IDENTIFICATION OF CHEST PAIN PATIENTS APPROPRIATE FOR AN EMERGENCY DEPARTMENT OBSERVATION UNIT

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Chest pain is the second commonest chief complaint presenting to US emergency departments (ED), accounting for 5.2% of visits in 1996 equal to 5 million people. From 10% to 31% have acute coronary ischemia (ACI) as the cause of their visit. Acute coronary ischemia (ACI) encompasses the syndromes of acute myocardial infarction (AMI) and unstable angina (UA). The challenge is to identify the patient with acute coronary ischemia out of all of those presenting with chest pain and to recognize atypical presentations (e.g., dyspnea, weakness, syncope, palpitations, and confusion). The rate of discharge of AMI patients ranges from 1.9% to 3.8% with up to 25% suffering death or complications. Patients inadvertently released with an AMI have a mortality rate of nearly twice those correctly diagnosed and admitted. Failure to diagnose and treat AMI continues to account for the largest amount of dollars paid for claims against emergency physicians.

Once the diagnosis of ACI is suspected, the second goal is appropriate triage. This is based on immediate need for intervention, risk of death or serious complications, cost-effectiveness, and resource utilization. The cost of care of patients unnecessarily admitted to the CCU has been estimated at nearly $3 billion annually whereas the total estimated cost of liberal admissions to rule out AMI in low-risk patients has been estimated at up to $13 billion annually. The setting (e.g., CCU, intermediate care unit, monitored hospital ward, ED Chest Pain Observation Unit [CPOU], or the outpatient setting) and pace of work up for ACI are based on the risk of short-term, life-threatening cardiac...
events (e.g., myocardial infarction, malignant arrhythmia, recurrent ischemia, need for revascularization, pump failure, and death). The focus on this article is on the clinical factors and technologies currently available in the ED to stratify the probability of ACI for these patients. It discusses the impact of specific features of the history, physical examination, and ECG on decision making as well as existing algorithms and prediction models. Last, it will address the roles of echocardiography and perfusion imaging currently being defined.

Risk Stratification

Six features are crucial in the ideal risk stratification model for myocardial ischemia. It should be composed of diagnostic and prognostic indicators for coronary ischemia available in the ED and possess the features listed here:

1. A high sensitivity to reduce risk and delay in diagnosis
2. Adequate specificity to avoid the panic, expense, and morbidity inherent in false-positive results
3. Minimal intrusiveness and modest expense
4. A clinical impact on triage, outcome, and cost
5. The ability to identify the disease at a stage at which intervention can lead to patient benefit
6. Applicability to the population at large (e.g., women, minorities, and the elderly)

Unfortunately, no single or combination of prognostic indicators meets all these criteria. The needs for higher sensitivity, specificity, and cost-containment have been the driving forces behind the inception of CPOU. Risk stratification models estimate probabilities of ACI, AMI, short-term cardiac complications, and death in judging the most appropriate patient disposition.

PATHOPHYSIOLOGY OF ACUTE CORONARY SYNDROMES

The extent of coronary artery disease is an independent predictor of cardiac ischemia. The extent of coronary disease increases both the likelihood of a cardiac event as well as the morbidity and mortality. Coronary events are more common and more likely to be fatal with significant disease of multiple arteries because of decreased available collateral flow and a higher degree of left ventricular (LV) impairment. Endothelial integrity and function, plaque stability, and the relationship between thrombosis and thrombolysis determine the clinical course of coronary ischemia in addition to the number and severity of lesions. Coronary artery stenoses of 50% to 70% are considered clinically significant, but visual interpretation of the angiogram has been shown to be imprecise and poorly reproducible particularly for stenoses in the 40% to 80% range. Intracorony plaque is generally slow growing, averaging roughly 3% reduction in coronary artery lumen diameter per year. Although no coronary angiographic findings are pathognomonic for unstable angina, it is often associated with more complex lesions, more coronary thrombus, and more significant progression on angiography than those seen with patients with stable angina. In addition to the characteristic of coronary artery plaque, the degree of stenosis, recently has been recognized as a determinant of the progression of coronary artery disease and ischemic events. A critical point is that prospective angiographic studies have
shown acute plaque rupture with subsequent vessel occlusion to be more common at sites of only relatively moderate stenosis. In studies with sequential angiography, nearly two thirds of lesions responsible for unstable angina or infarction were less than 50% occlusive during the days to weeks before the event. Fibrous plaque is gradually occlusive, whereas the lesions responsible for most acute ischemic events consist of a soft lipid core and a thin fibrous cap that is prone to rupture. Angiography alone is ineffective at assessing the plaque composition and vulnerability. Angiographic studies using intracoronary ultrasonography have been able to demonstrate anatomic details of plaque, including the size of lipid core and the thickness of the fibrous plaque. Currently, however, this technology is experimental and not widely used for this purpose. A history of extracardiac vascular disease (e.g., stroke, peripheral vascular occlusive disease, mesenteric ischemia) raises the likelihood of coronary artery disease to an intermediate level in patients with symptoms suggesting ACI.

**RISK STRATIFICATION: THE STILL-DOMINANT ROLE OF THE HISTORY AND PHYSICAL EXAMINATION**

**Pain Characteristics**

World Health Organization (WHO) criteria for the diagnosis of AMI remain the current standard. It states that the diagnosis of myocardial infarction requires that the patient meets at least two of three criteria: Chest pain consistent with AMI, diagnostic ECG changes consistent with AMI, or a rise and fall in serum markers (specifically CK-MB). Cardiac enzyme markers continue to play a confirmatory role and have little usefulness in identifying the patient who has not yet sustained myocardial injury. The poor sensitivity of a single CK-MB for AMI and even lower sensitivity for USA make them much less useful in the initial ED diagnostic evaluation and risk stratification. The sensitivity of plasma CK-MB for diagnosis of AMI within the first 4 hours of onset of chest pain is reported to be as low as 25%.

The diagnosis of coronary ischemia presently is based on elements found in the history. The nature, duration, and tempo of the discomfort have the most diagnostic and prognostic implications. In the Multicenter Chest Pain Study, chest discomfort that is similar to a prior MI or worse than the patient's usual angina remains the strongest independent risk factors for MI and the likelihood of acute coronary ischemia. Time since onset of pain < 4 hours, pain described as "pressure," radiation of pain to the left arm, shoulder, neck, or jaw all identify patients at higher risk for AMI and ischemia. It is more useful for the clinician to characterize the symptoms in terms of a "discomfort" as many patients will deny pain even in the setting of significant chest symptoms. The physician's overall assessment of the discomfort as definite angina, probable angina, probably not angina, or not angina likewise has a major impact on risk stratification. The patient is at a lower risk if the chest pain is pleuritic or "stabbing," localized with one finger, reproduced by movement or palpation of the chest wall or arms, primarily or solely located in the middle or lower abdominal region, or radiating into the lower extremities. Unfortunately, the presence of these historical elements does not completely exclude acute coronary ischemia as the source of symptoms. Figure 1 illustrates the percentage of patients with ischemic and nonischemic chest pain presenting with "typical" AMI pain. In the Multicenter Chest Pain Study, of patients subsequently found to have AMI up to 22% presented with sharp or stabbing pain, 13% of patients
with some pleuritic quality to the pain, and 7% of patients with reproduction of their pain by palpation. The term *sharp* always needs further investigation. It can refer either to the character of the pain, the intensity of the pain, or both, depending on the patient's age and background. There are numerous reasons for patients to misperceive or misrepresent the nature and quality of chest discomfort. These include social, cultural, level of education and intelligence, presence of other comorbid process, fear of cardiac diagnosis, coupled with cardiac neurophysiology, which can sometimes cause chest discomfort to be perceived atypically. Prolonged episodes of severe chest pain indicate the patient is at higher risk for ACI. Episodes lasting longer than 20 or 30 minutes have been shown to carry a worse prognosis, but discomfort lasting constantly for days or for just a few seconds is significantly less likely to represent ischemic pain. The tempo of the discomfort is one of the most valuable predictors of risk for MI and other short-term cardiac events. Active or recurrent pain has been shown to be a high-risk predictor of life-threatening complications.

The single best historical predictor of ACI is a known history of AMI or known coronary artery disease. The risk of a coronary event is five times more likely in persons with established coronary artery disease. Prior MI based on history or significant ECG Q waves, sudden death, or other known history of coronary artery disease are major independent risks for the presence of acute ischemia and short-term cardiac complications. A history of AMI within the last 14 days was found on multivariate analysis to be the strongest predictor of major cardiac events in a population of patients with unstable angina (e.g., death, AMI, ventricular fibrillation, cardiogenic shock, heart failure, ventricular tachycardia, or fibrillation). In a British population-based survey of 7735 men with nearly 15 year follow-up, the patients recall of a prior ischemic heart diagnosis yielded an odds ratio of 3.98 (95% CI = 3.36–4.71) for a subsequent major ischemic heart disease event. In the same study, prior chest pain symptoms remained predictive of future major ischemic events, even in the absence of a previous cardiac diagnosis. Assessment of LV function is the single strongest
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predictor of subsequent cardiac death in patients with coronary artery disease (CAD) owing to the lower cardiac reserve seen with impaired function. Details of prior testing that aid in the stratification process include prior assessments of LV function and coronary anatomy, and prior revascularization procedures.

TRADITIONAL FRAMINGHAM RISK FACTORS FOR CORONARY ARTERY DISEASE

Traditional risk factors from the Framingham study (e.g., age, male gender, smoking, HTN, DM, hypercholesterolemia, family history) have been shown to be predictive patients who will develop of coronary artery disease over a 14-year period in an outpatient setting. They were never developed or intended to identify which chest pain patient in the ED had acute cardiac ischemia. They have been shown to perform poorly in this setting.

No single specific risk factor has the power to predict AMI or ACI independently. Their benefit lies in their cumulative effect. The number of risk factors (specifically diabetes, smoking, hypercholesterolemia, and hypertension) is a useful historical feature in assessing the likelihood of CAD. In a study of chest pain patients presenting to the ED, Jayes et al found the traditional Framingham risk factors to be only weakly predictive of the likelihood of acute ischemia in men. In this study, diabetes (relative risk 2.4) and family history (relative risk 2.1) were the best predictors followed by smoking history. No risk factors were found to be significant predictors of acute ischemia in women owing to low sample size. Thus, the risk factor profile cannot be depended on in isolation to risk stratify or to predict the presence of ischemic coronary artery disease in the ED. The presence or absence of risk factors should not be used to decide whether an individual patient should be admitted or treated for ACI.

Age as a risk factor warrants further consideration. Both the likelihood and severity of CAD increase with age. More important than its value in predicting the presence of ACI, age is an independent prognosticator of outcome. Multiple studies have found age to be predictive of severe complications or mortality. Eighty percent of fatal MI's occur in patients over the age of 65 years, most of whom are over 75 years old. Advanced age is likely an independent risk marker for unfavorable outcome due to lowered cardiac and physiologic reserves and concurrent comorbidities. In addition, people over the age of 65 years are more likely to have atypical presentations with delayed or missed diagnoses.

The impact of recently identified factors such as elevated homocysteine levels remain to be determined for the ED chest pain population. Homocysteine is an amino acid derived from ingestion of meat and dairy products. It directly injures endothelial cells, enhances LDL cholesterol oxidation, promotes growth of smooth muscle cells, increases thrombogenicity, and inhibits thrombolysis. It appears to be a significant and probably independent risk factor for CAD. Between 10% and 25% of the population risk for CAD is attributable to elevated homocysteine elevation.

The history is presently the best tool to predict survival. The four most important factors related to survival from an acute ischemic event include the LV function, extent of obstructive CAD, age, and comorbid factors. Comorbidities such as renal failure, COPD, cerebrovascular disease, malignancy, and other systemic diseases decrease the patient's likelihood of survival if an ischemic cardiac event occurs. Table 1 outlines the risk of coronary artery disease based on historical features.
Table 1. LIKELIHOOD OF SIGNIFICANT CORONARY ARTERY DISEASE BASED ON HISTORICAL ELEMENTS IN PATIENTS WITH SYMPTOMS SUGGESTING UNSTABLE ANGINA

<table>
<thead>
<tr>
<th>High Likelihood</th>
<th>Intermediate Likelihood</th>
<th>Low Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>(e.g., 0.85-0.99)</td>
<td>(e.g., 0.15-0.84)</td>
<td>(e.g., 0.01-0.14)</td>
</tr>
</tbody>
</table>

Any of the Following:

- History of prior MI, sudden death, or other known history of CAD
- Definite angina: males ≥60 or females ≥70 years of age
- Transient hemodynamic changes during pain

Absence of High Likelihood Features and Any of the Following:

- Definite angina: males <60 or females <70 years of age
- Angina in patients with diabetes
- Chest pain probably not angina and two or three risk factors other than diabetes

Probable angina: males ≥Chest pain probably not angina

Extracardiac vascular disease

"Coronary artery disease risk factors include diabetes, smoking, hypertension, and elevated cholesterol.

Note: Estimation of the likelihood of significant coronary artery disease is a complex, multivariable problem that cannot be fully specified in a table. The table therefore is meant to illustrate major relationships rather than offer rigid guidelines.


THE VALUE OF PRIOR CARDIAC TESTING AND INTERVENTIONS

Many ED patients with chest pain have had prior interventions (e.g., CABG, angioplasty, stent, atherectomy) or testing (e.g., stress testing). The role of prior testing and interventions remains uncertain. The impact of these interventions on risk stratification is unclear. Although revascularization with CABG or PTCA has been effective in relieving the symptoms of angina, it has not been shown to decrease the risk of subsequent AMI. The presence of angiographically significant stenoses on catheterization is predictive of future cardiac events despite the fact that these high-grade lesions are less likely to be responsible. Rather, they serve as a marker for overall plaque burden and for less significant stenoses that usually accompany and outnumber the hemodynamically significant lesions. PTCA has a reported initial success rate of 90% and a 6-month restenosis rate of 31%. The use of intracoronary stents has led to improved outcomes, with corresponding values of 96% and 16%, respectively. The 6-month event-free survival rate is 79% for angioplasty alone and 89% for angioplasty with stent placement. In another provocative study, however, Jain et al used an atrial pacing stress test ECG to assess the presence of ischemia immediately after successful PTCA in 50 patients with known ACI. Despite angiographically successful PTCA, 28% of the patients demonstrated inducible ischemia.
though a meta-analysis comparing angioplasty and CABG in moderate risk patients found no difference in prognosis, the PTCA group had a 1.6 times higher rate of recurrent angina and a tenfold higher risk of requiring revascularization at 1 year. The prognostic impact of a recent negative stress test with or without myocardial imaging is unclear, particularly in patients with known cardiac disease who might undergo routine or annual studies and subsequently develop chest pain symptoms warranting evaluation. The situation can be further muddied by the patients’ recollection or understanding of their actual results. The standard treadmill exercise test has a reported sensitivity of 65% to 70%, whereas the addition of myocardial perfusion imaging or stress echocardiography increases the sensitivity for detecting coronary artery disease to 80% to 85%. Multiple studies have demonstrated that the best predictor of future cardiac events (cardiac death or AMI) is the number of transient thallium-201 defects on stress thallium testing in groups both with and without documented coronary artery disease. The presence of a single or multiple transient or reversible defects confers a 6- to 12-fold increased risk of cardiac death or AMI. Other studies have shown the presence of fixed defects to be a significant predictor of future cardiac events as well. Increased lung uptake of thallium-201 is an even stronger predictor of future cardiac events and a marker for severe CAD. Conversely, the cardiac event rate of death or AMI in patients with known or suspected cardiac disease but a normal stress thallium study is 1% per year, only slightly above that of the general population. Thus, a normal study identifies a very-low-risk group. In addition to detecting CAD, stress testing aids in delineating prognosis. Patients who can exercise to a high workload without evidence of ischemia generally have a favorable prognosis, whereas those with evidence of ischemia at a lower workload (Bruce stage 1 or 2) have an increased risk of severe disease and short-term cardiac complications. In a review by Iskander of 14 studies with over 12,000 patients with stable symptoms, normal stress SPECT scanning was associated with an annual event rate of 0.6% for death or nonfatal MI. Patients with abnormal images had a 12-fold higher annual event rate of up to 7.4%. The risk was increased in proportion to the magnitude of the abnormality and both fixed and reversible defects had prognostic importance. They noted that these results were similar to those obtained with studies of thallium-201 imaging. This study did not address the need for revascularization in this group. The published average sensitivity of exercise echocardiography for detecting coronary artery disease is similar to that of the nuclear imaging procedures.

THE PHYSICAL EXAMINATION

The physical examination adds relatively little to the assessment and risk stratification of ACI in the ED as abnormal physical findings are uncommon in the majority of presenting patients. Most predictive features are related to the presence of hypotension or other evidence of LV impairment. Hypotension is an independent predictor of complications. Congestive heart failure (CHF), typically defined by new or worsening rales, an S3, or chest radiograph, is an independent risk factor for complications. A precordial lift, S4, or S3 during an episode of discomfort or a new or worsening mitral regurgitant murmur specify a higher likelihood of significant CAD. Palpation of the chest wall can alter the likelihood of acute coronary ischemia but does not exclude it. In general, the smaller the area of discomfort localization and point tenderness, the less likely it is to
represent cardiac ischemia. In one Danish study of 204 patients admitted with acute chest pain but without MI, chest wall syndromes were ultimately diagnosed in over 28%. The finding of bruits (e.g., carotid, aortic, peripheral) or pulse deficits increases the likelihood of CAD.

**RISK STRATIFICATION**

**Unstable Angina Classification Systems**

Historically, ED chest pain patients have been classified by using unstable angina classification systems. Unfortunately, these classifications are based on patients whose chest pain is eventually proved to be due to an acute coronary syndrome. By virtue of this, these are "retrospective" classification systems and perform poorly when applied prospectively to an ED population of undifferentiated chest pain patients. This population requires classification tools that are developed for prospective use; these are discussed later. It is still important, however, to understand the different classes of unstable angina and their implications.

Braunwauld defined unstable angina as one of the following (1) progressive angina with a distinct increase in the frequency, severity, or duration of chest pain, usually with relief by rest; (2) new-onset angina (<2 mo); or (3) rest or nocturnal angina within 1 week of presentation. More commonly used is the Canadian Cardiovascular Society Classification of Angina (CCSC), which is:

- **Class I**—angina only with strenuous activity
- **Class II**—angina leading to slight limitation of ordinary activity
- **Class III**—angina leading to marked limitation of ordinary activity
- **Class IV**—angina that restricts any activity and occurs at rest

For unstable angina, short term mortality rates are 2% to 4%, based on observational studies and clinical trials. Up to 6% to 8% of patients presenting with unstable angina will have a nonfatal MI or die within the first year of diagnosis. The risk of death, MI, arrhythmia, and CHF are greatest at the time of presentation, then diminish over the next 1 to 2 weeks, and then approximate those for patients with chronic angina by 2 months. Rest pain lasting > 20 minutes within the past week or a class II worsening of angina are greater risk presenting features. Angina that remains exertion related yet at a lower workload signifies a lower risk of short-term complications. The elderly, longstanding diabetics, African-Americans, and patients with altered cognition or language barrier represent important exceptions because they are much less likely to present with or to report chest discomfort. Patients with nonchest pain presentations of ACI have up to a threefold increase in mortality.

**The 12-lead ECG**

Despite limited sensitivity and specificity, the 12-lead ECG is the standard initial technology to evaluate the presence of ACI. The ACEP guidelines for the ED evaluation of chest pain recommend an ECG for men over the age of 33 years, women over the age of 40 years, and for patients with risk factors for coronary disease. The advantages of the ECG are that it is universally available, rapid, noninvasive, readily interpretable in the ED, repeatable, and can be coupled with interpretive software. Proper interpretation of the ECG is paramount. In studies by McCarthy et al and Lee et al of missed AMI in the ED, up
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Of note, in the former study, 25% of patients with subsequent missed AMI were sent home with symptoms believed to be due to ischemic heart disease. The sensitivity and specificity of the standard 12-lead ECG is moderate for AMI but poor for unstable angina. The ECG’s diagnostic ability for AMI depends on the defining criteria used. If the more stringent criteria of new Q-waves or new ST-segment elevation in two or more leads are used, the sensitivity varies from 41% to 77% with specificity from 95% to 98%. If more liberal criteria such as any old or new ST- or T-wave abnormality, the sensitivity increases to 72% to 99% but with significant loss of specificity (23%–85%). Of note, these values are for AMI and not USA. A nondiagnostic ECG is seen in roughly 50% of patients presenting with AMI. The likelihood of significant CAD disease based on ECG changes is outlined in Table 2.

Overall, the ECG changes associated with the highest mortality and complications are ST-segment elevation, followed in declining order by, Q waves, ST-segment depression, and T-wave inversion. Savonitto et al studied 12,142 patients with acute chest pain and reported the 30-day incidence of death and MI to be 12.4% in those with ST-segment elevation and depression, 10.5% in those with ST-segment depression, 9.4% in those with ST-segment elevation, and 5.5% in those with isolated T-wave inversion (P < 0.001). Defined ECG markers of high likelihood for CAD include ST-segment elevation or depression ≥1 mm, deep symmetric T-wave inversion in multiple precordial leads, or any dynamic ECG change occurring during pain. Marked symmetric precordial T-wave inversion strongly suggests acute ischemia particularly from a proximal LAD stenosis.

Dynamic ST–T wave changes (particularly shifts in ST segment with ≥1 mm of depression or elevation or T-wave inversions that resolve when symptoms are

Table 2. LIKELIHOOD OF SIGNIFICANT CORONARY ARTERY DISEASE BASED ON ECG FEATURES WITH SYMPTOMS SUGGESTING UNSTABLE ANGINA

<table>
<thead>
<tr>
<th>Intermediate Likelihood (e.g., Low Likelihood 0.15–0.84)</th>
<th>High Likelihood (e.g., 0.85–0.99)</th>
<th>Very High Likelihood (e.g., 0.99–1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of any of the following: ST-depression, Q waves, 21 mm in leads with reversible ST-segment elevation</td>
<td>Any of the following: Absence of high or any of the following: ST-depression, Q waves, 21 mm in leads with reversible ST-segment elevation, T-wave inversion in multiple precordial leads, or any dynamic ECG change occurring during pain</td>
<td>Marked symmetric precordial T-wave inversion strongly suggests acute ischemia particularly from a proximal LAD stenosis.</td>
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relieved) portend a very high-risk group that should be admitted to at least a stepdown unit bed.\textsuperscript{5, 108} In the TIMI IIIB study, reversible ST-segment depression was associated with an increase by a factor of three to six in the likelihood of death, MI, ischemia at rest, or provokable ischemia during a provocative test.\textsuperscript{95} Gorgels et al found that the number of leads with ST-segment deviations and the amount of ST-segment deviation in the ECG obtained during pain showed a positive correlation with the number of diseased coronary arteries in patients with new rest angina pectoris with dynamic changes.\textsuperscript{39} When the total amount of ST-segment change was above 12 mm, the positive predictive accuracy for three-vessel or left mainstem CAD rose to 86%. A liberal use of repeat ECGs in patients with ongoing symptoms is usually the most rapid means of diagnosing AMI and predicting complications, the need for intervention, and admission to an intensive care setting.\textsuperscript{19, 111}

Brush et al prospectively studied 469 patients with suspected ischemia to assess the prognostic utility of the initial ECG.\textsuperscript{9} They classified the initial ECG into a positive or negative group. Negative ECGs were defined as normal, or having nonspecific ST-segment or T-wave alterations (i.e., downsloping ST depression or T-wave flattening) or were unchanged from a prior ECG available at the time of admission. Positive ECGs were defined by the presence of pathologic Q waves, ST-segment elevation, ST-segment depression, T-wave inversion (consistent with infarction, ischemia, or strain), LVH, left bundle branch block, or a paced rhythm. Endpoints included sustained or nonsustained (\geq 3 beat) ventricular tachycardia, ventricular fibrillation, pump failure, heart block (Mobitz type II or complete), conduction disturbances (first, second, third, fascicle or bundle), atrial arrhythmias, recurrent chest pain, or as need for intervention (i.e., cardioversion, pacer, swan, balloon pump). Of the group, 167 (39\%) had negative ECG and 302 (64\%) had an ECG classified as positive. In the positive ECG group, 171 (57\%) had AMI and 42 (14\%) had immediate life-threatening complications (e.g., ventricular fibrillation, sustained ventricular tachycardia, and heart block). In the negative ECG group, 25 patients had infarcts (15\%), and 1 patient (0.6\%) had immediate life-threatening complications. Whereas the negative ECG defined a lower-risk group for infarction, immediate and delayed complications, and need for intervention, up to 48\% of the group was diagnosed with unstable angina, for a total ACI rate of nearly 63\%. Therefore, the negative criteria espoused did not effectively exclude an ischemic cause of chest pain. This work subsequently has been confirmed by others.\textsuperscript{19, 111} The inclusion of the LVH group in the positive ECG cohort is supported by other work showing that electrocardiographic changes characteristic of LVH carry a short-term ACI rate of 26\% and a mortality rate of 7.5\%, making this a higher-risk presentation than a normal ECG.\textsuperscript{40}

Markers of intermediate likelihood include ST-segment depression $\geq 0.5$ mm but $\leq 1$ mm, T-wave inversion $\geq 1$ mm in leads with dominant R waves, and nonspecific ST- and T-wave changes. Nonspecific ST- and T-wave changes (usually defined as ST-segment deviation or T-wave inversion $< 1$ mm) are less helpful. In the Multicenter Chest Pain Study and the Multicenter Acute Ischemia Predictive Instrument Trial, roughly 25\% of patients with these changes were ultimately diagnosed with acute ischemic heart disease.\textsuperscript{61, 81} Jayes et al studied the ECGs of 1,743 men and women without prior history of CAD presenting with chest pain to six hospital EDs.\textsuperscript{47} They found the presence of ST-segment flattening or elevation $< 0.1$ mV(1mm) conferred a relative risk of acute ischemia of 8.7 for men (95\% CI = 5.0–14.8) and 3.9 for women (95\% CI = 2.2–6.9). Similarly, T-wave peaking or inversion $\leq 0.5$ mV conferred a relative risk of acute ischemia of 5.3 for men (95\% CI = 3.1–8.8) and 4.0 for women (95\% CI = 2.2–7.4). To
compound the confusion on the issue, nonspecific or minor ST- or T-wave changes can be transient in the general population. In a study of 173 asymptomatic men with such ECG changes, only 36 (20%) still had them on a follow-up ECG at 1 year.15

A normal ECG has inadequate sensitivity to exclude ACI and even AMI. The false-negative discharge rate of patients with suspected ACI and a normal ECG is as high as 6% to 7%, and the missed AMI rate up to 2% in the same group.74 In a study by Sazaki et al, the AMI rate was reported to be as high as 15% for patients presenting to the ED with chest pain and a normal ECG.90 Patients presenting with suspected ACI with a normal ECG have a death rate from cardiac complications of up to 1.1%, a life-threatening cardiac complication of 0% to 4%, and an AMI rate of up to 6%.60, 74, 85 Whereas the normal ECG cannot be used to exclude AMI and certainly not ACI, it does identify a cohort with low mortality and risk of cardiac complications.9, 49, 109, 113

Thus, despite its shortcomings, the ECG is still one of the most powerful predictors of complications and life-threatening events for patients presenting with suspected ACI.18, 97, 111, 113 but the ECG should always be considered to supplement rather than supplant physician judgment. The standard tracing does not fully sample myocardium, particularly the right ventricle, posterior basal, lateral walls. It lacks sensitivity in the distribution of the circumflex artery. It can miss small areas of ischemia or injury even in areas it is able to sample. Interpretation can be hindered by left ventricular hypertrophy, early repolarization pattern, electrolyte abnormalities, bundle branch blocks and other conduction defects, and existing Q waves. The ECG is also an interpreter-dependent test. In a study comparing ED physicians’ readings with those of expert electrocardiographers, the ED physicians’ readings recognized ST-segment and T-wave changes with sensitivities of only 59% and 64% respectively, with corresponding specificities of 86% and 83% against the “gold-standard” interpretation.48, 102 The impact of these differences on actual care decisions is unknown. One of the best strategies for risk reduction in patients with suspected ACI is a disciplined review of the ECG. Incorrect ECG interpretation by the ED physician is responsible for up to 25% of missed ACI or AMI.66, 74 Lateral and posterior infarctions are among the most frequently missed diagnoses, as well as patients with prior ischemic changes that alter the baseline. Availability of a prior tracing is useful and usually readily available to the clinician in the age of fax machines and archival ECG retrieval systems. It was shown by Lee et al to reduce unnecessary without reducing appropriate admissions.62 Fesmire et al studied 258 patients admitted for suspected AMI and grouped the ECGs according to the Brush criteria.18 They found that change from a prior tracing in the negative ECG group conferred a 2.1 times greater risk of requiring intervention (e.g., IV lidocaine, IV nitroglycerin, pressor support, temporary pacing, Swan–Ganz catheter monitoring, intra-aortic balloon pump insertion, cardioversion, angioplasty, CABG, thrombolytic therapy, or ventilator support) than those with an unchanged negative ECG. The effect was even more striking in the group with a positive initial ECG that had changed from a prior tracing. This group had a greater risk for interventions (2.0 times), complications (2.6 times), life-threatening complications (4.2 times), and AMI (6.6 times) than did the sum of patients in all other ECG categories. They found that change from a prior tracing helped predict need for intervention in patients with negative Brush criteria ECGs and for intervention, complications, and AMI in positive Brush criteria ECGs. Another study, however, by Hoffman et al, found the availability of a prior ECG did not significantly affect disposition decisions by the physician.41 Fax machines also serve as a means of obtaining rapid consultation of questionable electrocar-
### Table 3. AHCPR TRIAGE GUIDELINES AND SHORT-TERM RISK OF DEATH OR NONFATAL MI FOR PATIENTS WITH UNSTABLE ANGINA

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>High-Risk Feature but Must Have Any of the Following:</th>
<th>Intermediate-Risk Feature but May Have Any of the Following Features:</th>
<th>Recommended Triage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Risk</strong></td>
<td>Prolonged (&gt;20 min) rest angina, now resolved, with moderate or high likelihood of CAD</td>
<td>Increased angina frequency, severity, or duration</td>
<td>Admission to an ICU or telemetry bed</td>
</tr>
<tr>
<td></td>
<td>Rest angina (&gt;20 mins or relieved with rest or sublingual nitroglycerin)</td>
<td>Angina provoked at a lower threshold</td>
<td>Chest pain observation unit.</td>
</tr>
<tr>
<td></td>
<td>Nocturnal angina</td>
<td>New-onset angina with onset ≤2 weeks to ≤2 months</td>
<td>Consider outpatient treatment if close follow-up</td>
</tr>
<tr>
<td></td>
<td>Angina with dynamic T-wave changes</td>
<td>Normal or unchanged ECG prior to presentation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>New onset Canadian Cardiovascular Society Class I or IV angina in the past 2 weeks with moderate or high likelihood of coronary artery disease</td>
<td>Pathologic Q waves or resting ST depression 1 mm in multiple lead groups (anterior, inferior, lateral)</td>
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</tr>
<tr>
<td></td>
<td>Age &gt;65 years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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diagrams, although the effectiveness of this approach has not been studied. Used alone, the ECG has insufficient sensitivity for AMI and ACI. A negative, nonspecific, or even normal ECG should not be relied on solely to exclude ACI. Having the suspicion to order an ECG, interpreting it carefully, obtaining an old ECG, ordering serial ECGs to screen for dynamic changes in patients with continued discomfort, and obtaining necessary consultation for questionable cardiograms all increase the utility of this tool. The main benefit of the ECG is in the rapid identification of AMI or changes specific for ACI and to prognosticate for short-term, life-threatening complications.

CONSENSUS-BASED TOOLS: AHCPR GUIDELINES FOR UNSTABLE ANGINA

National guidelines with recommendations for triage in patients with suspected unstable angina were published in 1994 by the Agency for Health Care Policy and Research (AHCPR) and are included as Table 3. The triage decision is based on the estimated risk of death or nonfatal MI and divided into high-, intermediate-, and low risk. Only 6% to 15% of all ED chest pain patients fall into the low-risk category per the AHCPR guidelines. The 30-day event rate for death or nonfatal MI in this group is less than 1%.6,50

Katz et al retrospectively applied the AHCPR guidelines to a consecutive sample of 457 patients presenting with symptoms suggestive of cardiac ischemia and compared their performance to the Acute Cardiac Ischemia-Time Insensitive Predictive Instrument (ACI-TIPI) scoring Table 4 outlines the final diagnosis and 30-day follow-up endpoints for patients in each AHCPR guideline class as well as the mean ACI-TIPI probability for each class. Only 4% (1/28) of patients thought to be low risk by the guidelines were actually discharged. The overall classification agreement for the AHCPR guidelines for USA with the ACI-TIPI was found to be only 54% (Spearman correlation coefficient 0.16). ACI-TIPI tended to put less patients in the low-risk group (only 16% of guideline low-risk group patients were in ACI-TIPI low-risk group) and less in the high-risk group (only 27% of guideline high-risk group were labeled high risk by TIPI stratification). Patients who are at a low risk of cardiac ischemia by AHCPR guidelines, and who have been asymptomatic for > 24 hours could be candidates for outpatient testing with close follow-up depending on comorbidities and healthcare access.6,21 Patients with increased age, comorbidities, and complex presentations can benefit from a more complete ED evaluation.

VALIDATED TOOLS: MULTICENTER CHEST PAIN STUDY TOOLS

The reported sensitivity for physician diagnosis and triage of AMI is 87%, with a specificity of 78%.101 These data stem from work done in 1985. A more modern estimate of the predictive ability for ACI by emergency physicians yielded sensitivities of 95% to 100% and a broad range of specificity from 16% to 73%.40,93 In attempts to improve on both the sensitivity and specificity in the diagnosis of ACI, mathematical models based on clinical and ECG variables have been developed. The best known of these is the computer-derived protocol by Goldman et al to identify clinical factors predicting complications requiring ICU in ED chest pain patients.29 Nine clinical and two ECG variables were derived from 50 prospectively collected variables from 1379 ED chest pain
Table 4. PERFORMANCE OF THE AHCPR GUIDELINES

| Risk Each Group Agreement No. in CHF Tachyarrhythmia Readmission Revascularization | ACI-TIPI | AHCPR Number in Grouping Ventricular ED/Hospital |
|---|---|---|---|---|---|---|---|---|---|
| Low risk | 28 (6) | 4 (16) | 0 | 8 (29) | 0 | 0 | 6 |
| Intermediate | 247 (54) | 178 (78) | 12 (5%) | 131 (53) | 7 (3) | 7 |
| High risk | 182 (40) | 45 (27) | 28 (15%) | 65 (35) | 44 (24) | 9 (5) | 49 (28) | 16 (10) | 3 (1.7%) |


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patients presenting to diverse hospitals. Recursive partitioning was used to create 14 risk stratification groups, with AMI defined by enzymes, new ECG Q waves, technetium-99m stannous pyrophosphate, or sudden death within 72 hours of presentation as the endpoints. A cut-off of a 7% or greater probability of AMI was used for CCU admission. In a prospective study of the protocol, the sensitivity of the protocol and physicians' judgment for AMI were essentially equal (88%), but the specificity (74% and 71% respectively, $P < 0.00001$) and overall accuracy (76% vs. 73% respectively, $P < 0.00001$) were significantly higher for the algorithm, thereby potentially reducing unnecessary CCU admissions. The algorithm suffers from being somewhat unwieldy and only speaks to the probability of a given patient suffering AMI rather than ACI. Figure 2 outlines the elements of the protocol.

Goldman et al further refined these criteria in a derivation set of 10,682 patients at seven diverse hospitals participating in the Multicenter Chest Pain Study from 1984 to 1986. The purpose was to again identify clinical factors that predict patients with suspected ACI who will have complications requiring an intensive care setting. They identified two ECG variables and three clinical risk factors that stratified patients into four risk groups for major complications in the first 12 hours. The validation set included a separate set of 4,676 patients from one of the original participating hospitals. The clinical and electrocardiographic features in the ED associated with an increased risk of complications are listed here:

**Electrocardiographic features**
1. Suspected MI on the initial ECG: Defined as ST-segment elevation of 1 mm or more or pathologic Q waves in two or more leads, with neither finding known to be old.
2. Suspected ischemia on ECG on the initial ECG: Defined as ST-segment depression of 1 mm or more or T-wave inversion in two or more leads on the electrocardiogram, with neither finding known to be old.

**The three risk factors included one historical variable and two physical examination findings**
1. Systolic blood pressure < 110 mm Hg.
2. Rales heard above the bases on initial ED examination
3. Known unstable ischemic heart disease: Defined as worsening of previously stable angina, new-onset post-infarction angina or angina after a coronary revascularization procedure, or pain that was the same as that associated with a prior MI.

Major complications in the study were defined in three groups: arrhythmia (e.g., ventricular fibrillation, cardiac arrest, new complete heart block, insertion of a temporary pacemaker, emergency cardioversion), pump failure (e.g., cardiogenic shock, use of an intra-aortic balloon pump, intubation) and ischemia (e.g., recurrent ischemic chest pain requiring CABG or PTCA within 72 hours after admission or cardiac catheterization followed by CABG or PTCA before discharge). The algorithm successfully stratified patients into a high, moderate, low, or very low risk of major complications in the first 24 hours after presentation with statistically significant differences between each risk group in the 4,676 patients validation set. The group identified as high risk had a major event rate of 16.1% in the validation set compared with 21.5% in the derivation set. The moderate risk group's major event rate was 7.8%, whereas the stratified low and very low groups' rates were 3.9% and 0.6%, respectively. The high-risk group was the only one in which the derivation and validation groups differed appreciably in the major event rate ($P = 0.04$). Figure 3 outlines the algorithm.
ST elevation or Q waves (not known to be old) in 2 or more leads

High (77)

Yes

High (24)

No

Longest pain episode

21 hour

Yes

Low (3)

1

Low (3)

No

Pain worse than usual angina or the same as an earlier MI

High (21)

Yes

No

Pain is stabbing

Low (3)

Figure 2. See legend on opposite page

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Suspected MI on ECG?

No factors

Suspected ischemia on ECG?

Two or more T waves

No factors

Two or more factors

No risk

Very low risk

Moderate risk

Figure 3. Risk of complications in ED chest pain patients. Myocardial infarction was suspected if the ECG showed ST-segment elevation of 1 mm or more or pathologic Q waves in 2 or more leads, and these findings were not known to be old. Ischemia was suspected if the ECG showed ST-segment depression of 1 mm or more or T-wave inversion in 2 or more leads, and these findings were not known to be old. Risk factors included systolic blood pressure below 110 mm Hg, rales heard above the bases bilaterally on physical examination, and known unstable ischemic heart disease, defined as a worsening of previously stable angina, the new onset of postinfarction angina or angina after a coronary-revascularization procedure, or pain that was the same as that associated with a prior myocardial infarction. The difference between each adjacent pair of risk groups was significant (P < 0.001). (Adapted from Goldman L, Cook EF, Johnson PA, et al: Prediction of the need for intensive care in patients who come to the emergency department with acute chest pain. N Engl J Med 334:1498–1504, 1996; with permission.)

Because the function of the algorithm is to identify patients requiring intensive care, it does not speak to risk stratification for the identification of unstable angina and is not able to address nonchest pain or atypical presentations, which can account for up to 26% of ED patients with ACL. Similarly, the algorithm did not address how the risk factors performed in identifying important intermediate events (Mobitz II second-degree heart block, sinus bradycardia requiring medication, pulmonary edema without hypotension, recurrent ischemia not meeting the criteria for a major event, or infarct extension or reinfarction without a major event). Although the algorithm supports statistically significant risk discrimination, it does not speak to the intangible characteristics of human decision making, such as the risk tolerance of the treating physician. A difference among a 3.9%, 7.8%, and 16.1% chance of a potentially lethal event is not likely

Figure 2. Risk stratification protocol for AMI. The protocol is based on a recursive partitioning model. The numbers in parentheses indicates the percentage of patients with AMI. (Adapted from Goldman L, Cook EF, Brand DA, et al: A computer protocol to predict myocardial infarction in emergency department patients with chest pain. N Engl J Med 318:797–803, 1988; with permission.)
to affect the decision making of the physician given the consequences of mistriage, and indeed it did not when studied. The algorithm did not change care or resource utilization in a separate prospective trial by Lee et al of 1,921 patients with acute chest pain.64

**VALIDATED TOOLS: THE ORIGINAL ACI PREDICTIVE INSTRUMENT AND ACI-TIPI**

In the early 1980s, Pozen et al developed a predictive instrument using clinical data available in the ED to increase diagnostic specificity without compromising sensitivity. The resulting tool was developed from 7 of 59 clinical variables in 2,801 study subjects presenting to the EDs of six participating hospitals. The outcome examined was the clinical diagnosis of myocardial ischemia or infarction. The variables included the presence of chest pain, pressure, or left arm pain and whether any of these were the chief complaint. Additional variables included prior history of MI or nitroglycerin use as well as ECG ST-segment and T-wave morphology. The variables in the original ACI predictive instrument are listed here:

**Questions**
- Presence of chest pain or pressure, or left arm pain?
- Were the above the chief complaint?
- Prior history of heart attack?
- Prior history of NTG use?

**ACI ECG Variables**
- ST-segment flattening or straightening
- ST-segment elevation or depression ≥ 1 mm
- Hyperacute T waves (> 50% of the R wave)
- T waves inverted ≥ 1 mm
- Absence of any of the above ECG features

A multivariate logistic regression model was developed, allowing a percentage estimate (0%-100%) of the probability of ACI. The ACI predictive instrument has been shown prospectively to improve diagnostic performance and specificity without increasing the number of patients discharged home with ACI. It is accurate and has good evidence of its impact on ED decision making but was not designed for use in retrospective review of care. The ACI predictive instrument is one of the first tools to assess ACI rather than AMI, more fully meeting the needs of emergency physician decision making. The instrument originally used a programmable calculator, and its acceptability was limited because it was thought to be too complicated and cumbersome. Prospective testing in the ED showed that its use could decrease the rate of false-positive diagnoses and CCU admissions by up to 30% without increase in false-negative discharges. In a Netherlands prehospital study, Grijseels et al prospectively tested the ACI-TIPI criteria to 1,005 patients triaged by general practitioners and prehospital ECG and constructed a receiver operating characteristic (ROC) curve based on actual calculated probabilities. In this environment, the instrument demonstrated only a 43% sensitivity and 78% specificity for ACI.

In 1991, Selker revised the original predictive instrument to allow real-time

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†ECG features must be present in two leads, excluding a VR.
calculation and for inclusion in an ECG-based program. This new model was developed to be valid for both prospective and retrospective use and thus is time insensitive. The incorporation of the computerized software into ECG machines allowed more detail in the ACI-TIPI's measurement of the ST segment and T waves. This in turn allowed more weight and higher probability predictions for ECG ST and T changes suggestive of AMI. The variables used in ACI-TIPI are essentially the same as in the original predictive instrument but include a more quantitative assessment of the ST and T changes on the ECG. These are listed here:

- Age
- Sex
- Presence or absence of chest pain or pressure or left arm pain
- Whether these are the patient's chief complaint or a secondary complaint
- Presence or absence of Q waves
- Presence and degree of ECG ST-segment elevation or depression
- Presence and degree of ECG T-wave elevation or inversion

In a test phase study on 2320 ED chest pain patients, the instrument performed exceedingly well, with a ROC area of 0.88 and performance comparable to that of the physicians. The instrument discriminated well between those proved to have acute ischemia and those without as shown by mean TIPI probabilities of 59% and 21% respectively (P< 0.0001). Table 5 outlines the percentage of patients subsequently found to have ischemia in each of four TIPI risk-stratified test group of 2,320 patients. In the same study, the ACI-TIPI performed equally as well as the original ACI instrument and provided greater differentiation between those with and without ischemia.

In a prospective study of 10,689 chest pain patients in 10 EDs, Selker et al found the use of the ACI-TIPI to reduce CCU, telemetry, and hospital admissions in patients without cardiac ischemia while not compromising diagnostic accuracy. It performed best with unsupervised residents at hospitals with high monitored bed capacity. Because the instrument was meant to be used in conjunction with physician decision making, no probability cut-off defining a low-risk or very-low-risk group was reported. A subsequent study by Cairns et al showed an ACI-TIPI score of ≥ 38% to have a 93% sensitivity and 69% specificity for AMI and AMI complications and to perform better than physician judgment for ICU triage. Aufderheide et al tested the performance of the ACI-TIPI score generated by a specially programmed ECG machine in a prospective study of 362 chest pain patients in the prehospital setting. They found that patients with

<table>
<thead>
<tr>
<th>TIPI Score Outcome</th>
<th>ACI Probability Group</th>
<th>ACI (%)</th>
<th>AMI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low I 0-10</td>
<td>5.0</td>
<td>1.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Medium I1 10-25</td>
<td>17.5</td>
<td>12.0</td>
<td>4.4</td>
</tr>
<tr>
<td>I11 25-55</td>
<td>40.0</td>
<td>36.7</td>
<td>12.3</td>
</tr>
<tr>
<td>High IV 55-100</td>
<td>77.5</td>
<td>81.6</td>
<td>53.3</td>
</tr>
</tbody>
</table>

*Adapted from Selker HP, Griffith JL, D'Agostino RB: A tool for judging coronary care unit admission appropriateness, valid for both real-time and retrospective use. A Time-Insensitive Predictive Instrument (TIPI) for Acute Cardiac Ischemia: A multicenter study. Med Care 29:610-627, 1991; with permission.*
a low ACI-TIP1 probability score (0%–9%) had no AMIs, a 2.3% incidence of angina, and no prehospital life-threatening events. Only 6.1% of patients, however, were classified as low risk. The performance of the system was similar to that of two study investigators blinded to patient outcome.

Any predictive instrument is limited in assessing the probability of ACI in patients without chest pain. This is particularly important in the elderly population, and thus is an increasing problem as this group increases. The existing models speak in terms of probability only, so there is no specific cut-off point that corresponds directly to a specific triage decision. The result of both the ACI-TIP1 and the original ACI predictive instrument is measured as a percent probability, which still leads to some margin of individual physicians' risk tolerance. Although these approaches are able to stratify patients into low- and high-risk groups for infarctions and cardiovascular complications, physician judgment must still decide how low a risk they are willing to take before discharging a patient with suspected ACI from the ED. Still, by offering relative ease of use and consistency, the guidelines allow the patient to be better informed of the short-term risks so that they can participate in the decision making. The cost savings represents a major advantage because most systems are relatively inexpensive to apply and can safely decrease inappropriate utilization of the cardiac intensive care unit.

OTHER ECG DECISION-MAKING MODELS

An artificial neural network takes computer-based decision making even further. Baxt and Skora used such a network to identify AMI in 1,070 consecutive patients presenting with anterior chest pain. The sensitivity was 96% versus 73.3% by the physician for identifying patients ultimately diagnosed with AMI. The specificities for the network and physician were 96% and 81.1%, respectively. The study did not address the clinical importance of this difference; that is, how many patients with AMI were discharged versus simply admitted as unstable angina rather than as non-Q-wave AMI? Also, this model did not test the broader, more complex decision of whether ACI were present, but focused only on AMI. Hirshberg used a computer expert system using a criteria-based expert shell for assessment of ED chest pain patients and found it to have a sensitivity of 100% and a specificity of 39% in diagnosing ischemic cardiac disease. This study had only 59 patients and the difference amounted to the ED physicians recommending admission for 54 patients and the computer criteria recommending that only 47 be admitted. The major limitation rests in the networks' ability to deal with atypical presentations. Physicians have not generally accepted strategies using artificial intelligence. The accuracy and quality of the entered data limit any such system. In the study by Baxt and Skora, up to 10% of original data entries were deemed incorrect and required reentry. Their strength rests in the capacity to manage large numbers of weighted variables to ascertain a probability analysis.

RISK STRATIFICATION WITH 2-DOPPLER ECHOCARDIOGRAPHY

The use of echocardiography in the setting of ACI is based on the tenet that ischemic myocardium develops hypokinesis or dyskinesis and thus demonstrates regional wall abnormalities. During ischemia, the muscle can fail to
thicken or can appear thinner during systole than diastole. These changes have been shown to predict the culprit coronary artery. The echocardiogram is insensitive in distinguishing new ischemia from old injury. Therefore, most prospective clinical trials of echocardiography in the ED setting excluded patients with prior MI or CAD. The sensitivity of echocardiographic studies performed during chest pain for ACI and AMI respectively were 85% and 88% and 86% and 92% respectively in groups with normal or nonspecific ECGs. The corresponding specificities were 74% and 78% and 53% and 82% for ACI and AMI. On et al studied 26 patients presenting with ED chest pain and nondiagnostic ECGs and found 5 patients with regional wall motion abnormalities all who subsequently ruled in for non-Q-wave AMI. An additional two patients evolved non-Q-wave AMI without wall motion abnormalities, however. Horrowitz et al found regional wall motion abnormalities in 31 of 33 patients with AMI, and Loh et al found regional wall motion abnormalities in 10 of 12 with subsequent non-Q-wave AMI. In a study by Sabia et al that did not exclude patients with known CAD 4% of patients with normal echocardiograms had MIs. Thus, regional wall abnormalities persisting after pain can help to predict AMI in a group with normal ECGs and initial enzyme studies, but a negative study result during pain does not exclude ACI or AMI. In addition, changes in wall motion can be difficult to detect and caused by factors other than ischemia (i.e., conduction abnormalities, right ventricular overload, and movement of adjacent segments. Bedside echocardiography can help to prognosticate and predict both early complications by assessment of LV function. Ejection fractions of <40% have been shown to be an independent predictor of early mortality and complications in patients with AMI. A recent study by Kontos et al examined the predictive ability of echocardiography performed within 4 hours of presentation in 260 ED patients. Positive echocardiograms were defined as having regional wall motion abnormalities or an ejection fraction of less than 40%. It is unclear from the protocol which percentage of patients had chest discomfort at the time of echocardiography. The sensitivity of the echocardiogram for predicting MI or need for revascularization was 91% (95% CI = 79%–97%) with a specificity of 75% (95% CI = 69%–81%). Excluding patients with abnormal ECGs did not significantly alter the sensitivity or specificity of echocardiography. They found the sensitivity of echocardiography in predicting MI or need for revascularization to be significantly higher than the ECG but with a lower specificity. It is most useful in patients with nondiagnostic ECG changes, left bundle-branch block, or paced rhythm. In addition, the echocardiogram has the ability to obtain information rapidly about important complications of infarction such as papillary muscle rupture, ventricular septal rupture, pseudoaneurysm, intracardiac thrombus, cardiac rupture, and valvular regurgitation. It can provide evidence of alternative serious diagnoses like pericardial effusion or tamponade, aortic dissection, critical aortic stenosis or regurgitation, and pulmonary embolism with right heart strain.

The limitations of ED sonography include cost, study availability, operator dependence of both image acquisition and interpretation, time required to obtain the study, and body habitus restrictions in the acoustic window. Getting real-time interpretation from an expert represents a significant limitation to ED utility. Echocardiography is poor at distinguishing active ischemia from old ischemic wall dysfunction. The scoring system used in most prospective studies is too complex to be reproduced practically on a universal basis. Most important, the wall motion abnormalities seen in ischemia can resolve quickly in patients who are pain free at the time of presentation, making the test less useful in a significant number of patients. In many of the earlier studies, ED echocardiogra-
phy helped to triage patients being admitted with ACI but lacked adequate sensitivity to exclude ACI or even AMI in this setting. It is not currently recommended by the National Heart Attack Alert Working Group Report for the ED diagnosis of acute cardiac ischemia, and its role in selected populations is still being defined.

VALIDATED TOOLS: SESTAMIBI PERFUSION IMAGING PROTOCOLS

Technetium-99m–labeled sestamibi is a myocardial perfusion tracer that is taken up by the myocardium in proportion to the degree of regional blood flow. Sestamibi uptake is a marker of cell membrane and mitochondrial integrity and reflects myocardial perfusion at the time of injection, even if the patient is imaged several hours later. Because of its prolonged retention, patients can be injected after stabilization with a gamma counter for up to 4 hours after injection of the isotope. Patients with transient myocardial ischemia still can demonstrate tracer uptake abnormality owing to the time required restoring the cellular membrane impairment. Studies showing perfusion defects with associated wall motion abnormalities or thickening are considered positive. Sestamibi is not taken up by either acutely or chronically infarcted myocardium, and the quantified size of the defects correlates with infarct size, CK release amount, and postinfarction LVEF. It has an advantage over thallium-201 of providing superior image quality in obese patients. The addition of single-photon emission computed tomography (SPECT) imaging allows demonstration of segmental abnormalities of LV and measurement of LV function using gated images. Kontos et al found a similar sensitivity for detecting AMI (92%) with serial cardiac troponin (cTnI) determinations and resting sestamibi scanning in 620 ED patients presenting with chest pain. The sestamibi study had higher sensitivity for predicting need for revascularization or significant CAD than cTnI, but lower specificity for all endpoints. Its most promising role appears to be in patients with equivocal chest pain histories and nondiagnostic ECG findings, particularly those having chest pain at the time of the study. Varetto et al studied the utility of early ED imaging in 64 ED chest pain patients with nondiagnostic ECGs and found a sensitivity of 100%, specificity of 92%, and 90% accuracy for identifying patients ultimately diagnosed with ACI. In this study, no patient with a normal perfusion scan had a major cardiac event in the 18-month follow-up period. Hilton et al studied 102 patients presenting to an ED with active symptoms of angina and nondiagnostic ECGs with sestamibi scanning. The test demonstrated a high sensitivity (94%), specificity (83%), and accuracy (85%) for predicting adverse cardiac events (e.g., AMI, need for revascularization or thrombolysis, death) with a risk ratio of 13.9 (P = 0.0001). In this study, the 99mTc sestamibi scan could stratify chest pain patients with nondiagnostic ECGs into very high (>70%) and very low (<2%) risks for cardiac events. In fact, it was the only independent predictor of adverse cardiovascular events during hospitalization. Kontos et al studied the diagnostic performance of rest sestamibi imaging in 532 consecutive ED patients with chest pain and normal or nondiagnostic ECG. Perfusion imaging was positive in 32% and represented the only predictor of AMI on multivariate analysis. The sensitivity for AMI was 93% (95% CI = 77%–98%), and was 81% for the composite endpoint of AMI or revascularization (95% CI = 71%–88%). The corresponding negative predictive values were 99% (95% CI = 98%–100%) and 95% (95% CI = 92%–97%) respectively. Hilton et al followed 87 chest pain patients with a nondiagnostic or
normal ECGs and normal sestamibi scans for 90 days and found no short-term cardiac events (e.g., death, nonfatal AMI, or need for revascularization in this low-risk group. Of note, all patients in the study were injected with tracer during symptoms.

Tatum et al studied the efficacy of an evaluation strategy using immediate resting sestamibi in 1,187 ED patients with no prior history of chest pain presenting with chest pain and nondiagnostic ECGs. Patients with low probability of AMI but low to high probability of UA were assigned to undergo immediate resting technetium-99-labeled sestamibi imaging. Patients did not have to have active chest pain to be entered in the study. They found the sensitivity of immediate resting myocardial imaging to be 100% (95% CI = 64%-100%) for AMI with a specificity of 78% (74%-82%). The test was able to predict AMI or need for revascularization with a sensitivity of 82% (95% CI = 67%-91%) and a specificity of 83% (95% CI = 79%-87%). Only 2.1% of patients in the group with a normal perfusion study had 30-day AMI or revascularization, compared with 32% of the group with abnormal studies. Patients with negative sestamibi studies (n = 338) had a 1-year revascularization rate of 3% and no MI or deaths, whereas patients with abnormal imaging studies (n = 100) had an 11% MI rate and a cardiac death rate of 8%. A normal test had a high negative predictive value of 97% (95% CI = 95%-98%) for combined cardiac events over the next year. Of note, only three patients with normal resting myocardial sestamibi perfusion scans required revascularization within the first year of follow-up, and none died or sustained an AMI. Table 6 outlines their results. An abnormal scan is associated with a 50-fold increased risk of AMI and a 14.5-fold increase in the risk of revascularization over the next 30 days, as well as a 30-fold increase in 1-year mortality. Use of sestamibi resulted in a 20% reduction in unnecessary hospitalizations without a significant difference in false-negative assessments. In a recent study by Kosnik et al, the use of sestamibi in 69 ED patients with chest pain and nondiagnostic ECGs demonstrated good specificity (92%) and moderate sensitivity (71%) at predicting MI, death, or need for revascularization during the index hospitalization and subsequent year-long follow-up. The positive predictive value was 50% with a negative predictive value of 97%; the overall accuracy was 90%. The subsequent risk of an adverse cardiac event (e.g., AMI, death, need for revascularization) was only 3% in the group with a normal scan, compared with 62% in the group with an abnormal scan. There were no statistical differences in age, sex, prior history of angina, characteristics of the chest discomfort, or ACI-TIP1 score between the positive and negative sestamibi groups.

Tatum et al compared the performance of ED echocardiography and resting sestamibi perfusion in chest pain patients with nondiagnostic ECGs and found a high degree of agreement (concordance 89%, kappa coefficient 0.66). Both tests identified all patients with AMI or requiring acute PTCA, but the sensitivity for a combined endpoint (e.g., AMI, angiographically significant disease on catheterization, or an abnormal stress imaging study) decreased to 71% for both imaging modalities (95% CI 50%-86%). An appreciable number of these patients were pain free at the time of echocardiographic or perfusion imaging; however, the study lacked the power to show that the two techniques were equivalent.

The problems with resting sestamibi perfusion imaging involve the time required for preparation of the isotope, equipment and personnel expense, radiation safety concerns, usual need for transport, time delay of 1 to 3 hours between administration and imaging and cost. The test is unable to determine the age of an injury and can miss small areas of ischemia. The sensitivity of sestamibi depends on active pain. The logistics of having an available technician
### Table 6. RESULTS OF AN EVALUATION STRATEGY USING IMMEDIATE RESTING SESTAMIBI IN ED CHEST PAIN PATIENTS WITH NO PRIOR HISTORY OF CHEST PAIN AND NONDIAGNOSTIC ECGs

<table>
<thead>
<tr>
<th>No. with Total No.</th>
<th>No. with Cardiac</th>
<th>With No.</th>
<th>Probability Disposition</th>
<th>Diagnostic Strategy</th>
<th>No. with MI</th>
<th>Revascularization</th>
<th>Death Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients of MI</td>
<td>Probability of UA &amp; Disposition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Very High</td>
<td>Very High</td>
<td>ECG; Admit to ICU</td>
<td>29 (96)</td>
<td>15 (56)</td>
<td>2 (6)</td>
<td>26 (96)</td>
</tr>
<tr>
<td>191</td>
<td>High</td>
<td>High</td>
<td>Serial ECG, enzymes; Admit to ICU</td>
<td>25 (13)</td>
<td>56 (29)</td>
<td>0</td>
<td>64 (34)</td>
</tr>
<tr>
<td>160</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Serial ECG, enzymes, resting sestamibi perfusion imaging; Admit to ICU</td>
<td>5 (3)</td>
<td>27 (17)</td>
<td>0</td>
<td>28 (18)</td>
</tr>
<tr>
<td>282</td>
<td>Low</td>
<td>Low to moderate</td>
<td>&quot;Fast track ECG, enzymes&quot;, resting sestamibi; ED workup</td>
<td>2 (0.7)</td>
<td>7 (2.5)</td>
<td>0</td>
<td>8 (2.8)</td>
</tr>
<tr>
<td>527</td>
<td>Very Low</td>
<td>Very Low</td>
<td>As appropriate</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; UA, unstable angina.


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and isotope in the necessary window are potentially formidable and represent
the greatest limitation of this exciting technology. The accuracy of the test
depends on the quality of the images and the expertise and experience of the
interpreter. The study by Kosnik et al reported good interrater reliability, as
measured by a kappa value of 0.83 ($P < 0.001$) in nuclear medicine physicians
at three different institutions. Sensitivities derived in experienced centers might
not be generalizable. The test is expensive, with typical costs ranging from $500
to 800 dollars and charges roughly double those. Several studies have shown
the addition of rest technetium-99m-labeled sestamibi scanning to ED chest pain
strategies be cost effective.

The ED CHEST PAIN OBSERVATION UNIT

The ED CPOU is best suited for patients at low to moderate risk of ACI
and low risk for complications. The ED CPOU has been shown to be safe,
cost-effective, and has a high sensitivity for acute cardiac ischemia in this
group. The reported missed MI rate reported in the chest pain evaluation
registry (CHEPER) study of ED CPOUs was reported by Graff et al to be 0.4%.
One of the benefits of the CPOU is that it allows serial biomarker studies with
increased sensitivity for AMI. It should be cautioned, however, that serial
ECGs and biomarkers alone are insensitive for ACI. In a study of patients at
low risk (<10%), Gaspoz et al reported a 1.6% incidence of patients discharged
with subsequent MI within 72 hours. An important feature of this group was
that none of these patients underwent provocative testing prior to discharge.
The desire to simply do an "enzyme only" evaluation must be avoided for this
reason. Immediate exercise testing after cardiac enzyme rule-out can facilitate
discharge of up to 85% of low-risk patients, at a savings of nearly $2000 per
patient not requiring admission. In addition, the hospital work-up for the 15%
of patients requiring admission after immediate stress testing is facilitated, and
the stay shortened. Patients with an intermediate likelihood of and moderate
risk needs to have ACI ruled in or out rapidly in the most cost-effective
setting without compromising safety. This has typically been accomplished in
the inpatient setting, but Farkouh et al studied 424 ED chest pain patients
stratified into an intermediate-risk group using the AHCPR criteria and random-
ized one half to hospital admission and one half to a chest pain unit (CPU)
protocol with aspirin, heparin, serial enzymes, continuous ST-segment monitor-
ning, and exercise testing. There was no difference in the number of cardiac
events between the inpatient (8.5%) and CPU (6.6%) group during the 6 month
follow-up, but resource utilization was significantly lower in the CPU group. Of
note, 54% of the CPU group required admission for continued chest pain,
abnormal enzymes, or failed stress tests. Because up to 54% of all patients
presenting with chest pain can have an intermediate risk (7%) of death or
nonfatal MI within 30 days, it is in this group that the greatest strides in safety
and cost efficiency may be realized.

The National Heart Attack Alert Program Working Group reviewed tools
used to diagnose acute cardiac ischemia (Table 7), and the quality of the
evidence concerning each technology was reviewed and weighted. A rating of
A was given for prospective controlled clinical studies of high quality, whereas
B was used for evidence involving substantial clinical studies. The C rating was
SUMMARY

There are no perfect tests or algorithms to exclude ACI. Because acute coronary occlusion often occurs in patients with low-grade coronary stenosis, the diagnostic goal of a chest pain diagnostic protocol is not to identify patients with CAD, but rather to identify patients who may be safely discharged home without the development of complications such as MI, unstable angina, death, shock, or CHF over the next 1 to 6 months. There is an advantage to evaluating patients at the time of their symptoms. Patients who have a small plaque that is ruptured, leading to intracoronary thrombosis and ischemia, will manifest ischemia on diagnostic testing that could be missed in routine outpatient testing when their plaque were stable. The diagnosis and risk stratification of acute coronary ischemia in the ED depends on a careful history and interpretation of the ECG. Multiple regression models using readily available data (e.g., history, physical examination, and ECG) provide the best tools for risk stratification. If one is deciding how to select patients for an EDOU chest pain evaluation, diagnostic tools that have previously been tested and validated in this setting are preferable. These include the Multicenter Chest Pain Study derived tools (i.e., Goldman,
Lee), the ACI and ACI-TIPI tools, and sestamibi risk stratification tools. This is not to say that other tools may not play a role at individual institutions. It is probably better to select a consistent approach and evaluate its performance, rather than to allow random variation to dictate practice.

The future direction probably will involve standardization of the ED chest pain population. This allows outcome and cost-effectiveness comparative research of various strategies for patients with normal or nondiagnostic ECGs and normal biomarkers. Although this approach allows more precise stratification, the risk will never be zero, meaning that there will never be a substitute for good clinical judgment and close follow-up care.

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