# Pitfalls in Evaluating the Low-Risk Chest Pain Patient

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**KEYWORDS**

- Acute coronary syndrome • Atypical chest pain
- Chest pain in the elderly • Electrocardiogram
- Low-risk chest pain • Risk stratification

One of the most common causes of patients visiting an emergency department (ED) is a chief complaint of chest pain. Nationwide, more than 6 million ED visits a year involve patients presenting with chest pain, which is more than 5% of all ED visits. Only abdominal pain is seen more commonly.[1]

Chest pain has multiple causes ranging from benign to immediately life-threatening (**Box 1**). Immediately life-threatening causes of chest pain include acute coronary syndrome (ACS, defined as a spectrum of disease ranging from unstable angina to acute myocardial infarction [AMI]), pulmonary embolus, aortic dissection, tension pneumothorax, pericarditis with pericardial tamponade, and esophageal rupture. Less immediately life-threatening are pneumonia, anxiety, and musculoskeletal and gastrointestinal (GI, esophageal spasm, biliary colic, peptic ulcer disease) causes of chest pain. In a large percentage of patients, the cause of their chest pain is never found. The challenge for the physician evaluating a patient with acute chest pain is to rule out potential life-threatening causes and to formulate a diagnostic and management strategy that will allow for rapid and safe disposition of the patient.

In the case of most life-threatening causes of chest pain, rapidly available diagnostic tests clearly and reliably make or disprove the diagnosis. For example, when the physician considers a diagnosis of tension pneumothorax, pericardial tamponade,

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Emerg Med Clin N Am 28 (2010) 183–201
doi:10.1016/j.emc.2009.10.002 **emed.theclinics.com**
0733-8627/09/$ – see front matter 

**Box 1**
**Immediately life threatening causes of chest pain**

- Acute Coronary Syndrome (including unstable angina and acute myocardial infarction)
- Pulmonary Embolism
- Pericarditis with Tamponade
- Tension Pneumothorax
- Aortic Dissection
- Esophageal Rupture

or aortic dissection, tests such as a chest radiograph, chest computed tomography (CT), or bedside ultrasonography can be used to make a rapid and definitive diagnosis. Although historically a diagnostic challenge, the diagnosis of pulmonary embolism has also become more straightforward with the development of diagnostic strategies using a combination of clinical probability, D-dimer testing, lower extremity venous compression ultrasonography, or high-resolution multidetector pulmonary CT angiography (CTA). Recent studies have shown that this strategy can be used reliably and safely to exclude the diagnosis of pulmonary embolism.[2,3]

Although the diagnosis of chest pain is becoming more straightforward with many of these causes, the diagnosis remains problematic when chest pain arises from ACS. This is especially true in patients thought by the clinician to be at low risk of cardiac ischemia.

There is considerable literature that has attempted to define the patient population with low-risk chest pain and a newer body of literature that has begun to define a subset of patients at very low risk of cardiac ischemia. The focus of this article will be on defining these patient populations and identifying potential pitfalls in the recognition and management of the patient with low-risk chest pain.

## SCOPE OF THE PROBLEM

Heart disease is the leading cause of death for men and women. In 2005, cardiac ischemia was responsible for 20% of all deaths in the United States.[4] The number of new and recurrent myocardial infarctions (MIs) presenting to hospitals is estimated to be 935,000 per year. The direct and indirect cost of coronary artery disease (CAD) in the United States is estimated to be more than 165 billion dollars in 2009.[4] Because of the high prevalence of ischemic heart disease and the overwhelming morbidity, mortality, and cost associated with its management, there is no other disease process seen in the ED that has been more extensively investigated.

Numerous studies have demonstrated a fairly high rate of patients with missed cardiac ischemia who were discharged from the ED. This rate has been reported to vary from 2% to 4%, with significantly higher rates at individual centers.[5–7] Furthermore, patients discharged from an ED with undiagnosed cardiac ischemia have a high likelihood of death with mortality ranging between 10% and 25%.[7]

The significant morbidity and mortality associated with missing MI results in the highest overall cost to insurers of any missed diagnosis in emergency medicine.[8,9] Compounding this problem are the variable practice patterns amongst individual physicians in the management of patients with low-risk chest pain due to their fear of litigation. The literature has shown that emergency physicians' fear of being sued for missed ACS leads to considerable increased testing and inappropriate admission for patients in the population with low-risk chest pain.[10]

It is critically important that the emergency physician understand that a large percentage of patients defined as ''low risk'' in the literature are not at low enough risk to discharge home without further testing. The difficulty for the emergency physician is balancing clinical judgment, appropriate testing strategies, and evidence-based principles to manage this group of patients in a safe and cost-effective manner.

## CHARACTERIZING PATIENTS DISCHARGED FROM THE ED WITH MISSED CARDIAC ISCHEMIA

In an attempt to define the type of patient who is inadvertently discharged with a missed diagnosis of cardiac ischemia, many important studies have identified the same or similar factors that lead to misdiagnosis. Lee and colleagues[6] found that patients sent home with missed MI were younger, had atypical symptoms, and were less likely to have a history of prior angina or known CAD. Additionally, roughly half of these patients had missed signs of ischemia on initial electrocardiogram (ECG). McCarthy and colleagues[7] had similar findings albeit with a lower incidence of misinterpreted ECGs. Several of these patients were diagnosed with ischemia but were thought to have stable rather than unstable angina. In a large multicenter study, Pope and colleagues[5] had similar findings and also found a continuing trend showing decreasing rates of misinterpreted signs of ischemia on ECG. They identified several, additional, significant factors in patients with missed cardiac ischemia, including women younger than 55 years and a 2-fold increase in inappropriate discharge of patients of nonwhite race.

In a recent multicenter study of missed MI in Canada, Schull and colleagues[11] found a high disparity in the number of missed MIs that inversely correlated to overall ED volume. The overall rate of missed MI in this study was 2-fold higher in low-volume facilities and ranged from 0% in EDs with the highest volume of patients to a staggering 29% at one low-volume facility. The conclusion was that higher-volume facilities with improved expertise and access to testing and consultants have the greatest ability to detect patients with cardiac ischemia.

In addition to facility volume, data in the literature demonstrate that physicians with greater experience are less likely to miss ACS. One study of litigation against emergency physicians for missed MI showed that the average number of years of ED experience was 2.6 years for those missing the diagnosis versus 5.1 years of ED experience for controls. Furthermore, physicians sued for a missed diagnosis were less likely to document cardiac risk factors or chest pain descriptors or, in some cases, even obtain an ECG.[9]

In summary, patients discharged from EDs with missed ischemia are generally younger or have atypical symptoms. Women and individuals of nonwhite race make up a larger percentage of these patients. Although a trend is seen in decreasing misinterpretation of the initial ECG, it continues to be a problem. Facilities with lower volumes of patients and physicians with less experience of working in an ED also have higher incidence of inadvertent discharge of these patients (**Box 2**).

## DEFINING THE PATIENT WITH LOW-RISK AND VERY LOW-RISK CHEST PAIN

There is no single prospectively validated study or, for that matter, body of literature that defines comprehensively the patient with low-risk chest pain or specifies what an acceptable miss rate might be. In the eyes of the individual physician, the patient, and the patient's family, the miss rate should be low; ideally approaching zero. Clearly, this is a very difficult, if not impossible, task to accomplish, arising from several issues. Foremost is the complete lack of standardized reporting guidelines for studies

**Box 2**
**Characteristics associated with increased inadvertent discharge of a patient with missed cardiac ischemia**

Younger patient age

Atypical symptoms

Women

Nonwhite race

Physician inexperience

Lower-volume EDs

Failure to detect ischemia on initial ECG

Failure to obtain an ECG

*Data from* Refs.[5–9,11]

evaluating risk stratification in patients with potential ACS, which makes comparisons between studies difficult, and hence, no single risk stratification tool has gained widespread use in day-to-day clinical practice.[12]

There are several studies in the literature that have proposed various risk stratification schemes to identify patients with low-risk chest pain. All these studies have sought to identify a group of patients who are unlikely to have cardiac ischemia and/or AMI and therefore do not need intensive management or hospital admission. Several more recent studies have gone a step further in identifying a very low-risk subset of patients (<1% likelihood of ACS) who may be safe for discharge from the ED without additional testing beyond an ECG, thorough history and physical examination, assessment of cardiac risk factors, and if indicated, cardiac biomarkers.[13–15]

## RISK STRATIFICATION

In the 1960s, the focus of a chest-pain evaluation centered on the diagnosis of AMI as evidenced by history, physical examination, and ECG findings. In 1963, coronary care units (CCUs) were developed in the United States primarily to treat lethal arrhythmias associated with AMI with pharmacologic management and early defibrillation. Before this time, one-third of patients admitted to hospitals with AMI died there. Because of the high mortality associated with AMI at the time, a concept of precoronary care was evolving. In 1967, Bernard Lown and colleagues[16] published an article advocating early monitoring in emergency wards and ''immediate hospitalization on mere suspicion of myocardial infarction.'' At the same time, the use of cardiac biomarkers, first identified in the mid 1950s, and stress testing were still in their infancy and had not gained widespread clinical use. It was not until 1979 that the World Health Organization (WHO) officially recognized the application of an increase and decrease of cardiac biomarkers in the diagnosis of AMI.[17] Because of the difficulty in making a clear-cut diagnosis of AMI at the time and of working with less reliable data elements , very large numbers of patients with chest pain were admitted to the nations CCUs, most of whom did not have AMI.

Toward the end of this era, the first decision-making tools were developed to assist with risk stratification in patients presenting with chest pain. In 1982, Goldman and colleagues[18] published a computer-based algorithm to assist in identifying ED patients having an AMI. This tool was intended to aid the clinician in making the

diagnosis of AMI and to decrease admission to CCUs in patients identified as low risk. However, it did not address the issues of unstable angina or of patients who were safe to discharge home from the ED.

As it became clear that there was a need to exclude the entire spectrum of ACS and in the face of the extreme cost of admitting large numbers of patients with chest pain to CCUs, the focus shifted to the development of chest-pain units where patients could be evaluated with a combination of ECG, biomarkers, and exercise stress testing. During this time, the focus of risk stratification models changed to include the diagnosis of cardiac ischemia in addition to AMI. In 1998, Selker and colleagues[19] published the Acute Cardiac Ischemia Time-Insensitive Predictive Instrument (ACI-TIPI) using the combination of age, sex, presence of chest pain, and ST-segment abnormalities to predict the likelihood of ACS. Although the tool was proven to be useful in triaging patients with higher-risk chest pain needing admission, it also lacked an adequate degree of sensitivity to be used by itself in the decision to discharge a patient with chest pain home without additional testing. A subsequent review of the sensitivity of the Goldman and the ACI-TIPI chest-pain stratification models has shown that the sensitivity of Goldman's risk score for detecting AMI is 90% and the ACI-TIPI for detecting cardiac ischemia is 86% to 95%.[20] Clearly, neither of these models provides the sensitivity to identify a group of patients that can be safely discharged home without additional evaluation.

An additional risk stratification tool, the thrombolysis in MI (TIMI) risk score, was published in 2000 and was originally validated on a high-risk patient population with known unstable angina or non–ST-elevation MI.[21] The tool, based on a 7-point scale, incorporates various elements, including age, risk factors, chest pain, prior CAD, use of aspirin in the previous week, positive biomarkers and ECG changes, and it was used to predict major ischemic complications at 14 days. Use of the TIMI risk score has been studied retrospectively and prospectively to assist in risk stratification in the ED of patients with low-risk chest pain.[22,23] Although the tool is excellent for identifying the highest-risk patients, those with a TIMI risk score of zero had an unacceptably high 30-day major ischemic complication rate of 1.7% to 2.1%, making its use problematic in identifying patients needing no further evaluation.[22,23] Recent efforts to improve the sensitivity of the TIMI risk score by combining a low score with a clear-cut alternative noncardiac diagnosis have also been evaluated. The results of this study demonstrated that the addition of a clear-cut noncardiac diagnosis in patients with lower TIMI risk scores did not significantly reduce major ischemic complications at 30 days.[24] Thus, the TIMI risk score does not have the sensitivity to identify patients who can be sent home from the ED without further diagnostic testing.

Later, Sanchis and colleagues[13] proposed a risk score with a primary end point of death or AMI within 1 year. This risk score improves on the original TIMI risk score and includes the cardiac biomarker troponin and a chest-pain score based on previously validated elements of the chest-pain history. A small subset of this population (17%) with a risk score of zero was deemed to be at very low risk and had no reported adverse outcomes at 1 year. However, individuals characterized as low risk by this model with a score of one had a 1-year adverse outcome rate of 3.1%.

An analysis of a subset of patients enrolled in the Rule Out Myocardial Infarction Using Coronary Artery Tomography (ROMICAT) Study has compared the sensitivity of the Goldman, TIMI, and Sanchis models in detecting ACS in ED patients with chest pain deemed to be candidates for CTA.[25] In this subset of patients, none of these models was sufficiently sensitive in detecting ACS, with all three having sensitivities falling to less than 90%.

The holy grail in the management of the patient with low-risk chest pain is identifying a subset of patients (deemed to be very low risk) who need no additional evaluation beyond a thorough history, ECG, and if indicated, cardiac biomarkers. The Vancouver Chest Pain Rule[14] has recently proposed a risk stratification model that includes age less than 40 years, no history of CAD, and a normal initial ECG result to define a very low-risk group. In addition, a very low-risk subset of individuals older than 40 years was also identified. In patients older than 40 years, further criteria were applied along with the characteristics described earlier. These included a combination of low-risk chest-pain characteristics (nonradiating pain and pain reproduced by palpation or pain described as pleuritic) combined with an initial creatine kinase MB (CK-MB) value less than 3.0 μg/L or if the CK-MB was higher than this threshold, lack of ischemic changes on repeat ECG or upward trending CK-MB or troponin value at 2 hours. Patients fitting into these criteria were deemed to be at very low risk of ACS. In this study, the sensitivity for detecting this very low-risk population was reported to be 98.8%. Furthermore, one-third of patients with chest pain evaluated in this particular study fit these criteria.

Hess and colleagues[26] reviewed 8 ED, chest-pain, decision prediction rules, including the Vancouver and Sanchis rules. After reviewing the methodology of the studies and evaluating the sensitivity and specificity of each for detecting ACS, the authors of this study have concluded that none of these models can be recommended for use in clinical practice.

It is important for the physician to understand that many early risk-stratification models were derived using high-risk patients. It is equally important that the emergency physician not equate low-risk chest pain to "no risk."

As of early 2009, no single study in the literature has been prospectively validated for adequate sensitivity to identify a subset of patients at low enough risk for discharge from the ED without further testing that may include exercise treadmill testing, nuclear scintigraphy, or coronary CTA.

## CLINICAL HISTORY

The patient's history is one of the most important pieces of information available to the clinician evaluating acute chest pain in the ED. The quality, location, duration, and modifying factors associated with a patient's chest pain are critically important in establishing the correct diagnosis. Although certain aspects of the clinical history are important in identifying patients at high risk of ACS, the clinician must be aware of the pitfalls associated with placing too much reliance on symptoms thought to be less typical of the disease. This is especially true in higher-risk patients, including the elderly, patients with known CAD, diabetics, and women. Studies have repeatedly shown an increased incidence of missed ACS in patients because the physician viewed the patient's symptoms as atypical.

## TYPICAL CHEST PAIN

Although some historians pointed to the possibility of earlier descriptions of angina in the medical literature, most agree that angina pectoris was first clearly described in 1768 by William Heberden.[27] Although Heberden had no knowledge of the pathophysiology of the condition, his classic description of angina pectoris included left-sided substernal pain, described as a strangling sensation worsened by exertion and relieved by rest, that radiated to the left arm. The condition was commonly seen in men older than 50 years, and as it progressed over time, the patients would invariably expire. Textbook descriptions of typical angina are variable. There is

excellent information in the literature regarding elements of the chest-pain history increasing the likelihood that the pain is from cardiac ischemia. For example, pain radiating to the one or both arms significantly increases the likelihood of ACS.[28,29] Pain radiating to the right arm or both arms is far more predictive of ACS than pain radiating to the left arm. Furthermore, pain described as pressure only minimally increases the likelihood ratio that the pain is cardiac in nature.[29] Since Heberden's time, there has been a continual refinement in the accepted description of ischemic chest pain. Current guidelines published by The National Heart Attack Alert Program Coordinating Committee on recognition of symptoms potentially associated with cardiac ischemia describe the presentation as follows: Pain, if present, is described as pressure, tightness, or heaviness. It may radiate to the neck, jaw, shoulders, back, or one or both arms. The pain may also be described as indigestion or heartburn with associated nausea and/or vomiting. Additional symptoms in the absence of pain may include shortness of breath, weakness, dizziness, lightheadedness, or loss of consciousness.[30] This description serves as a useful tool and illustrates the wide constellation of symptoms associated with this disease process, many of which may be considered atypical by the inexperienced clinician.

## ATYPICAL CHEST PAIN

Many clinicians use the presence of typical features in helping establish the diagnosis of ACS and atypical features to help disprove it. Unfortunately, the literature has proven that things are not quite so black-and-white. Webster's dictionary defines atypical to mean unusual or not ordinarily encountered. Symptoms referred to as atypical chest pain include those signs and symptoms that do not fit the classically described complaints typically associated with myocardial ischemia. There is currently no consensus opinion on what exactly defines ''atypical'' chest pain.[29] Lee and colleagues[31] reviewed the clinical history of nearly 600 patients presenting with chest pain and found that a combination 3 variables defined a low-risk group with no identified cases of ACS: (1) sharp or stabbing pain; (2) no history of angina; and (3) pain reproduced by palpation or position. Without this combination of variables, 5% of patients whose pain was described as sharp, stabbing, or pleuritic, or could be reproduced by palpation were diagnosed with AMI.[31] A separate study of patients meeting the diagnostic criteria for costochondritis found that 6% of patients actually had enzyme-proven MI.[32] Furthermore, atypical symptoms, such as burning pain and indigestion, long considered to be more suggestive of a GI cause by many physicians, has been shown to be equivalent to pressure in patients with documented myocardial ischemia.[28,29,31]

One of the major problems with an individual's chest-pain symptoms is that they are subjective and will always be so. Cultural and ethnic differences and language barriers in different patient populations further complicate the issue. Underlying diseases, such as psychiatric illness, further cloud the picture. In one illustrative study, an actress portrayed the same chest-pain history in a businesslike and then in a histrionic fashion. Physicians were nearly 5 times less likely to believe a cardiac cause of the patient's pain in the histrionic patient.[33] It is critically important that the clinician evaluating acute chest pain understand that many of the symptoms classically regarded as atypical may in fact be representative of ischemia or could even be typical myocardial ischemia. Multiple reviewers have all come to the same conclusion regarding a patient's history. Specifically, there is no single historical element that can be used to safely discharge a patient with potential ACS without additional testing. In

patient with high-risk features, using the presence of atypical symptoms to exclude the diagnosis of ACS is fraught with danger.

## ACS IN THE ABSENCE OF CHEST PAIN

Complicating an already difficult problem is the issue of silent ischemia. Fully 25% of patients in the Framingham study, arguably the most studied group of patients in history, have been found to have a Q-wave MI on routine annual ECGs that was so atypical in presentation that it escaped medical detection.[34] More than half of these patients had no recollection of the event, signifying a truly silent MI. More sobering is the finding of a recent study using delayed enhancement cardiovascular magnetic resonance imaging in high-risk patients that has indicated an incidence of unrecognized non–Q-wave infarction that is 3-fold higher than unrecognized Q-wave infarction.[35] Extrapolated to the entire population, this represents a staggering number of unrecognized MIs.

Studying the presenting symptoms of patients with recognized infarction, Canto and colleagues[36] reviewed the clinical presentation of more than 434,877 patients reported in the National Registry of Myocardial Infarction 2 database (NRMI-2) between 1994 and 1998 with a diagnosis of AMI. Thirty three percent of these patients did not have chest discomfort or arm, neck, or jaw pain on initial presentation to the hospital. AMI patients presenting without chest pain were, on average, 7 years older and had a higher population of women and diabetics than these patients presenting with chest pain. Brieger and colleagues[37] reviewed more than 20,000 cases of ACS in the Global Registry of Coronary Events (GRACE) database. In this population, 8.4% did not have chest pain at presentation and almost a quarter of these were not recognized to have ACS on their initial presentation. The most common symptom in the absence of chest pain was dyspnea followed by diaphoresis, nausea, and syncope. Similar to Canto's findings, this group of patients was also far more likely to be elderly, female, hypertensive, diabetic, or have a history of congestive heart failure.

To summarize, the greatest pitfall for the emergency physician in evaluating a patient with ACS in the absence of chest pain is failing to consider the diagnosis of cardiac ischemia entirely. Specific symptoms by themselves in the absence of chest pain may in fact be anginal equivalents in certain patient populations. If the patient fits the criteria described earlier, such as an elderly diabetic with syncope or an 80-year-old man with unexplained dyspnea, the physician must have a high degree of suspicion and include ACS high on their differential diagnosis and must manage the patient aggressively.

## PRECIPITATING FACTORS

There are several activities that may precipitate acute ischemia. Culic[38] performed a meta analysis reviewing 17 different studies covering more than 10,000 patients with AMI and identified several important triggers. In this review, nearly 35% of patients with AMI were performing some kind of physical activity. Patients were found to be eating in 8.2% of cases and 6.8% of patients reported emotional stress before the event. The study also found that 20% of patients were awakened from sleep.

The important factor demonstrated here is that the physician should not discount emotional stress or eating as precipitating factors and assign an alternate cause for the patient's symptoms, such as anxiety or GI cause.

## RELIEVING FACTORS

Many individuals incorrectly assume that because a patient's chest pain is relieved with nitroglycerine, the pain is more likely to be cardiac in nature. In examining this question, Henrikson and colleagues[39] found a higher incidence of relief of chest pain in patients without ACS than those with active ischemia. Steele and colleagues[40] also found that nitroglycerine relieved chest pain in 66% of patients who were ultimately diagnosed with noncardiac chest pain. This data shows that chest-pain relief by nitroglycerine had no value in predicting or disproving ACS. Similarly, physicians have used the GI cocktail (a mixture of antacids and viscous lidocaine) to prove the likelihood of a GI cause and disprove the presence of ACS. There is no recent literature supporting the use of the GI cocktail for differentiating these types of pain, but the practice persists. Many physicians believe that burning substernal pain relieved by antacids is clearly caused by esophagitis or gastritis. Subsequent studies have actually shown that ''burning'' chest pain or pain described as ''indigestion'' may be as strong a descriptor of ischemia as chest pressure.[28,31] In a small descriptive study, Wrenn and colleagues[41] found indiscriminate use of the GI cocktail for various ED complaints. In this subset, a significant portion of patients who were subsequently admitted with possible myocardial ischemia reported total or partial relief after administration of a GI cocktail.

In summary, chest-pain relief with either nitroglycerine or GI cocktail does nothing to improve the diagnostic accuracy for ACS and should not be used to influence decision making.

## CARDIAC RISK FACTORS

There are a large number of conditions and behaviors that have traditionally been associated with the development of CAD. These classic risk factors are advanced age, male sex, diabetes mellitus, smoking, hypertension, hypercholesterolemia, and the presence of premature coronary disease in a first-degree relative. In addition to these well-recognized risk factors, a host of other conditions are known to be associated with the development of CAD, whereas others are now known to be involved in AMI in patients with normal coronary arteries (**Box 3**). It would seem intuitive that assessing risk factors or risk-factor burden can guide a physician's disposition of an individual patient and many physicians use the presence or absence of cardiac risk factors to guide management. Jayes and colleagues[42] examined whether the presence of classic cardiac risk factors had significant predictive value in diagnosis of acute ischemia in the ED. The findings of this study showed that except for diabetes and a positive family history in male patients, classical risk factors were of little additional value in predicting ischemia. Although these 2 risk factors were found to be important, they conferred only a 2-fold increase in risk for acute ischemia. This was far less than the relative risk of a compelling history or ECG abnormalities.[42] Nearly 20% of patients with known ischemic heart disease do not have conventional risk factors of CAD, which illustrates the potential pitfalls of over-reliance on risk factors in the acute setting.[43] The clinician must be aware that risk factors predict the development of CAD over a lifetime and do not correlate at all well with the risk of ischemia in a patient with acute chest pain.

One possible exception to this rule is the absence of cardiac risk factors in patients younger than 40 years. Several studies have shown that patients younger than 40 years without identifiable risk factors are at low risk of ACS.[14,15,44]

In looking at overall risk-factor burden, Han and colleagues[44] found increasing likelihood of ACS as the total number of risk factors increased. This was especially

**Box 3**
**Risk factors of CAD**

- Classic or traditional risk factors
  - Advanced age
  - Male sex
  - Hypertension
  - Diabetes mellitus
  - Hypercholesterolemia
  - Premature CAD in a first-degree relative
  - Cigarette smoking
- Nontraditional risk factors
  - HIV
  - Systemic lupus erythematosus
  - End-stage renal disease
  - Cocaine
  - Type A personality
  - Genetic and acquired thrombophilias

important in patients younger than 40 years. However, in patients older than 40 years, absence of risk factors was insufficient in itself to rule out ACS.

In patients older than 40 years, cardiac factors are of very little use in the acute setting in the diagnosis of ACS. Hence, they should not be used to alter physicians' judgment in this patient population.

## GENDER DIFFERENCES

In general, men develop coronary disease 7 to 10 years earlier than women. Clear differences do exist in the presentation of ACS between men and women. In a study of 1450 patients with documented MI, Goldberg and colleagues[45] defined differences in symptom presentation based on gender. Findings from the study showed that men were less likely to complain of neck, back, or jaw pain and were less likely to present with nausea. Canto and colleagues[46] confirmed these findings and found a higher proportion of women with ACS reporting indigestion, fatigue, palpitations, and weakness. Women with ACS also have a higher total number of associated symptoms and risk factors than men and generally present at a more advanced age.[46,47] Amongst individuals with advanced disease, women were less likely to be treated aggressively and had a higher mortality.[47]

## CHEST PAIN AND ACS IN YOUNG ADULTS

CAD is uncommon in individuals younger than 40 years, and in the United States, CAD in this age group has a prevalence of 0.8% in men and women.[4] It is important to be aware that MIs do occur with some frequency in younger patients and approximately 6% to 10% occur in patients younger than 45 years.[48] Most of these patients (80%) are men and have single-vessel coronary disease. Up to 20% of these patients do not have coronary atherosclerosis.[48] Berenson and colleagues[49] studied the presence

of coronary atherosclerosis in young adults at autopsy to identify risk factors for the development of CAD. In this population, elevated body mass index, hyperlipidemia, hypertension, and smoking were all strongly correlated with the development of premature CAD. Prior studies have also strongly linked poorly controlled diabetes to premature coronary atherosclerosis.[49]

In a study of clinical characteristics and outcomes of ED patients younger than 40 years with chest pain, Walker and colleagues[50] found a 4.7% incidence of ACS. Within this group, however, a population at very low risk of ACS was identified. Amongst this group of patients with chest pain and no history of cocaine use, individuals without a known history of CAD, a normal ECG result, no classic cardiac risk factors, and normal cardiac biomarker levels were found to have had less than 0.5% risk of ACS. Marsan and colleagues[15] prospectively validated Walker's original study. In this group, an adverse 30-day outcome was defined by the need for bypass surgery, angioplasty, or by AMI or death. Once again, the overall incidence of ACS in this cohort was not insignificant, with 5.4% of patients in the study being diagnosed with ACS, and the very low-risk patient group (normal ECG results, normal enzyme levels, and no cardiac risk factors) was found to have a very low rate (0.14%) of adverse events at 30 days.

In summary, the physician should be acutely aware of the potential for ACS in younger patients and that age, by itself, cannot and should not be used to assign a patient to a very low-risk group. Roughly 5% of patients younger than 40 years presenting with chest pain have cardiac ischemia. Although young patients are less likely to present with ACS, those with a compelling history and cardiac risk factors, either traditional or nontraditional, should prompt a careful evaluation.

## CARDIAC ISCHEMIA IN THE ELDERLY

The elderly patient population stands to gain the most from rapid recognition of and intervention in ACS, yet studies continue to indicate lower use of invasive treatments and cardiovascular medications amongst this patient population.[51] AMI carries a significantly higher risk of death in the elderly patient; 82% of patients who die from CAD are aged 65 years or older and one-third of deaths in this population are a result of ischemic heart disease.[4]

Difficulties arise in the evaluation of elderly patients with ACS primarily due to an increasing number of vague and atypical symptoms and the wide constellation of complaints that are associated with ACS in this patient group. ACS may also accompany another acute incident in the elderly, such as a fall or a cerebrovascular accident, and may therefore be missed. Age-related neurologic diseases, such as dementia, further cloud this picture. In a study of a large population of Medicare beneficiaries with unstable angina, Canto and colleagues[52] found that more than half had presentations that were categorized as atypical. These complaints included dyspnea, nausea, diaphoresis, syncope, or pain primarily localized to the arm, neck, jaw, or abdomen. Data from the NRMI has shown that only 60% of patients 85 years or older had no chest pain on initial presentation.[51] Amongst patients presenting with ACS in the absence of chest pain, up to 25% are missed on initial presentation.[37] Despite the importance of obtaining a rapid ECG, recent literature has demonstrated that the elderly are less likely to have an ECG performed in a timely fashion or to receive appropriate initial care.[53]

Most physicians recognize the elderly to be at high risk of ACS. The major pitfall in this group of patients is the wide variety of atypical presentations that may be seen and the physician's failure to recognize that these symptoms may be arising from cardiac ischemia.

## THE PHYSICAL EXAMINATION

As medicine has advanced, many think that the physical examination has taken on a less important role than sophisticated imaging and laboratory testing in a patient's evaluation. Although the physical examination is extremely important for many disease processes, it is of little benefit in establishing a diagnosis of ACS in the patient with low-risk chest pain, and results are often normal. Physical signs associated with ACS, such as heart failure, are rare in most patients with ACS. The most common finding in acute ischemia is the presence of a fourth heart sound.[54] However, the noisy ED environment is often a difficult place to hear subtle and often fleeting heart sounds. Furthermore, more recent information from a study using digitally recorded heart sounds on patients with chest pain showed no statistical association between abnormal heart sounds and ACS.[55] The physical examination is of limited use in establishing a diagnosis of ACS; its value however lies in assisting with finding or excluding an alternate diagnosis.

## PHYSICIANS INITIAL IMPRESSION AND JUDGMENT

To perform initial risk stratification of patients presenting with acute chest pain, physicians must rely on various immediately available data elements, including the patient's chest pain history, risk factor profile, physical examination, and initial ECG. Miller and colleagues[56] studied whether the physician's initial impression of noncardiac chest pain based on these data elements was sufficient information to send the patient home without further testing. The results of this study looked at physicians' impressions for 17,737 patients with chest pain older than 18 years enrolled in the multicenter chest-pain registry, Internet Tracking Registry of Acute Coronary Syndromes (i*trACS). In this study, patients were assigned to several categories, including definite unstable angina or AMI and high-risk, low-risk, or noncardiac chest pain. After the initial evaluation, physicians assigned 20.8% of patients to this noncardiac group. These patients had further evaluations, including biomarkers and stress testing, at the discretion of the treating physician. Adverse outcomes, including AMI, revascularization at 30 days, or cardiac death, were measured. Findings within this noncardiac chest-pain group showed that 2.8% had a definite cardiac event at 30 days. Further analysis of these patients showed that those who had adverse outcomes were older and more likely to have traditional risk factors of CAD or known CAD.

In another study, Hollander and colleagues[57] examined the relationship between the physician impression of a clear-cut alternative diagnosis and 30-day adverse outcomes for chest pain. After initial ED evaluation, including biomarkers if requested, physicians were asked if the patient had a clear-cut alternative diagnosis, such as gastroesophageal reflux, musculoskeletal pain, or other noncardiac cause. In this study 30% of patients were thought to have a clear-cut alternative chest-pain diagnosis, yet at 30 days, 4% had an adverse cardiac outcome.

Although physician judgment is critically important and can be used to improve risk stratification, it must be tempered with the evidence that in patients with advancing age, known CAD or risk-factor burden, an impression in itself, is not enough information to safely send a patient home without further testing.

## THE INITIAL ECG

Electrical activity in the heart was first recognized in the mid 1800s. In 1920, ST elevation was first described in association with a patient having an AMI.[58] Today,

the 12-lead ECG continues to be the single most important and most rapidly available diagnostic test used in the management of the patient with chest pain.

Any ECG changes should be considered important. Studies of patients discharged from the ED with a missed diagnosis of myocardial ischemia have shown that a major reason is misinterpretation of the ECG.[5–7] Virtually all risk stratification schemes assign higher risk to patients with abnormal ECG results.

Objective findings such as ST depression on presentation carry significant mortality. In one study of more than 250,000 patients in the NRMI database, patients with ST depression had an in-hospital mortality of 15.5%, which was equivalent to that of patients with an ST-segment elevation myocardial infarction (STEMI).[59] Furthermore, any T-wave abnormalities, including T-wave inversion and flattening, carry higher risks of cardiovascular events at 30 days.[60]

Several studies in the not-so-distant past have suggested that a normal or nonspecific ECG result portends low morbidity and mortality, and deferred outpatient testing in this patient population was recommended. Approximately 50% of patients with unstable angina and non–Q-wave MI do not have significant abnormalities on ECG. Welch and colleagues[61] reviewed initial ECG findings from the NRMI database in 391,208 patients with documented AMI. Within this patient population, 7.8% had a normal ECG result and 35.2% had nonspecific ECG findings on initial presentation. Based on this data, it is clear that a normal or nonspecific ECG finding cannot, by itself, be used to rule out ischemia.

Testing the hypothesis that the sensitivity of the ECG would be greater on symptomatic patients, Chase and colleagues[62] examined the prognostic value of a normal or nonspecific ECG obtained while the patient was experiencing chest pain. The results of this study indicated that patients with normal or nonspecific ECG findings obtained during pain had similar 30-day adverse outcome rates to those whose ECG had been obtained after their pain had subsided.

A normal or nondiagnostic ECG has been shown to be one of the most likely reasons that a patient was discharged with missed cardiac ischemia. The physician managing a patient with acute chest pain should recognize that an ECG represents a single snapshot in the patient's presentation and may be normal or nondiagnostic even in the face of active ischemia. Furthermore, ECG findings are often dynamic in patients with ACS. Strategies, such as continuous ST-segment trend monitoring and aggressive use of serial ECGs, may be of help but are less useful if a patient's pain has resolved. Physicians should not rely on a normal ECG alone in disposition of patients without further evaluation.

## CARDIAC BIOMARKERS

Cardiac biomarkers are an essential component in the initial workup of patients with possible ischemic chest pain. The first cardiac biomarkers were identified in 1954 but did not gain widespread clinical use for more than 20 years.[17] Through the 1970s, assays were plagued with issues with sensitivity and it was not until the age of immunoassays in the 1980s that the use of cardiac biomarkers realized their full potential.

Today, the gold standard biomarker for diagnosing AMI is troponin[63] and immunoassays for cardiac troponin. Troponin T and I can be used to detect myocardial necrosis with a high degree of sensitivity.

An early investigation[64] looked at the prognostic value of a negative troponin T or troponin I value at presentation in ED patients with acute chest pain. In this study, the investigators concluded that patients with negative troponin values were at low

risk and could safely be discharged from the ED with no additional testing. Several studies performed since then have shown that this is clearly not the case. Subsequent evaluations of the prognostic value by 2 larger studies have found that a normal initial troponin value had low sensitivity for predicting cardiac events.[65,66] Hence, although both studies found a normal troponin value to be beneficial in risk stratification, it does not assure a favorable prognosis and cannot be used by itself to guide management in the low-risk patient population.

The literature has shown that the use of serial biomarkers can assist in detection of ACS. Fesmire and colleagues[67] have devised a protocol using a combination of ECG findings, comparison of 2-hour serial cardiac biomarkers, and physician judgment with a sensitivity that approaches 85% for detecting ACS in high- and low-risk patients. An upward trend in biomarkers has been shown to have significant power for detecting ACS. Some physicians have incorporated the increased discriminatory power of serial markers in decision making to discharge low-risk patients without further workup. The authors caution against this practice without further testing in all but patients determined to be at very low risk.

Many physicians continue to obtain troponin and CK-MB. Storrow and colleagues[68] looked at the odds ratio (OR) for ACS with discordant values of CK-MB and troponin. Both groups of patients, one found to have elevated troponin and normal CK-MB level and the other, normal troponin and elevated CK-MB level, were at higher risk of ACS (OR 4.8 and 2.2, respectively). Additionally, the finding of elevated CK-MB level with a normal total CK value was also associated with a higher incidence of ACS.

In summary, a single normal cardiac biomarker level cannot be used to rule out ACS. Although serial biomarkers can improve the detection of ACS, the physician should use careful judgment of the patient population on which they can be used without further testing. Finally, the finding of discordant biomarkers identifies higher-risk groups that should undergo further testing.

## PRIOR NEGATIVE CARDIAC WORKUP

A frequent issue facing the emergency physician is a patient who presents to the ED with chest pain who has undergone a prior stress test or cardiac catheterization. Although cardiac catheterization remains the gold standard in diagnosing CAD and there is excellent literature on the favorable short-term prognosis of discharged patients who have undergone stress testing of all types, there is little information in the literature on the management of patients who return to the ED after a negative result in chest-pain workup.

In cases where the stress test result is abnormal or catheterization shows disease, the management is more straightforward. Patients who have known disease should never be considered low risk. In patients where a prior workup had negative results, the issue becomes more complex.

The 3-year event rate for patients with prior negative stress testing results has been reported as being between 5% and 15% in several small studies.[69,70] A negative stress test result by itself does not rule out coronary disease. A stress test can be considered valid during the time it is performed to rule out ischemia as the cause of a patient's chest pain during that visit. As a result, many physicians have a low threshold for repeating stress testing on subsequent chest-pain evaluations. In the only study examining the impact of a prior negative stress test result on physician management patterns for patients returning to the ED with chest pain, it was found that patients were admitted with a prior negative stress test result at the same rate as those who had never had a stress test.[71]

Many physicians take comfort in a prior normal cardiac catheterization and a belief that this portends very low risk for the patient re-presenting with chest pain. A small study of 17 patients with angiographically normal coronaries found that only 2 (11.7%) had developed coronary disease at the time of repeat angiogram (averaging 9 years between procedures).[72] A later study covering 1-year events rates in 7656 patients with mild CAD (<50% stenosis) or normal coronary arteries pooled from 3 large randomized trials found a serious event rate (defined as death or AMI) of 3.3% and 1.2% in these 2 groups, respectively.[73] These data are at odds with many physicians' belief that a normal angiogram equates to no short-term risk of ACS. It has been known for many years that by their very nature, angiograms may miss clinically important lesions,[74] and hence, the clinician should not be overly reliant on the results of a prior normal angiogram if clinical concern is sufficient.

In summary, although a prior negative angiogram may be helpful in risk stratification, in a patient with a compelling history or in a high-risk clinical situation, it cannot be used alone to discharge a patient without further testing.

## SUMMARY

Risk stratification and management of the patient with low-risk chest pain continues to be challenging despite considerable effort on the part of numerous investigators. At least, there is now evidence that a specific subset of young patients can be defined as a very low-risk group in whom further testing may not be necessary. For all other patients, the physician must have a high index of suspicion for ACS and understand the myriad of often subtle and atypical presentations of ischemic heart disease, especially in certain patient populations such as the elderly.

Although the initial history, ECG, and biomarkers are critically important, obtaining serial ECGs and biomarkers improves sensitivity in detecting ACS. However, physicians must always keep in mind that for many patients with atypical symptoms, relying on normal or unchanged ECG findings, negative cardiac biomarker levels, or the absence of cardiac risk factors, is not enough to safely discharge a patient without further workup. Hence, some type of objective testing such as exercise treadmill testing, nuclear scintigraphy, stress echocardiography, or coronary CTA, should be strongly considered before, or soon after, discharge in all patients who do not have a clearly explained reason for their chest pain.

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