluated serial CK testing [85,86]. Both used broad inclusion criteria but enrolled populations in which the prevalence of AMI was moderate to high. Test sensitivity was high (95%–99%) in serial tests performed over approximately 15 hours after presentation to the ED (or from the onset of symptoms), but was only modest (69%) in the one study that drew serial samples for 4 hours. Test specificity was modest in both studies (68% and 84%, respectively).

As a single test, CK is insensitive and only modestly specific for AMI. Serial testing appears to have higher sensitivity, although the specificity remains modest. The evidence is insufficient to evaluate serial CK measurements over a short time, however. Because high-serum CK levels represent infarcted myocardium, CK has not been evaluated for diagnosing ACI in the ED. There are no clinical impact studies for CK.

Table 2  
Summary of test performance studies of diagnostic technologies for ACI in the emergency department

Technology	Condition studied	No. studies (no. subjects)	Population category of studies <sup>a</sup>	Studies prevalence range, %	Sensitivity <sup>b</sup> (95% CI), %	Specificity <sup>b</sup> (95% CI), %	Diagnostic odds ratio <sup>b</sup> (95% CI)	Overall quality of evidence <sup>c</sup>
Prehospital ECG	ACI	5 (4311)	I/II	46-92	76 (54-89)	88 (67-96)	23 (6.3-85)	B
	AMI	10 (4481)	I/II	14-51	68 (59-76)	97 (89-92)	104 (48-224)	B
Continuous/serial ECG	ACI	2 (1271)	III	4-40	21-25 <sup>c</sup>	92-99 <sup>c</sup>	3.8-45 <sup>c</sup>	C
	AMI	1 (261)	III	11	39 <sup>c</sup>	88 <sup>c</sup>	4.9 <sup>c</sup>	B
Nonstandard lead ECG	ACI	1 (52)	IV	48	96 <sup>c</sup>	41 <sup>c</sup>	17 <sup>c</sup>	B
	AMI	4 (897)	IV	22-65	59-83 <sup>c</sup>	76-93 <sup>c</sup>	10-19 <sup>c</sup>	B
Exercise stress ECG	ACI	2 (312)	III	6-10	70-100 <sup>c</sup>	82-93 <sup>c</sup>	11-320 <sup>d</sup>	B
	AMI	12 (3195)	I/II/III/IV	7-41	37 (31-44)	87 (80-91)	3.9 (2.7-5.7)	B/C
CK (serial)	AMI	2 (786)	I	26-43	69-99 <sup>c</sup>	68-84 <sup>c</sup>	12-220 <sup>c</sup>	C
	ACI	1 (1042)	III	20	23 <sup>c</sup>	96 <sup>c</sup>	7.2 <sup>c</sup>	C
CK-MB (presentation)	AMI	19 (6425)	I/II/III/IV	6-42	42 (36-48)	97 (95-98)	25 (18-36)	B
	ACI	1 (1042)	III	20	31 <sup>c</sup>	95 <sup>c</sup>	8.5 <sup>c</sup>	C
Myoglobin (presentation)	AMI	14 (11,625)	I/II/III/IV	1-43	79 (71-86)	96 (95-97)	140 (65-310)	B
	AMI	18 (4172)	I/II/IV	6-62	49 (43-55)	91 (87-94)	11 (8.0-15)	B/C
Myoglobin (serial)	AMI	10 (1277)	I/II/IV	11-41	89 (80-94)	87 (80-92)	84 (44-160)	B
	AMI	4 (1149)	II/III/IV	6-39	39 (10-78)	93 (88-97)	11 (3.4-34)	B
Troponin I (presentation)	AMI	2 (1393)	III/IV	6-9	90-100 <sup>c</sup>	83-96 <sup>c</sup>	230-460 <sup>c</sup>	A/B
	AMI	6 (1348)	II/III/IV	6-78	39 (26-53)	93 (90-96)	9.5 (5.7-16)	C
Troponin T (serial)	AMI	3 (904)	I/III/IV	5-78	93 (85-97)	85 (76-91)	83 (33-210)	B
	AMI	3 (2283)	II/IV	9-28	83 (51-96)	82 (68-90)	17 (7.6-40)	B/C
CK-MB and myoglobin combination (presentation)	AMI	2 (291)	IV	11-20	100 <sup>d</sup>	75-91 <sup>d</sup>	4.3-14 <sup>d</sup>	A/B
	AMI	1 (263)	II	33	35 <sup>d</sup>	79 <sup>d</sup>	2.0 <sup>d</sup>	B
P-selectin	AMI	1 (263)	II	8.4	45 <sup>d</sup>	76 <sup>d</sup>	2.6 <sup>d</sup>	B
	AMI	2 (228)	III	3-30	70 (43-88)	87 (72-94)	20 (9-48)	C
Rest echocardiography	AMI	3 (397)	I/III	3-30	93 (81-91)	66 (43-83)	20 (7-62)	B
	AMI	3 (397)	I/III	3-30	93 (81-91)	66 (43-83)	20 (7-62)	B

Stress Technocardiography	AMI	1 (139)	III	4	90 <sup>d</sup>	89 <sup>d</sup>	68 <sup>d</sup>	C
Sestamibi (rest)	ACI	3 (702)	III	9–17	81 (74–87)	73 (56–85)	18 (11–29)	B
	AMI	3 (702)		2–12	92 (78–98)	67 (52–79)	26 (6–113)	
ACI-TIPI	ACI	4 (5496)	I	17–34	86–95 <sup>d,e</sup>	78–92 <sup>d,e</sup>	61–69 <sup>d,e</sup>	A
Goldman chest pain protocol	AMI	3 (5359)	I	12–20 (ACI 27–30)	88–91 <sup>d</sup>	70–74 <sup>d</sup>	20–23 <sup>d</sup>	A
Algorithm/protocols <sup>f</sup>	—	—	—	—	—	—	—	—
Computer-based decision aids	AMI	6 (3606)	I/II/III	7–42	52–98 <sup>d</sup>	58–96 <sup>d</sup>	4.4–90.4	A

<sup>a</sup> See text for definitions of population categories.

<sup>b</sup> Results from meta-analysis of several studies using random-effects calculations unless otherwise indicated.

<sup>c</sup> For purposes of calculation of diagnostic odds ratio, 0.5 was added to cells with 0 subjects.

<sup>d</sup> Point estimate from single study or a range of reported values, meta-analysis not performed.

<sup>e</sup> ACI-TIPI is not designed to provide sensitivity and specificity. Reported values here represent overall physician diagnostic performance.

<sup>f</sup> No data from prospective studies.

<sup>g</sup> A, highest quality (least bias); B, high quality (some bias); C, lower quality (significant bias).

**Abbreviations:** ACI, acute cardiac ischemia; ACI-TIPI, acute cardiac ischemia time-insensitive predictive instrument; AMI, acute myocardial infarction; CI, confidence interval; CK, creatine kinase; CK-MB, creatine kinase subunit.

Table 3  
Summary of clinical impact studies of diagnostic technologies for ACI in the emergency department

Technology	Condition studied	No. studies (no. subjects)	Population category <sup>a</sup>	Prevalence, %	Clinical outcomes studied	Clinical impact <sup>b</sup>	Quality of evidence <sup>c</sup>
Prehospital ECG	ACI AMI	~10 (~8000) <sup>d</sup>	I/II	46–100 15–51	Time to thrombolysis, ejection fraction, mortality	++ —	A —
Continuous or serial ECG	—	No study	—	—	—	Not known	—
Nonstandard lead ECG	—	No study	—	—	—	Not known	—
Exercise stress ECG	ACI AMI	3 (272) —	III —	0–6 0–1	Feasibility and safety	Not known Not known	C —
CK (single/serial)	—	No study	—	—	—	Not known	—
CK-MB (single)	—	No study	—	—	—	Not known	—
CK-MB (serial)	ACI	1 (1042)	III	20	Additional admissions or discharges of ACI and non-ACI patients	++	C
Myoglobin (single/serial)	AMI	—	—	6.4	—	—	—
Troponin I or T	—	No study	—	—	—	Not known	—
Other biomarkers	—	No study	—	—	—	Not known	—
Rest echocardiography	—	No study	—	—	—	Not known	—
Stress echocardiography	—	No study	—	—	—	Not known	—
Sestamibi imaging	—	No study	—	—	—	Not known	—
ACI-TIPI	ACI	4 (14,394)	I	17–59	CCU admission rate, inappropriate discharge	+++	A
Goldman chest pain protocol	AMI	1 (1921)	II	6.6	Hospitalization rate, length of stay, estimated costs	+	A

Algorithm/protocols	ACI	2 (602)	III	6–9	Length of stay, hospital charges, 30-day and 150-day mortality	Not known	B
Computer-based decision aids	ACI	1 (977)	III	48	30-day mortality	Not known	A
	AMI			30			

<sup>a</sup> See text for definitions of population categories.

<sup>b</sup> Clinical impact scores range from low (+) to high (+++).

<sup>c</sup> Quality of evidence scores range from low (C) to high (A).

<sup>d</sup> Different outcomes analyzed involved different number of studies and patients.

*Abbreviations:* ACI, acute cardiac ischemia; ACI-TIPI, acute cardiac ischemia time-insensitive predictive instrument; AMI, acute myocardial infarction; CCU, coronary care unit; CK, creatine kinase; CK-MB, creatine kinase subunit.

### *Creatine kinase subunit (CK-MB), single and serial measurements*

As with CK, the total sample sizes and number of studies on a single CK-MB measurement at presentation to the ED are large (Tables 2 and 3) [21]. The evidence suggests that the sensitivity of single CK-MB for AMI is low (47%), although specificity is high (96%). Studies reported a broad range of sensitivity for diagnosing AMI. Again, as for CK, limited evidence suggests that the sensitivity of CK-MB depends on the duration of the patient's symptoms; sensitivity increases with longer symptom duration. In general, studies reported a narrow range (92%–99%) of test specificity. Test performance across studies did not appear to vary by type of hospital, inclusion criteria, AMI prevalence, or test threshold.

The total sample sizes and number of studies of serial tests for CK-MB in the ED setting are large. Overall, serial testing has a modest sensitivity (87%) and high specificity (96%) for AMI. Test sensitivity is strongly related to the timing of serial testing, however. All studies that performed serial testing for at least 4 hours after presentation to the ED (or until at least 8 hours after symptom onset) found test sensitivity to be greater than 90%. Conversely, all studies that performed serial testing to at most 3 hours found test sensitivity to be less than 90%. The pooled sensitivity for serial testing to at least 4 hours is 96%; pooled sensitivity for serial testing until 3 hours is only 81%. In general, test specificity was in a narrow range across studies and was greater than 90%.

CK-MB as a single test is only modestly sensitive and specific for AMI; however, serial testing performed over 4 to 9 hours is highly sensitive and highly specific. Because serum CK-MB levels represent infarcted myocardium, CK-MB has not been tested for diagnosing ACI in the ED. There are no clinical impact studies for CK-MB.

### *Troponin T and troponin I*

The evidence for the diagnostic performance of troponin T is substantial in diagnosing AMI but rather limited in diagnosing ACI [21] (Tables 2 and 3). Data for troponin I are limited, but its performance is similar to that of troponin T. The sensitivity of presentation (initial) troponin T for diagnosing AMI in the ED is poor, but improves substantially if serial measurements are obtained for up to 6 hours after ED presentation. Most likely, the sensitivity is better for patients who have had symptoms for longer periods of time. The specificity of troponin T for AMI is approximately 90%.

### *Myoglobin*

The diagnostic performance of myoglobin has been well studied for diagnosing AMI but not for diagnosing ACI (see Tables 2 and 3) [21]. The sensitivity of myoglobin for diagnosing AMI in the ED is poor when a single initial measurement is obtained, but sensitivity improves greatly if a second

measurement is obtained 2 to 4 hours after the first one. The sensitivity for patients only recently symptomatic is poor, however, and a second measurement in 2 to 4 hours may still not be sufficiently sensitive to be useful. Specificity is very good, but not excellent, depending on the extent to which other reasons for elevated myoglobin are excluded a priori. A doubling of myoglobin levels as soon as 1 to 2 hours after the initial measurement is almost perfectly sensitive for AMI.

The evidence suggests that a normal myoglobin value 2 hours after presentation may be used safely to rule out AMI. A doubling of myoglobin as early as 1 to 2 hours after the baseline measurement establishes a diagnosis of AMI. A small-scale study suggested that normal myoglobin and CK-MB values 2 hours after presentation completely rule out AMI [87]. The incremental value of CK-MB compared with myoglobin alone cannot be evaluated given the small sample sizes. In a much larger study, Kontos et al [88] found no advantage for myoglobin over baseline and 3-hour CK-MB values.

#### *Other biomarkers*

Studies on P-selectin and malondialdehyde-modified low-density lipoprotein, C-reactive protein, B-type natriuretic peptide, and pregnancy-associated plasma protein A (PAPP-A) are just beginning to appear. There is only one ED study of P-selectin that reported low sensitivity and low specificity for AMI. In the future, tests for neurohormonal activation (B-type natriuretic peptide) and inflammation (C-reactive protein, PAPP-A) may augment physicians' ability to identify patients with ACI who are at risk for adverse events. The use of these markers could potentially augment physicians' ability to reserve the most expensive and aggressive therapies for patients who have the highest risk.

## **Cardiac imaging**

### *Echocardiography*

The total sample sizes and the number of studies evaluating echocardiography for the diagnosis of ACI are small (Tables 2 and 3) [21]. Limited evidence suggests that resting echocardiography has high sensitivity (93%) although only modest specificity (66%) for AMI. The availability of previous echocardiograms for comparison may improve the specificity [89]. Even if this improved specificity were verified with additional studies, the need for previous echocardiography would limit its applicability in the general ED setting. In addition, the data pertain mostly to patients with normal or nondiagnostic ECGs. The data for stress dobutamine echocardiography are even more limited; one study suggested that it may be the next diagnostic step for patients with a negative resting echocardiogram, normal

ECG, and normal enzyme levels. There is no clinical impact study for this technology.

#### *Technetium-99m sestamibi myocardial perfusion imaging*

Data on the diagnostic accuracy of resting technetium-99m sestamibi imaging in the ED is limited, and there are still no data on its clinical impact (see Tables 2 and 3). The test has been used in selected patient populations that generally have a low to moderate risk of ACI, no history of myocardial infarction, and a presenting ECG nondiagnostic for ACI. Thus, the generalizability of the current evidence is limited, and the test should be reserved for these circumscribed populations. In these patients, the test has excellent sensitivity for AMI, and very good, but not perfect, sensitivity for coronary disease in general. Specificity is modest for AMI, and although it may be a little better for ACI, it is still far from excellent.

### **Computer-based decision aids**

#### *Acute cardiac ischemia time-insensitive predictive instrument*

The acute cardiac ischemia time-insensitive predictive instrument (ACI-TIPI) [26] computes a 0% to 100% probability that a given patient has ACI (ie, either acute AMI or UAP) (Tables 2 and 3). It is based on a logistic regression equation that uses presenting symptoms and ECG variables and is applicable to any ED patient presenting with any symptom that suggests ACI. Originally in hand-held calculator form, the instrument is now incorporated into conventional ECGs so that the patient's ACI-TIPI probability is printed with the standard ECG header text. In large-scale controlled interventional trials in a wide range of hospitals, its use by ED physicians has been shown to reduce unnecessary admissions of patients without ACI and patients with stable angina, while not reducing appropriate hospitalization for patients with ACI. It has also been shown to help the triage speed and accuracy of less-trained and less-supervised residents. The wider dissemination and use of ACI-TIPI could result in significant positive impact on the triage of ACI patients in the ED.

#### *Goldman chest pain protocol*

The Goldman chest pain protocol is based on a computer-derived model using recursive partitioning analysis to predict myocardial infarction in patients with chest pain (Tables 2 and 3) [4]. It has good sensitivity (about 90%) for AMI but it was not developed to detect UAP. In a clinical impact study of “low-intensity, noninvasive intervention” performed at a teaching hospital ED, no differences in hospitalization rate, length of stay, or estimated costs were demonstrated between the experimental group, which used the protocol, and the control group [15].

### *Other computer-based decision aids*

Several investigators have reported various computer-based decision aids to diagnose AMI (see Tables 2 and 3). The artificial neural network by Baxt et al [90] was found to have high sensitivity and high specificity for AMI in a prospective study, but the clinical impact has not been demonstrated.

## **Identifying acute cardiac ischemia in patient subgroups**

### *Gender*

Knowing whether gender influences the likelihood that a given ED patient has ACI, and whether any specific presenting clinical features are differentially associated with ACI in women compared with men, can aid clinicians in the accurate diagnosis of ACI. The incidence of AMI in the general population has been shown to be higher in men than women [91–94], but until recently it has not been clear whether this gender difference holds among symptomatic patients who come to the ED.

Several studies have looked at gender differences in the presentation of patients with AMI [95–99]. In a retrospective analysis of patients with confirmed AMI, women had higher rates of atypical presentations, such as abdominal pain, paroxysmal dyspnea, or congestive heart failure (CHF) [43,92,100–102]. In a group of ED patients with typical presentations, such as chest pain, the prevalence of AMI was lower in women [33,103]. In another study of ED patients with chest pain, however, when adjustments were made for other presenting clinical features (specifically ECG), the gender difference was no longer significant [95]. From these results, it is difficult to assess whether the gender-specific differences in AMI prevalence among symptomatic ED patients were the result of gender-specific biology or limitations in a particular study's patient selection.

Zucker et al's [104] study of 10,525 patients aged 30 years or older, who presented to the ED with chest pain or other symptoms suggestive of ACI, found that AMI was almost twice as common in men as women (10% versus 6%). Among women with ST-segment elevation or signs of CHF, however, AMI likelihood was similar to that in men with these characteristics. This finding suggests that the presence of CHF should be given substantial weight in assessing the likelihood of AMI in women presenting to the ED with symptoms suggestive of ACI. Pope et al [3] found that among the patients with AMI who present to the ED, women were more likely than men to have been discharged. In addition, among all patients with ACI, women younger than 55 years were at highest risk for not being hospitalized.

### *Race*

Blacks have high levels of risk factors for CAD, but how this finding influences diagnosis in patients presenting to the ED with symptoms

suggesting ACI is not well understood [105,106]. Studies that have included only patients with chest pain and not other symptoms that suggest ACI have found no significant differences in presentation, natural history, or final diagnosis of AMI between black and white patients [107]. Evaluating chest pain and establishing the diagnosis of coronary heart disease in blacks is often difficult given the presence of excess hypertension and left ventricular hypertrophy and the increased occurrence of out-of-hospital cardiac arrest in blacks [108–111]. Furthermore, the paradoxical finding of severe chest pain without significant angiographic CAD complicates diagnosis and treatment of blacks with symptoms that suggest ACI [106]. In another analysis of the ACI-TIPI trial data, Maynard et al [112] found that black patients were 8 to 10 years younger and that a higher percentage were women than was the case among white patients, which may partially explain why physicians might be less inclined to suspect the presence of ACI in black patients. Finally, Pope et al [3] found that among patients with ACI, the adjusted risk of being sent home was more than two times as high among nonwhite as among white patients; among those with AMI, the risk was more than four times as high among nonwhite as among white patients. In this study, 5.8% of the black patients with AMI were not hospitalized, compared with 1.2% of the white patients with infarction.

### Clinical outcomes

Each year in the United States, over 6 million patients with chest pain or other symptoms suggesting ACI (ie, Imminent Myocardial Infarction Rotterdam (IMIR) Study inclusion symptoms) [25] present to EDs [9]. These patients can have various clinical outcomes ranging from discharge home to hospital admission after thrombolytic therapy or angioplasty. Table 4 shows the final diagnosis for the ACI-TIPI trial [2] control subjects by ED triage disposition. These data were employed to develop a flowchart (Fig. 1) to represent the diagnoses and triage dispositions of ED patients presenting with chest pain or other symptoms that suggest ACI.

Table 4  
Final diagnosis (%) for ACI-TIPI trial control subject by ED triage disposition ( $N = 5951$ )

Triage disposition	Control		
	AMI ( $n = 496$ )	UAP ( $n = 898$ )	Non-ACI ( $n = 4557$ )
Home	3	8	41
Ward	1	2	6
Telemetry	31	61	43
CCU	66	29	10

*Abbreviations:* ACI, acute cardiac ischemia; ACI-TIPI, acute cardiac ischemia-time-sensitive predictive instrument; AMI, acute myocardial infarction; CCU, coronary care unit; ED, emergency department; UAP, unstable angina pectoris.

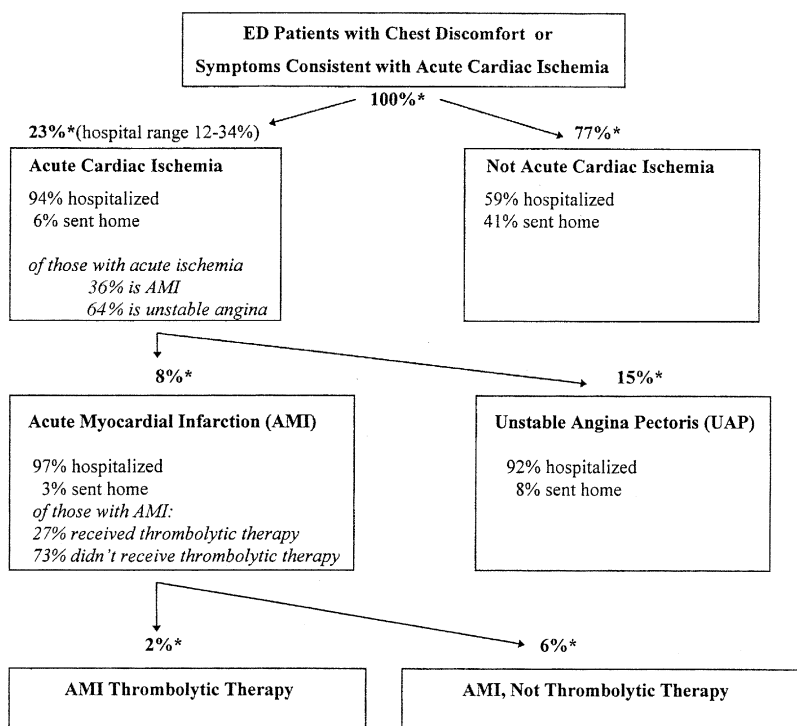


Fig. 1. Flowchart illustrating diagnoses and triage dispositions of patients presenting to the emergency department (ED) with chest pain or other symptoms suggesting acute cardiac ischemia (ACI). \*Percentage of ED patients in the control group with chest pain or symptoms consistent with ACI.

The flowchart demonstrates that of all ED patients with suspected ACI, only 23% of patients (hospital range, 12%–34%) had ACI at final diagnosis, of which 94% were hospitalized and 6% were sent home. Conversely, 77% did not have ACI at final diagnosis; of these patients, 59% were hospitalized and 41% were sent home. In the ACI group of patients, 36% of patients had AMI and 64% had UAP. This represented 8% and 15%, respectively, of the overall group. In the AMI group, 97% were hospitalized and 3% were sent home; in the UAP group, 92% were hospitalized and 8% were sent home. Of those with AMI, 27% received thrombolytic therapy, representing 2% of the overall group.

The current authors' work with Pozen et al [7] from 1979 to 1981, at the same hospitals as the present report, demonstrated a 7% ED discharge rate for patients with a final diagnosis of ACI; McCarthy et al [18] found that 2% of these subjects had AMI at final diagnosis. In the mid-1980s, Lee et al [5] reported a 4% AMI discharge rate. Our study [2] found a 6% discharge rate for ACI and a 3% AMI discharge rate, demonstrating stability of these

figures over the decade. The proportions of AMI and UAP in the present study (36% AMI, 64% UAP) were essentially identical to those from the authors' work with Pozen et al [7] in 1979 to 1984 (35% AMI, 65% UAP). Finally, in an analysis of the ACI-TIPI trial data for failure to make the diagnosis of ACI, the current authors found that the missed diagnosis rate for ACI was 2.2% (2.1% for AMI, 2.3% for UAP) [3].

## **Summary**

A better understanding of coronary syndromes allow physicians to appreciate UAP and AMI as part of a continuum of ACI. ACI is a life-threatening condition whose identification can have major economic and therapeutic importance as far as threatening dysrhythmias and preventing or limiting myocardial infarction size. The identification of ACI continues to challenge the skill of even experienced clinicians, yet physicians continue (appropriately) to admit the overwhelming majority of patients with ACI; in the process, they admit many patients without acute ischemia [2], overestimating the likelihood of ischemia in low-risk patients because of magnified concern for this diagnosis for prognostic and therapeutic reasons.

Studies of admitting practices from a decade ago have yielded useful clinical information but have shown that neither clinical symptoms nor the ECG could reliably distinguish most patients with ACI from those with other conditions. Most studies have evaluated the accuracy of various technologies for diagnosing ACI, yet only a few have evaluated the clinical impact of routine use. The prehospital 12-lead ECG has moderate sensitivity and specificity for the diagnosis of ACI. It has demonstrated a reduction of the mean time to thrombolysis by 33 minutes and short-term overall mortality in randomized trials. In the general ED setting, only the ACI-TIPI has demonstrated, in a large-scale multicenter clinical trial, a reduction in unnecessary hospitalizations without decreasing the rate of appropriate admission for patients with ACI. The Goldman chest pain protocol has good sensitivity for AMI but was not shown to result in any differences in hospitalization rate, length of stay, or estimated costs in the single clinical impact study performed. The protocol's applicability to patients with UAP has not been evaluated. Single measurement of biomarkers at presentation to the ED has poor sensitivity for AMI, although most biomarkers have high specificity. Serial measurements can greatly increase the sensitivity for AMI while maintaining their excellent specificity. Biomarkers cannot identify most patients with UAP. Finally, diagnostic technologies to evaluate ACI in selected populations, such as echocardiography, sestamibi perfusion imaging, and stress ECG, may have very good to excellent sensitivity; however, they have not been sufficiently studied.

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