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<p>For patients who have acute coronary syndromes (ACS), risk stratification is key to initiating appropriate treatment. For ST-segment elevation MI, immediate reperfusion therapy is needed, and thus rapid identification of ST elevation on the ECG is critical. Then, having a standardized protocol for rapid treatment—with either primary percutaneous coronary intervention or thrombolysis—is critical. For unstable angina/non-ST elevation ACS, after first identifying the patients who have a higher likelihood of actually having an ACS (as opposed to noncardiac chest pain) stratification to high versus lower risk is needed to choose appropriate therapies. Thus, it is important for risk stratification to be a central part of all management of patients who have ACS.</p>	
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<p>Each year in the United States, over 8 million patients present to the emergency department (ED) with complaints of chest discomfort or other symptoms consistent with possible acute coronary syndrome (ACS). While over half of these patients are typically admitted for further diagnostic evaluation, fewer than 20% are diagnosed with ACS. With hospital beds and inpatient resources scarce, these admissions can be avoided by evaluating low- to moderate-risk patients in chest pain units. This large, undifferentiated patient population represents a potential high-risk group for emergency physicians requiring a systematic approach and specific ED resources. This evaluation is required to appropriately determine if a patient is safe to be discharged home with outpatient follow-up versus requiring admission to the hospital for monitoring and further testing.</p>	
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Failure to diagnose patients who have acute coronary syndromes (ACSs)—either acute myocardial infarction (AMI) or unstable angina pectoris (UAP)—who present to the

emergency department (ED) remains a serious public health issue. Better understanding of the pathophysiology of coronary artery disease has allowed the adoption of a unifying hypothesis for the cause of ACSs: the conversion of a stable atherosclerotic lesion to a plaque rupture with thrombosis. Thus, physicians have come to appreciate UAP and AMI as parts of a continuum of ACSs. This article reviews the state of the art regarding the diagnosis of ACSs in the emergency setting and suggests reasons why missed diagnosis continues to occur, albeit infrequently.

## **Use of Biomarkers in the Emergency Department and Chest Pain Unit**

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Allan S. Jaffe

The use of biomarkers of cardiac injury in the emergency department (ED) and observation unit settings has several nuances that are different and, therefore, worthy of its own set of use guidelines. The markers that are used, however, are the same. The primary marker of choice continues to be cardiac troponin (Tn). Other markers that have been used because of the need in the ED for rapid triage have been myoglobin and fatty acid binding protein. In addition, some centers still prefer less sensitive and less specific markers such as creatine kinase myocardial band (CK-MB). More recently, a push has occurred to develop markers of ischemia, such as ischemia modified albumin (IMA), to determine which patients have ischemia, even in the absence of cardiac injury. As troponin assays become more sensitive and method for use becomes better understood, the use of these other markers are being relegated to lesser and lesser roles. Markers of ischemia are useful, but at present, despite some enthusiasm, are not ready for routine use. Before describing the recommendations for clinical use of biomarkers in the ED, a basic understanding of some of the science and measurement issues related to these analytes is helpful.

## **Point-of-Care Testing and Cardiac Biomarkers: The Standard of Care and Vision for Chest Pain Centers**

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Gerald J. Kost and Nam K. Tran

Point-of-care testing (POCT) is defined as testing at or near the site of patient care. POCT decreases therapeutic turnaround time (TTAT), increases clinical efficiency, and improves medical and economic outcomes. TTAT represents the time from test ordering to patient treatment. POC technologies have become ubiquitous in the United States, and, therefore, so has the potential for speed, convenience, and satisfaction, strong advantages for physicians, nurses, and patients in chest pain centers. POCT is applied most beneficially through the collaborative teamwork of clinicians and laboratorians who use integrative strategies, performance maps, clinical algorithms, and care paths (critical pathways). For example, clinical investigators have shown that on-site integration of testing for cardiac injury markers (myoglobin, creatinine kinase myocardial band [CK-MB], and cardiac troponin I [cTnI]) in accelerated diagnostic algorithms produces effective screening, less hospitalization, and substantial savings. Chest pain centers, which now total over 150 accredited in the United States, incorporate similar types of protocol-driven performance enhancements. This optimization allows chest pain centers to improve patient evaluation, treatment, survival, and discharge. This article focuses on cardiac biomarker POCT for chest pain centers and emergency medicine.

## **Markers of Cardiac Ischemia and Inflammation**

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Tracy Y. Wang, Wael A. AlJaroudi, and L. Kristin Newby

Because biomarkers of myocardial necrosis only become positive in the setting of myocardial necrosis and disruption of cellular integrity, the diagnosis of myocardial infarction can only be made in retrospect. Ideally, one would like to identify patients at risk for complications before myocardial necrosis occurs. Insights into the pathophysiology of atherothrombosis have allowed development of novel markers to detect not only early ischemia without myocyte death but also early indicators of coronary inflammation in patients who have preclinical atherosclerosis.

<b>Exercise Testing in Chest Pain Units: Rationale, Implementation, and Results</b>	<b>503</b>
Ezra A. Amsterdam, J. Douglas Kirk, Deborah B. Diercks, William R. Lewis, and Samuel D. Turnipseed	

Chest pain units are now established centers for assessment of low-risk patients presenting to the emergency department with symptoms suggestive of acute coronary syndrome. Accelerated diagnostic protocols, of which treadmill testing is a key component, have been developed within these units for efficient evaluation of these patients. Studies of the last decade have established the utility of early exercise testing, which has been safe, accurate, and cost-effective in this setting. Specific diagnostic protocols vary, but most require 6 to 12 hours of observation by serial electrocardiography and cardiac injury markers to exclude infarction and high-risk unstable angina before proceeding to exercise testing. However, in the chest pain unit at UC Davis Medical Center, the approach includes "immediate" treadmill testing without a traditional process to rule out myocardial infarction. Extensive experience has validated this approach in a large, heterogeneous population. The optimal strategy for evaluating low-risk patients presenting to the emergency department with chest pain will continue to evolve based on current research and the development of new methods.

<b>Imaging in the Evaluation of the Patient with Suspected Acute Coronary Syndrome</b>	<b>517</b>
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Over the last decade, major advances have been made in the treatment of acute coronary syndromes (ACSs). However, effective implementation of these treatments requires timely and accurate identification of the high-risk patient among all those presenting to the emergency department (ED) with symptoms suggestive of ACS. The opportunity for improving outcomes is time-dependent, so that early identification of the patient who has true ACS is essential. This necessity further increases the need for rapid triage tools, especially in the current setting of ED and hospital overcrowding that has become the norm in large urban centers.

<b>Echocardiography in the Evaluation of Patients in Chest Pain Units</b>	<b>531</b>
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Using percutaneous angioplasty to induce the ischemic cascade in the cardiac catheterization laboratory, echocardiographic wall motion abnormalities have been documented to precede electrocardiographic abnormalities and angina. Therefore, detection of cardiac wall motion abnormalities is potentially more sensitive than the history, physical examination, and ECG for identification of myocardial ischemia. Echocardiography is highly reliable for assessing cardiac wall motion and, thus, it has been used for diagnosis and risk assessment in patients presenting to the emergency department (ED) with symptoms suggestive of myocardial ischemia. In patients who have acute ST-elevation myocardial infarction (MI), echocardiography is comparable to invasive left ventriculography for detecting wall motion abnormalities. However, the usefulness of echocardiography in the low-risk population that has chest pain of uncertain origin and a nondiagnostic initial presentation is less well established.

<b>Newer Imaging Methods for Triage Patients Presenting to the Emergency Department with Chest Pain</b>	<b>541</b>
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The usefulness of electron beam CT (EBCT) for the risk stratification of patients in the emergency department (ED) who have possible acute coronary syndrome has been evaluated in three small studies. The results of these studies are promising, as patients who have no coronary calcium detected by EBCT essentially had no adverse cardiac events.

Although the negative predictive value of EBCT was excellent, the limited positive predictive value that would lead to further diagnostic testing makes this strategy less attractive if applied to a broad population. Further larger studies may help define which patients in the ED who have chest pain and nondiagnostic ECGs can be effectively evaluated by EBCT. Recent advances in noninvasive coronary angiography by multislice computed tomography are of considerable interest in the ED evaluation of patients with undefined chest pain, but the utility of this method in this setting awaits clinical studies.

### **Chest Pain Units: Management of Special Populations**

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Deborah B. Diercks, J. Douglas Kirk, and Ezra A. Amsterdam

Chest pain units provide an important alternative to traditional hospital admission for patients who present to the emergency department with symptoms compatible with acute coronary syndrome and a normal or inconclusive initial evaluation. Although patient subgroups such as women, diabetics, those with established coronary artery disease, and those with symptoms related to stimulant use present unique challenges, management in a chest pain unit appears to be appropriate in these populations. Judicious application of accelerated diagnostic protocols and current testing methods can promote safe, accurate, and cost-effective risk stratification of special populations to identify patients who can be safely discharged and patients who require hospital admission for further evaluation.

### **Management of the Patient with Chest Pain and a Normal Coronary Angiogram**

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Eric H. Yang and Amir Lerman

Angina in the setting of a normal coronary angiogram (NOCAD) occurs in 20% to 30% of patients undergoing coronary angiography. The management of these patients can be challenging and requires a correct diagnosis of the etiology. The differential diagnosis of NOCAD can be classified anatomically into three categories: (1) epicardial disease, (2) coronary microvascular dysfunction, and (3) noncoronary disease. The pathophysiology of NOCAD and a systematic diagnostic approach to these patients is reviewed. Potential therapeutic options and prognosis are also discussed.

### **Using the Emergency Department Clinical Decision Unit for Acute Decompensated Heart Failure**

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W. Frank Peacock

Acute decompensated heart failure (ADHF) is a complex disease of epidemic proportions. In the United States, it accounts for more than 1 million hospitalizations annually, and heart failure represents the single greatest cost to the Centers for Medicaid and Medicare Studies. Half of the annual costs are estimated to be the result of hospitalization. Compared with other pathology, heart failure has a very high hospitalization rate, with 80% of emergency department ADHF patients being admitted. This high rate has resulted from the lack of successful management predictors available to the emergency physician and the lack of any disposition option other than hospitalization for the ADHF patient. The emergency department observation unit offers an alternative to hospitalization for patients with ADHF. Validated protocols have demonstrated that in ADHF, intensive short-term therapeutic, diagnostic, and educational protocols result in a marked improvement in hospitalization rates, while at the same time decreasing costs. New risk stratification data can aid in the identification of the appropriate candidate. The observation unit now represents a nonhospitalization disposition option for patients presenting to the emergency department with ADHF.

## **Cost Effectiveness of Chest Pain Units**

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Sandra Sieck

Health care facilities face many challenges in their attempts to provide cost-effective care without sacrificing quality. One key factor in producing quality outcomes while maintaining economic profitability is the establishment of a cost-effective outpatient care environment. Chest Pain Units (CPUs) have evolved to provide a streamlined approach to acute cardiac care that emphasizes optimal efficiency initiated at the point of entry. The Centers for Medicare and Medicaid Services have structured new reimbursement approaches designed to shift care from the inpatient setting and “reward” efficient and appropriate care delivered in the outpatient arena. These new reimbursement strategies have transformed the CPU into an economically viable entity for the acute care facility and also have afforded opportunities to enhance the quality of care delivered to the acute cardiac patient.

## **Medical Error Prevention in ED Triage for ACS: Use of Cardiac Care Decision Support and Quality Improvement Feedback**

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Denise H. Daudelin and Harry P. Selker

Medical errors in the care of patients who present with acute coronary syndrome (ACS) include errors in emergency department (ED) triage, such as the decision to send home a patient who presents with ACS or to hospitalize a patient who does not have ACS to the cardiac care unit (CCU), and errors in treatment, such as the failure to promptly use reperfusion therapy for patients who present with ST-elevation acute myocardial infarction (AMI). ECG-based acute cardiac ischemia time-insensitive predictive instrument (ACI-TIPI) and thrombolytic predictive instruments (TPIs), with a linked TIPI information system (TIPI-IS), provide real-time, concurrent, and retrospective decision support tools and feedback for the prevention of medical errors in the care of patients who present with ACS. In real-time, ACI-TIPI probabilities printed on the ECG header for the ED physician, provide an additional piece of information for triage decision making, and the ACI-TIPI Risk Management form reduces liability risk by prompting consideration and documentation of key clinical factors in the diagnosis of ACI. Also in real-time, the TPI increases overall coronary reperfusion therapy use. Concurrent flagging by TIPI-IS uses electronically acquired ECG and hospital data to provide concurrent alerts about potential misdiagnosis or mis-triage of patients with ACS. Retrospectively TIPI-IS-based feedback reports allow performance improvement. These examples of information technology tools integrated into ECG equipment already used in hospitals to deliver patient care demonstrate the potential to adapt other existing equipment or other patient care activities to enhance patient safety and error reduction.

## **Cumulative Index 2005**

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## Foreword Chest Pain Units



Michael H. Crawford, MD  
*Consulting Editor*

Chest pain units have been enthusiastically embraced by some medical centers and disdained as marketing ploys by critics. Whether you have one or not, this issue should be of interest. If you already have one, you may get some ideas for improvement or widening the scope of your operation. If you don't have one, this issue will help with the decision of whether to pursue establishing one. One clear benefit of chest pain centers is that they decrease unnecessary hospital admissions by allowing patients to be evaluated further without bogging down the emergency department or being admitted. As pointed out in one of the articles, this concept is not unique to chest pain but can also be applied to heart failure exacerbation patients.

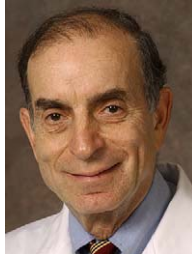
Drs. Amsterdam and Kirk from cardiology and emergency medicine, respectively, at the University of California at Davis School of Medicine are leaders in this area and both are very active in the growing Society of Chest Pain Centers. They have assembled a panel of experts to cover every aspect of chest pain centers,

including articles on cost effectiveness, medical errors, and the employment of various types of diagnostic imaging. New noninvasive methods for imaging the coronary arteries are adding a new dimension to the evaluation of chest pain patients. Newer biomarkers are also changing the triage of patients with chest pain. They are discussed in three articles. After more than 102 years of use, is the ECG ready for the medical museum? Will biomarkers and imaging replace the ECG in triaging chest pain patients? Read on.

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Preface  
Chest Pain Units



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*Guest Editors*

Although time-dependent therapy is an overarching principle of the management of acute coronary syndromes (ACS), fulfillment of this concept remains incomplete [1]. Delays in recognition of ACS and initiation of therapy entail patient, physician, and systemic factors [2]. This problem is particularly pertinent to the treatment of non-ST elevation (non-STE) ACS in which the history and ECG may be ambiguous. Although the high-risk patient is the primary clinical focus, most patients who present with chest pain have a noncardiac etiology that is frequently benign. The clinical dilemma posed by this situation has often been resolved by unnecessary admissions to avert missed diagnoses of ACS, resulting in suboptimal patient care and resource use [3]. The development and growth of chest pain units (CPUs) is a response to this problem by application of a systematic approach to optimize management of patients presenting with symptoms compatible with ACS by affording: (1) prompt identification and treatment of those with an ischemic syndrome and (2) early and accurate discharge of individuals without evidence of myocardial ischemia.

Through its recently implemented process, the Society of Chest Pain Centers has accredited almost 150 CPUs in this country [4] and, based on the current growth rate, it is anticipated that this number will reach 200 or more by the end

of this year. Although these units differ in certain respects, their common basis is a protocol-driven patient evaluation by an accelerated diagnostic strategy, including clinical observation, sequential ECGs, and serial cardiac injury markers. These basic methods are being extended by rapidly emerging technologies with the promise of earlier and more accurate diagnostic capability, thereby further enhancing the use of CPUs. This volume of *Cardiology Clinics* encompasses these advances in presenting the contemporary status of CPUs and associated methodology from the perspectives of an outstanding group of clinician scientists who have made major contributions to this field.

In his introductory chapter, Cannon synthesizes current understanding of ACS in terms of pathophysiology, clinical presentation, and risk stratification. To achieve the latter goal, he considers the roles of basic clinical tools, guidelines, and critical pathways while maintaining focus on the individual patient for optimal management. Blomkalns and Gibler elucidate the rationale of the CPU concept and the practical aspects of its implementation. They relate how these strategies can differ based on institutional variation in methods of staffing, structure, and administration to meet the CPU goals. In the next two articles, Pope and Selker (1) delve further into the diagnostic challenges and current systems for evaluating patients presenting with chest pain and (2)



explore the crucial problem of missed ACS and inadvertent discharge from the emergency department. In the latter context, they identify the principal factors associated with these clinical errors and methods to prevent them. The pivotal role of cardiac injury markers is developed by Jaffe who describes the most recent advances in this area and charts a rational application based on an understanding of the value and limitations of these essential clinical tools. These concepts are extended by Kost and Tran who analyze the rapidly advancing area of point-of-care testing for cardiac injury markers and the remarkably rapid results while maintaining diagnostic accuracy. Wang, Aroudi, and Newby then explore the increased understanding of inflammation in ACS and the growing body of markers that reflect this process, some of which are already being applied clinically.

The next series of articles is devoted to the varieties of cardiac stress testing and imaging as applied in the CPU setting. Our group reviews the extensive clinical experience in multiple centers confirming the utility of treadmill testing as the final element of accelerated diagnostic protocols and we note our results with the immediate exercise test in low-risk patients. The central role of myocardial scintigraphy in many CPUs is addressed by Kontos and Tatum who demonstrate the efficacy of this method in their innovative approach to risk stratification. Rest and stress echocardiography has had substantial application in the assessment of patients who present with chest pain and the indications and accuracy of this technique are evaluated by Lewis. New imaging methods, such as coronary artery calcium scoring and the emergence of noninvasive coronary angiography by computed tomography, are receiving major attention and McCord and Amsterdam provide a perspective on the potential of these techniques.

Because of their unique clinical characteristics, populations such as women, the elderly, and those with documented coronary heart disease, have required specific investigation to determine if the CPU concept applies to their presentations. Diercks and colleagues demonstrate that the CPU strategy is appropriate in these other groups with special clinical features. A large proportion of patients who present to the emergency department with chest pain do not have obstructive coronary artery disease. Yang and Lerman delineate these distinctive syndromes and impart a systematic approach to their etiology, prognosis, and management. A new dimension that has recently been added to the CPU is the management of patients with acute

decompensated heart failure, which is detailed by Peacock in his presentation of the rationale, indications, and results of this innovation.

Reduction of medical errors is an imperative of the CPU and Daudelin and Selker clarify current research in this area. Although their clinical utility has been demonstrated, the complex question of whether CPUs are cost-effective has received limited attention. Sieck reviews this issue in terms of its medical and administrative aspects and their relation to the larger framework of the health care system.

This volume provides a current understanding of the implementation and efficacy of CPUs and the integration of new technology into this approach. These results have provided the basis for continuing advances toward the optimal strategy for the management of patients presenting to the emergency department with chest pain.

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# Acute Coronary Syndromes: Risk Stratification and Initial Management

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In the United States, there are approximately 1.68 million patients admitted every year to hospitals with acute coronary syndromes (ACS) [1]. Of these, one quarter present with acute myocardial infarction (MI) associated with ECG ST-segment elevation (STEMI), whereas three quarters, or approximately 1.3 million patients, have unstable angina/non-ST elevation MI (UA/NSTEMI) [1]. The former is most commonly caused by acute total occlusion of a coronary artery and therefore urgent reperfusion is the mainstay of therapy, whereas UA/NSTEMI is usually associated with a nonocclusive thrombus [2]. Among patients who have UA/NSTEMI, between 40% and 60% will have evidence of myocardial necrosis with elevated troponin, and are thus diagnosed with a NSTEMI [3,4].

In the past several years, there have been many advances in the diagnosis and management of this patient population, as summarized in part in the 2002 update of the American College of Cardiology (ACC) and the American Heart Association (AHA) UA/NSTEMI guidelines, and the 2004 ACC/AHA STEMI guidelines.

The approach to the patient, especially at the first presentation in the emergency department (ED) or chest pain unit, involves careful risk stratification. This assessment actually involves two steps: assessment of the likelihood that the patient's symptoms represent ACS (as opposed to noncardiac chest pain), and risk stratification of the patients who have ACS to identify high- versus lower-risk patients. The guidelines recommend that specific therapies and treatment can be targeted to only high-risk patients, with other

treatments recommended for all patients. The treatments recommended include anti-ischemic, antithrombotic therapy and what strategy should be followed (ie, whether to pursue an invasive versus conservative approach), and reperfusion therapy for STEMI.

## Assessment of likelihood of coronary artery disease

Approximately 6 to 7 million persons per year in the United States present to EDs or chest pain units with a complaint of chest pain or other symptoms suggestive of possible ACS. Of these, approximately 20% to 25% have a final diagnosis of unstable angina or MI [5,6]. Thus, the first step in evaluating patients who have possible UA/NSTEMI is to determine the likelihood that coronary artery disease (CAD) is the cause of the presenting symptoms. The 2002 ACC/AHA guidelines list factors associated with increased likelihood that the patient actually has unstable angina (Table 1).

Numerous prediction rules using clinical and ECG variables have also been developed to assess the likelihood of CAD in patients presenting to the ED with chest pain [7–14]. One algorithm, the acute cardiac ischemia time-insensitive prediction instrument (ACI-TIPI) has been integrated into ECG devices. It provides a quantitative likelihood of the patient having ACSs (ie, STEMI and UA/NSTEMI) [12,13]. One randomized trial has shown that ACI-TIPI reduced unnecessary hospital and coronary care unit admissions [13]. Other studies have suggested that good clinical judgment is as good as the computer algorithms [9,10], emphasizing the importance of obtaining a good

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Table 1  
Estimating the likelihood that the suspected acute coronary syndrome event is secondary to coronary artery disease

	High likelihood	Intermediate likelihood	Low likelihood
Feature	Any below:	No high-likelihood features but any below:	No high- or intermediate-likelihood features but may have:
History	Typical angina; known history of coronary artery disease including myocardial infarction	Probable angina; age > 70 years; male diabetes mellitus	Atypical symptoms
Examination	Congestive heart failure	Peripheral vascular disease, cerebrovascular accident	Pain on palpation
ECG	New ECG changes	Old ECG abnormalities	Normal ECG
Cardiac markers	Positive	Normal	Normal

From Braunwald E, Mark DB, Jones RH, et al. Unstable angina: diagnosis and management. Rockville MD: Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute, US Public Health Service, US Department of Health and Human Services; 1994; AHCPR Publication No. 94-0602.

clinical history when assessing patients who have chest pain.

### Risk stratification

Based on data from a global registry, the outcomes of patients who have ACS fall on a spectrum of risk, ranging from 30-day mortality of 1.7% for patients who have unstable angina to 7.4% for those who have NSTEMI and 11.1% for those who have STEMI [15]. Within clinical trials in which inclusion criteria select higher-risk patients, rates of death by 30 days ranged from 3.5% to 4.5% and of new MI from 6% to 12% [16–18]. However, patients who have UA/NSTEMI constitute a wide spectrum of patients and risk [19–21]; thus, the ACC/AHA guidelines strongly recommend risk stratification as important to characterize the patient's prognosis and to select appropriate therapy. Boxes 1 through 3 list the three recommended stratifications for risk of death/MI in UA/NSTEMI.

The rationale for risk stratification is to target some of the more aggressive therapies to the higher-risk patients. This approach has been seen in multiple studies with several of the agents for management of UA/NSTEMI. In STEMI, most of the treatments are similar based on the patient's risk, beginning with reperfusion therapy and including antithrombotic and anti-ischemic therapies, which are similar to that of UA/NSTEMI.

Thus, among patients who have been identified as having a moderate or high likelihood of having an ACS, the ACC/AHA guidelines highlight risk stratification as a key step that can target the intensity of medical and interventional therapies

to higher-risk patients. Factors associated with a high risk for death or nonfatal MI in patients who have UA/NSTEMI are prolonged rest pain, ST-segment changes, elevated cardiac biomarkers (eg, troponin), diabetes, evidence of congestive heart failure, and age over 75 years. Low-risk patients present without rest pain [22], ECG changes, or evidence of heart failure (see Box 3). Other factors are highlighted as markers of long-term risk, such as extent of CAD, left ventricular dysfunction, and elevated markers of inflammation.

In UA/NSTEMI, use of troponin alone has been a powerful tool for risk stratification and targeting of therapies. Studies have found that high-risk patients benefit from the more aggressive treatments. For low molecular weight heparin (LMWH), glycoprotein (GP) IIb/IIIa inhibitors, and an early invasive strategy, there is a greater benefit of these interventions in patients who have a positive troponin, and almost no benefit in patients who have a negative troponin [3,23–26]. For example, with the GP IIb/IIIa inhibitors, there was a 50% to 70% reduction in death or MI in patients who were troponin-positive and were receiving GP IIb/IIIa inhibitors compared with patients not receiving these agents, with no benefit of GP IIb/IIIa inhibitors in those who did not have a positive troponin [24,25]. A different pattern has been seen with the oral antiplatelet agents, in that aspirin and clopidogrel benefit low-, intermediate-, and high-risk patients and those who have positive or negative cardiac markers [27–29]. Thus, aspirin and clopidogrel have been recommended for all patients regardless of risk, whereas GP

**Box 1. Short-term high risk for death/myocardial infarction in unstable angina/NSTEMI**

*At least one of:*

History

Accelerating tempo of ischemic symptoms in preceding 48 hours

Character of pain

Prolonged ongoing (>20 min) rest pain

Clinical findings

Pulmonary edema, most likely caused by ischemia

New or worsening mitral regurgitation murmur

S<sub>3</sub> or new/worsening rales

Hypotension, bradycardia, tachycardia

Age over 75 years

ECG

Rest angina with transient ST changes greater than 0.05 mV

Bundle branch block

New sustained ventricular tachycardia

Cardiac markers

Markedly elevated (eg, Troponin T or Troponin I >0.1 ng/mL)

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*From Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). J Am Coll Cardiol 2000;36:970-1062; with permission.*

**Box 2. Short-term intermediate risk for death/myocardial infarction in unstable angina/NSTEMI**

*No high-risk features, but must have one of:*

History

Prior myocardial infarction, peripheral vascular disease, or cerebrovascular disease

Coronary artery bypass grafting

Prior aspirin use

Character of pain

Prolonged (>20 min) rest angina, now resolved, with moderate or high likelihood of coronary artery disease

Rest angina (<20 min) or relieved with rest or sublingual nitroglycerin

Clinical findings

Age over 70 years

ECG

T-wave inversions greater than 0.2 mV

Pathologic Q waves

Cardiac markers

Slightly elevated (eg, Troponin T >0.01 ng/mL but <0.1 ng/mL)

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*From Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). J Am Coll Cardiol 2000;36:970-1062; with permission.*

IIb/IIIa inhibitors are recommended for use only in high-risk patients or those undergoing percutaneous coronary intervention (PCI) (Fig. 1).

**Risk scores**

Integrating all the risk factors identified in the ACC/AHA guidelines as low-, intermediate-, or high-risk, comprehensive risk scores have been

developed using clinical variables and ECG and initial serum cardiac marker data [30,31]. The Thrombolysis in Myocardial Infarction (TIMI) risk score was developed using multivariate analysis to predict the occurrence of death, MI, or recurrent ischemia leading to urgent revascularization in the TIMI 11B trial. Seven independent risk factors emerged: age over 65 years, more than three risk factors for CAD, documented CAD at

**Box 3. Short-term low risk for death/myocardial infarction in unstable angina**

*No high or intermediate risk feature, but may have any of:*

History

None indicated

Character of pain

New-onset Canadian Cardiovascular Society class III or IV angina in past 2 weeks without prolonged (>20 min) rest pain, but with moderate or high likelihood of coronary artery disease

Clinical findings

None indicated

ECG

Normal or unchanged ECG during chest discomfort

Cardiac markers

Normal

*From Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). J Am Coll Cardiol 2000;36:970-1062; with permission.*

catheterization, prior ASA, more than two episodes of angina in the last 24 hours, ST deviation more than 0.5 mm, and elevated cardiac markers. This scoring system was able to risk stratify patients across a ten-fold gradient of risk, from 4.7% to 40.9% ( $P < .001$ ) [31]. More importantly, the relative benefit of enoxaparin as compared with unfractionated heparin increased as the risk increased [31]. Similar findings have now been seen using the TIMI risk score to predict the benefit of GP IIb/IIIa inhibitors [32] and an early invasive strategy [3]. Thus, these findings support the ACC/AHA guideline recommendations that risk stratification be the first task in evaluating patients who present with UA/NSTEMI [33].

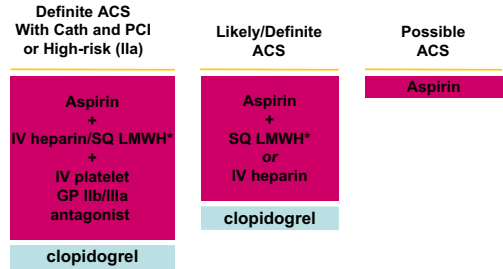


Fig. 1. 2002 American College of Cardiology/American Heart Association guideline recommendations for antithrombotic therapy for unstable angina/non-ST elevation acute coronary syndrome. (From Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). J Am Coll Cardiol 2000;36:970-1062; with permission.)

**Antithrombotic and medical therapy**

Initial treatment for patients who have UA/NSTEMI should include aspirin, which leads to a 50% to 70% reduction in death or MI as compared with placebo [34]. Current data on aspirin indicate the drug is beneficial for long-term treatment at doses as low as 75 mg/d [27]. New data from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial indicates that lower doses of aspirin (eg, 81 mg) are associated with a 50% lower rate of major bleeding over 1 year of treatment than doses of 200 to 325 mg [35]. Thus, for acute management in-hospital, 160 to 325 mg daily is recommended, but at hospital discharge and during follow-up, the new data suggest a dose of 81 mg may be safer.

The 2002 ACC/AHA guideline included a new Class I recommendation for the use of clopidogrel in addition to aspirin. Clopidogrel blocks the ADP pathway by blocking the P<sub>2</sub>Y<sub>12</sub> component of the ADP receptor, which in turn decreases platelet activation and aggregation. The CURE trial found that clopidogrel plus aspirin led to a 20% relative risk reduction in cardiovascular death, MI, or stroke compared with aspirin alone [28]. This benefit was seen in low- and high-risk patients [29] and was seen as early as 24 hours [36], with the Kaplan-Meier curves for event rate in the two treatment groups diverging after just 2 hours.

This benefit has also been seen in two other trials. In the CREDO trial of patients undergoing PCI, clopidogrel was associated with a significant 27% relative reduction in the combined risk for death, MI, or stroke at 1 year ( $P = .02$ ) [37]. Similarly, in the CAPRIE trial, clopidogrel alone had a significant reduction in these events versus aspirin through 3 years of follow-up in patients who had prior atherothrombotic disease [38]. Thus, there is strong evidence from large double-blind, randomized trials that clopidogrel plus aspirin is the new optimal long-term antithrombotic regimen.

Intravenous GP IIb/IIIa inhibitors have also been shown to be beneficial in treating UA/NSTEMI [39]. For “upstream” management (ie, initiating therapy when the patient first presents to the hospital), the small molecule inhibitors eptifibatid and tirofiban clearly show benefit, whereas abciximab was of no benefit in an unselected UA/NSTEMI patient population [40] and is in fact contraindicated for patients approached with a noninvasive strategy [41].

Unfractionated heparin (UFH) or LMWH is recommended for patients who have UA/NSTEMI [42]. Comparative trials of enoxaparin (a LMWH) versus UFH have demonstrated superiority of enoxaparin in reducing recurrent cardiac events [43,44]. Based on these data, the 2002 Updated ACC/AHA UA/NSTEMI practice guidelines have made a Class IIA recommendation that enoxaparin is the preferred antithrombin over UFH [41].

Anti-ischemic therapy with nitrates is also recommended, with the use of intravenous nitrates for ongoing ischemic pain and beta-blockade early and during long-term follow-up [33].

In STEMI, benefits of early angiotensin-converting enzyme inhibition are considerable. In the GISSI-3 [45] trial, early initiation of lisinopril was associated with a 12% mortality reduction, and in ISIS-4 [46], captopril therapy resulted in a 7% mortality reduction. Benefits were more pronounced in patients who had anterior MI. However, in patients who had NSTEMI, no benefit was observed in the ISIS-4 study.

### Invasive versus conservative strategy: non-ST elevation acute coronary syndrome

For patients who have UA/NSTEMI, nine randomized trials have assessed the merits of an invasive strategy involving routine cardiac catheterization with revascularization (if feasible) versus a conservative strategy where angiography and revascularization are reserved for patients who

have evidence of recurrent ischemia either at rest or on provocative testing. Of these, six of the last seven have all shown a significant benefit of the invasive strategy (Fig. 2), especially in higher-risk patients [3,35,47]. Accordingly, the 2002 ACC/AHA guideline has added ST-segment changes and positive troponin to the list of high-risk indicators that would lead to a Class I recommendation for an early invasive strategy, as shown in Box 4 [41]. With regard to the timing of an invasive strategy, the results from the Intracoronary Stenting with Antithrombotic Regimen Cooling-Off study found a benefit of an immediate invasive strategy with an average time to catheterization of 2 hours, compared with a delayed invasive strategy with an average time to catheterization of 4 days [48]. Randomized studies have not yet evaluated whether an immediate invasive approach is better than catheterization 24 to 48 hours postadmission.

### Summary—acute therapy for non-ST elevation acute coronary syndrome

Summarizing the ACC/AHA guidelines, there are now five baseline therapies for all patients: aspirin; clopidogrel; heparin or LMWH (with enoxaparin the preferred antithrombin); beta-blockers; and nitrates (Fig. 3) [23]. Then there are two treatments that are best targeted by risk

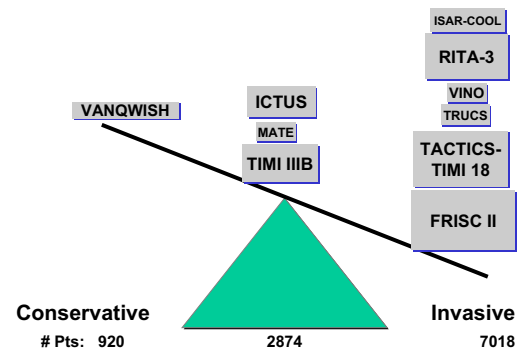


Fig. 2. The “weight of the evidence” showing benefit of an invasive versus conservative strategy in patients who have unstable angina/non-ST elevation acute coronary syndrome. The size of the boxes for each of the nine randomized trials corresponds to the number of patients enrolled. (Modified from Cannon CP, Turpie AG. Unstable angina and non-ST-elevation myocardial infarction: initial antithrombotic therapy and early invasive strategy. *Circulation* 2003;107:2640–5; with permission.)

**Box 4. ACC/AHA guideline recommendations for an early invasive strategy for unstable angina/non-ST elevation myocardial infarction**

*Class I*

Any of the high-risk indicators (level of evidence: A)

- Recurrent angina at rest/low-level activity despite treatment
- Elevated Troponin T or Troponin I
- New ST-segment depression
- Recurrent angina/ischemia with congestive heart failure symptoms, rales, mitral regurgitation
- Positive stress test
- EF less than 0.40
- Decreased blood pressure
- Sustained tidal volume
- PCI less than 6 months, prior coronary artery bypass grafting

*From Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). J Am Coll Cardiol 2000;36:970–1062; with permission.*

stratification: the invasive strategy and the IIb/IIIa inhibitor, where the benefit is in the higher-risk patients.

**ECG ST-segment elevation: reperfusion therapy**

In STEMI, the coronary artery is in most cases 100% occluded with a fresh thrombus at the site of a ruptured plaque. To restore perfusion to the myocardium, immediate reperfusion of the infarct-related artery is needed.

There are two approaches: use of fibrinolytic therapy or primary PCI. Time is critical with either therapy, where the sooner reperfusion is achieved, the greater the chance of reducing morbidity and increasing survival.

*Primary percutaneous coronary intervention*

At present, the preferred method of achieving coronary reperfusion is the use of primary PCI.

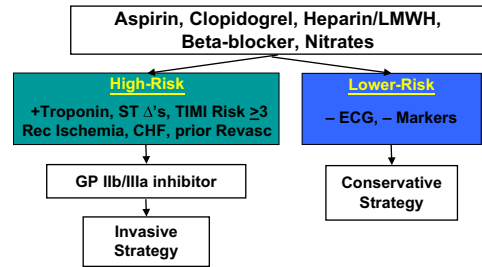


Fig. 3. Evidence-based risk stratification to target therapies in unstable angina/non-ST elevation acute coronary syndrome, as recommended in the American College of Cardiology/American Heart Association guidelines. (From Cannon CP. Evidence-based risk stratification to target therapies in acute coronary syndromes. *Circulation* 2002;106:1588–91; with permission.)

Many randomized controlled trials have compared pharmacologic and mechanical reperfusion during STEMI. A meta-analysis of 23 of these trials found that primary PCI was superior to thrombolytic therapy in reducing mortality; non-fatal reinfarction; stroke; and the combined endpoint of death, nonfatal reinfarction, and stroke [49]. The benefits of PCI in reducing mortality and recurrent MI were particularly striking.

At present, however, only 20% to 25% of hospitals have primary PCI capabilities. Therefore, hospitals that do not have PCI capabilities can either treat patients who have STEMI with immediate thrombolysis, or emergently transfer them to a site where PCI can be performed. Recent clinical trials have also found that if door-to-balloon times are within 2 to 3 hours, that primary PCI is superior to fibrinolysis with a 40% to 50% reduction of the combined end point [50–52].

**Thrombolysis**

Thrombolysis has been shown to reduce mortality in several large placebo-controlled trials using streptokinase (SK) and tissue plasminogen activator (t-PA). These benefits persist through at least 10 years of follow up. The Fibrinolytic Therapy Trialists' overview of all the major placebo-controlled studies showed a 2.6% absolute reduction in mortality for patients who have STEMI treated within the first 12 hours after the onset of symptoms [53]. Patients presenting with new left bundle branch block and a strong clinical history for acute MI also derive a substantial benefit from thrombolysis. Patients who have non-ST

elevation ACS, however, do not benefit from thrombolysis.

SK was the initial fibrinolytic drug, with newer agents later developed. The fibrin-specific thrombolytic agents, such as alteplase (t-PA), were seen in the TIMI-1 trial to have twice the rate of infarct-related artery patency as SK [54]. In the GUSTO I trial, accelerated tPA plus heparin led to a highly significant 14% reduction in mortality. Reteplase and tenecteplase are molecular modifications of t-PA designed to have longer plasma half-lives that allow double or single bolus administration, respectively. However, the newer agents did not lead to a further reduction in mortality rates compared with t-PA.

Similarly, use of the combination of half-dose fibrinolysis and GP IIb/IIIa receptor inhibitors did not improve mortality, and this more complicated regimen is not widely used. The use of other adjunctive agents with full-dose fibrinolysis is being actively studied, with enoxaparin being compared with UFH in the EXTRACT-TIMI 25 trial, and clopidogrel being added to standard regimens versus placebo in the CLARITY-TIMI 28 trial.

### Choice of reperfusion therapy

In summary, although thrombolysis is more widely available, is simple to administer, and produces results that are independent of operator experience, primary PCI in experienced hands is associated with less-recurrent infarction and ischemia; lower short-term mortality; and less stroke and intracranial hemorrhage than thrombolysis. PCI also results in higher early infarct-related artery patency rates and reduced residual stenosis compared with thrombolysis. The current ACC/AHA guidelines recommend invasive strategy with PCI if a timely intervention can be performed; that is, if door-to-balloon time is less than 90 minutes or if the delay to PCI compared with on-site thrombolysis is less than 1 hour. Primary PCI is also generally preferred for patients in cardiogenic shock, who have contraindications to thrombolysis, and in whom thrombolysis is unlikely to produce meaningful benefit (eg, symptom onset more than 3 hours before presentation).

### Summary

For patients who have ACS, risk stratification is key to initiating appropriate treatment. For STEMI, immediate reperfusion therapy is needed,

and thus rapid identification of ST elevation on the ECG is critical. Having a standardized protocol for rapid treatment—with either primary PCI or thrombolysis—is critical. For UA/NSTEMI, one first has to identify the patients who have a higher likelihood of actually having an ACS as opposed to noncardiac chest pain. There are many modalities for this assessment, as reviewed in this issue. Among patients who have a moderate or high likelihood of ACS, stratification to high versus lower risk is needed to choose appropriate therapies. Thus, it is important for risk stratification to be a central part of all management of patients who have ACS.

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## Chest Pain Unit Concept: Rationale and Diagnostic Strategies

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Each year in the United States, over 8 million patients present to the emergency department (ED) with complaints of chest discomfort or other symptoms consistent with possible acute coronary syndrome (ACS). While over half of these patients are typically admitted for further diagnostic evaluation, fewer than 20% are diagnosed with ACS. With hospital beds and inpatient resources scarce, these admissions can be avoided by evaluating low- to moderate-risk patients in chest pain units (CPUs) [1–5].

This large, undifferentiated patient population represents a potential high-risk group for emergency physicians requiring a systematic approach and specific ED resources. This evaluation is required to appropriately determine if a patient is safe to be discharged home with outpatient follow-up versus requiring admission to the hospital for monitoring and further testing.

The concept of rapid diagnostic and treatment protocols for specific disease processes is not new. For instance, analogous approaches for trauma patients have been accepted widely for many years, resulting in decreased morbidity and improved survival for these patients. The same tenants of early evaluation, appropriate risk stratification, and intervention are appropriate for the patient presenting with possible ACS to the ED. Just as trauma centers have adopted strict protocols for diagnosis and treatment of the injured patient, CPUs should have basic principles for evaluation and treatment of patients who

present with possible ACS. The evaluation of patients who exhibit symptoms consistent with ACS requires a protocol that includes testing for myocardial necrosis, rest ischemia, and exercise-induced ischemia.

### Implementation

Implementation of a CPU approach in an emergency setting is nearly as challenging as evaluating the patients themselves. Several synergistic components are required to adequately, efficiently, and cost-effectively evaluate this patient population, including

- 1) Sufficient and dedicated space to evaluate and observe the patients
- 2) Nursing staff and other ED personnel that are knowledgeable and dedicated to this approach
- 3) Emergency physician staff that can be responsible for these patients
- 4) Collaboration of cardiologist colleagues on the protocols, testing, follow-up, and admission procedures
- 5) Availability of nuclear cardiology and radiology colleagues for the emergent performance and reading of nuclear imaging studies
- 6) Laboratory personnel to run serial cardiac biomarker measurements
- 7) Primary care physicians that understand the scope and limitations of a CPU evaluation for follow-up

Various physical models exist for CPUs. Several of these models are illustrated in [Table 1](#) and [Figs. 1](#) and [2](#). In [Table 1](#), the Medical College of Virginia protocol integrates the use of radionuclide

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Table 1  
Medical College of Virginia CPU protocol

Level	AMI risk	ACS risk	Strategy	Disposition
1	Very high	Very high	Fibrinolysis/PCI	CCU
2	High	High	ASA, heparin, NTG, GP IIb/IIIa	CCU
3	Moderate	Moderate	Markers + nuclear imaging	9-h observations
4	Low	Mod or low	Nuclear imaging	Home and OP stress test
5	Very low	Very low	As needed	Home

Abbreviation: AMI, acute myocardial infarction.

testing into a five-level risk stratification program. Figs. 1 and 2 demonstrate protocols for the University of Cincinnati and the Mayo Clinic, respectively. Both protocols integrate myocardial necrosis testing by cardiac biomarkers and functional exercise testing. Each model takes into account the specific patient population, cardiologist collaboration, nuclear imaging availability, and ED resources to design the optimal CPU for that hospital.

Most of these units are located in an area adjacent to, but separate from, the general emergency patient population. Often the CPU protocol patients are evaluated in conjunction with other observation unit (OU) protocols. As these patients are frequently in the ED for 6 hours or more, it is desirable to provide many of the in-hospital comforts generally not available in a traditional ED. These comforts may include hospital beds, meals, television sets, and telephones, which greatly improve patient satisfaction. This space allocation and additional patient resources may

be prohibitive for some hospital physicians, nurses, and administrations considering the start-up of a new CPU and, thus, some of these protocols are performed within the regular department using basic ED resources. This alternative can be suboptimal as the increased time required for CPU protocols can hamper ED patient throughput, lowering patient satisfaction.

A successful CPU also requires a nursing staff dedicated to the care of these patients with special needs. These patients require frequent assessment, close monitoring, noninvasive testing, and serial cardiac biomarker testing and ECG acquisition. These tasks are generally in excess of those expected for a typical emergency patient and may require additional training and staffing as appropriate for the individual institution and ED. The overall success of the unit depends on adherence to the systematic evaluation protocol by nursing personnel.

Although most of these patients are placed on CPU protocols that do not require constant

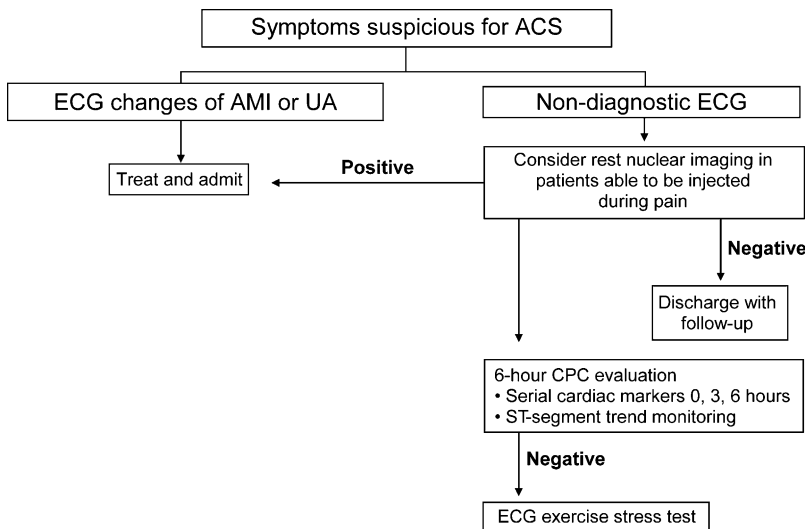


Fig. 1. University of Cincinnati "Heart ER" strategy. Data from [5] Gibler et al, Ann Emerg Med 1995;25:1-8 and [17] Storrow et al, Circulation 1998;98:I-425.

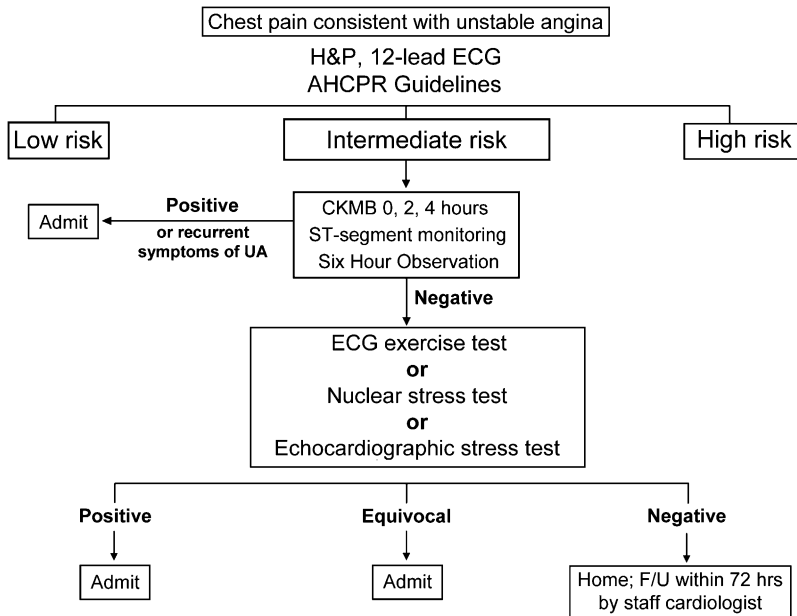


Fig. 2. Mayo Clinic Strategy.

emergency physician interaction, they must be continually re-evaluated and re-assessed while in the CPU. ACS is a dynamic process and can easily progress over the course of the patient's stay in the CPU. Symptom changes, cardiac biomarker positivity, and ECG ST-segment variation should prompt immediate therapy and potential intervention in the cardiac catheterization laboratory. The emergency physician must stay integrally involved with the patient to provide this increased level of therapy. A successful CPU requires the cooperation of many health care professionals in the ED and around the participating institution. An absolutely critical component of successful CPU operation is the collaboration and cooperation of cardiologists and radiologists. Cardiology involvement in CPU protocols is necessary for many reasons. Formulation, knowledge, and acceptance of CPU protocols particular for each institution requires active participation and expertise of the cardiologists. In addition, many CPU protocols successfully use provocative testing with radionuclide echocardiography, or standard graded exercise testing, and these tests generally require the interpretation of a cardiologist [5–10].

While collaboration between emergency medicine and cardiology is intuitive, integration with nuclear cardiologists and radiologists is also pivotally important to the success of every CPU.

Radionuclide perfusion imaging has emerged as an important tool in many centers for assessing patients who present with and without known cardiovascular disease and also in evaluating the patient presenting to the ED with possible ACS. Technetium-99 (Tc-99) sestamibi tomographic imaging is the most common agent currently being used in patients presenting to the ED with suspected ACS [11,12]. Studies have shown that positive rest perfusion imaging accurately identifies patients at high risk for adverse cardiac events [13]. Radionuclide perfusion imaging has thus become a cornerstone of evaluation for many units [14,15].

The diagnostic sensitivity of myocardial perfusion imaging is, in part, dependent on the timing of injection in relation to the cessation of chest pain. The major obstacles for radionuclide studies have traditionally included cost and accessibility. The perfusion agents have a 6- to 12-hour shelf life and, thus, have to be prepared several times a day to be available for acute imaging. Collaboration with nuclear cardiology and radiology colleagues is paramount for this reason. Timely evaluation of these patients requires immediate access to these studies and timely reading and reporting of the results by expert readers.

The laboratory must also be supportive of a CPU. Ideally, bedside point-of-care testing for cardiac biomarkers provides rapid data collection

for these patients as creatine-kinase myocardial band (CK-MB) and, in particular, the troponins I (TnI) and T (TnT) allow risk stratification to be performed expeditiously [16]. A collaborative relationship between emergency physicians and laboratorians can ensure a consistent and effective evaluation of patients in the CPU.

Finally, primary care physicians must be supportive of the CPU and willing to have patients evaluated in this protocol-driven process. Communication between emergency physicians and the patient's primary care physician can then assure careful follow-up and patient compliance with lifestyle changes and treatment recommendations after evaluation.

#### *Examples of chest pain units*

Over the years, several manifestations of CPUs have evolved. Each of these models has been successfully adopted by specific institutions for its patient populations. An individual institution should carefully evaluate their patient population, physician expertise, physical structure, staffing model, and hospital environment to most adequately determine their optimal CPU protocol.

For instance, the University of Cincinnati Center for Emergency Care "Heart ER," established in October 1991, was one of the first ED-based CPUs. Patients at low to moderate risk for ACS are admitted to the Heart ER for a protocol-driven evaluation of their chest discomfort. The serial cardiac biomarkers CK-MB and troponin T levels are drawn at 0, 3, and 6 hours after presentation to the ED. The original protocol used continuous ST-segment trend monitoring, which has since been discontinued. Graded exercise testing or Tc-99 sestamibi radionuclide scanning is now performed depending on patient's functional status and test availability. Patients having negative evaluations in the Heart ER are released to home with careful follow-up as an outpatient [5].

In the first 2131 consecutive patients evaluated over a 6-year period, 309 (14.5%) required admission and 1822 (85.5%) were released to home from the ED. Of admitted patients, 94 (30%) were found to have a cardiac cause for their chest pain. Follow-up of 1696 patients discharged from the Heart ER to home yielded 9 cardiac events (0.53%, confidence interval [CI], 0.24%–1.01%; 7 percutaneous transluminal coronary angioplasty, 1 coronary artery bypass grafting, 1 death) [17]. These data suggest that the Heart ER program provides a safe and effective means for evaluating

low- to moderate-risk patients who present with possible ACS to the ED.

Other institutions also have developed effective chest pain center strategies. The Medical College of Virginia has an elegant protocol that triages chest pain patients into five distinct levels (see Table 1) [14,18]. Level 1 patients have ECG criteria for acute myocardial infarction (AMI) while level 5 patients have clearly noncardiac chest discomfort. The triage level dictates further diagnostic measures and treatment. Intermediate level patients (levels 2 and 3) include individuals with variable probability of unstable angina. These patients are admitted to the CCU for diagnostic testing for ACS while less acute patients (level 4) undergo serial cardiac biomarker determination and Tc-99 sestamibi radionuclide imaging from the ED.

The University of California at Davis protocol uses a novel use of immediate exercise treadmill testing without serial cardiac biomarker determination. In a recent study of 1000 patients, 13% were positive and 64% were negative for ischemia. The remaining 23% of the patients had non-diagnostic tests. No adverse effects exist from exercise testing and no mortality occurred in either of the patient evaluation groups at 30-day follow-up. The authors concluded that immediate exercise testing of low-risk patients is safe and accurate for the determination of which patients can be safely discharged from the ED [6]. A careful history is required to ensure that only low- to moderate-risk patients for ACS are exercised acutely in the ED.

The Mayo Clinic separates patients into low-, intermediate-, and high-risk categories according to Agency for Health Care Policy Research (AHCPR) guidelines. Intermediate-risk patients are evaluated with CK-MB levels at 0, 2, and 4 hours while undergoing continuous ST-segment monitoring and 6-hour observation. If this evaluation is negative, an ECG exercise test, a nuclear stress test, or an echocardiographic stress test is performed. Patients with positive or equivocal evaluations are admitted, whereas patients having negative evaluations are discharged to home with a 72-hour follow-up [19].

Lastly, Brigham and Women's Hospital divides patients into three groups: unstable angina or AMI, possible ischemia, and nonischemic. Patients with unstable angina or AMI are admitted, whereas nonischemic chest pain patients are discharged from the CPU. The intermediate, or "possible ischemia," group either undergoes

exercise treadmill testing with a 6-hour period of observation or a 12-hour period of observation. At the end of the observation period, stable patients are discharged to home. Nichol and colleagues [20] evaluated the impact of this pathway approach in a retrospective cohort of 4585 patients and found that a 17% reduction in admissions and an 11% reduction in length of stay would occur if even fewer than 50% of eligible patients for observation and exercise testing had participated.

Each institution has constructed its CPU protocols to suit its patient population, physician expertise, and resource availability to optimize chest pain evaluation. Each hospital and patient population represents a unique environment with specific needs and resources that must be reflected in the ultimate CPU design and implementation.

Once the patient “passes” the CPU protocol and apparently does not have ACS, the individual can be discharged safely to home and appropriate follow-up arranged. Adequate attention must be given to the cause of the patient’s discomfort even if it is determined not to be cardiac in nature. Testing for other noncardiac chest pain, including gastrointestinal or psychiatric disease, must then be performed. Patients also require outpatient provocative testing, if not received in the CPU protocol, to further delineate their cardiac risk caused by fixed coronary artery lesions. These tests must be followed and acted on by a primary care physician.

## Efficacy

The protocols developed for CPUs must provide testing to evaluate every patient who presents with potential ACS for three possibilities: myocardial necrosis, rest ischemia, and exercise-induced ischemia. Numerous studies in several different hospital environments have validated the use of the CPU. Even early CPUs without the benefits of cardiac troponins and immediate nuclear imaging were successful in safely evaluating patients who are at low probability for AMI [21].

Early myocardial necrosis “rule-out” protocols challenged the traditional notion of a 24-hour period required to detect AMI. Lee and colleagues’ [22] multicenter trial validated a 12-hour algorithm using CK and CK-MB in patients identified as “low-risk” through assessment of clinical characteristics in the ED. “Low-risk” was defined as the probability of AMI less than

7%. Patients who have CK-MB levels lower than 5% of the total CK without recurrent chest pain after 12 hours had a 0.5% missed AMI rate while identifying 94% of AMI patients [22]. Far-kouh and colleagues [19] demonstrated the use of a CPU protocol and CK-MB measurements for patients identified as intermediate risk for adverse cardiac events. In this study, patients underwent 6 hours of observation followed by provocative testing. This protocol identified all patients who experienced short and long term cardiac events while using fewer resources over a 6-month period [19].

Symptom onset to patient presentation is a crucial factor in the use of cardiac biomarker protocols. Marker release kinetics vary with time and as time to ED presentation may be as short as 90 minutes or as long as several days, no single biomarker determination is suitable for adequately “ruling-out” myocardial necrosis [5,23,24]. In one of the first studies with CPU protocols, Gibler and colleagues [5] used a 9-hour protocol with serial CK-MB levels performed at 0, 3, 6, and 9 hours along with continuous 12-lead ECG monitoring, echocardiography, and graded exercise testing. The authors found that serial cardiac biomarkers alone had a sensitivity and specificity for AMI of 100% and 98%, respectively [5,23,24]. Serial cardiac biomarker determinations are now recommended to increase sensitivity for detecting necrosis rather than a single determination on ED presentation.

Several other studies have examined the value of cardiac biomarkers in the risk stratification of heterogeneous patients who present to the ED with chest pain. In a multicenter study of over 5000 patients in 53 EDs, the relative risk for ischemic complications and death for ED patients who have positive CK-MB at 0 or 2 hours was 16.1 and 25.4, respectively [25]. Serial CK-MB results also have proved to be sensitive in AMI detection when collected at 0 and 3 hours after ED presentation. Young and colleagues [26] found a 93% and 95% sensitivity and specificity when combining 0, 3, and net change in CK-MB levels. As expected, the sensitivity improved with increased time from symptom onset [26]. Serial cardiac biomarker measurements and comparison of biomarker elevation over 3 to 6 hours also improved sensitivity for MI [27–29]. Even minor elevations of CK-MB as small as twice the upper limit of normal are associated with an increased 6-month mortality when compared with those with normal levels [30].

Serial CK/CK-MB protocols have become the diagnostic standard for AMI in the CPU setting. Most all of studied protocols use a specific threshold above which is diagnostic for AMI. Fesmire and colleagues [29] studied a promising new approach that included the change in CK-MB levels within the normal range over the course of ED evaluation. In his population of 710 CPU patients, a CK-MB increase or delta of 1.6 ng/mL over 2 hours was more sensitive for AMI than a second CK-MB drawn 2 hours after patient arrival (93.8% versus 75.2%) [29]. Validation of these and other novel protocols will add further to the use of biomarkers in the CPU setting.

The beneficial attributes of myoglobin have made it a commonly used biomarker in CPU protocols. The diagnostic strength of myoglobin lies in its early release kinetics and sensitivity, whereas its primary weakness is a lack of specificity. Davis and colleagues [31] showed that serial myoglobin levels were 93% sensitive and 79% specific in detecting AMI in patients within 2 hours of arrival. Similarly, Tucker and colleagues [32] showed a myoglobin sensitivity of 89% in patients who had nondiagnostic ECGs within 2 hours of ED presentation. Myoglobin seems to achieve maximal diagnostic accuracy within 5 hours after symptom onset [33].

Therefore, it is reasonable and recommended that myoglobin should be combined with other more specific cardiac biomarkers when used in CPU protocols. Brogan and colleagues [34] found that a combination of carbonic anhydrase III and serum myoglobin was more sensitive and equally specific as CK-MB in patients presenting early, within 3 hours of symptom onset. In contrast, Kontos and colleagues [3] reported less encouraging results from a study of 2093 patients combining CK, CK-MB, and myoglobin obtained at 0, 3, 6, and 8 hours. A CK-MB level greater than 8.0 ng/mL at three hours was 93% sensitive and 98% specific for AMI; adding myoglobin decreased the specificity to 86% with no significant increase in sensitivity.

Much like the other cardiac biomarkers, myoglobin levels become increasingly useful when drawn in a serial fashion. In a study of 133 consecutive admitted chest pain patients, myoglobin levels were obtained at 2, 3, 4, and 6 hours after symptom onset. This regimen was found to be 86% sensitive for AMI at 6 hours. The negative predictive value (NPV) in patients who have negative myoglobin levels during 6 hours of evaluation, and without doubling over any 2-hour

period, was 97% [32]. As CPUs continue to evolve, aggressive and innovative biomarker strategies have been developed. McCord and colleagues [35] found that AMI can be excluded 90 minutes after patient presentation using point-of-care myoglobin and cardiac troponin I.

Data from protocols using myoglobin measurements in patients who have a lower risk for AMI are sometimes conflicting. In a study of 3075 low-risk CPU patients with AMI prevalence of 1.4%, a 4-hour serial myoglobin protocol was reported as 100% sensitive for AMI [9]. Conversely, in a study of 368 patients whose AMI prevalence was 11%, the sensitivity and specificity of myoglobin at 0 and 2 to 3 hours was only 61% and 68%. Myoglobin change or increase did not improve diagnostic performance either [28].

Myoglobin in the CPU setting is probably best used in a serial fashion along with another biomarker of necrosis such as troponin which is highly specific for cardiac injury. It is most valuable when used in patients presenting early in the time course of symptoms and less so for remote events, as the myoglobin elevation can be normalized within 12 hours after symptom onset through renal clearance.

TnI and TnT have revolutionized the risk stratification of chest pain patients in CPU protocols and now are a cornerstone of serial evaluation. They have proved extremely valuable and sensitive in the diagnosis of myocardial necrosis [36,37]. In addition to diagnosis of myocardial necrosis in ACS, the troponins are valuable in risk stratification of low- and high-risk patient populations. Troponin release kinetics mimic CK-MB, but elevated levels persist for up to 12 days after AMI as a result of the breakdown of the contractile apparatus over this period.

The main two issues surrounding the cardiac troponins are: (1) cutoff values for TnI and TnT and (2) appropriately defining the time of chest pain onset in the context of the ED presentation. Most large studies and analyses have determined that TnI and TnT can identify patients at risk for adverse cardiac events [36–39].

Cardiac TnT is detected at slightly lower serum levels than most TnI assays and has proved valuable in the emergency setting for early identification of myocardial necrosis. The GUSTO-II Investigators compared TnI and TnT in short-term risk stratification of ACS patients. This model compared troponins collected within 3.5 hours of ischemic symptoms. Ohman and colleagues found that TnT showed a greater



association with 30-day mortality ( $\text{Chi}^2 = 18.0$ ,  $P < .0001$ ) than TnI ( $\text{Chi}^2 = 12.5$ ,  $P = .0002$ ) [40]. These authors concluded that TnT is a strong, independent predictor of short-term outcome in ACS patients, and serial levels were useful in determining the risk for adverse cardiac events [41].

As with all new cardiac biomarkers, initial studies on troponin risk stratification were performed initially on patients who have known ACS. Studies using TnI in ACS patients showed a statistically significant increase in mortality among those patients who have levels greater than 0.4 ng/mL [42]. TnT was an extremely effective test for risk stratification of patients who have ACS in a large trial [43]. Stubbs and colleagues [44] showed that patients who have elevated baseline TnT levels had up to 4 times higher mortality than ACS patients with normal values.

While the increased risk for troponin positive patients is well-established, the degree of risk varies greatly between studies and patient populations. Meta-analyses have helped consolidate conclusions and clinically useful parameters when using troponins for the evaluation of patients. One such analysis in high-risk patients performed by Wu [45] demonstrated a cumulative odds ratio of a positive TnT for the development of AMI or death from hospital discharge to 34 months was 4.3 (2.8–6.8 95% CI). The cumulative odds ratio of a positive TnT for predicting need for cardiac revascularization within the same period was 4.4 (3.0–6.5 95% CI). Another analysis involving greater than 18,000 patients in 21 ACS studies found that troponin positive patients had an odds ratio of 3.44 for death or MI at 30 days. Troponin positive patients with no ST-segment elevation and patients with unstable angina carried odds ratios of 4.93 and 9.39 for adverse cardiac outcomes [39].

Benamer and colleagues [46] compared the prognostic value of TnI combined with C-reactive protein (CRP) in patients who present with unstable angina. They found that while 23% of patients with elevated TnI had major in-hospital cardiac events, there was no such prognostic significance associated with CRP [46].

Troponin applications in low- to moderate-risk patients presenting to EDs have shown similar encouraging results. Tucker and colleagues [47] used a comprehensive marker strategy including myoglobin, CK-MB, TnI, and TnT in ED patients over 24 hours after arrival. As expected within the first 2 hours of presentation,

CK-MB and myoglobin maintained better sensitivity. The troponins were useful only when measured 6 or more hours after arrival, exhibiting sensitivities and specificities of 82% and 97% for TnI, and 89% and 84% for TnT [47]. Troponin use seems to be more beneficial in later or delayed patient presentations. In a study of 425 patients using serial TnI and CK-MB over 16 hours, Brogan and colleagues [48] showed no increase in sensitivity or specificity between troponin and CK-MB in patients with symptoms less than 24 hours. However, in patients presenting with greater than 24 hours of symptoms, TnI had a sensitivity of 100% compared with CK-MB (56.5%) [48].

Sayre and colleagues showed that patients who exhibited a TnT level of 0.2ng/L or greater were 3.5 times more likely to have a cardiac complication within 60 days of ED presentation [49]. In a CPU population, Newby and colleagues [50] determined that TnT positive patients had angiographically significant lesions (89% versus 49%) and positive stress testing (46% versus 14%) more frequently than TnT negative patients. Long-term mortality was also higher in TnT positive patients (27% versus 7%) [50]. Johnson and colleagues [37] studied a heterogeneous patient population admitted from an urban teaching hospital and found that TnT was elevated in 31% of patients who presented without AMI and who had major short-term complications as compared with CK-MB activity and mass [37].

Other investigators have found that while patients with troponin positivity are at higher risk for adverse cardiac events, the test in isolation lacks sensitivity. Kontos and colleagues [51] found that while TnI positive patients were more likely to have significant complications (43% vs 12%), the sensitivity for these end points was low (14%). Similarly, Polanczyk and colleagues [52] demonstrated that peak TnI greater than 0.4 ng/mL was associated with only a 47% sensitivity and 80% specificity for a major cardiac event within 72 hours of presentation.

The recent publication of the “redefinition” of MI has brought troponin to the forefront of diagnosis and risk stratification in this patient population [53]. In a re-analysis of the data from PARAGON B, GUSTO IIa, and CHECKMATE studies, patients with baseline troponin elevation without CK-MB elevation were found to be at increased risk for early and short term adverse outcomes [43,54–56]. McCord and colleagues [57] found that troponin and myoglobin measurement

over a 9-hour period was most predictive of adverse events in their CPU population.

CPUs likely will incorporate a multimarker approach that includes some combination of myoglobin, CK-MB, and troponin, and an inflammatory marker such as CRP [46,58–60]. Additional biomarkers, such as brain natriuretic peptide (BNP), myeloperoxidase, and albumin cobalt binding assays, have been investigated and also show promising results [59–64].

The evaluation of patients for rest ischemia is also extremely important in the CPU setting. Rapid perfusion imaging using radionuclide testing has been a revolutionary step for CPUs. Perfusion imaging with agents, such as sestamibi, has been used in various CPU settings and protocols with great success [11–15]. Tatum and colleagues [14] found that patients with normal imaging findings had a 1-year event rate of 3% no MI or death compared with 42% with 11% experiencing MI and 8% cardiac death. Obtaining multiple 12-lead ECGs can also be an effective method for detecting rest ischemia in patients who present with possible ACS [5,65]. Other imaging modalities, such as computed tomography and MRI, may also improve diagnostic performance in the emergency setting [66,67]. In an ED in Rio de Janeiro, Brazil, a neural diagnostic tree offered an innovative approach to the evaluation of ACS in 566 patients, achieving sensitivities of 99% and 93% for ACS and AMI respectively, with a negative predictive value of 98% for both [68].

Finally, a CPU program must ultimately evaluate patients for exercise-induced ischemia. Fixed coronary artery atherosclerotic lesions may make a patient symptomatic only with exercise. Standard graded exercise testing is extremely useful for these patients [5–7,9]. Many programs use treadmill or chemical stress testing with radionuclide imaging or echocardiography to identify exercise-induced ischemia [3,10–15].

One frequently overlooked advantage of the CPU, is the potential to educate patients about atherosclerosis risk factors during their evaluation. For many patients, coming to the ED represents a key “interventional moment” where education about coronary artery disease and risk modification may be particularly effective [69].

### **Cost effectiveness**

Continued economic constraints and scarce inpatient resources discourage unnecessary

inpatient admissions, making CPU protocols more prevalent and important for effectively managing the large number of patients presenting to the ED with chest discomfort. “Rule-out MI” is no longer an acceptable diagnosis to assign for low and moderate risk patients with chest pain on admission. Increased financial pressures exerted by federal and private insurers on physicians and hospitals have indicated the need for more such units. Emergency physicians, in particular, have been challenged to develop more efficient and cost-effective strategies to evaluate these patients [70,71].

Admissions for ultimately diagnosed “noncardiac” chest pain cost our society billions of dollars annually [72]. The CPU has allowed physicians to condense a hospital admission into a 6- to 12-hour evaluation, risk stratification, and observation period. Even CPUs of a decade ago proved to have significant economic advantages over hospital admission [9,73,74]. Roberts and colleagues [75] determined that accelerated diagnostic protocols for low-risk patients with chest pain saved total hospital costs while reducing hospitalization rates and patient length of stay. Each CPU must be formulated and evaluated based on the target patient population, hospital occupancy and resources, and reimbursement patterns. Initial critics of CPUs contend that this evaluation is expensive and cost prohibitive in some studies [76]. These conclusions were largely based on previously immature protocols. CPUs, by their innovative nature, constantly must undergo a continuous evolution toward optimal patient care and cost savings.

In general, protocol and guideline driven medicine is effective for the evaluation of multiple disease processes in the ED, chest discomfort included. Continuous quality improvement should be an integral part of the continued assessment of every CPU. The 2002 ACC/AHA guidelines for non-ST-segment elevation MI and unstable angina should be reflected in every CPU protocol’s diagnostic and treatment strategies [77].

Finally, it should be mentioned that CPUs are intended for the evaluation of low- to moderate-risk patients, and not “no-risk” patients. Evaluating all patients presenting with chest discomfort in a CPU would indeed be an inefficient use of ED and hospital resources. Continuous assessment of alternative, more effective, and possibly less expensive protocols will improve care standards for these units over time. Already, the last decade has seen a remarkable evolution of cardiac biomarker

regimens and diagnostic and prognostic testing for the evaluation of patients who present with possible ACS. As more and more reports of successful CPUs are published and evidence expands for cost-effectiveness, likely it will be an expectation, rather than an exception, that EDs and hospitals have such units.

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## Acute Coronary Syndromes in the Emergency Department: Diagnostic Characteristics, Tests, and Challenges

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Failure to diagnose patients who have acute coronary syndromes (ACSs)—either acute myocardial infarction (AMI) or unstable angina pectoris (UAP)—who present to the emergency department (ED) remains a serious public health issue. AMI is the leading cause of death for men and women in the United States, with as many as 1.2 million patients having myocardial infarctions (MIs) annually [1] and about half of whom come to EDs for their initial care. In addition, nearly twice as many patients come to EDs having UAP. However, only 25% of patients who present to the ED with symptoms suggestive of an ACS, either AMI or UAP, will have a confirmed diagnosis of the same on discharge [2]. The missed diagnosis rate for AMI and UAP in this setting is about 2% each [3]. Thus clinicians have the unenviable task on the one hand of identifying, treating, and hospitalizing (in the appropriate unit) those patients who have a true ACS and on the other hand of avoid filling hospital telemetry, step-down units, and coronary care units (CCUs) mostly with patients who have symptoms suggestive of an ACS but who in fact do not have one of these syndromes.

For many years, the diagnosis of ACSs was of more prognostic than therapeutic importance. Over the past 3 decades, physicians' diagnostic and triage decisions for patients who have suspected cardiac ischemia have reflected two tendencies. First, as the number of acute interventions for

treating dysrhythmias and preventing or limiting the size of AMI has grown, clinicians have tended to admit all patients who have even a low suspicion of acute ischemia. As a result, clinicians have generally admitted nearly all (92% to 98%) patients presenting with AMI [4–9] and nearly 90% of those presenting with ACSs (including those who have AMI and those who have UAP) [6,7,10]. The conscious strategy of maintaining a high diagnostic sensitivity (ie, that any error be toward overdiagnosis) has the intended effect: among patients who have AMI who seek attention in EDs, the diagnosis is generally missed in 2% [3]. High diagnostic sensitivity has been achieved at the cost of admitting many patients who do not have ACSs (low diagnostic specificity). Only 18% to 42% (typically about 30%) of the 1.5 million patients admitted annually to CCUs [11] actually experience AMI [7,12–16], and only 50% to 60% have acute cardiac ischemia (ACI) [6,7,10,12].

Investigating the causes, progression, and treatment of ACSs continues to be a national research priority, and this research continues to produce substantial progress in the areas of prevention, diagnosis, and treatment of ACI and in advances in understanding its molecular and cellular aspects. Over the past decade, there has been a virtual revolution in our understanding of the pathophysiology and management of coronary artery disease (CAD) [17]. The conversion of a stable atherosclerotic lesion into a ruptured plaque with thrombosis has provided a unifying hypothesis for the cause of ACSs. The understanding of ACSs has evolved from this thesis. Thus, UAP (eg, rest angina, new-onset angina, increasing

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angina) and AMI are now well appreciated as parts of a continuum of myocardial ischemia. The overarching diagnosis of ACS has provided a framework for understanding the pathogenesis, clinical features, treatment, and outcome of patients across the spectrum of myocardial ischemia. For emergency triage, the diagnosis of ACS better identifies patients for CCU or telemetry/step-down unit admission than does the diagnosis of AMI alone. This fact is partly because of the difficulty in differentiating unstable angina from infarction, and partly because of intent, as it helps to reverse ischemia and prevent frank infarction. For patients who have ACSs and prolonged chest pain without infarction, the medium- and long-term mortality may be as poor or worse than for those who actually have AMI [3,18]. In clinical medicine, much research has been focused on the early diagnosis and treatment of ACSs. This research has shown that early diagnosis and treatment of UAP is beneficial and may prevent AMI.

For clinical reasons, to promote the optimal use of a limited resource, and to reduce unnecessary expenditure, research has focused on improving physician's diagnostic and triage accuracy. However, there remains a need for improved methods of diagnosis that can reduce unnecessary hospitalization for patients incorrectly presumed to have acute ischemia without increasing the number of patients who have acute ischemia who are sent home inappropriately [19]. To this end, and as mandated by Congress, in 1991 the National Heart, Lung, and Blood Institute of the National Institutes of Health instituted the National Heart Attack Alert Program to focus on issues related to the rapid recognition and response to patients who have symptoms and signs of ACSs in emergency settings, and made reports in 1997 [20] and 2000 [21] on technologies for identifying ACI in such settings.

For as many as 50% of women and a small percentage of men who have a suspected ACSs, other mechanisms of illness are at work, including vasospastic angina, microvascular endothelial dysfunction, transient left ventricular apical ballooning syndrome, and mitral valve prolapse. The accurate identification of these syndromes in the ED or other acute care settings challenges the skill of even the most seasoned clinician. Clinical features, patient demographics, physical examination findings, and a firm understanding the strengths and limitations of the standard ECG can greatly assist with the identification of patients who have ACSs. Biochemical markers,

cardiac imaging, myocardial performance indices, and computer-based decision aids remain under-evaluated adjuncts to, but not substitutes for, clinicians' judgment regarding diagnosis and triage of patients who have symptoms suggestive of ACSs. However, despite 2 decades of focused research and without compelling evidence for a noncardiac cause, there remains no single way to discriminate perfectly between those who should be admitted to exclude ACSs and those who could be managed safely without admission. In essence, for the continuum of patient risk for ACSs, the investigators have developed a matched continuum of triage options for each patient, from short-stay chest pain evaluation units to multiday admissions for more intensive evaluations. This article reviews the state of the art regarding the diagnosis of ACSs in the emergency setting and suggests reasons why missed diagnosis continues to occur, albeit infrequently, and outlines strategies to deal with the remaining "continuum of risk" for patients who have suspected ACSs.

### Methodologic Issues

Consideration of the specific methods used in studies of patients who have ACSs is vital when critically reviewing studies of the diagnosis/misdiagnosis and triage of patients in the ED who have suspected cardiac ischemia. The key methodologic issues for applicability of study results are:

- Representative patient sample
- Representative prevalence of ischemic heart disease
- Broad patient inclusion criteria, not just chest pain
- Study setting includes a range of settings
- Diagnostic end point includes unstable angina and acute infarction
- Completeness of follow-up
- Follow-up data appropriate and significant
- Validation of findings in generalizable trials

Central to any study is whether the patient sample studied is representative of patients in the ED who are seen in actual practice. Also, the positive predictive value (ie, the proportion of patients that actually has ACSs among all those who have a positive test or attribute) of a symptom, sign, or test result depends on the prevalence of ischemic heart disease in the study population [22]. Thus, the proportion of patients who have

false-positive results will be higher (and positive predictive value lower) in a population that has a low prevalence of ischemia (all patients in the ED) compared with a population that has a high prevalence (patients in the CCU). Even studies performed in EDs may not be comparable when ACSs prevalence is significantly different. Inclusion criteria can limit studies of patients in the ED if, for example, only patients who have chest pain are studied [23–25], compared with the use of broad entry criteria, including multiple symptoms that could be anginal equivalents such as any chest discomfort, epigastric pain, arm pain, shortness of breath, dizziness, or palpitations [26]. Study setting (eg, urban versus rural hospital, teaching versus community hospital) can also affect the applicability of any findings to various practice settings.

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

Finally, validation of the findings of clinical studies is critical, especially for prediction rules and diagnostic aids; findings may be center- or data-dependent. The ideal validation study is a prospective trial of a finding's or prediction rule's effects on patient care in diverse settings [29].

### **Clinical presentation**

The clinically obtained history must be concise, yet detailed enough to establish the probability of ACSs, and obtained expeditiously so as not to delay implementation of therapy.

### **Chest discomfort**

Of all the symptoms for which patients seek emergency medical care, chest pain or discomfort

is one of the most common and complex, accounting for about 5.6 million ED visits annually [1]. It is important to keep in mind that many patients will not admit having chest “pain,” but will acknowledge the presence of chest “discomfort” because of their definition of pain. Published reports suggest that up to 5% of visits to the ED involve complaints relating to chest discomfort [30]. The complaint of chest discomfort encompasses many varying conditions, ranging from insignificant to high-risk in terms of threat to the patient's life, including, but not limited to, acute coronary syndromes (AMI and UAP), thromboembolic disease (pulmonary embolism), aortic dissection, pneumothorax, pneumonia, myocarditis, and pericarditis. Chest discomfort may be perceived as pain with descriptions such as crushing, vice-like constriction; a feeling equivalent to an “elephant sitting on the chest”; tightness; pressure; heartburn; or indigestion, or as discomfort most noticeable for its radiation to an adjacent area of the body such as the neck, jaw, interscapular area, upper extremities, or epigastrium. Elderly patients or those who have diabetes may have altered ability to specifically localize discomfort [31]. Individuals of each gender and different cultural groups vary in their expression of pain and ability to communicate with health professionals, so that presentation may range from merely bothersome to cataclysmic for conditions that seem nearly equivalent when objective criteria are matched. The level of discomfort does not necessarily correlate with the severity of illness, making identification of potentially life-threatening conditions difficult in certain patients. Because of the serious nature of many conditions presenting with chest discomfort and the potential for significant reduction in morbidity and mortality with early diagnosis and treatment, clinical policies have been developed to guide clinicians with their initial evaluation of chest discomfort, emphasizing prompt triage, assessment, and initiation of therapy [32]. This article only reviews the policies that apply to ACSs.

It is sometimes difficult to distinguish cardiac from noncardiac chest discomfort, even though chest pain is the hallmark of ACSs. Taking the time to elicit the exact character of the sensation (without prompting the patient, if possible) and any pattern of radiation (if present) is most helpful. Typically, the chest discomfort of acute ischemia has a deep visceral character, preventing the patient from localizing the discomfort to a specific region of the chest. It is often described



as a pressure-like or heavy weight on the chest, a tightness, a constriction about the throat, or an aching sensation that is not affected by respiration, position, or movement and that comes on gradually, reaches its maximum intensity over a period of 2 to 3 minutes, lasts longer than 30 minutes rather than seconds, may wax and wane, and may be remitting. It may be described as indigestion and occasionally may be relieved by belching. In a large study of patients in the ED who had suspected ACSs, Pope and colleagues [2] found that the 76% of patients who presented with the complaint of chest pain or discomfort (including arm, jaw, or equivalent discomfort) had a 29% incidence of ACSs at final diagnosis (10% AMI, 19% UAP). In 69% of patients, chest pain or discomfort was the chief complaint, and this group had a 31% incidence of ACSs (10% AMI, 21% UAP). In 21% of patients, it was the only complaint, and this group had a 32% incidence of ACSs (9% AMI, 23% UAP). Furthermore, chest pain or discomfort as the chief complaint or presenting symptom was more frequently associated with a final diagnosis of ACS (88% ACS versus 62% non-ACS and 92% ACS versus 71% non-ACS, respectively;  $P = .001$ ). Sharp, stabbing, or positional pain is less likely to represent ischemia [33] but does not exclude it. Lee and colleagues [34] found that among patients in the ED who had sharp or stabbing pain, 22% had acute ischemia (5% AMI, 17% UAP). Among those who had partially pleuritic pain, 13% had acute ischemia (6% AMI, 7% UAP), and among the group that had fully pleuritic pain, none was shown to have acute ischemia. Of the patients whose pain was fully reproduced by palpation, 7% nonetheless had acute ischemia (5% AMI, 2% UAP), and 24% had pain partially reproduced with palpation had ischemia (6% AMI, 18% UAP). Patients who describe their discomfort as similar to previous episodes of cardiac ischemia are more likely to have ACSs [16,35], but any chest discomfort carries a higher risk than no discomfort [6,26,36].

Combinations of variables improved discrimination in these patients [24]. In patients who had sharp or stabbing pain that was also pleuritic, positional, or reproducible by palpation, 3% had UAP and none had AMI. Furthermore, if these same patients had no history of ischemic heart disease, none had acute ischemia. The “partially” and “fully” groups were subjective and small in number.

Exact location of chest pain is not significantly different in patients who have or do not have AMI

[37], but chest pain that radiates to the arms or neck does increase the likelihood [38–40]. In the study by Sawe [37] that looked at admitted patients who had AMI, 71% had pain radiation to arms or necks, whereas 39% of admitted patients who experienced pain radiation did not have AMI. Consistent with the classical description, 33% of patients who proved to have infarction had radiation to both arms, 29% had pain radiating to the left arm only, and 2% to the right arm only [37].

Some investigators believe that a significant number of patients who have cardiac ischemia can present with abdominal pain as their chief complaint [23,24]. However, Pope and colleagues [2] found that 14% of study patients had this complaint. This group had a 15% incidence of ACSs at final diagnosis (6% AMI, 9% UAP), but less than 1% of these patients complained of abdominal pain as their chief or only complaint and had a 4% incidence of ACI (2% AMI, 2% UAP). Abdominal pain as a chief complaint or presenting symptom was associated with a higher incidence of a non-ACS final diagnosis (0.6% non-ACS versus 0.1% ACS; 16% non-ACS versus 9% ACS, respectively;  $P = .001-.002$ ). Esophageal reflux and motility disorders are common masqueraders of ACS. In a study of all patients discharged from a CCU with undetermined causes of chest pain, over half had esophageal dysfunction [41]. When these patients' presenting complaints were compared with those of patients who did not have ACSs, those who had esophageal disorders were more likely to complain of a lump in their throat, acid taste, overfullness after eating, a hacking cough, and chest pain that caused awaking at night, and they were less likely to report effort-related chest pain, a history of nitroglycerin use, or reliable chest pain relief with its use.

### Anginal pain equivalents

Dyspnea, present in about one third of patients who have infarction in some series [24,38,42], is the most important angina equivalent. In their multicenter ED trial, Pope and colleagues [2] found that 16% of patients who had suspected ACSs presented with a chief complaint of shortness of breath and had an 11% incidence of ACSs at final diagnosis (6% AMI, 5% UAP); in 8%, this was the only complaint, with a 10% incidence of ACS (5% AMI, 5% UAP). However, a final diagnosis of ACSs was not more frequent in

patients who had a presenting symptom of shortness of breath (56% ACS versus 56% non-ACS;  $P = .5$ ); as a chief complaint, shortness of breath was more commonly associated with a final diagnosis of non-ACS (18% non-ACS versus 7% ACS;  $P = .001$ ), possibly reflecting a high prevalence of patients who have lung disease in the study population. Yet, because 4% to 14% of patients who have AMI [23,24,26] and 5% of patients who have UAP present only with sudden difficulty breathing [2], ACSs should be considered as a cause of unexplained shortness of breath.

Diaphoresis and vomiting, when associated with chest pain, increase the likelihood of infarction [15,29,38]. Diaphoresis occurs in 20% to 50% of patients who have AMI [39,43]. One study showed that the presence of nausea without vomiting did not discriminate, but vomiting was significantly more frequent in patients who “ruled in” [38]. Pope and colleagues [2] found nausea in 28% of patients who had suspected ACSs. Patients who had nausea as a presenting symptom had a 26% incidence of ACSs at final diagnosis (10% AMI, 16% UAP); patients who had nausea or vomiting as chief complaint (2%) had a 15% incidence of ACSs (11% AMI, 4% UAP); and less than 1% of patients had nausea or vomiting as their only symptom. The same study found vomiting present in 10% of patients. Patients who had vomiting as a presenting symptom had a 23% incidence of ACSs (13% AMI, 10% UAP) and patients who had vomiting as the chief or only complaint had less than 1% incidence. Furthermore, investigators showed that a chief complaint of nausea or vomiting was more frequently associated with a final diagnosis of non-ACS (0.5% non-ACS versus 0.3% ACS;  $P = .15$ ), yet a presenting complaint of nausea was more commonly associated with a final diagnosis of ACSs (30% ACS versus 27% non-ACS;  $P = .004$ ); a presenting complaint of vomiting did not show this association (10% ACS versus 10% non-ACS;  $P = .7$ ). In a CCU study, 43% of patients who had Q-wave infarction and only 4% of patients who had non-Q-wave infarctions or prolonged angina had vomiting [44].

So-called “soft clinical features,” such as fatigue, weakness, malaise, dizziness, and “clouding of the mind,” are surprisingly frequent, occurring in 11% to 40% of patients who have AMI [29,37,38,42]. Prodromal symptoms (those occurring in the preceding days or weeks) are also frequent: 40% report unusual fatigue or weakness, 20% to 39% dyspnea, 14% to 20% “emotional

changes,” 20% a change in appearance (ie, “looked pale”), and 8% to 10% dizziness [24,42]. Pope and colleagues [2] found that 28% of patients who had suspected ACSs presented to the ED with dizziness and had a 16% incidence of ACSs (5% AMI, 11% UAP). Dizziness was the primary complaint in 5% of study patients, with a 4% incidence of ACSs (2% AMI, 2% UAP), and it was the only symptom in 1% of patients (2% AMI, 0% UAP). In the same study, dizziness or fainting as a chief complaint were more commonly associated with a final diagnosis of non-ACS (7% non-ACS versus 1% ACS,  $P = .001$ ). Similarly, dizziness or fainting as a presenting symptom was more frequently associated with final diagnoses of non-ACS (31% non-ACS versus 19% ACS; 8% non-ACS versus 2% ACS; respectively;  $P = .001$ ). ECG evaluation is helpful in low-prevalence patients who have these vague complaints.

### Atypical presentations

Few studies address what proportion of patients in the ED who have ACSs present with atypical symptoms—a group for which the diagnostic/triage decision is often most problematic. Among hospitalized patients who have AMI, 13% to 26% had no chest pain or had chief complaints other than chest pain (eg, dyspnea, extreme fatigue, abdominal discomfort, nausea, syncope) [23,24]. In a large ED study of patients presenting with a wide range of clinical symptoms, Pope and colleagues [2] found that 31% of patients who had suspected ACSs presented without chest pain, with a 26% incidence of ACSs at final diagnosis (18% infarction, 8% unstable angina), and had chief complaints other than chest pain (eg, shortness of breath, abdominal pain, nausea, vomiting, dizziness, fainting). Subanalysis of this same data by Coronado and colleagues [31] found pain to be absent in 6.2% of patients who had acute ischemia and 9.8% of patients who had AMI. These investigators found that age and heart failure were independently associated with painless ACSs, in addition to diabetes mellitus among those who had AMI, and that lack of pain predicted increased hospital mortality. Finally, in a large group of patients on Medicare who were hospitalized with confirmed UAP, Canto and colleagues [45] found over half of these patients had atypical presentations. Independent predictors of atypical presentation for patients who had UAP were older age, history of dementia, and absence of

prior MI, hypercholesterolemia, or family history of heart disease. Patients who had atypical presentation received aspirin, heparin, and beta-blocker therapy less aggressively, but there was no difference in mortality.

Among patients in the ED, no single atypical symptom is of overwhelming diagnostic importance, although combinations of symptoms can identify high-risk patients who should be admitted regardless of ECG findings. Pope and colleagues [2] ranked atypical presenting symptoms in decreasing order of association with ACI at final diagnosis as follows: nausea (26%), shortness of breath (24%), vomiting (23%), dizziness (16%), abdominal pain (15%), and fainting (65%). Canto and colleagues [45], in their study of patients who had UAP, found the most frequent symptoms to be dyspnea (69%), nausea (38%), diaphoresis (25%), syncope (11%), and pain in the arms (12%), epigastrium (8%), shoulder (7%), or neck (6%).

Data from community-based epidemiologic studies [25,46–48] suggest that 25% to 30% of all Q-wave infarctions go clinically unrecognized. Of these, half were truly silent and half were associated with atypical symptoms in retrospect [25,46]. Because Q waves often resolve (in the Framingham Study)—10% of patients were discharged after anterior infarction and 25% of those discharged after inferior infarction lost their Q waves within 2 years—the true incidence was underestimated [49].

The rate of erroneous discharge from the ED of patients who have AMI may be a marker for atypical cases, but such studies are limited by inclusion criteria, small numbers, and lack of complete follow-up. Rates of 2% [50], 4% [9], and as high as 8% [8] have been reported. In a large ED series [3], patients who had suspected ACSs reported rates of erroneous discharge of 2% (2.1% AMI, 2.3% UAP). The early mortality (30-day) for these missed AMIs may be as high as 10% to 33% [3,8,9].

Finally, in a large ED study of patients who had UAP, Pope and colleagues [3] found that 2.3% were not hospitalized. Over three fourths of the patients were evaluated by an attending physician, and more than one fourth by a consulting cardiologist. Although there was disagreement over the interpretation of 16% of the ECGs on subsequent review by an experienced cardiologist, this was not believed to be clinically significant in any of the cases. Given that most of the patients who were not hospitalized had Canadian Cardiovascular

Society class 3 angina with new symptoms or symptoms that changed within 3 days before presentation, inaccuracies in the clinician assessment of the dynamic nature of anginal symptoms may have contributed to the failure to hospitalize patients who had UAP.

### Past medical history

In addition to the presenting clinical features, the presence of a CAD risk factor has traditionally been considered diagnostically helpful in the ED setting. In a large ED series [2] an association was shown between patients having a past history of diabetes mellitus (31% ACS versus 18% non-ACS;  $P = .001$ ), MI (45% ACS versus 20% non-ACS;  $P = .001$ ), or angina pectoris (63% ACS versus 29% non-ACS;  $P = .001$ ), and a final diagnosis of ACSs; however, these findings require careful interpretation. From the Framingham Study, it is well known that the risk for developing ischemic heart disease is increased over decades by male gender, advancing age, a smoking habit, hypertension, hypercholesterolemia, glucose intolerance, ECG abnormalities, a type A personality, a sedentary lifestyle, and a family history of early CAD [24,51,52]. Clinicians customarily assess these factors when providing preventive care because they predict the incidence of future coronary disease. However, coronary risk factors were established to provide an estimate of risk over years. Thus, the Framingham Study showed that hypertension increases the risk for ischemic heart disease twofold over 4 years [25], but only a very small portion of this risk applies to the few hours of acute illness that the patient in the ED experiences. A patient's report of coronary risk factors is also subject to biases and inaccuracies. This history is presumably less reliable than the methods used to assign risk in longitudinal studies.

In a multicenter study, Jayes and colleagues [53] found that most of the classic coronary risk factors have little predictive value for ACSs when used in the ED setting. Except for diabetes and a positive family history in men, no coronary risk factor significantly increased the likelihood that a patient had acute ischemia. Diabetes and family history each confer only about a twofold relative risk for acute ischemia in men, whereas chest discomfort, ST-segment abnormalities, and T-wave abnormalities confer relative risks of about 12-, 9-, and 5-fold, respectively. Because these results run counter to the prevailing clinical

wisdom, it is possible that physicians who give risk factor history great weight may inappropriately diagnose/triage patients in the ED, which is an issue that deserves further attention and investigation.

Finally, a past history of medication use for coronary disease increases the likelihood that the current chest pain is an ACS. In the Boston City Hospital and the multicenter predictive instrument trials, a history of nitroglycerin use was found to be one of the most powerful predictors of ACSs [6]. Although nitrates are an accepted mainstay in treating acute and chronic coronary disease, the diagnostic and prognostic value of chest pain relief with nitroglycerin has been poorly studied. In the largest study to date, Henrikson and colleagues [54] found that chest pain relief with nitroglycerin did not accurately predict active CAD or subsequent outcomes in a general population presenting to an ED. Nitrates can cause dramatic relief of chest pain from esophageal spasms [55], thus further questioning their diagnostic ability in ischemic heart disease.

### Physical examination

The physical examination is generally not helpful in diagnosing ACSs when compared with the value of historical data and ECG findings, except when it points to an alternate process. On the other hand, clinicians must not be lulled into a sense of security by chest pain that is partially or fully reproduced by palpation, because 11% may have infarction or UAP [26]. Pope and colleagues [2] found the pulse rate to be lower in patients who had a final diagnosis of ACSs versus those who had a final diagnosis of non-ACS ( $P = .02$ ), but this difference was not considered clinically significant.

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

In a large series of patients in the ED who had suspected ACS, median first and highest systolic blood pressures (SBPs) were higher in patients who had a final diagnosis of ACSs [2]. This finding suggests that the adrenergic excess associated with ACSs might be greater than that associated with non-ACS diagnoses. However, to use this hypothesis as a predictive factor, clinicians must have some idea of their patient's baseline blood pressure, which is not the case in most ED evaluations. Thus, the usefulness of this observation may be limited.

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

Pope and colleagues [3] found that median first, median highest, and median lowest SBPs of patients who had AMI and were subsequently classified as Killip class 4 (cardiogenic shock) were above the threshold of this classification (SBP  $\leq 90$  mmHg) for these three blood pressure observations. This finding suggests that the adrenergic excess associated with ACSs may be greater than that associated with non-ACS diagnoses. Although the number of such patients in this analysis was small, it did suggest that patients who have ACSs can present with apparently normal blood pressures and can go on to develop cardiogenic shock.

Abnormal vital signs and certain combinations of these have been shown to be critical observations in clinical outcome prediction. The reported probability of infarction decreases with a normal respiratory rate [38] and increases with diaphoresis [15], but other signs mainly help identify high-risk patients who have infarction [56]. In the predictive instrument for AMI mortality proposed by Selker and colleagues [36], blood pressure, pulse, and their interaction figured prominently in three of the six clinical variables used to develop the prediction instrument.

Finally, rales (of any degree), but not S3 gallops, have been more frequently seen in patients who have a final diagnosis of ACSs [2]. This finding is not surprising, as several clinical syndromes of pump failure can complicate ACSs. The investigators'

failure to find association between an S3 gallop rhythm and ACSs at final diagnosis is surprising, but it may have to do with a failure to document this finding consistently in the medical record on the part of the physicians in the EDs at study sites.

## ECG

### *Standard 12-lead ECG*

A complete summary of evidence related to the diagnostic usefulness of the standard ECG was recently published [20,57], and this background will not be repeated in this article. However, the National Heart Attack Alert Program (NHAAP) Working Group on "Evaluation of Technologies for Identifying Acute Cardiac Syndrome" [57] found that most studies evaluate the accuracy of the technologies and only a few evaluate the clinical impact of routine use. Furthermore, the group concluded that although the standard ECG is a safe, readily available, and inexpensive technology with a high sensitivity for AMI, it is not highly sensitive or specific for ACSs. However, the ECG findings remain an integral, if not the most important, part of the evaluation of patients who have chest pain, and the Working Group recommended that they remain the standard of care for evaluating patients who have chest pain in the ED.

The ECG provides essential information when the diagnosis is not obvious by symptoms alone [58], despite one study noting that the results of the ECG infrequently changed triage decision based on initial clinical impressions [59]. The generally dominant weights given to ECG variables in mathematic models for predicting ACSs substantiate this impression [6,7,10,15,16]. Moreover, the initial ECG is increasingly important in intrahospital triage because of its value in predicting complications of AMI [60–62].

The fundamental limitations in the standard ECG include:

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

First, it is a single brief sample of the whole picture of the changing supply-and-demand characteristics of unstable ischemic syndromes. If a patient who has UAP is temporarily pain-free when the ECG is obtained, the resulting tracing

may poorly represent the patient's ischemic myocardium.

Second, 12-lead ECG is limited by its lack of perfect detection [63]. Small areas of ischemia or infarction may not be detected; conventional leads do not examine satisfactorily the right ventricle [64] or posterior basal or lateral walls (eg, AMIs in the distribution of the circumflex artery) [65,66].

Third, some ECG baseline patterns make interpretation difficult or impossible, including prior Q waves, early repolarization variant, left ventricular hypertrophy, bundle branch block, and dysrhythmias [67]. Lee and colleagues [9] demonstrated that when the current ECG shows ischemic findings, availability of a prior comparison ECG improved triage.

Fourth, ECG waveforms are frequently difficult to interpret, causing disagreement among readers—so-called "missed ischemia." In a study of patients who had AMI and were sent home, ECGs tended to show ischemia or infarction not known to be old, with 23% of the missed diagnoses owing to misread ECGs [8]. Jayes and colleagues [53] compared ED physician readings of ECGs with formal interpretations by expert electrocardiographers, and calculated sensitivities of 0.59 and 0.64 and specificities of 0.86 and 0.83 for ST-segment and T-wave abnormalities, respectively. McCarthy and colleagues [18] and a review of litigation in missed AMI cases [68] emphasized this factor of incorrect ECG interpretation. In the largest study to date of ACSs in the ED, Pope and colleagues [3] found that although the rate of missed diagnoses of ACSs (2.1% AMI, 2.3% UAP) was low, there was a small but important incidence of failure by the ED clinician to detect ST-segment elevations of 1 to 2 mm in the ECGs of patients who had MI (11%). Correct ECG interpretation by ED physicians is doubly important today because of the need to use interventions such as thrombolytic agents and percutaneous coronary intervention appropriately in ACSs.

Fifth, the implications of the ECG findings must be interpreted in their clinical context, a process performed intuitively by clinicians and formally stated in Bayesian analysis. When symptoms alone strongly suggest ischemia, a normal or minimally abnormal ECG will not substantially decrease the probability of ischemia. Conversely, when the presentation is inconsistent with acute ischemia, an abnormal ECG (unless diagnostic abnormalities are present) will only modestly increase the likelihood of ischemia. Bayes' rule

tells us that the ECG will have the greatest impact when symptoms are equivocal [69].

Finally, the ECG suffers from imperfect sensitivity and specificity for ACS. When interpreted according to liberal criteria for MI (ie, ECGs that show any of the following as positive for AMI: nonspecific ST-segment or T-wave changes abnormal but not diagnostic of ischemia; ischemia, strain, or infarction, but changes known to be old; ischemia or strain not known to be old; and probable AMI), the ECG operates with high (but not perfect) sensitivity (99%) for AMI, at the cost of low specificity (23%; positive predictive value 21%; negative predictive value 99%). Conversely, when interpreted according to stringent criteria for AMI (only ECGs that show probable AMI), sensitivity (61%) drops and specificity equals 95% (positive predictive value 73%; negative predictive value 92%) [20].

Despite its usefulness, the ECG is insufficiently sensitive to make the diagnosis of ACSs consistently. The ECG should not be relied on to make the diagnosis but rather should be included with history and physical examination characteristics to identify patients who appear to have a high risk for ACSs (ie, a supplement to, rather than a substitute for, physician judgment). In rule-out AMI patients, a negative ECG carries an improved short-term prognosis [60,70–73]. Providing the interpreter with old tracings would intuitively seem to be of value because baseline abnormalities make current evaluation difficult. However, Rubenstein and Greenfield [74], in a study of 236 patients presenting to EDs with the complaint of chest pain, found that only a small proportion might have benefited from having a previous baseline ECG available (5% might have avoided unnecessary admission). Furthermore, there was no patient for whom a baseline ECG would have aided in avoiding an inappropriate discharge. ECG sampling should be periodic, not just static. The pitfalls of not ordering ECGs in younger, atypical patients, and of misinterpretation should be anticipated. Finally, clinicians should not be reluctant to obtain a second opinion—by fax transmission if necessary—for difficult tracings.

#### *ST-segment and T-wave abnormalities*

ST-segment and T-wave abnormalities are the sine quo non of ECG diagnosis of ACSs. Numerous studies [63,73,75] have found that 65% to 85% of CCU patients who have ST-

segment elevation alone will have had an infarction. Other investigators found that if Q waves and ST-segment elevation were present, 82% to 94% actually sustained AMI [63]. However, it must be remembered that ST-segment elevation can occur in the absence of ischemia (ie, “early repolarization” variant, pericarditis, left ventricular hypertrophy, and previous infarction even in the absence of a ventricular aneurysm) [76]. Conversely, Pope and colleagues [2] showed that a large percentage of patients who have ACS (20% AMI, 37% UAP) can present with initial normal ECGs.

In their study of patients in the ED who had suspected ACS, Pope and colleagues [2] found that ST-segment elevation of either 1 to 2 mm or more than 2 mm was more frequently associated with a final diagnosis of ACSs (9% ACS versus 7% non-ACS; 5% ACS versus 1% non-ACS, respectively;  $P = .001$ ). A full 30% of patients who have ST-segment elevation of 1 mm or greater had a final diagnosis of AMI. In addition, in a study of missed diagnosis of ACSs in the ED, Pope and colleagues [2] found a small but important incidence of failure by the ED clinician to detect ST-segment elevations of 1 to 2 mm in the ECGs of patients who had AMI (11%). This incidence represents an important and potentially preventable contribution to the failure to admit such patients.

ST-segment depression usually indicates subendocardial ischemia. If these abnormalities are new, persistent, and marked, the likelihood of AMI increases. About 50% to 67% of admitted patients who have new or presumed new isolated ST-segment depression have infarctions [64,75]; even more patients have probable ischemia. Pope and colleagues [2] found that all degrees of ST-segment depression (0.5, 1, 1–2, and  $\geq 2$  mm) were more commonly associated with a final diagnosis of ACSs (12% ACS versus 7% non-ACS; 8% ACS versus 3% non-ACS; 2% ACS versus 0% non-ACS, respectively;  $P = .001$ ). A full 19% of patients who had ST-segment depression of at least 0.5 mm or greater had a final diagnosis of AMI. Quantitative ST-segment depression and cardiac Troponin T status have been found to be complementary in assessing risk among ACS patients [77]. ST-segment depression may also occur in nonischemic settings, including patients who are hyperventilating, those taking digitalis, those who have hypokalemia, and those who have left ventricular strain (without voltage criteria) [76].

Inverted T waves may reflect acute ischemia. One study showed that isolated T-wave inversion

occurred in 10% of CCU admissions, of whom 22% had AMI [78]. T-wave changes may reflect prior myocardial damage or left ventricular strain [76]. The study by Pope and colleagues [2] found that certain T-wave patterns (inverted 1–5 mm, inverted  $\geq 5$  mm, or elevated) were more frequently associated with a final diagnosis of ACS (32% ACS versus 17% non-ACS; 1% ACS versus 0% non-ACS; 4% ACS versus 1% non-ACS, respectively;  $P = .001$ ). Flattened T waves did not have the same association with an ACS final diagnosis (18% ACS versus 20% non-ACS;  $P = .001$ ). Furthermore, 39% of patients who had inverted T waves of at least 1 mm or greater had a final diagnosis of AMI.

### Q waves

Q waves are diagnostic of MI, but what is the age of the Q wave? In the Multicenter Investigation of the Limitation of Infarct Size (MILIS) study of admitted patients in the CCU, isolated new or presumed-new inferior or anterior Q waves were associated with acute infarction in 51% and 77% of patients, respectively [63]. Other findings of the MILIS study that should be kept in mind are: 12% of healthy young men have inferior Q waves [76,78,79]; pathologic Q waves can be from a previously unrecognized infarction and can mask new same-territory ischemia; Q waves alone do not identify ACSs and are rarely the sole manifestation of AMI (6% in the MILIS study); and, finally, infarction can occur in the absence of Q waves [80,81]. The investigators' ED study [2] showed that Q waves were more commonly associated with a final diagnosis of ACS (25% ACS versus 11% non-ACS;  $P = .001$ ) and that 29% of patients who had Q waves present on their ECGs had a final diagnosis of AMI.

### “Nondiagnostic” ECG patterns

“Nondiagnostic” ST-segment and T-wave abnormalities may be defined as follows: not having 1 mm or greater (0.1 mV) ST-segment elevation or depression in two contiguous leads, not having new T-wave inversion in two contiguous leads, absence of significant Q-waves ( $> 1$  mm deep and 0.3 s duration) in two contiguous leads, not having second- or third-degree heart block, and not having a new conduction abnormality (eg, bundle branch block). These patterns are the most difficult to interpret and can result in

overdiagnosis (no comparison ECG available) and underdiagnosis (baseline abnormality obscuration of ischemia) [82]. Lee and colleagues [34] found that emergency patients who had chest pain and nondiagnostic ECG abnormalities had a low risk for AMI but a significant risk for ACSs. Pope and colleagues [3] found that 53% of patients in the ED who had a missed diagnosis of AMI had normal or nondiagnostic ECGs, as did 62% of patients who had a missed diagnosis of UAP.

### Normal ECG

Among patients in the ED who had normal ECGs (ie, lacking Q waves; primary ST-segment and T-wave abnormalities; and criteria for nondiagnostic abnormalities), 1% [34] to 6% [82] had AMI. Among admitted patients who had normal ECGs, 6% to 21% had AMI [12,78,81–83]. Of patients discharged home with a normal ECG, only 1% had acute infarction [82]. Patients who have a normal ECG and a suggestive clinical presentation still have a significant risk for ACI, especially if the ECG was obtained when the patient was pain free. On the other hand, a truly normal ECG in a patient unlikely to have acute ischemia provides strong evidence against ACS [34].

In their series, Pope and colleagues [2] found that patients who had normal ST-segment and T waves and no Q waves more commonly had a final diagnosis of non-ACS, yet 20% of these patients had AMI and 37% had UAP at final diagnosis.

### Prehospital 12-lead ECG

The NHAAP Working Group on Evaluation of Technologies for Identifying ACSs [57] found that the diagnostic accuracy of prehospital ECG for AMI and ACSs, as expected, is similar to that of the standard 12-lead ECG, which is the standard of care in the management of patients suspected of having ACS (Tables 1 and 2). The accumulation of evidence is substantial in the total sample size and quality, and the data have been gathered from patient populations with few exclusion criteria. The evidence shows that obtaining a prehospital ECG does not prolong time in the field or delay transport to the ED. In addition, prehospital ECG-guided thrombolytic therapy can be administered 45 minutes to 1 hour earlier than hospital-based thrombolytics. Prehospital thrombolysis has a modest but significant impact

Table 1  
Summary of test performance studies of diagnostic technologies for acute cardiac ischemia in emergency departments

Technology	Condition studied	Number of studies (subjects)	Population category of studies <sup>a</sup>	Studies' prevalence range (%)	Sensitivity <sup>b</sup> (95% CI) (%)	Specificity <sup>b</sup> (95% CI) (%)	Diagnostic odds ratio <sup>b</sup> (95% CI)	Overall quality of evidence
Prehospital 12-lead ECG	ACI	5 (4311)	I/II	46–92	76 (54–89)	88 (67–96)	23 (6.3–85)	B
	AMI	10 (4481)	I/II	14–51	68 (59–76)	97 (89–92)	104 (48–224)	B
Continuous/serial ECG	ACI	2 (1271)	III/IV	4–40	21–25 <sup>c</sup>	92–99 <sup>c</sup>	3.8–45 <sup>c</sup>	C
	AMI	1 (261)	III/IV	11	39 <sup>c</sup>	88 <sup>c</sup>	4.9 <sup>c</sup>	B
Nonstandard lead ECG	ACI	1 (52)	IV	48	96 <sup>c</sup>	41 <sup>c</sup>	17 <sup>c</sup>	B
	AMI	4 (897)	IV	22–65	59–83 <sup>c</sup>	76–93 <sup>c</sup>	10–19 <sup>c</sup>	B
Exercise stress ECG	ACI	2 (312)	III	6–10	70–100 <sup>c</sup>	82–93 <sup>c</sup>	11–320 <sup>d</sup>	B
CK (presentation)	AMI	10 (2885)	I/II/III	7–41	36 (29–44)	88 (80–93)	4.0 (2.6–6.2)	C
CK (serial)	AMI	2 (786)	I	26–43	69–99 <sup>c</sup>	68–84 <sup>c</sup>	12–222 <sup>c</sup>	C
CK-MB (presentation)	ACI	1 (1042)	III	20	23 <sup>c</sup>	96 <sup>c</sup>	7.2 <sup>c</sup>	C
	AMI	10 (2504)	I/II/III	6–42	44 (35–53)	96 (94–97)	23 (17–32)	B
CK-MB (serial)	ACI	1 (1042)	III	20	31 <sup>c</sup>	95 <sup>c</sup>	8.5 <sup>c</sup>	C
	AMI	7 (3381)	I/II/III	1–53	87 (67–95)	96 (94–97)	171 (58–505)	B
Myoglobin (presentation)	AMI	10 (1395)	I/II/III	12–413	49 (41–57)	93 (88–96)	13 (7.9–21)	B
Myoglobin (serial)	AMI	5 (831)	I/II/III	23–37	90 (78–96)	90 (78–96)	140 (66–300)	C
Troponin I (presentation)	AMI	2 (874)	II/III	6–39	23–66 <sup>c</sup>	89–95 <sup>c</sup>	5.7–14 <sup>c</sup>	A
Troponin I (serial)	AMI	1 (773)	III	6	100 <sup>c</sup>	83 <sup>c</sup>	— <sup>d</sup>	A
Troponin T (presentation)	AMI	5 (1171)	II/III	6–39	44 (32–56)	92 (88–95)	10 (5.9–18)	B
Troponin T (serial)	AMI	2 (1440)	II/III	5–6	80–93 <sup>c</sup>	65–90 <sup>c</sup>	35–120 <sup>c</sup>	A/C
P-selectin	ACI	1 (263)	II	33	35 <sup>c</sup>	79 <sup>c</sup>	2.0 <sup>c</sup>	B
	AMI	same study		8.4	45 <sup>c</sup>	76 <sup>c</sup>	2.6 <sup>c</sup>	
Rest echocardiography	ACI <sup>e</sup>	2 (228)	III	3–30	70 (43–88)	87 (72–94)	20 (9–48)	C
	AMI	3 (397)	I/III	3–30	93 (81–91)	66 (43–83)	20 (7–62)	B
Stress echocardiography	AMI	1 (139)	III	4	90 <sup>c</sup>	89 <sup>c</sup>	68 <sup>c</sup>	C
	Sestamibi (rest)	ACI	3 (702)	III	9–17	81 (74–87)	73 (56–85)	18 (11–29)
ACI-TIPI	ACI	4 (5496)	I	17–34	86–95 <sup>c,e</sup>	78–92 <sup>c,e</sup>	61–69 <sup>c,e</sup>	A
	Goldman chest pain protocol	AMI	3 (5359)	I	(ACI 27–30) 12–21	88–91 <sup>c</sup>	70–74 <sup>c</sup>	20–23 <sup>c</sup>
Algorithm/protocols	No data from prospective studies							
Computer-based decision aids	AMI	6 (3606)	I/II/III	7–42	52–98 <sup>c</sup>	58–96 <sup>c</sup>	4.4–9.04	A

Abbreviations: ACI-TIPI, acute cardiac ischemia time-insensitive predictive instrument; CK, creatine kinase; CK-MB, creatine kinase subunit.

<sup>a</sup> Population categories: I: all patients who have symptoms suggestive of ACI; II: chest pain; III: chest pain with nondiagnostic ECG; IV: selected subpopulation.

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

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

<sup>d</sup> Upper range cannot be estimated because of a study with 100% sensitivity.

<sup>e</sup> ACI-TIPI is not intended to provide sensitivity and specificity. The results reported incorporate physicians' triage decisions and are not reflective of diagnostic test performance only.



Table 2  
Summary of clinical impact studies of diagnostic technologies for acute cardiac ischemia in emergency departments

Technologies	Condition studied	Number of studies (subjects)	Population category <sup>a</sup>	Prevalence (%)	Clinical outcomes studied	Clinical impact	Quality of evidence
Prehospital 12-lead ECG	ACI	~ 10 studies <sup>b</sup>	I/II	46–100	Time to thrombolysis, ejection fraction, mortality	++	A
Continuous/serial ECG	AMI	~ 8000 pts <sup>b</sup> No study	—	15–51	—	Not known	—
Nonstandard lead ECG		No study	—		—	Not known	—
Exercise stress ECG	ACI	3 (272)	III	0–6	Feasibility and safety	Not known	C
CK (single/serial)		No study	—		—	Not known	—
CK-MB (single)		No study	—		—	Not known	—
CK-MB (serial)	ACI	1 (1042)	III	20	Additional admissions or discharges of ACI and non-ACI patients	++	C
Myoglobin (single/serial)		No study	—		—	Not known	—
Troponin I or T		No study	—		—	Not known	—
Other biomarkers		No study	—		—	Not known	—
Rest echocardiography		No study	—		—	Not known	—
Stress echocardiography		No study	—		—	Not known	—
Sestamibi		No study	—		—	Not known	—
ACI-TIPI	ACI	5 (14450)	I	17–59	CCU admission rate, inappropriate discharge	(+++)	A
Goldman chest pain protocol	AMI	1 (1921)	III	6.6	Hospitalization rate, length of stay, estimated costs	(+)	A
Algorithm/protocols	ACI	2 (602)	III	6–9	Length of stay, hospital charges, 30-day and 150-day mortality	Not known	B
Computer-based decision aids	ACI	1 (977)	III	48 (AMI 30)	30-day mortality	Not known	A

Clinical impact scores range from low (+) to high (+++).

Quality of evidence scores range from low (C) to high (A).

*Abbreviations:* ACI-TIPI, acute cardiac ischemia time-insensitive predictive instrument; CK, creatine kinase; CK-MB, creatine kinase subunit.

<sup>a</sup> Population categories: I: all patients who have symptoms suggestive of ACI; II: chest pain; III: chest pain with non-diagnostic ECG; IV: selected subpopulation.

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

on early mortality, with approximately 60 patients requiring prehospital treatment compared with hospital thrombolysis to save one additional life in the short-term. Short-term, beneficial effects of thrombolysis on left ventricular ejection fraction have not been reported in randomized trials. The long-term survival benefits of prehospital thrombolysis remain uncertain. Although it has promise, the Working Group [57] believed that its best use would be in areas with long EMS transport times and perhaps in conjunction with prehospital thrombolytic therapy. Its routine use was not recommended.

### Continuous ECG/Serial ECG

The Working Group [57] found that two studies evaluated the test performance of continuous/serial 12-lead ECG in the ED, but there was no clinical impact study (see Tables 1 and 2). One study by Gibler and colleagues [84] included a large retrospective population of 1010 participating in a 9-hour protocol. The serial ECG consisted of a 20-second interval between readings. The second study [85] included patients from a veterans' hospital in which two ECGs were taken 4 hours apart. The prevalences of ACSs in these studies were very different (4% and 40%, respectively) given the low-risk populations. The sensitivity for ACSs was low (21% and 25%, respectively) and the specificity was high (92% and 99%, respectively). With the limitations and the varied source of data, a conclusion about the usefulness of this technology cannot be drawn.

### Non-standard-lead ECG

The data on the diagnostic performance of non-standard-lead ECG from the four studies reported vary too much to draw any conclusion [57]. The studies used 15, 18, 22, and 24 leads and were conducted with selected patients for admission (see Tables 1 and 2). The prevalence is reflective of this selective population: it ranged between 22% and 65% for AMI. There are no clinical impact studies on non-standard ECGs.

### Exercise stress ECG

The data on the diagnostic performance of exercise stress testing to detect ACSs in the ED are limited to only two studies (see Tables 1 and 2) [86,87]. The overall data include a small sample size of a low-risk population. Although the

diagnostic performance is encouraging, it would be premature to make conclusions regarding this technology until additional high-quality studies are conducted.

There are also limited data on the clinical impact of exercise testing for ACSs. Two studies [88,89] had no cardiac events and included very small sample sizes: 28 and 35, respectively. Adding a third study [86], these investigations comprised only 272 subjects and are of low methodologic quality; the clinical impact of this technology is unclear.

### Biochemical markers

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

There is a large amount of evidence on creatine kinase (CK) as a single test administered at presentation to patients in the ED (see Tables 1 and 2) [57]. The evidence suggests that the sensitivity of a single CK reading for AMI is low (36%), and specificity is modest (88%). Limited evidence suggests that the sensitivity of the test depends on the duration of the patient's symptoms; sensitivity increases with longer symptom duration. Test performance across studies did not appear to vary by type of hospital, inclusion criteria, AMI prevalence, or test threshold.

Only two studies have evaluated serial CK testing [90,91]. These studies used broad inclusion criteria but enrolled populations in which the prevalence of AMI was moderate to high. Test sensitivity was high (95%–99%) in serial tests performed over about 15 hours after presentation to the ED (or from the onset of symptoms), but was only modest (69%) in the one study that drew serial samples for 4 hours. Test specificity was modest in both studies (68% and 84%).

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

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

As is the case with CK, the total sample size and number of studies on a single CK subunit (CK-MB) measurement at presentation to the ED

are large (see Tables 1 and 2) [57]. The evidence suggests that the sensitivity of single CK-MB for AMI is low (47%), although specificity is high (96%). Studies reported a broad range of sensitivity for diagnosing AMI. Again, as is the case for CK, limited evidence suggests that the sensitivity of CK-MB depends on the duration of the patient's symptoms; sensitivity increases with longer symptom duration. In general, studies reported a narrow range (92%–99%) of test specificity. Test performance across studies did not appear to vary by type of hospital, inclusion criteria, AMI prevalence, or test threshold.

The total sample size and number of studies of serial tests for CK-MB in the ED setting are large. Overall, serial testing has a modest sensitivity (87%) and high specificity (96%) for AMI. However, test sensitivity is strongly related to the timing of serial testing. All studies that performed serial testing for at least 4 hours after presentation to the ED (or until at least 8 hours after symptom onset) found test sensitivity to be greater than 90%. Conversely, all studies that performed serial testing to at most 3 hours found test sensitivity to be less than 90%. The pooled sensitivity for serial testing to at least 4 hours is 96%; pooled sensitivity for serial testing until 3 hours is only 81%. In general, test specificity was in a narrow range across studies and was above 90%. A recent report found that a 2-hour delta CK-MB level (sensitivity 93%; specificity 94%) outperformed a myoglobin level in the early identification of AMI when troponins are used as the criterion standard [92].

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

#### *Troponin T and troponin I*

The cardiac troponins have expanded the spectrum of detectable myocardial injury and enhanced the clinician's ability to identify patients who have ACSs and are at higher risk for death or recurrent ischemic events even with low-level elevation of cardiac troponin T or I [93,94]. The notion that any reliably detected troponin elevation results from myocyte necrosis serves as the basis for the recent revision of diagnostic criteria

for AMI. However, further research is necessary to conclusively refute the possibility that the release of cardiac troponins may also occur in the setting of reversible myocyte injury resulting from cellular ischemia [95]. Cardiac troponins offer extremely high tissue specificity but do not discriminate between ischemic and nonischemic mechanisms of myocardial injury; thus, presently the clinician must assess whether a patient's presenting symptoms are consistent with ACSs. In addition, renal failure does not appear to diminish the prognostic value of troponins among patients who have a high clinical probability of ACSs regardless of patient's creatinine clearance [96].

The evidence for the diagnostic performance of troponin T is substantial in diagnosing AMI but rather limited in diagnosing ACSs (see Tables 1 and 2) [57]. Data for troponin I are limited, but its performance is similar to that of troponin T. The sensitivity of presentation troponin T for diagnosing AMI in the ED is poor, but improves substantially if serial measurements are obtained for up to 6 hours after ED presentation. Most likely, the sensitivity is better for patients who have had symptoms for longer periods of time. The specificity of troponin T for AMI is in the range of 90%.

#### *Myoglobin*

The diagnostic performance of myoglobin has been well studied for diagnosing AMI, but not for diagnosing ACSs (see Tables 1 and 2) [57]. The sensitivity of myoglobin for diagnosing AMI in the ED is poor when a single initial measurement is obtained, but sensitivity improves greatly if a second measurement is obtained 2 to 4 hours after the first one. However, the sensitivity for patients only recently symptomatic is poor, and a second measurement in 2 to 4 hours may still not be sufficiently sensitive to be useful. Specificity is very good, but not excellent, depending on the extent to which other reasons for elevated myoglobin are excluded a priori. A doubling of myoglobin levels as soon as 1 to 2 hours after the initial measurement is almost perfectly sensitive for AMI.

The evidence suggests that a normal myoglobin value 2 hours after presentation may be used safely to rule out AMI. A doubling of myoglobin as early as 1 to 2 hours after the baseline measurement establishes a diagnosis of AMI. A small study [97] suggests that normal myoglobin and CK-MB values 2 hours after presentation

completely rule out AMI. The incremental value of CK-MB compared with myoglobin alone cannot be evaluated given the small sample sizes. In a much larger study, Kontos and colleagues [98] found no advantage for myoglobin over baseline and 3-hour CK-MB values. In a subanalysis of patients who had non-ST-elevation ACS, serum myoglobin above the MI detection thresholds was associated with increased 6-month mortality and thus may be useful for early risk stratification.

#### *Biomarkers of neurohumoral activation and inflammation*

In addition to markers of myonecrosis, markers of neurohumoral activation and inflammation may provide important prognostic and possibly diagnostic information in ACS. Studies on P-selectin [99,100], malondialdehyde-modified low-density lipoprotein, high-sensitivity C-reactive protein (hsCRP) [101–104], B-type natriuretic peptide [105], pregnancy-associated plasma protein A (PAPP-A) [106], serum amyloid A (SAA) [107], soluble CD-40, myeloperoxidase [108], glutathione peroxidase 1 [109], placental growth factor (PIGF) [110], matrix metalloproteinases [111], and monocyte chemoattractant protein-1 (MCP-1) [112] are just beginning to appear.

P-selectin in platelets and endothelial cells mediates adhesion interaction with leukocytes to form thrombi. There is only one ED study of P-selectin that reported low sensitivity and low specificity for AMI. Traditionally, hsCRP has been thought of as a bystander marker of vascular inflammation, without playing a direct role in the cardiovascular disease. More recently, accumulating evidence suggests that hsCRP may have direct proinflammatory effects, which is associated with all stages of atherosclerosis, including plaque destabilization [104,107]. Laterza and colleagues [106] studied ED patients who had suspected ACSs and found pregnancy-associated protein A, a potential proatherosclerotic metalloproteinase, to be only a modest predictor of adverse events, with a sensitivity of 67% and a specificity of 51%. It is thought that cellular antioxidant enzymes such as glutathione peroxidase 1 and superoxide dismutase have a central role in the control of reactive oxygen species. In vitro data and studies in animal models suggest that these enzymes may protect against atherosclerosis, but little is known about their relevance to human disease. In a prospective study of patients who have suspected ACSs, Blankenberg and colleagues [109]

found that a low level of red-cell glutathione peroxidase 1 was independently associated with an increased risk for cardiovascular events. Experimental data suggest that PIGF, a member of the vascular endothelial growth factor family, acts as a primary inflammatory instigator of atherosclerotic plaque instability and thus may be useful as a risk-predicting biomarker in patients who have ACSs. In a subanalysis of data from the CAPTURE Trial, Heesch and colleagues [110] found PIGF to be an independent marker of adverse outcome in patients who have suspected ACSs. Myeloperoxidase, an abundant leukocyte enzyme, is elevated in culprit lesions that have fissured or ruptured in patients who had sudden death from cardiac causes. Numerous lines of evidence suggest mechanistic links between myeloperoxidase and inflammation and cardiovascular disease. In a prospective assessment of patients in the ED who had suspected ACSs, Brennan and colleagues [108] found that a single initial measurement of plasma myeloperoxidase independently predicted the early risk for MI and the risk for major adverse cardiac events in the ensuing 30-day and 6-month periods.

In the future, tests for neurohormonal activation (B-type natriuretic peptide) and inflammation (C-reactive protein, PAPP-A, MCP-1, SAA) may augment the ability to identify patients who have ACSs and are at risk for adverse events. The use of these markers alone or in combination (a multi-marker approach) could potentially augment the ability to reserve the most expensive and aggressive therapies for patients who have the highest risk [113].

### **Cardiac imaging**

#### *Echocardiography*

The total sample size and the number of studies evaluating echocardiography for the diagnosis of ACSs are small (see Tables 1 and 2) [57]. Limited evidence suggests that resting echocardiography has high sensitivity (93%), although only modest specificity (66%) for AMI. The availability of previous echocardiograms for comparison may improve the specificity [114]. But even if this improved specificity were verified with additional studies, the need for previous echocardiography would limit its applicability in the general ED setting. In addition, the data pertain mostly to patients who have normal or non-diagnostic ECGs. The data for stress dobutamine

echocardiography are even more limited. One study suggests that it may be the next diagnostic step for patients who have a negative resting echocardiogram, normal ECG, and normal enzyme levels. There is no clinical impact study for this technology.

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

Data on the diagnostic accuracy of resting technetium (Tc) 99m sestamibi imaging in the ED are limited (see [Tables 1 and 2](#)). The test has been used in selected patient populations that generally have a low-to-moderate risk for an ACS, no history of MI, and a presenting ECG nondiagnostic for an ACS. Thus, the generalizability of the current evidence is limited, and the test should be reserved for these circumscribed populations. In these patients, the test has excellent sensitivity for AMI and very good, but not perfect, sensitivity for coronary disease in general. Specificity is modest for AMI, and although it may be a little better for ACSs, it is still far from excellent. In a prospective ED trial, Udelson and colleagues [115] showed that resting Tc 99m sestamibi imaging improved ED triage decision making for patients who had symptoms suggesting ACSs but no obvious abnormalities on the initial ECG by reducing unnecessary admissions without reducing appropriate admissions.

### **Myocardial performance index**

#### *Central aortic pressure*

One index of myocardial contractility is the rate of increase of intraventricular pressure during isovolumetric contraction (left ventricular dP/dt; arterial dP/dt). dP/dt represents the rate of change of pressure during ejection [116–119]. It has been shown previously that cardiac contractility and dP/dt decrease during acute cardiac ischemia [116,118]. Preliminary work by Gorenberg and Marmor [120] suggests that a noninvasive device that quantifies central aortic pressure through brachial artery sensors may be a technique that could be used in selected patient populations that have a low-to-moderate risk for ACSs, no history of MI, and a presenting ECG nondiagnostic for ACSs. However, the generalizability of the current evidence is limited because of study size and design.

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

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

The acute cardiac ischemia time-insensitive predictive instrument (ACI-TIPI) [26] computes a 0% to 100% probability that a given patient has ACS (either acute MI or unstable angina pectoris) (see [Tables 1 and 2](#)). Applicable to any patient in the ED presenting with any symptom suggestive of ACS, it is based on a logistic regression equation that uses presenting symptoms and ECG variables. Originally in hand-held calculator form, it is now incorporated into conventional electrocardiographs so that the patient's ACI-TIPI probability is printed with the standard ECG header text. In large controlled interventional trials in a wide range of hospitals, its use by ED physicians has been shown to reduce unnecessary admissions of patients who do not have ACSs and patients who have stable angina, while not reducing appropriate hospitalization for patients who have ACSs. It has also been shown to help the triage speed and accuracy of less-trained and less-supervised residents. Although this decision aid is a widely available software option offered by all the major ECG machines manufacturers in the United States, it has not been widely used in clinical practice. The greater dissemination and use of ACI-TIPI could result in significant positive impact on the triage of patients who have ACSs in the ED.

#### *Thrombolytic predictive instrument*

Correctly diagnosing STEMI for prompt use of coronary reperfusion therapy can be lifesaving. In EDs this can be difficult, especially for less obvious candidates [121–123]. Efforts by physician leaders, the NHAAP, health care organizations and monitoring entities, and pharmaceutical companies [123–132], have helped increase use and promptness of reperfusion therapy [133]. Further improvement is needed [133,134], however, particularly for other than anterior STEMI, the category for which thrombolytic therapy first was recognized as effective [121,122] and for women who have received less coronary reperfusion therapy than men [134,135]. Also, a need remains for ways to support prompt and accurate coronary reperfusion therapy decisions in hospitals and pre-hospital EMS settings where consultation with off-site physicians is required.

Selker and colleagues [136] developed the thrombolytic predictive instrument (TPI), a collection of five component predictive instruments designed to accurately assess the patient-specific likely benefits and risks from the use of thrombolytic therapy for STEMI. The TPI helps clinicians identify patients for coronary reperfusion therapy based on their probabilities of benefits and complications and facilitates earliest possible use of reperfusion therapy [123,136]. In conventional computerized ECGs when significant ST segment elevation of STEMI is detected, the TPI predictions are automatically computed and printed on the ECG header: probabilities for acute (30-day) mortality either treated with thrombolytic therapy or untreated; 1-year mortality rates treated with thrombolytic therapy; cardiac arrest treated with thrombolytic therapy and untreated; thrombolytic therapy-related stroke and major bleeding requiring transfusion.

To test whether the ECG-based TPI improves ED selection of patients for coronary reperfusion therapy and promptness of treatment, the authors ran a 22-month randomized controlled clinical effectiveness trial of its impact on the use of thrombolytic therapy and overall coronary reperfusion therapy. The trial ran in EDs at 28 urban, suburban, and rural hospitals across the United States, from major cardiac centers to small community hospitals. Study endpoints were percentages of patients receiving (a) thrombolytic therapy; (b) thrombolytic therapy within 1 hour of ED presentation; and (c) all coronary reperfusion therapy, either by thrombolytic therapy or PTCA.

At participating hospitals, software generating TPI predictions was installed on their conventional computerized ECGs. When a significant ST elevation characteristic of STEMI was automatically detected, the ECG randomly assigned the patient to the control or intervention group. If assigned to the intervention group, the ECG automatically prompted the user to enter information needed to compute the TPI predictions: age, sex, history of hypertension or of diabetes, blood pressure, and time since ischemic symptom onset. The remaining variables, based on ECG waveform measurements, were automatically acquired by the ECG. Then the ECG was printed with TPI predictions on its header.

Among the 1197 patients who developed STEMI, the trial showed that the TPI increased use of thrombolytic therapy, use of thrombolytic therapy within 1 hour, and use of overall coronary reperfusion therapy by 11% to 12% for patients

who have developed inferior STEMI, 18% to 22% for women, and 30% to 34% for patients who have an off-site physician [137]. Although the TPI's effect was minimal on patients who had high baseline coronary reperfusion therapy rates, such as men who present with anterior STEMIs, for the groups needing the most improvement in their rates of recognition for coronary reperfusion, women and those with less obvious STEMIs, and where involved physicians were off-site, the TPI increased recognition of STEMI and use and timeliness of coronary reperfusion therapy. It is hoped that as TPI-capable ECGs become more widely available in ED and EMS settings, its use will facilitate the accuracy and speed of recognition and treatment of these patients.

#### *Goldman Chest Pain Protocol*

The Goldman Chest Pain Protocol [7] is based on a computer-derived model using recursive-partitioning analysis to predict MI in patients who have chest pain (see Tables 1 and 2). It has good sensitivity (about 90%) for AMI, but was not developed to also detect UAP. In a clinical impact study of "low-intensity, non-intrusive intervention" performed in the ED of a teaching hospital [16], no differences in hospitalization rate, length of stay, or estimated costs were demonstrated between the experimental group that used the protocol and the control group. Goldman and colleagues [35] eventually switched to predicting the need for intensive or other levels of care. They found that clinicians who had higher levels of training had a higher sensitivity for detecting AMI, but at the expense of decreased specificity [138]. Reilly and colleagues [139] developed a consensus to adapt the Goldman prediction rule and found a favorable impact on physicians' hospital triage decisions solely by different triage decisions for very low-risk patients. Unfortunately, any algorithm that incorporates only clinical elements and the ECG findings at presentation is likely to be suboptimal because of the substantial proportion of patients who present with atypical symptoms or with no or minimal ECG abnormalities.

#### *Other computer-based decision aids*

Several investigators have reported various computer-based decision aids to diagnose AMI (see Tables 1 and 2). The artificial neural network by Baxt and Skora [140] had high sensitivity and high specificity for AMI in a prospective study,

but the clinical impact has not been demonstrated. A predictive model with automatic ECG interpretation has been shown to increase the use of fibrinolytic therapy for acute ST-segment elevation MI, especially in historically undertreated patients, such as those who have inferior AMI and women who have AMI [141].

### *Women*

It is becoming apparent that one of the major contributing factors for the misdiagnosis of ischemic heart disease in women is pathophysiologic differences that appear to exist between men and women who have these syndromes and between the various ischemic syndromes themselves. Obstructive CAD continues to be a major public health problem in women and has represented the leading cause of death and disability for more than a decade [1,142,143]. In the United States alone, more than a quarter of a million women die of coronary heart disease (CHD) each year, translating into 1 death every 2 minutes [1]. Increased awareness of these statistics and a recent focus on women's health issues in general have resulted in renewed interest in trying to understand important gender differences in patients who have ACSs. Although women have a lower prevalence of obstructive CAD compared with men who have similar symptoms [144–146], women have a higher frequency of angina/chest pain than men partly because of the higher prevalence of the less common causes of ischemia, such as vasospastic angina and microvascular endothelial dysfunction; transient left ventricular apical ballooning syndrome (takotsubo cardiomyopathy) [147]; and syndromes of nonischemic chest pain, such as mitral valve prolapse [148]. Add to this the fact that young women who have obstructive CAD experience a significantly worse outcome with regard to prognosis after MI compared with men [149], and that older women who have obstructive CAD often have greater comorbidities that influence their outcome adversely after AMI or myocardial revascularization than do men [150–153]. Furthermore, women presenting with ACSs are less likely to receive effective acute diagnostic and treatment strategies than men [3,154,155]. When women develop obstructive CAD, they have a greater functional expression of their disease and disability compared with men. Most women who do not have obstructive CAD at angiography continue to have symptom-related disability and consume considerable health

care resources [156–158], partly because the pathophysiology of ischemia in women is incompletely understood and gender-specific diagnostic and treatment strategies are underdeveloped [159]. Gender differences with regard to ischemic heart disease appear to exist in several areas, including established and novel risk factors; the metabolic syndrome; the physiology of endogenous reproductive hormones; the role of endothelial dysfunction in producing obstructive macrovascular CAD, myocardial ischemia, chronic chest pain syndromes, and ACS; genetic factors; proteomics; the menstrual cycle and reproductive status; pain threshold/perception; neurohumoral control; and behavioral/psychosocial factors.

The diagnostic evaluation of women who have suspected ACSs continues to be a major challenge. Knowing whether gender influences the likelihood that a given patient in the ED is having ACSs, and whether any specific presenting clinical features are differentially associated with ACSs in women compared with men, can aid clinicians in the accurate diagnosis of ACSs. The incidence of AMI in the general population has been shown to be higher in men than women [160–163], but until recently it has not been clear whether this gender difference holds among symptomatic patients who come to the ED. In addition, several studies have looked at gender differences in the presentation of patients who have AMI [157,164–167]. In a retrospective analysis of patients who have confirmed AMI, women had higher rates of atypical presentations, such as abdominal pain, paroxysmal dyspnea, or congestive heart failure [46,160,168–170]. In a group of patients in the ED who had typical presentations such as chest pain, the prevalence of AMI was lower in women [34,171]. However, in another study of patients in the ED who had chest pain, when adjustments were made for other presenting clinical features (specifically ECG), the gender difference was no longer significant [166]. From these results it is difficult to assess whether the gender-specific differences in AMI prevalence among symptomatic patients in the ED were the result of gender-specific biology or limitations in a particular study's patient selection.

One reason for such challenges is that chest pain in women is neither sensitive nor specific in predicting the presence of underlying CHD. The highest sensitivity is found in women presenting with symptoms of typical angina pectoris, whereas the highest specificity is found in women presenting with nonspecific symptoms. In fact, although

women who have ACSs may present with symptom patterns that differ from men (ie, atypical symptoms), for most women, typical symptoms are the strongest symptom predictors of ACSs [172–174]. A further challenge is gender differences in reporting pain, including but not limited to chest pain. Gender differences in endogenous pain-modulating systems may contribute to differences in pain perception. Regarding biomarkers, there is a suggestion that women who have obstructive CHD may have a different pattern of presenting biomarkers compared with men. In a TACTICS-TIMI 18 subanalysis examining patients who have UA/NSTEMI, there was a different pattern of presenting biomarkers between the sexes: men were more likely to have elevated CK-MB and troponins, whereas women were more likely to have elevated C-reactive protein and brain natriuretic peptide, suggesting that a multimarker approach to diagnosis may improve triage in the ED. Lastly, the Women's Ischemic Syndrome Evaluation Study Group and others have suggested that those women who have chest pain without flow-limiting lesions by angiography may have associated microvascular endothelial dysfunction (cardiac syndrome X) [175] and impaired coronary flow reserve [176,177]. Preliminary data suggest that coronary microvascular dysfunction is associated with an increased rate of hospitalization for chest pain, poor quality of life, and ongoing health care costs. Newer technologies, such as MR spectroscopy and gadolinium cardiac MRI, may allow for the identification of abnormalities in vascular function and structure not identifiable by coronary angiogram that can cause or contribute to development of myocardial ischemia, and may aid in the initial risk assessment of UA/NSTEMI, especially in women [178].

Finally, numerous studies have found that women have poorer outcomes than men after a diagnosis of ACSs. Explanations have included gender differences in pathophysiology and response to treatment; prehospital delays in symptom recognition and action; and gender differences regarding evaluation and treatment in emergency medical services. Recent reports of similar or better outcomes in women who have ACSs compared with men suggest that pathophysiologic differences can be overcome with early, aggressive therapy [153,179]. The diagnosis of ischemia influences prognosis differently in various clinical ischemic syndromes. In unstable angina the detection of ischemia indicates the likelihood of persistence or recurrence of plaque instability and hence carries

much more severe prognostic implications than in chronic stable angina, whereas although angina in patients who have normal coronary angiograms is not associated with increased short-term risk of infarction or sudden death, these patients may be crippled by pain. Inconsistent response to nitrates and antianginal drugs indicates the need for research on the various potential causes of coronary vascular dysfunction that burden women disproportionately, to facilitate development of rational forms of therapy.

### Race

Blacks have high levels of risk factors for CAD, but how this finding influences diagnosis in patients presenting to the ED with symptoms suggesting ACSs is not well understood [180,181]. Studies that have included only patients who have chest pain and not other symptoms suggestive of ACSs have found no significant differences in presentation, natural history, or final diagnosis of AMI between black and white patients [182]. Evaluating chest pain and establishing the diagnosis of CAD in blacks is often difficult given the presence of excess hypertension and left ventricular hypertrophy and the increased occurrence of out-of-hospital cardiac arrest in blacks [183–186]. Furthermore, the paradoxical finding of severe chest pain without significant angiographic CAD that can be seen in 30% to 40% of men [187] complicates diagnosis and treatment of blacks who have symptoms suggestive of ACSs [180,183]. In subanalysis of the ACI-TIPI Trial data, Maynard and colleagues [188] found that black patients were 8 to 10 years younger and that a higher percentage were women than was the case among white patients, which may partially explain why physicians might be less inclined to suspect the presence of ACSs in black patients. Finally, Pope and colleagues [3] found that among patients who have ACSs, the adjusted risk for being sent home was more than two times as high among nonwhite as whites. Among those who had AMI, the risk was more than four times as high among nonwhites as whites. In this study, 5.8% of the black patients who had AMI were not hospitalized, as compared with 1.2% of the white patients who had infarction.

### Outcomes

Each year in the United States, over 6 million patients who have chest pain or other symptoms



suggesting ACSs (eg, IMIR Study inclusion symptoms) [23] present to EDs [4]. These patients can have various clinical outcomes ranging from discharge home to hospital admission after thrombolytic therapy or percutaneous coronary intervention. Table 3 shows the final diagnosis for the ACI-TIPI Trial [2] control subjects by ED triage disposition. These data were employed to develop a flowchart (Fig. 1) to represent the diagnoses and triage dispositions of patients in the ED presenting with chest pain or other symptoms suggestive of ACSs. Although these data are not recent and the triage and intervention options have expanded over the last decade, the proportions have remained remarkable similar.

The flowchart (see Fig. 1) demonstrates that of all such patients, only 23% of patients (hospital range 12%–34%) had ACSs at final diagnosis, of which 94% were hospitalized and 6% were sent home. Conversely, 77% did not have ACSs at final diagnosis, of which 59% were hospitalized and 41% were sent home. In the ACSs group of patients, 36% of patients had AMI and 64% had UAP, which represented 8% and 15%, respectively, of the overall group. In the AMI group, 97% were hospitalized and 3% were sent home; in the UAP group, 92% were hospitalized and 8% were sent home.

The authors' work with Pozen and colleagues [6] from 1979 to 1981 at the same hospitals as the present report demonstrated a 7% ED discharge rate for patients who had a final diagnosis of ACSs; McCarthy and colleagues [18] found that 2% of these subjects had AMI at final diagnosis. In the mid-1980s, Lee and colleagues [9] reported a 4% AMI discharge rate. The authors' study found a 6% discharge rate for ACSs and a 3% AMI discharge rate, demonstrating stability of these figures over the decade. The proportions of AMI and UAP in the authors' present study (36% AMI, 64% UAP) were essentially identical to those from their work with Pozen and

colleagues [6] in 1979 to 1981 (35% AMI, 65% UAP). Finally, in an analysis of the ACI-TIPI Trial data for failure to make the diagnosis of an ACS, the authors found that the missed diagnosis rate for ACSs was 2.2% (2.1% for AMI, 2.3% for UAP) [3].

Recent approaches to patient safety emphasize "systems thinking" rather than focusing on individual cognitive mistakes. The goal is to prevent human errors, which are commonly made by competent clinicians [189,190]. Suggested approaches include diagnostic protocols and pathways, decision aids, novel approaches to staffing, chest-pain units, and other systems changes.

#### *Missed diagnosis of ACS*

Several factors, listed in Box 1, have been associated with inappropriate discharge of patients who have symptoms suggestive of ACSs from EDs and other acute care settings. These factors include younger age (<55 years), female gender, nonwhite ethnicity, atypical symptoms, no previous MI, normal or nondiagnostic ECG findings, misinterpretation of the ECG (failure to recognize minimal ST-segment elevation), and failure to appreciate the dynamic nature of anginal symptoms, obtain multiple ECGs tracings over time, obtain previous ECG tracings for comparison, appreciate the dynamic nature of anginal symptoms, and appreciate nonobstructive cardiac ischemic syndromes [3].

Although women tend to develop obstructive CAD 10 years later than men, Pope and colleagues [3] found that women under the age of 55 years were at the highest risk for not being hospitalized with ACSs. Physicians must try not to pigeonhole patients into set categories, and remember that low risk for ACSs is not zero risk. Furthermore, because about 50% of women and a small percentage of men who have symptoms suggestive of ACSs have nonobstructive syndromes, it is important that this subset of patients not be overlooked as is has been previously, and that these patients are referred to cardiologists for definitive diagnosis and therapy. In addition, these researchers found that the risk for being sent home was twice as high for nonwhites and whites, citing younger age and higher percentage of women as possible reasons for lowering clinical suspicions about ACSs. Although most patients, including women who have ACSs, present in a typical fashion, many can present in an atypical fashion with complaints of shortness of breath [191].

Table 3  
Final diagnosis (%) for acute cardiac ischemia time-insensitive predictive instrument trial control subjects by emergency department triage disposition

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

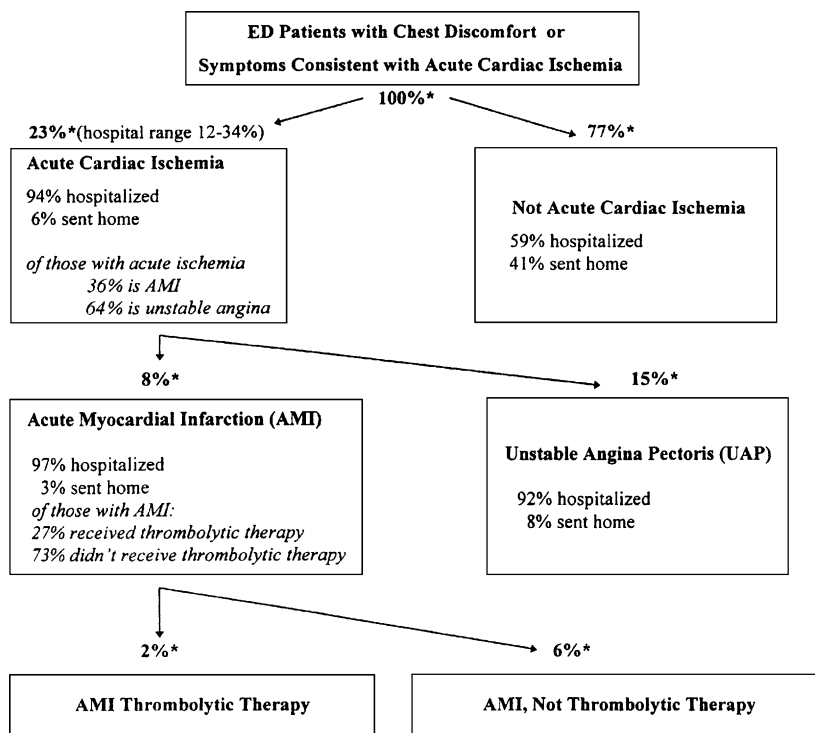


Fig. 1. Flowchart illustrating diagnoses and triage dispositions of patients presenting to the ED with chest pain or other symptoms suggesting ACI. \*Percentage of ED patients in the control group who have chest pain or symptoms consistent with ACI.

Because about 25% of patients who are mistakenly discharged are sent home after an error in interpretation in their ECG [192], improving the analysis and interpretation of ECGs could improve decision making. Finally, some investigators have

suggested that as many as 3% of patients who have suspected noncardiac chest pain will go on to experience a adverse cardiac event within 30 days of that assessment [193], and suggest that features such as male gender, hypercholesteremia, advanced age, CHD, heart failure, features that are not typically associated with noncardiac chest pain, and a higher calculated ACI-TIPI score. However, safe noncardiac chest pain criteria have yet to be derived and validated. Clinicians must at least consider the possibility of the diagnosis of ACSs in patients who have these factors, especially if a less serious cause for the patient's symptoms is not readily apparent.

### Box 1. Factors contributing to the misdiagnosis of acute coronary syndromes

- Younger age (<55 years of age)
- Female sex
- Nonwhite ethnicity
- Atypical symptoms
- No previous MI
- Normal or nondiagnostic ECG findings
- Misinterpretation of the initial ECG
- Failure to obtain multiple ECGs and obtain previous tracings
- Failure to appreciate the dynamic nature of anginal symptoms
- Failure to appreciate nonobstructive cardiac ischemic syndromes

### Summary

Failure to diagnose patients who have ACSs, either AMI or UAP, who present to the ED remains a serious public health issue. Better understanding of the pathophysiology of CAD has allowed the adoption of a unifying hypothesis for the cause of ACSs: the conversion of a stable atherosclerotic lesion to a plaque rupture with

thrombosis. Thus, physicians have come to appreciate UAP and AMI as parts of a continuum of ACSs. However, for as many as 50% of women who have a suspected ACSs, other mechanisms of illness are at work, including vasospastic angina, microvascular endothelial dysfunction, transient left ventricular apical ballooning syndrome, and mitral value prolapse. The accurate identification of these syndromes in the ED or other acute care settings challenges the skill of even the most seasoned clinician. Clinical features, patient demographics, physical examination findings, and a firm understanding the strengths and limitations of the standard ECG can greatly assist with the identification of patients who have ACSs. Biochemical markers, cardiac imaging, myocardial performance indices, and computer-based decision aids remain undervalued adjuncts to, but not substitutes for, clinicians' judgment regarding diagnosis and triage of patients who have symptoms suggestive of ACSs. Several factors have been associated with inappropriate discharge of patients who have symptoms suggestive of ACSs from EDs and other acute care settings, including younger age (<55 years of age), female gender, nonwhite ethnicity, atypical symptoms, no previous MI, normal or nondiagnostic ECG findings, misinterpretation of the ECG, and failure to appreciate the dynamic nature of anginal symptoms. However, safe noncardiac chest pain criteria have yet to be derived and validated. Despite 2 decades of focused research and without compelling evidence for a noncardiac cause, there remains no single way to discriminate perfectly between those who should be admitted to exclude ACSs and those who could be managed safely without admission. For the continuum of patient risk for ACSs, there is a matched continuum of triage options for each patient, from short-stay chest pain evaluation units to multiday admissions for more intensive evaluations.

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## Use of Biomarkers in the Emergency Department and Chest Pain Unit

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The use of biomarkers of cardiac injury in the emergency department (ED) and observation unit settings has several nuances that are different and, therefore, worthy of its own set of use guidelines. The markers that are used, however, are the same. The primary marker of choice continues to be cardiac troponin (Tn). Other markers that have been advocated for use in the ED because of the need for rapid triage have been myoglobin and fatty acid binding protein. In addition, some centers still prefer less sensitive and less specific markers, such as creatine kinase myocardial band (CK-MB). More recently, a push has occurred to develop markers of ischemia, such as ischemia modified albumin (IMA), to determine which patients have ischemia, even in the absence of cardiac injury. As troponin assays become more sensitive and how to use them becomes better understood, the use of other markers are being relegated to lesser and lesser roles. Markers of ischemia would be useful but at present, despite some enthusiasm, they are not ready for routine use. Before describing the recommendations for clinical use of biomarkers in the ED, a basic understanding of some of the science and measurement issues related to these analytes is helpful.

### Background

#### *Troponin*

The Tns are a complex of three proteins (I, C, and T) that regulate the calcium mediated

interaction of actin and myosin [1]. Tissue-specific isoforms of each troponin exist; however, the cardiac form of troponin C is shared by smooth muscle, so it lacks cardiac specificity [2,3]. For cardiac troponin I (cTnI), the cardiac isoform is structurally different due to the presence of a 32-amino acid posttranslational tail [4] and sequence dissimilarity with other isoforms [5]. Various monoclonal antibodies have been developed that are highly specific and have no cross-reactivity with other forms [6]. Since cTnI has not been found in any tissue outside of the heart, even in response to tissue injury, it has unique specificity for the heart [7,8].

Three different genes control the expression of cardiac troponin T. These genes and alternative mRNA splicing produce a series of isoforms with varying sequences [9]. Cardiac muscle contains four of these isoforms, but only one is characteristic of the normal adult heart, and that is the one against which antibodies have been made [10]. Some of the other cardiac troponin T (cTnT) isoforms are expressed in other tissues, including skeletal muscle in response to injury [11], and the initial assay for cTnT detected some of these and cross-reacting skeletal muscle TnT [12]. However, it has been established with immunohistochemistry and PCR, that the antibodies used in the present iteration of the assay do not detect these forms [13,14]. Accordingly, cTnI and cTnT have high specificity for the heart.

In addition to having high specificity, these proteins have high sensitivity. Most of the troponin is complexed to the contractile apparatus. A small amount (3% for cTnI and 6% for cTnT) exists which is not structurally bound [15,16]. This “small amount” has been termed the “cytosolic

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pool," although its localization was not proved definitively. The relative amount of troponin in this pool is similar to that of CK-MB [15]. This pool is released acutely. Because it is of the same magnitude as CK-MB, troponin might be expected to have similar sensitivity, but the sensitivity of the troponins is substantially better because a greater percentage of what is lost from the heart eventually resides in blood (ie, the so-called "release ratio" is higher) [17]. Subsequently, prolonged elevations of troponin occur as a result of degradation of the contractile pool in the area that has been injured. The cytosolic pool permits the early kinetics of release similar to that of CK-MB or even earlier with more sensitive assays. The persistence of elevation is due to release from the structural pool, since the half life of troponin in the circulation is short [18]. The degree of persistence varies tremendously and is somewhat longer for cTnT [19] than for some of the cTnI assays. For cTnI, the degree of persistence in part depends on which forms are measured and which epitopes the antibodies used in the assay are targeted toward. A 7- to 10-day time window during which elevations may be present, however, is a reasonable estimate. Accordingly, if the initial troponin in a patient who presents with chest pain is elevated, it may be from a prior event or from an acute event. In that situation, a rising pattern is helpful in determining if the event is acute.

The heterogeneity of assays indicated above is of particular importance. Different assays detect different forms, and various complex formations and protein modifications exist that can alter the relative sensitivity and specificity of one assay compared with another. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) group has published quality specifications for troponin assays and an analysis of the presently available assays [20,21]. Clinicians must understand which assay is being used in their center to understand how to use the data optimally [22]. As lower values are used, such as the recommended value of the 99th percentile as recommended by the ESC/ACC Committee on the Redefinition of MI [23,24], the assays invariably perform with less precision. This puts clinicians and patients at risk for false-positive and false-negative results. Accordingly, a recommendation has been made that the 99th percentile be measured with a less than 10% coefficient of variability (CV). This measurement will eliminate many false-positive and false-negative values and has been recommended until all assays can achieve

detection of the 99th percentile of a normal reference population with that level of precision [21,25]. At present, only one assay meets that specification. In general, the 10% CV value is close to the 99th percentile but how close they are varies assay to assay (Table 1). Thus, clinicians must know the characteristics of the assay that they rely on. In addition, other analytic issues exist that can confound assays. Good laboratories should be able to help trouble-shoot potential problems. The most common problem is fibrin interference, which may on occasion require additional centrifugation of the sample to remove cross-reacting fibrin.

In addition, it should be appreciated that troponin elevations indicate cardiac injury but do not define the nature of the cardiac injury. In patients who present with chest pain, most troponin elevations likely are related to coronary artery disease. The astute clinician must be aware, however, that elevations in troponin can occur from acute pulmonary embolism, myocarditis, and congestive heart failure to name just a few common entities that can confound the diagnosis of acute myocardial infarction [26]. Thus, the idea that an elevated troponin is synonymous with

Table 1

Concentrations corresponding to 10% CV imprecision and 99th percentile reference limit for the evaluated troponin assays

Platform	99th percentile limit* (µg/L)	10% total CV concentration (µg/L)	Ratio of 10% CV concentration to 99th percentile limit
AxSYM	0.30	1.22	4.1
Centaur	0.10	0.33	3.3
Access	0.04	0.06	1.5
Vidas	0.10	0.36	3.6
Dimension	0.07	0.26	3.7
RxL			
Stratus CS	0.07	0.10	1.4
Alpha Dx	0.15	ND	
E170	0.01	0.04	4.0
AIA21	0.06	0.09	1.5

*Abbreviations:* CV, coefficient of variability; ND, not determined.

\* Data obtained from manufacturer's package insert or through personal communications with manufacturers.

Data from Panteghini M, Pagani F, Yeo KT, et al. Evaluation of imprecision for cardiac troponin assays at low-range concentrations. *Clin Chem* 2004;50:327-32.

coronary artery disease can lead to missed diagnoses and suboptimal patient care.

### **Creatine kinase myocardial band**

CK-MB [27] served us well for many years, and facile assays exist that are reasonably sensitive. The percentage of CK-MB depleted from the heart that ends up in the blood, however, is modest (15% in the absence of reperfusion and 30% with reperfusion), limiting its sensitivity compared with troponin. In addition, because there is CK-MB in skeletal muscle, individuals have a circulating constitutive level and CK-MB elevations can be diagnosed only when that broad normal range is exceeded. This further limits sensitivity, but it also has implications for specificity. Elevations can occur as a result of skeletal muscle damage in patients with renal failure and abnormalities in clearance associated with hypothyroidism. In addition, re-expression of the B-chain gene in skeletal muscle when damage to muscle occurs can increase the percentage of CK-MB and confound diagnosis. The use of the relative index, which relies on the percentage of CK-MB with respect to total CK, improves specificity, but because there is so much CK in skeletal muscle, it diminishes sensitivity in individuals who may have coronary and skeletal muscle diseases [28]. In addition, a multiplicity of assay issues for CK-MB exist that assay issues often are more complex than those related to troponin. The role of CK-MB in 2005 is unclear beyond its role in helping to evaluate the timing of events in patients who present with chest discomfort.

### **Myoglobin**

Myoglobin [27] is a 17.8 kd protein that is released from all tissues ubiquitously. It is released rapidly and has a short persistence in the circulation (< 20 minutes in studies in which it has been injected) and, therefore, a pattern of increases and reductions are common. This protein responds rapidly and quickly to insults, and if the insults are sustained, elevations will persist. Because it has cleared renally, abnormalities in renal function can cause substantial elevations, and because it is ubiquitous, it lacks specificity for the heart. Myoglobin can and has been used as a nonspecific marker to screen for disease in patients who often have been poorly triaged. In addition, many studies have used high, rather than conventional,

troponin cutoff values in their studies, which amplifies the value of the testing [29,30]. As better troponin assays have been developed, the amount of time saved by a nonspecific marker like myoglobin has progressively diminished [31].

### **Fatty acid binding protein**

Fatty acid binding protein [27] is similar to myoglobin in its release kinetics, but a much larger percentage exists in the heart relative to skeletal muscle. This increased percentage has led some to claim an increased degree of specificity for elevations. Again, with more sensitive assays for troponin, it is unclear how much time measuring fatty acid binding protein might save.

### **Markers of ischemia**

The only test presently approved for detection of ischemia by the Federal Drug Administration (FDA) is IMA. Based on experimental data, it has been argued that ischemia injures the amino terminal end of albumin, which inhibits it from binding cobalt [32]. This fact has been taken advantage of in an assay that looks at the percentage of delivered cobalt that becomes bound. The argument is that this test can provide information concerning whether ischemia has occurred in the absence of necrosis. In response to ischemia, elevations of IMA do occur. They are short lived (roughly four hours), however, and then diminish [33]. These elevations, it is argued, can be used to define if ischemia has occurred and, thus, could be helpful in the triage of patients in the ED setting, especially in excluding ischemia. The problem with these studies is the lack of a clear gold standard. In addition, low levels of IMA seem protective and high levels seem to have some prognostic significance for eventual troponin elevations [34]. In the high pretest probability high-risk group, however, it is unclear whether this test is necessary to further define risk. In the low-risk group, a similar question can be posed. Most of the patients in whom clinicians are unsure, however, have values in the middle range and it is unclear how well they separate those with ischemia from those without ischemia. Furthermore, ischemia in other tissues also stimulates abnormalities in albumin binding also and assay issues exist related to the effect of lactate and pH [35]. These issues are why the FDA-approval was predicated on the fact that a negative test excludes ischemia. The argument,

has been made, therefore, that if a test is performed and fails to show an elevation, that those patients are probably safe to be sent home without further testing. Various studies, some of which are commented on in later discussion, have attempted to prove that postulate. On the other hand, what should be done with a positive test is less clear. Obviously, if markers of cardiac injury subsequently show that necrosis exists, then the patient is triaged easily. Suppose, however, that no evidence of necrosis exists. Is there a reason, based on the fact that an ischemic bed exists somewhere, to do more work on that particular patient? Perhaps this is the group that requires stress testing? Do these patients require evaluation of other organ systems also? These questions require answers before advocacy for the widespread use of the test.

These markers of cardiac injury need to be intertwined within the overall risk assessment of patients who present to the ED.

**Clinical use of troponin and other biomarkers in specific patient subsets seen in the emergency department or chest pain unit**

The use of biomarkers is predicated in large part on the underlying nature of the patients being evaluated. The following suggestions are developed predicated on risk stratification.

*Patients with ST elevation and myocardial infarction*

Patients who present with ST elevation myocardial infarction (STEMI) do not need biomarker measurements before the initiation of therapy. Therapy should be started before the return of biomarker data to ensure the most rapid initiation of therapy, which is critical in this setting. Recent data suggests that troponin elevations identify patients at high risk for adverse events. Patients who have elevated troponins have a lower rate of coronary recanalization with thrombolysis [36] or in response to direct percutaneous coronary intervention (PCI) (Fig. 1) [37]. The largest part of this effect probably is related to the fact that it takes time for elevations of troponin to develop, and therefore, patients who present with elevated troponin, are patients who present later than those who do not manifest elevations. Time from the onset of symptoms to treatment is the most critical determinant of the success or failure of recanalization and limitation of infarction size, which is likely the largest reason why patients who present with

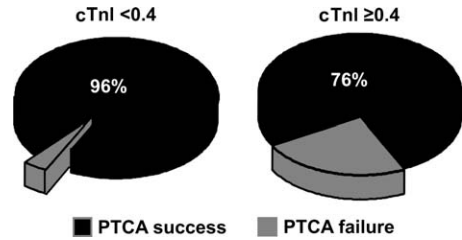


Fig. 1. Frequency of successful direct PCI when troponin is elevated (cTnI > .4 ng/ml) compared with when it is “normal” (< 0.4ng/ml). From Matetzky S, Sharir T, Domingo M, et al. Elevated troponin I level on admission is associated with adverse outcome of primary angioplasty in acute myocardial infarction. *Circulation* 2000;102:1611–6; with permission).

elevated troponins do poorly. In analyses where one attempts to correct for the time from the onset of infarction to presentation, however, a major adverse effect of having an elevated troponin still exists (Fig. 2) [38]. The ability to determine when the onset of symptoms has occurred may be inaccurate or it may be that other pathophysiology exists related to how infarction is initiated, which mediates this effect. Nonetheless, knowing that the troponin is elevated in patients who present with STEMI predicts a lower likelihood of recanalization, a lower TIMI flow grade with reperfusion [39], and an adverse short- and long-term prognosis. The therapeutic implications of this phenomenon are unclear at this time, but in one study, stenting seemed to have a positive impact [40]. No

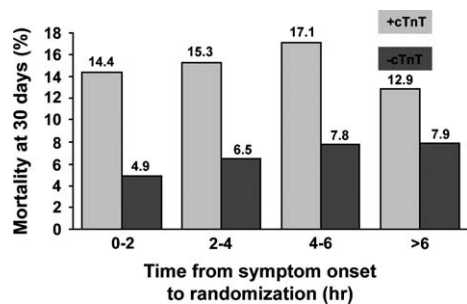


Fig. 2. Relationship between the time of onset of symptoms, troponin and mortality. Note at any given time from the onset of symptoms to randomization there is an increased risk associated with an elevated troponin. From Ohman EM, Armstrong PW, White HD, et al. Risk stratification with a point-of-care cardiac troponin T test in acute myocardial infarction. GUSTO III Investigators. Global use of strategies to open occluded coronary arteries. *Am J Cardiol* 1999;84:1281–6; with permission.

data exist about this issue with biomarkers other than troponin.

#### High-risk patients with acute coronary syndromes

The high-risk patient group that has been well represented in most of the major intervention trials. These patients are often elderly, have had chest discomfort at rest, have transient ST segment changes or bundle branch block, an increase in the tempo of their symptoms or signs, and can have evidence of hemodynamic instability or arrhythmias. This group often has a high frequency of elevated troponins in the range of 50% to 60% [41–44]. If so, they fulfill the definition of non-STEMI per the ESC/ACC [23,24].

In this patient subset, as with STEMI, an elevated troponin often is unnecessary for decisions concerning admission. Information suggests, however, that elevated troponin values define a subset at high risk [41–45] and provide important information with which to guide therapy. Patients who present with elevated troponins have adverse coronary anatomy as assessed angiographically with more thrombus, reduced TIMI grades of perfusion, more complex lesions, and more extensive disease (Fig. 3) [46]. Thus, they require and are more apt to benefit from the use of more sophisticated therapies. These patients have fewer ischemic events if treated with low molecular weight heparin rather than unfractionated heparin [47]. These studies do not show a mortality benefit. IIB/IIIA agents also have been found to markedly reduce death and recurrent MI in these patients, but, again, the benefit is almost

exclusively in the recurrent event category. The effects of IIB/IIIA agents are particularly strong in those patients who undergo percutaneous intervention [48]. Their use, then, is the present standard of care for patients who present with acute coronary syndromes and elevated troponins [49]. Patients who present without elevated troponins do not seem to benefit from the adjunctive use of low molecular weight heparin or IIB/IIIA agents in the setting of acute coronary syndromes. The recent accelerating use of clopidogrel has raised questions about whether the results of these previous studies would be the same if clopidogrel had been used adjunctively. Clopidogrel recapitulates the benefits of IIB/IIIA agents, it could be argued. Alternatively, it is possible that synergism exists between clopidogrel and IIB/IIIA agents and that patients would benefit even more from the combination. Until ongoing trials answer this key question, the standards and guidelines proposed by the American Heart Association/American Cardiac College would recommend that patients who present with an acute coronary syndrome and an elevated troponin receive IIB/IIIA agents [49]. In the CURE trial, clopidogrel seemed to benefit patients who presented with and without troponin elevations [50].

As might be expected, because short-term benefit is associated with the use of these agents so is long term benefit [51]. In addition, recent data has substantiated that the use of early invasive therapy, which in the United States means cardiac catheterization within the next 12 to 24 hours and interventional therapy (with stenting and a PCI or coronary artery bypass grafting),

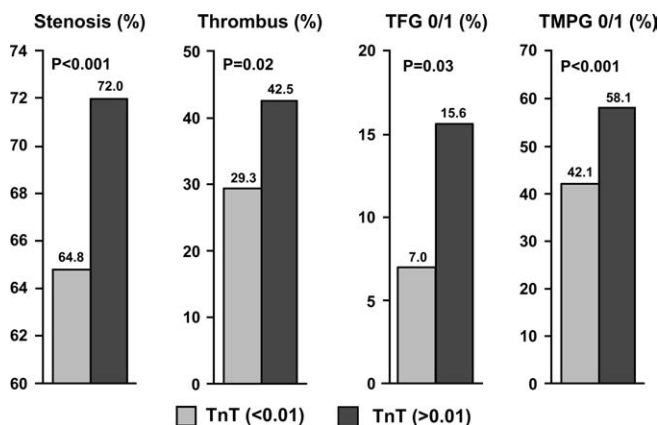


Fig. 3. Angiographic relationships with troponin in patients with acute coronary syndromes. From Scirica BM, Morrow DA. Troponins in acute coronary syndromes. *Prog Cardiovasc Dis* 2004;47:177–88; with permission.

leads to substantial benefit in patients who present with acute coronary syndromes and elevated troponins [52,53]. This benefit is not generally observed in patients who present without elevations. The one exception recently published is that women who more often present with normal values of troponin but elevated BNP or CRP may, nonetheless, benefit from an early aggressive invasive strategy (Fig. 4) [54]. Unfortunately, the data were based not on serial troponin data but on only the initial sample. Few other data exist at present to substantiate this claim.

*Intermediate and low risk for the patient subsets*

The intermediate and low-risk subsets of patients are the groups that usually are problematic in the ED or chest pain unit. The intermediate risk group often does not have rest pain or ongoing pain and lacks ECG changes, although this group may have a high pretest probability of having coronary artery disease. In contrast, the low-risk group usually has normal ECGs or only minimal T changes and often may not have impressive risk factors. Nonetheless, because of the need to diagnose as many patients as possible at risk for acute infarction given its morbidity and potential mortality, these patients need to be triaged and evaluated aggressively. In addition, this group is where a high percentage of malpractice dollars are lost. For these reasons, a conservative approach often is mandated. The downside of this

approach is that it is costly to admit a large number of patients solely because of this concern.

In this setting, troponin markers are again the markers of choice. In a landmark study of 733 consecutive patients who presented with chest discomfort, Hamm and colleagues [55] demonstrated that almost all patients at short-term risk could be identified using troponin (Fig. 5). Several caveats existed that were important in that study. The first caveat was that at least one troponin value needed to have been obtained at least 6 hours after the onset of symptoms to make sure that there had been time for the marker to rise. Unless the onset of symptoms is totally clear, it is wise to start the clock at the time of presentation. A second important caveat was the troponin value used was the limit of detectability (ie, a highly sensitive standard). Although the assays involved were less sensitive than contemporary assays, the concept probably is still correct. With modern assays, the use of the so-called 10% CV value is advocated [21,25]. When there is a high pretest probability of disease, as in the patients with overt acute coronary syndromes, the data are clear that using the lowest level of troponin detectable, (ie, the 99th percentile), provides greater predictive accuracy [56]. The pretest probability of a given elevation, being a true positive rather than a false positive, is high in the group with severe disease. When one deals with a patient population where the pretest probability of disease is somewhat less, severe disease is less likely. In that

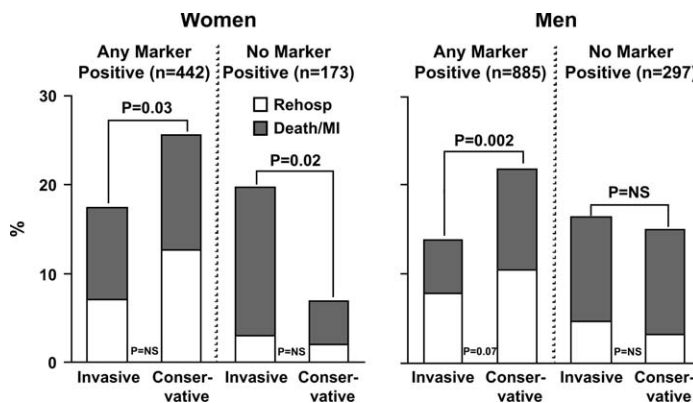


Fig. 4. Outcomes of therapy by gender. Note patients with any positive marker (troponin, BNP or CRP) benefited. Some suggestion of detriment exists in an invasive therapy in patients without an elevations in any marker. From Wiviott SD, Cannon CP, Morrow DA, et al. Differential expression of cardiac biomarkers by gender in patients with unstable angina/non-ST-elevation myocardial infarction: a TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction 18) substudy. *Circulation* 2004;109:580-6; with permission.



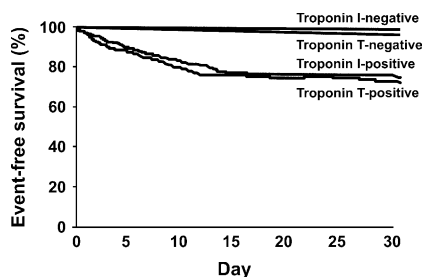


Fig. 5. Survival of patients evaluated to include or exclude acute myocardial infarction. *From Hamm CW, Goldmann BU, Heesch C, et al. Emergency room triage of patients with acute chest pain by means of rapid testing for TnT or troponin I. N Engl J Med 1997;337:1648–53; with permission.*

population, if one uses values where the assays are imprecise, the percentage of false-positive elevations is far greater. For that reason, in this population, it is important to use what is known as the 10% CV value rather than the 99th percentile, which is a level where few, if any, false-positive elevations are caused by imprecision. Most would advocate using the 10% CV level (which is usually close to the 99th percentile) in all patients with the recognition that in patients who are at high risk clinically even lower levels may have a prognostic and therapeutic significance. In the intermediate and lower-risk groups, however, if one uses the lower level (ie, the 99th percentile), an unacceptably high percentage of patients is apt to have false positives. The 99th percentile and the 10% CV values for present assays are shown in [Table 1](#) [21]. Caution is advised because the assays themselves and, thus, the values, presented change frequently.

Many of the studies that have been done have used high cutoff values for troponin in evaluating ED patients. Recently, a study from Johns Hopkins [57] evaluated patients who had low levels and patients who had intermediate levels between the 99th percentile and what is known as the ROC determined cutoff value for MI, a level initially used when the assays were novel to match the sensitivity of CK-MB. As with almost every other study that has been done, a substantial short- and long-term adverse prognostic effect was observed with even minor elevations of troponin ([Fig. 6](#)). More of these studies are needed, but they were consonant with the vast body of clinical information that suggests the elevated troponin values usually have important prognostic significance.

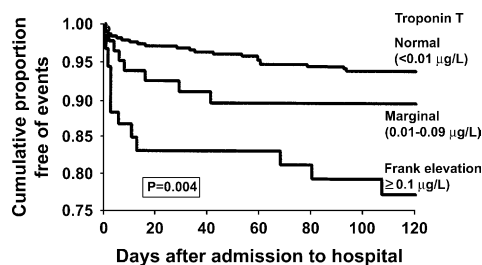


Fig. 6. Events in patients with various troponin values. Note even what are called in this figure marginal elevations have prognostic significance. *From Henrikson CA, Howell EE, Bush DE, et al. Prognostic usefulness of marginal troponin T elevation. Am J Cardiol 2004;93:275–9; with permission.*

Intermediate or low-risk patients who present with an elevated troponin may or may not have acute ischemic heart disease. Many etiologies exist for troponin elevations, and many of them may need to be evaluated as part of an evaluation in the ED or chest pain center. Two of the more common ones are pulmonary embolism [58,59] and congestive heart failure [60,61]; these can mimic the presentation of an acute coronary syndrome and both are associated with an adverse prognosis when troponin elevations occur. In general, the troponin elevations observed are modest. Elevations associated with pulmonary embolism resolve rapidly (by 40 hours) [62]. Elevations in patients who present with congestive heart failure persist for a longer period and are found in patients with and without coronary artery disease. Chest pain and elevated troponins in patients may be caused by some of these other etiologies for elevated troponins, but no overt coronary artery disease angiographically were at accentuated risk in the Tactics-TIMI-18 trial [63]. The coronary angiogram may not be, in every instance, totally reliable for the detection of acute coronary artery disease, especially when a delay exists between the onset of symptoms and implementation of the diagnostic procedure. Nonetheless, these data suggest that the due diligence of any good clinician seeing a patient who presents with an elevated troponin in these intermediate and lower-risk groups is not only to determine whether or not the patient is at risk for acute ischemic heart disease. The physician must also make sure that the elevations are not a result of other causes that may require different types of therapy (see later discussion).

Extensive evaluations of low risk patients have not been common. In an important study, however, the group from Galveston [64] evaluated a cohort of over 400 patients who presented with a low-risk history and normal or near normal ECG. They selected their inclusion criteria to be associated with a 5% to 7% incidence of MI. They then evaluated the frequency of coronary artery disease by offering angiography to all those patients with an elevated troponin and enrolling a control group that was selected from similar patients with chest pain but without elevated troponins as a comparison group. In that study, which used a higher troponin than has been advocated by this author, patients who presented with an elevated troponin had a 90% frequency of angiographic coronary artery disease. In two thirds, it was double or triple vessel disease. In addition, during follow up, these individuals had a 33% incidence of ischemic events caused by coronary heart disease (Fig. 7). These data demonstrate the importance of an elevated troponin in patients who present with chest pain, even those at low risk. Had the investigators used a lower cutoff value, the 10% CV value for example, it is possible there may well have been a larger number of patients with increases attributable to diseases other than acute ischemic heart disease. However, it is possible that the frequency of coronary artery disease seen in the control group of 23% would have been substantially diminished. Thus, it seems likely that the use of the low cutoff values may help to identify patients who are at risk when they present with chest discomfort.

No comparable data exist with any other markers in either risk group.

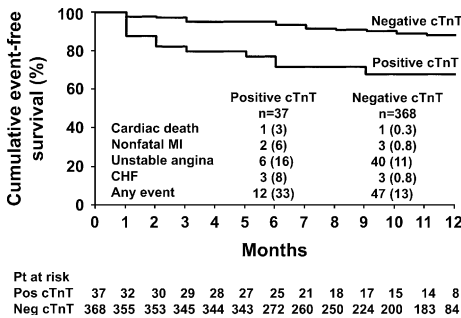


Fig. 7. Prognostic significance of troponin elevations in patients with normal or near normal electrocardiograms. From deFilippi CR, Tocchi M, Parmar RJ, et al. Cardiac troponin T in chest pain unit patients without ischemic electrocardiographic changes: angiographic correlates and long-term clinical outcomes. *J Am Coll Cardiol* 2000;35:1827-34; with permission.

*Patients with renal failure*

The most common cause of death in patients who present with renal failure is cardiovascular [65]. Coronary artery disease is common and events tend to occur during the period when patients have a longer interval between dialysis visits [65,66]. In patients who present with acute coronary syndromes, the interpretation of troponin elevations should not be altered by the presence of renal failure [67].

Other dialysis patients at risk who do not have acute coronary syndromes can often also be identified by having an elevated troponin [68,69]. These patients invariably have pathologic evidence of cardiac injury [70]. This group manifests differences in the frequency of elevations of cTnT and cTnI [68]. Many more elevations of cTnT occur than cTnI, and this has led some people to believe that the elevations of cTnT are false positives. With the initial iteration of the assay this might have been the case but is no longer a credible explanation. The present iteration of the assay has been shown not to cross-react with noncardiac isoforms of cTnT [10-14], nor does it detect the isoforms of cardiac cTnT that can be re-expressed in response to skeletal muscle injury. The epitopes for detection of cTnI may be lost in the milieu of renal failure. A substantial percentage of patients on dialysis, therefore, have elevations of troponin, especially cTnT, posing a difficult problem in the ED because the initial samples in these patients may indicate an elevation. Having a baseline cTnT is helpful. The FDA has approved the use of cTnT for risk stratification in patients who are on dialysis, and it is recommended that baseline values be available for comparison. If baseline values are not available, looking for a change in serial values is helpful. Patients who experience rising elevations are far more likely to have acute events than those whose values stay the same. This information does not imply that the latter are false positives only that they are less apt to be associated with an acute event. In a group, such as dialysis patients, where elevations in the absence of acute ischemic heart disease are common, this is a helpful approach to determine which patients require admission or urgent care and which do not. This same principle seems to be the case in patients who seem to be at risk for re-infarction [71]. Initial guidelines suggested the use of other markers to help in this area, but it is clear clinically, although extensive collaborating data have yet to be

developed in the literature, that using rising values are an effective strategy. Thus, dialysis patients who present with rising values are those in need of aggressive care. Patients who present with more chronic elevations can be evaluated more electively assuming no other clinical signs exist pointing to acute disease. This evaluation can include considerations of all other entities capable of causing elevations in troponin, such as pulmonary embolism, congestive heart failure, and the like.

These caveats apply only to patients who are on dialysis. Although there are an increased number of elevations of troponin in patients who present with significant renal dysfunction, most seem to be caused by concomitant comorbidities and are not synonymous with the chronic elevations seen in dialysis patients. Accordingly, the caveats above should be applied to dialysis patients only. The concept that elevations in troponin with milder forms of renal dysfunction can be attributed to this chronic process is at present unsupported by data. The potential etiologies of troponin elevations in dialysis patients likely are related to the metabolic milieu of dialysis, concomitant endothelial dysfunction, severe hypertension with LVH, acute ventricular stretch, and various other mechanisms that occur in patients who present with renal dysfunction. Delayed clearance of the troponin by way of the kidneys is an unlikely cause of the troponin elevations.

#### *Other etiologies for elevated troponins*

As indicated in earlier discussion and in **Box 1**, acute ischemic heart disease is only one reason for elevations. Many other reasons exist that need to be considered [26]:

1. Many of the entities listed involve some degree of ischemia but it is not ischemia necessarily caused by acute coronary abnormalities. For example, patients who present with left ventricular hypertrophy, whether caused by hypertension, aortic stenosis, or hypertrophic cardiomyopathy, and so forth, are known to have an underperfused subendocardium. Thus, patients may be at risk if rapid heart rates, hypotension, or hypertension for elevated troponins as a result of injury to the sub-endocardium. When patients have arrhythmias, a similar mechanism could be involved. This mechanism is probably the mechanism for elevations by

#### **Box 1. Elevations of troponins without overt ischemic heart disease**

- Trauma (including contusion; ablation; pacing; ICD firings, such as atrial defibrillators, cardioversion, endomyocardial biopsy, cardiac surgery, after-interventional-closure of ASDs)
- Congestive heart failure—acute and chronic
- Aortic valve disease and HOCM with significant LVH
- Hypertension
- Hypotension, often with arrhythmias
- Postoperative noncardiac surgery patients who seem to do well
- Renal failure
- Critically ill patients, especially with diabetes, respiratory failure
- Drug toxicity (eg, adriamycin, 5 FU, herceptin, snake venoms)
- Hypothyroidism
- Coronary vasospasm, including apical ballooning syndrome
- Inflammatory diseases (eg, myocarditis, including Parvovirus B19, Kawasaki disease, sarcoid, smallpox vaccination, or myocardial extension of BE)
- Post-PCI patients who seem to be uncomplicated
- Pulmonary embolism, severe pulmonary hypertension
- Sepsis
- Burns, especially if TBSA greater than 30%
- Infiltrative diseases, including amyloidosis, hemachromatosis, sarcoidosis, and scleroderma
- Acute neurologic disease, including CVA, subarachnoid bleeds
- Rhabdomyolysis with cardiac injury
- Transplant vasculopathy
- Vital exhaustion

which pulmonary embolism albeit in the right rather than the left ventricle, induces injury.

2. Cardiac toxicity as a result of drugs, snake bites, or other toxins in the environment are certainly capable of causing troponin

elevations. Heat shock protein or TNF are believed to participate in cardiac injury seen with sepsis.

3. Myocarditis, acute or chronic, can cause troponin elevations and a series of patients who might be confused with those suffering with STEMI has been published. The diagnosis should be considered in patients initially suspected of having acute coronary syndromes who have normal coronary arteries.
4. Cardiomyopathies, congestive or infiltrative, and congestive heart failure likely caused by wall stress and reduced subendocardial perfusion are also capable of leading to elevated troponins and have significant prognostic significance.
5. Critically ill patients. A large body of information suggests that elevations in troponin are common and highly prognostic in patients who are critically ill whether in the hospital or ED.

**The use of other markers**

Many studies previously done suggest that because increases in short-acting markers, such as myoglobin or fatty acid binding protein, or in the past, isoforms of CK increase more rapidly than troponin that they may save time in the ED

or chest pain clinic [27,29,30,72]. The value of this approach is predominantly to exclude infarction at an earlier point in time because these analytes lack cardiac specificity and often are falsely positive. Thus, what has been relied on is their negative predictive value, which is fairly high. A critical issue in this area has been that many of these studies done evaluating these analytes have used insensitive troponin assays or high cutoff values despite the use of sensitive assays. Recent data suggest that as one begins to use cutoff values, such as the 99th percentile and 10% CV that the difference in timing associated with these other laboratory tests becomes more modest than previously suggested (Fig. 8) [31]. A similar approach relying on the negative predictive value of nonelevated values has been taken with IMA [32–34], which is a marker of ischemia rather than necrosis. The influence of more sensitive troponin assays on the timing of elevations can also influence the amount of time saved with this analyte. The time saved which is now more modestly worthwhile compared with the cost and the confounds associated with the frequent false positives. The studies done with IMA have used more contemporary troponin assays and cutoff values [32–34] but continuing issues exist concerning the proper cutoff values for the test, analytic issues related to pH and lactate [35] and concern

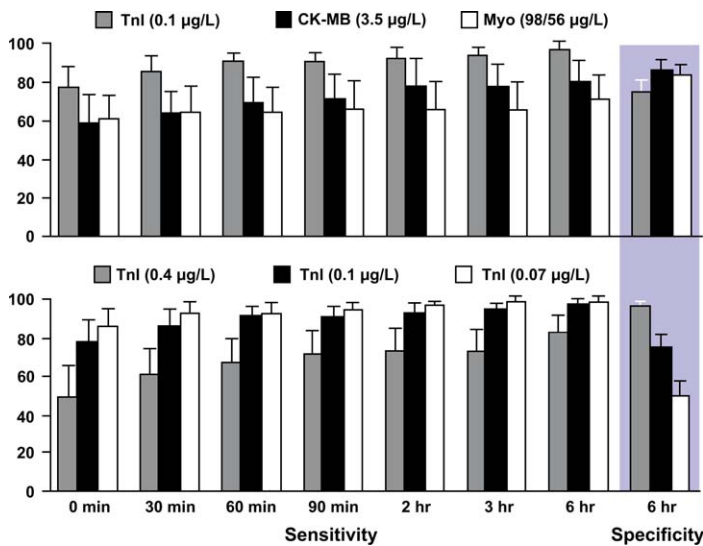


Fig. 8. Sensitivity of cTnI, CK-MB and myoglobin over time using modern prognostic cutoff values. Note that 0.7 ng/ml is the 99th percentile for the assay used. From Eggers KM, Oldgren J, Nordenskjold A, et al. Diagnostic value of serial measurement of cardiac markers in patients with chest pain: limited value of adding myoglobin to troponin I for exclusion of myocardial infarction. Am Heart J 2004;148:574–81;with permission.

about what should be done if a patient has an elevated IMA without an elevated troponin. Accordingly, a much simpler, more cost-effective paradigm would be to measure troponins on two occasions: (1) when the patient first presents and (2) 6 hours later or earlier if the onset of symptoms is totally clear. Additional data likely will shorten this time somewhat also. This paradigm would be a highly sensitive, highly specific, and cost-effective way of triage but requires thoughtful consideration of the etiologies of the potential troponin elevations, some clinical judgment, and a knowledge of the assays that are used locally.

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## Point-of-Care Testing and Cardiac Biomarkers: The Standard of Care and Vision for Chest Pain Centers

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Point-of-care testing (POCT) is defined as testing at or near the site of patient care [1]. POCT decreases therapeutic turnaround time (TTAT), increases clinical efficiency, and improves medical and economic outcomes [2,3]. TTAT (Fig. 1) represents the time from test ordering to patient treatment [2]. POC technologies have become ubiquitous in the United States, and, therefore, so has the potential for speed, convenience, and satisfaction, strong advantages for physicians, nurses, and patients in chest pain centers. POCT is applied most beneficially through the collaborative teamwork of clinicians and laboratorians who use integrative strategies, performance maps, clinical algorithms, and care paths (critical pathways) [2–5]. For example, clinical investigators [6–9] have shown that on-site integration of testing for cardiac injury markers (myoglobin, creatinine kinase MB isoenzyme [CK-MB], and cardiac troponin I [cTnI]) in accelerated diagnostic algorithms produces effective screening, less hospitalization, and substantial savings. Chest pain centers [10], which now total over 150 accredited in the United States [11], incorporate similar types of protocol-driven performance enhancements. This optimization allows chest pain centers to improve patient evaluation, treatment, survival, and discharge [12]. This

article focuses on cardiac biomarker POCT for chest pain centers and emergency medicine.

POC test clusters encompass electrolytes (eg,  $K^+$ ,  $Ca^{++}$ ), metabolites (glucose, lactate), function monitors (acid-base, hemostasis), and several biomarkers [2]. Hospital penetration of POC cardiac biomarker testing increased from 4% in 2001 to 12% in 2004, a threefold change [13,14]. Now, with a strong annual growth rate, cardiac biomarker POCT represents one of the most rapidly expanding areas in clinical diagnostics. The growth rate, estimated as 10% to 20% [13,15], could double use quickly. Sales are expected to grow from about \$200 million in 2003 to around \$400 to \$500 million in 2008, an increase of over 100% in five years. The current market trend is driven by the following: (a) an evolving standard of care for the timeliness of evaluation and treatment in chest pain centers and EDs; (b) motivation to produce cost-effective medical solutions for acute coronary syndromes (ACS) and other cardiovascular conditions, such as congestive heart failure; (c) need to reduce medicolegal risk in emergency department (ED) settings where acute myocardial infarction (AMI) is missed too frequently; (d) physician and nurse demands for rapid response testing and consistently fast test results, day and night; (e) emphasis on the total value of diagnostic information (versus piecemeal costs of individual tests); (f) smaller, smarter, faster, and cheaper portable devices with improved technologies for POCT, such as critical care profiling, faster immunotesting, and integrated multimarker indexing; (g) a continuing paradigm shift to the “hybrid

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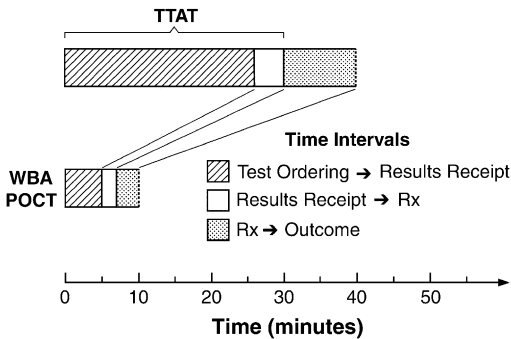


Fig. 1. Therapeutic turn around time (TTAT) is time from test ordering to appropriate treatment (Rx). If blood specimens are obtained first or before verbal orders are documented after, as may occur in critical situations, TTAT starts with collection. POCT and whole-blood analysis (WBA) shorten TTAT. The interval from Rx to outcome typically also decreases, thereby enhancing efficiency of patient care and usually improving medical and economic outcomes.

laboratory” [2] where laboratorians work more closely on-site with clinicians who perform bedside testing; (h) increasing penetration of POC cardiac biomarkers in a niche hospital market previously characterized by slow growth; and (i) physician expectations, patient empowerment, health consciousness, and early detection extending even to the home because too many patients succumb to AMI before reaching the hospital.

An important goal of this article is to help optimize the guidelines- and evidence-based clinical practice of POCT [16] in chest pain centers through systematic planning and implementing of POC cardiac biomarker testing. Themes include: (a) POCT should be applied broadly to reduce medical risk; (b) POCT for cardiac biomarkers is evolving into the standard of care; and (c) whole-blood analysis (WBA) time ultimately determines the minimum time interval for rapid response testing. This article delineates POC cardiac test clusters; describes clinical priorities for their application; summarizes handheld, portable, and transportable instruments and test kits; and identifies future needs that must be fulfilled to serve acute care patients efficiently and efficaciously. Current heavy investment in commercial development raises unique opportunities for creative interdigitation of POCT, bedside decision making, and evidence-based therapy in chest pain centers. Active leadership participation during this dynamic phase of expansion of cardiac

biomarker POCT will help maximize future benefits.

### Status of cardiac biomarker point-of-care testing

In 2004, an Enterprise Analysis Corporation [13] telephone interview survey of 493 United States hospitals with bed size of at least 150 showed that cardiac biomarkers were evaluated for use more frequently but rejected more commonly than other types of POCT, which implies that devices offered fall short of meeting needs [14]. Of hospitals deciding not to install a new POCT system, 75% (82 of 110) evaluated cardiac biomarkers [13]. Reasons for not installing included: (a) lack of improved turnaround time (TAT), (b) high costs, (c) inaccuracy, (d) not user friendly for nonlaboratorians, and (e) laboratory unwillingness to relinquish test control. Nonetheless, as noted above, between 2001 and 2004, hospital penetration of POC cardiac marker testing by discipline trebled with smaller hospitals (150 to 299 beds) most frequently adopting POCT. Sites where hospitals used cardiac biomarker POCT included: (a) ED (56%), (b) core laboratory (52%), (c) outpatient area (8%), (d) stat laboratory (6%), (e) cardiac catheterization laboratory (3%), (f) intensive care unit (2%), and (g) operating room (2%)—sum of 129% because of multiple sites. Overall, Biosite Diagnostics (San Diego, CA) led the market in cardiac biomarkers with B-type natriuretic peptide (BNP) on the Triage Cardiac Panel platform. Note that EDs holding their own Clinical Laboratory Improvements Act licenses were not contacted in the survey; therefore, the frequency of distributed testing in EDs may exceed 56%.

According to the United States survey [13], cardiac biomarker tests performed included: (a) cardiac troponin (cTn) alone (24% of hospitals using cardiac biomarker POCT); (b) cTn, CK-MB, and myoglobin (67%); and (c) BNP (74%). Forty-five percent reported they would switch BNP to the main laboratory if possible. Average POC cTn test volume (5227) represented about twice that of BNP (2766), but all types constituted 20% or less of total cardiac biomarker test volume in 58% of institutions. Overall, hospitals streamlined the number of POCT systems (average about three) under pressures for training, quality control, maintenance, integration, and oversight. Of those hospitals projecting rapid or very rapid growth, speed and improved technology were cited

most frequently. Thus, the survey showed that high accuracy, speed, improved technology, user friendliness, broad test menu, cost-effectiveness, quality control, and information integration, as well as faster quantitative analysis, represent key design specifications to be fulfilled by cardiac biomarker POC devices. Other important features include built-in data management and quality control, plus error alerting [17]. Use of POCT does not excuse inaccuracy or errors. Clinicians and laboratorians should insist on accuracy and reliability irrespective of where testing is performed.

### **Technologies for cardiac biomarker point-of-care testing**

#### *Instruments, decision levels, and applications*

Handheld, portable, and transportable instruments and devices available for cardiac biomarker POCT are summarized in Table 1 [18–38]. Test clusters, methods, analysis times, sample types, and other pertinent information are shown. Disposable qualitative test kits are shown also. For additional details of POC analytic principles, see Tang and colleagues [39] and for an earlier analysis of technology, see the University HealthSystem Consortium report by Cummings and colleagues [40]. Note that several of the devices and test kits in Table 1 may be used in near-patient laboratories or at the bedside. Before implementation, operators should check with manufacturers regarding regulatory constraints, decision thresholds, and test classifications. Currently, none of the tests listed qualify for so-called waived status under federal statutes governing diagnostic testing [41]. Thus, testing must be performed by licensed, certified, and validated personnel in accredited facilities with attention to required daily quality control, and should be supervised by POC coordinators who assure high-quality, satisfy inspection requirements, and incorporate proficiency testing (objective external performance review). Nurses and POCT coordinators and, often, experienced medical technologists, have become indispensable partners stitching these aspects of POCT together and maintaining the fabric of excellence in testing irrespective of where it is performed [42,43]. Chest pain centers should not attempt to implement and manage POCT without the assistance of an experienced POCT coordinator who provides valuable liaison with laboratory medicine and essential continuity of POCT throughout the hospital.

Several areas for potential improvement in the POC cardiac biomarker repertoire are identified in Table 1. Miniaturized bedside immunochemistry has just passed its infancy and integrated multimarker test clusters have appeared only recently on portable and handheld devices. Despite over one decade of development [44], WBA times for immunochemistry remain prolonged, in the order of 15 minutes. Following the precedent set in other clinical applications, such as biosensor-based bedside glucose testing, analysis time should be reduced to just a few minutes while analytic sensitivity (minimum detection level) should be improved. These potentially conflicting goals may justify the use of novel nano- or microfluidics, microarray, or optical approaches heretofore not commonly present on POC devices. Complex manufacturing and funding hurdles stall efforts to combine cardiac biomarkers with other critical care analytes, such as electrolytes (eg,  $K^+$  and  $Ca^{++}$ ), blood gases, and pH. Currently, these analytes can be measured with exchangeable cartridge-based systems (eg, i-STAT) but should be fully integrated on other instruments for the evaluation, diagnosis, and monitoring of critically ill patients.

The inconsistency in qualitative and quantitative decision levels is emphasized in Table 2. In this phase of rapid growth, standardization of cardiac biomarker measurements and decision levels should occupy a position of high priority. Standardization, which demands consideration of subject reference levels and assay characteristics (eg, epitopes, antibodies, and matrices, all producing in the case of cTnI, varying specificities for different forms released), improves the consistency of diagnostic interpretation, reduces the potential for errors, and allows physicians to follow trends if different assays are used for testing after patients are admitted. Inadequate computer interfacing of devices and lack of critical results alerting represent two additional weaknesses. Full integration with hospital computerized systems is required for settings using an electronic medical record. As noted in later discussion of risk, missed diagnoses resulting from poor communication and other root causes can result in significant financial penalties. Examples of special situations where cardiac biomarker POCT is being developed or can help facilitate unusual clinical problem solving are presented in Table 3 [45–58]. Generally, per test cost for POCT exceeds that on larger main-frame chemistry analyzers found in clinical laboratories. Despite high costs, POCT can improve overall cost-effectiveness [3,6–9], discussed below.

Table 1  
Cardiac Biomarker POCT

Test/Device name	Biomarker(s)	Device characteristics	Reference notes
Cardiac Reader <ul style="list-style-type: none"> <li>• Cardiac T</li> <li>• Cardiac M</li> <li>• Cardiac D</li> <li>• NT-proBNP (Portable)</li> </ul> Roche Diagnostics	cTnT Myoglobin D-dimer NT-proBNP <sup>a</sup>	Sample: 150 µL heparinized or EDTA WB Analysis time: 12 min, TnT; 8 min, myoglobin; and 8 min, D-dimer Method: Immunoassay and photosensor	Cardiac Reader interprets Cardiac T/M/D rapid assay strips. Comparison between the rapid test and a established laboratory-based method showed sufficient agreement of results with a correlation of $r = 0.89$ for troponin T and $r = 0.912$ for myoglobin [18]. The Cardiac T exhibited $Sn = 100\%$ and $Sp = 76.2\%$ for MI [19]. See also [20].
TropT sensitive (Handheld, disposable) Roche Diagnostics Indianapolis, IN <a href="http://www.roche.com">www.roche.com</a>	cTnT (QUAL)	Sample: 150 µL heparinized or EDTA WB Analysis time: 15 min Method: Immunoassay	Out of 34 patients who present with AMI, the TropT sensitive test showed positive quantitative results for 20 patients versus 29 patients when the Cardiac Reader was used [21]. At 3 hours after onset of symptoms for AMI, $Sn = 50\%$ , $Sp = 96.3\%$ , $PPV = 80\%$ , and $NPV = 86.7\%$ for AMI [22].
Cardiac STATus (Handheld, disposable) Spectral Diagnostics Toronto, Ontario, CAN <a href="http://www.spectraldx.com">www.spectraldx.com</a>	Myo + cTnI Myo + cTnI + CK-MB (test clusters) cTnI CK-MB	Sample: 150 µL heparinized WB, heparinized plasma or serum Analysis time: 15 min Method: Lateral flow based immunoassay	Qualitative results from CK-MB and myoglobin test cards were comparable diagnostically to quantitative results from the Ciba Corning ACS-180 and Dade Stratus IIIntellect [23]. cTnI tests showed 98% concordance with ELISA [24]. In comparison with Roche TropT, the Cardiac STATus proved more effective in early diagnosis of AMI [25]. The Cardiac STATus had a sensitivity of 96% for the detection of AMI within 3 hours of presentation [26].
<i>i-Lynx</i> (Handheld, portable) Spectral Diagnostics Toronto, Ontario, CAN <a href="http://www.spectraldx.com">www.spectraldx.com</a>	NA	The system consists of two interfaced components; a handheld electronic device to capture and analyze an image from the current Cardiac STATus rapid test strip, and a local area network compatible docking station to automate data capture communication	The <i>i-Lynx</i> is a connectivity solution with full QC functionality in open architecture, including system maintenance, user ID, QC log, lockout, passcode protection, universal barcode, and connectivity by way of TCP-IP for POC Coordinators (Chris Wayne, Spectral Diagnostics, e-mail communication.)

Cholestech LDX (Portable) Cholestech Corp. Hayward, CA <a href="http://www.cholestechn.com">www.cholestechn.com</a>	CRP	Sample: 50 µL WB or 40–50 µL plasma Analysis time: 7 min Other analytes: Total cholesterol, HDL, triglycerides, ALT, and glucose. Method: Reflectance photometry, immunoassay	WB and plasma samples showed a concordance rate of 94% and 90%, respectively, with results from Dade Behring BN100 [27].
i-STAT 1 and PCA (Handheld) i-STAT East Windsor, NJ <a href="http://www.i-stat.com">www.i-stat.com</a>	cTnI	Sample: 16 mL heparinized WB or plasma Analysis time: 10 min, cTnI Other analytes: Na <sup>+</sup> , K <sup>+</sup> , Cl <sup>-</sup> , Ca <sup>2+</sup> , glucose, creatinine, lactate, BUN, Hct, Hb, pH, pCO <sub>2</sub> , pO <sub>2</sub> , ACT, and PT Method: ELISA	cTnI test performance proved insensitive to hematocrits between 0 to 65%, but higher hematocrits produced imprecision [28].
LifeSign MI (Handheld, disposable) PBM Princeton, NJ <a href="http://www.pbmc.com">www.pbmc.com</a>	cTnI + myo CK-MB + myo CK-MB + myo + cTnI (test clusters) MLC-1 <sup>b</sup> NT-proBNP <sup>b</sup>	Sample: 120 µL WB, plasma, or serum Analysis time: 15 min Method: Chromatographic immunoassay	Each test cluster is equipped with a built in control for quality assurance [29].
Nycocard Reader II (Portable) Axis-Shield Oslo, Norway <a href="http://www.axis-shield.co.uk">www.axis-shield.co.uk</a>	CRP D-dimer	Sample: 5 µL heparinized/EDTA/ citrate WB or serum (dilution to 50 µL required) Analysis time: 3 min Other analytes: HbA1c, microalbumin Method: Reflectometric immunoassay	Nycocard Reader II interprets CRP and D-dimer test strips.
Nexus Dx (Handheld, disposable) Syn X Pharma Inc. Toronto, CAN <a href="http://www.synxpharma.com">www.synxpharma.com</a>	cTnI + myo <sup>a</sup> cTnI + myo + CK-MB <sup>a</sup> (test clusters) cTnI <sup>a</sup> NT-proBNP <sup>a,b</sup>	Sample: 120 µL WB, plasma or serum for cTnI Analysis time: 15 min, cTnI Method: Chromatographic immunoassay	NT-proBNP test was approved in Europe mid-2004 and is pending FDA approval in the United States. Other tests are available only in Canada and Europe [30].
One-Step Marker Test (Handheld, disposable) ACON Labs San Diego, CA <a href="http://www.aconlabs.com">www.aconlabs.com</a>	cTnI + myo + CK-MB <sup>a</sup> (test cluster)	Sample: 120 µL WB, plasma, or serum Analysis time: 15 min Method: Chromatographic immunoassay	Device is only available outside the United States. Quality controls are built into the test card.

(continued on next page)

Table 1 (continued)

Test/Device name	Biomarker(s)	Device characteristics	Reference notes
RAMP Reader (Portable) Response Biomedical British Columbia, CAN <a href="http://www.responsebio.com">www.responsebio.com</a>	Myoglobin CK-MB cTnI	Sample: 70 µL WB Analysis time: ~15 min Other analytes: WNV antigen Method: Fluorescence-based immunoassay	At 95% CI, Sn (cTnI) = 90%, Sp (cTnI) = 86%, Sn (CK-MB) = 59%, and Sp (CK-MB) = 90% for AMI [31].
RAPICHEK <sup>b</sup> (Handheld, disposable) Dainippon Pharmaceuticals Suita City, Osaka, Japan <a href="http://www.dainippon-pharm.co.jp">www.dainippon-pharm.co.jp</a>	H-FABP	Sample: 150 µL WB Analysis time: 15 min Method: Chromatographic immunoassay	H-FABP panel test achieved 98.4% agreement with H-FABP mass concentration ELISA [22,32]. At 3 hours following onset of symptoms of AMI, RAPICHEK had Sn = 100%, Sp = 63%, PPV = 44%, and NPV = 100%. RAPICHEK versus TropT sensitivity were 100% versus 50%, respectively.
Stratus CS STAT (Transportable NPT) Dade Behring Deerfield, IL <a href="http://www.dadebehring.com">www.dadebehring.com</a>	CK-MB Myoglobin cTnI D-dimer <sup>a</sup>	Sample: 2.7 mL heparinized WB or plasma Analysis time: 14 min for first result, 4 min for each additional result Other analytes: β-hCG Method: Fluorescence-based immunoassay	Device correlated well with cTnI tests performed in a central laboratory; imprecision of troponin method has a CV of less than 10% at the 99 <sup>th</sup> percentile of the reference population [33,34].
Triage Cardiac Panel (Portable) Biosite Diagnostics San Diego, CA <a href="http://www.biosite.com">www.biosite.com</a>	CK-MB + myo + cTnI cTnI + CK-MB + myo + BNP (test clusters) D-dimer  TBA	Sample: 225 µL EDTA WB or plasma Analysis time: ~15 min Other analytes: acetaminophen, amphetamines, methamphetamines, cocaine, opiates, phencyclidine, tetrahydrocannabinol, barbiturates, benzodiazepines, propoxyphen, tricyclic antidepressants Method: Fluorescence-based immunoassay Sample: fingerstick WB Analysis time: 2–5 min Method: under development	Triage MeterPlus interprets Triage Cardiac Panels, includes built-in quality controls, and provides simultaneous analyses of multiple analytes. Study showed Triage Cardiac Panel comparable to established methods for detection of AMI [35]. Sn for cTnI, CK-MB, and Myo were 98%, 95%, and 81% respectively, and the Sp were 100%, 91%, and 92% respectively for AMI [35,36].  A faster quantitative fingerstick-based test strip using whole blood is being developed (Julie Doyle, M.D., Biosite Diagnostics, e-mail communication.)

*Abbreviations:* ACT, activated clotting time; ALT, alanine aminotransferase; β-hCG, β-human chorionic gonadotropin; BUN, blood urea nitrogen; ELISA, enzyme-linked immunoabsorbant assay; F, female; Hb, hemoglobin; Hct; hematocrit; HDL, high density lipoprotein; H-FABP, human-type fatty acid binding protein; M, male; MLC-1, myosin light chain-1; myo, myoglobin; NA, not available; NPT, near-patient testing; NPV, negative predictive value; PPV, positive predictive value; PT, prothombin time; QC, quality control; QUAL, qualitative; Sn, sensitivity; Sp, specificity; TBA, to be announced; TnI, troponin I; WB, whole blood; and WNV, West Nile Virus.

*Notes:* a) Under development, b) Not available in US, +) Indicates test cluster. Methods were provided by manufacturers or their web sites. Reference 20 cited for completeness. No current information available for the First Medical Alpha Dx system [37,38]. Chemometrics data given for emergency room or early diagnostic applications. See Jaffe chapter for general information of sensitivity, specificity, and predictive values.

Table 2  
Clinical decision levels for cardiac biomarker POCT

Biomarker	Device(s)	Qualitative	Quantitative	Decision level
BNP	Triage Cardiac Panel		X	100 pg/mL
CK-MB	Cardiac STATUS	X		5.0 ng/mL
	LifeSign MI	X		5.0 ng/mL
	Nexus Dx <sup>a,b</sup>		X	Under development
	One-Step Marker Test	X		5.0 ng/mL
	RAMP Reader		X	5.0 ng/mL
	Stratus CS STAT		X	3.5 ng/mL
	Triage Cardiac Panel		X	4.3 ng/mL
CRP	Cholestech LDX		X	Under development
	NycoCard CRP	X		Not available
cTnI	Cardiac STATUS	X		0.5 ng/mL
	i-STAT 1 and PCA		X	0.1 ng/mL
	LifeSign MI	X		1.5 ng/mL
	One-Step Marker Test	X		0.5 ng/mL
	RAMP Reader		X	0.12 ng/mL
	Stratus CS STAT		X	0.06 ng/mL
	Triage Cardiac Panel		X	0.4 ng/mL
	Nexus Dx <sup>a,b</sup>		X	Under development
cTnT	Cardiac Reader		X	0.1 ng/mL
	TropT Sensitive	X		0.1 ng/mL
D-dimer	Cardiac Reader		X	0.5 µg/mL
	NycoCard D-dimer	X		Not available
	Triage Cardiac Panel		X	100 ng/mL
	Stratus CS STAT <sup>a</sup>		X	Under development
H-FABP	RAPICHECK		X	6.2 ng/mL
MLC-1	LifeSign MI <sup>b</sup>	X		Not available
Myoglobin	Cardiac Reader		X	76 ng/mL (M), 64 ng/mL (F)
	Cardiac STATUS	X		80 ng/mL
	LifeSign MI	X		50 ng/mL
	Nexus Dx <sup>a,b</sup>		X	Under development
	One-Step Marker Test	X		50 ng/mL
	RAMP Reader		X	99.3 ng/mL
	Stratus CS STAT		X	98 ng/mL (M), 56 ng/mL (F)
	Triage Cardiac Panel		X	107 ng/mL
NT-proBNP	Cardiac Reader <sup>a</sup>		X	Under development
	LifeSign MI <sup>b</sup>	X		Not available
	Nexus Dx <sup>a,b</sup>		X	Under development

*Abbreviations:* CRP, C-reactive protein; cTnT, cardiac troponin T; F, female; H-FABP, human-type fatty acid binding protein; M, male; MI, myocardial infarction; MLC-1, myosin light chain-1; NT-proBNP, N-terminal proBNP; TnI, troponin I; TnT, troponin T.

*Notes:* a) Under development; b) Not available in United States.

*Disclaimer:* Tables 1 through 3 were compiled from reliable sources including company web sites and cited literature. However, during evaluation before implementation users should update and verify all data directly from manufacturers and product inserts. Users also should verify decision levels and reference methods, as well as FDA-approved clinical applications of each cardiac biomarker.

*Qualitative versus quantitative testing: the American College of Cardiology/American Heart Association guidelines*

Cardiac biomarkers linked with efficient triage and treatment strategies can facilitate resource use, risk stratification, therapeutic management, and clinical outcomes [59–64]. The American

College of Cardiology/American Heart Association (ACC/AHA) 2002 guideline update [65] for patients who present with unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI) states that “point-of-care assays at present are qualitative or, at best, semiquantitative. The evolution of technology

Table 3  
Special applications of cardiac biomarker POCT

Special applications	Biomarker/concept	Device/index
<i>ACS.</i> Rapid test for ACS risk stratification utilizing cardiac myoglobin and CAIII for early specificity and sensitivity (Chris Wayne, Spectral Diagnostics, e-mail communication).	cMyo	Spectral Dx cMyo Test (under development)
<i>CHF.</i> Patients who died or were readmitted tend to have an increase in BNP concentration during their hospitalization ( $+ 239 \pm 233$ pg/mL). Patients who had successful treatment tend to have decreases in their BNP concentration during their hospitalization ( $-216 \pm 69$ pg/mL). The difference between these two groups were significant ( $P < .05$ ). Therefore, POCT of BNP may be an effective way to improve in-hospital management of patients with decompensated CHF [45].	BNP	Triage BNP
<i>Correctional facility.</i> When the Cardiac STATus is combined with EKG results and medical history, a positive result leads to early diagnosis and subsequently faster, more effective treatment. A negative result can provide the confidence needed to safely treat the inmate on premises. In the end the correctional facility saved substantial funds (Chris Wayne, Spectral Diagnostics, e-mail communication).	Multivariate analysis	Cardiac STATus
<i>Diabetes risk.</i> Bhalla and colleagues [46] state BNP to be the most significant ( $P < .001$ ) predictor of all-cause mortality in diabetic patients suspected of cardiac dysfunction.	BNP	Triage BNP
<i>Diagnostic synthesis.</i> "MMX" combines multiple biomarker test results in a continuous parameter that shows potential to discriminate patients with ACS from those without ACS (Julie Doyle, M.D., Boisite Diagnostics, e-mail communication). From ROCs, MMX AUC appears to outperform individual analyte (cTnI, CK-MB, myoglobin, or BNP) AUCs in ACS versus non-ACS and in other comparisons, such as MI versus UA or non-ACS, including for subsets of patients within 6 hours after the onset of chest pain. MMX algorithms have the potential to aid in the differential diagnosis of other conditions, such as stroke. Independent multimarker analysis also can be used for risk stratification [47,48].	Multimarker index	MMX (Anderberg J. and colleagues. AACC Oak Ridge Conference, 2005;63)
<i>Early dysfunction.</i> Mueller and colleagues [49] showed NT-proBNP comparable to BNP biomarkers for differential diagnosis in symptomatic and asymptomatic structural heart disease. However, results also suggested NT-proBNP was able to discern early cardiac dysfunction compared to BNP.	NT-proBNP	(Roche Elecsys) POCT under development
<i>General practice environment.</i> Dahler-Eriksen and colleagues [50] showed CRP testing in general practice identified significantly ( $P = .002$ ) more new diseases (eg, infectious disease, inflammatory disease) compared to the control group. Additionally, cost-effectiveness analysis showed a reduction of \$110,000 per year.	CRP	NycoCard Reader

Table 3 (continued)

Special applications	Biomarker/concept	Device/index
<i>Home testing.</i> Each year, more than a million persons in the United States have a heart attack, and about 50% of them die [51]. About 50% who die do so within 1 hour of the start of symptoms, such as pre-infarction angina. Home testing could improve outcomes.	Various cardiac biomarkers	Waived tests (to be developed)
<i>Military.</i> Cardiac troponin T can help exclude myocardial damage in patients who experience an elevated CK caused by skeletal muscle trauma [52].	cTnT	TropT Sensitive and Cardiac T
<i>Military.</i> The Cardiac STATus is available to every surface ship in the entire US Navy fleet (Chris Wayne, Spectral Diagnostics, e-mail communication).	Multimarker Analysis	Cardiac STATus
<i>Mobile intensive care unit.</i> When used within 2 to 12 hours from the onset of symptoms, the CK-MB/myoglobin multimarker test can prevent misdiagnosis of AMI or unnecessary hospitalization [53].	Multimarker Analysis	Cardiac STATus
<i>Paramedic use.</i> Use of the cTnI test helps Onslow County paramedics to quickly diagnose chest pain, and confidently rule-in or rule-out heart attacks while patients are in transit to the hospital. In certain cases, if the paramedic or ED physician confirms the patient is having a heart attack they can, following a protocol, implement therapy before they reach the hospital doors (Chris Wayne, Spectral Diagnostics, e-mail communication).	cTnI	Cardiac STATus
<i>Potential new biomarker.</i> For the diagnosis of AMI, quantitative ELISA-based measurement of H-FABP has been shown to be more sensitive than myoglobin or CK-MB, and more specific than myoglobin [22]. However, the ELISA process takes $\geq 90$ minutes whereas the RAPICHEK takes 15 minutes. Additionally, the RAPICHEK test exhibited superior negative predictive values, which reached nearly 100% for patients in all time frames. Seino and colleagues [22] concluded that the H-FABP could be useful for emergencies.	H-FABP	RAPICHEK
<i>Prehospital admission.</i> Prehospital cTnT testing appears to be an objective marker for patients with poor outcomes [54].	cTnT	TropT Sensitive and Cardiac T
<i>Renal dysfunction.</i> McCullough and colleagues [55] showed myoglobin and CK-MB correlated with corrected creatinine clearance ( $r = -0.36$ , $P < 0.01$ , and $r = -0.10$ , $P = .01$ , respectively), while cTnI did not ( $r = -0.10$ , $P = .12$ ). Multiple receiver operating characteristic curve testing showed cTnI to be the most consistent marker of myocardial injury over all strata of renal dysfunction including end-stage renal disease on dialysis [56]. Therefore, cTnI is applicable and superior to myoglobin or CK-MB in the evaluation of chest pain in patients with renal dysfunction [55].	cTnI	Triage Cardiac Panel
<i>Renal failure.</i> In patients with severe renal failure, cTnT could not be broken down and cleared by the kidneys, resulting in high serum cTnT levels [56].	cTnT	TropT Sensitive and Cardiac T

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Table 3 (continued)

Special applications	Biomarker/concept	Device/index
<i>Secondary referral.</i> European Society of Cardiology recommendations include BNP testing to refer patients to secondary care.	BNP	BNP
<i>Thrombosis.</i> As a cardiac biomarker, Dempfle and colleagues [57] found the Roche Cardiac D Rapid Assay was also useful as a rule-out diagnostic tool for patients with suspected acute thrombosis [58]. The Roche Cardiac D Rapid Assay also can be used for diagnostic work-up for deep vein thrombosis [57].	D-dimer	Cardiac D

*Abbreviations:* AUC, area under curve; CAIII, cardiac anhydrase III; cMyo, cardiac myoglobin; CorrCrCl, corrected creatinine clearance; CRP, C-reactive protein; cTnT, cardiac troponin T; ELISA, enzyme-linked immunoabsorbant assay; F, female; H-FABP, human-type fatty acid binding protein; M, male; MI, myocardial infarction; MMX, multi-marker index; NA, not available; NT-proBNP, N-terminal pro B-type natriuretic peptide; ROC, receiver operator curve; and UA, unstable angina.

that will provide quantitative assays of multiple markers that are simple to use will improve the diagnosis and management of patients with suspected acute coronary syndrome (ACS) in the ED". The 2004 ACC/AHA guidelines [66] for the management of patients with STEMI stated, "Although handheld bedside (point-of-care) assays may be used for a qualitative assessment of the presence of an elevated level of a serum cardiac biomarker, subsequent measurements of cardiac biomarker levels should be performed with a quantitative test.... in general, bedside assays are less sensitive and less precise than quantitative assays". Further, "A positive bedside test should be confirmed by a conventional quantitative test" [66]. These guidelines statements regarding qualitative assays allude to the various types of handheld formats and disposable test kits noted for convenience [67] and listed in Table 1. Qualitative versus quantitative assays are identified in Table 2. Much room for improvement exists in the detection of minor myocardial damage. The sensitivity and precision at the cutoff concentrations of qualitative and quantitative assays should be checked and deemed clinically appropriate before implementation [68] in chest pain centers.

Assay types, clinical applications, and testing sites create many alternatives, and the relevance of published studies will depend in part on the configuration and staffing of individual chest pain centers. Hamm and colleagues [69] found qualitative POC cardiac troponin T (cTnT) and cTnI tests to be sensitive and useful for ED triage. Schwartz and colleagues [70] documented diagnostically similar results from CK-MB and myoglobin qualitative testing in the ED and quantitative testing in the laboratory. Panteghini

and colleagues [25] studied the potential usefulness of rapid bedside qualitative myoglobin/CK-MB and cTnT tests in initiating revascularization therapy. James and colleagues [48] found rapid qualitative cTnI suboptimal for prediction of subsequent cardiac events at suspicion of unstable coronary syndromes. Hirschl and colleagues [71] found reliable clinical performance of qualitative cTnT testing, whether performed in laboratories or by nurses and physicians in critical care units. For "patients with suspicious AMI," Seino and colleagues [22] showed improved early sensitivity with a rapid whole-blood quantitative assay for heart-type fatty acid binding protein versus qualitative cTnT testing. Wu and colleagues [31] reported equivalent results for quantitative cardiac biomarker POCT and laboratory testing. Other studies [21,72] address quantitative bedside testing. Additionally, POCT encompasses near-patient testing (NPT), such as in ED satellite laboratories, where automated analyzers that provide quantitative testing (eg, Stratus CS STAT) often are placed.

In the ED, analytically sensitive quantitative cTn assays have blurred the distinction between patients who present with and without classically defined acute myocardial infarction (AMI) and have focused attention on the continuum of ACS from angina to transmural Q-wave myocardial infarction (MI) [73,74]. With first-draw specimens in the ED and qualitative POCT, Kratz and colleagues [75] showed that triple cardiac biomarkers (ie, a test cluster) may be needed to avoid weak positive predictive values for individual tests, and quantitative confirmation in the clinical laboratory yields additional improvement. In a five-hospital study of acute chest pain patients, Goldman and colleagues [18] reported equivalent

results for quantitative POC cTnT and myoglobin testing in the ED versus testing in the clinical laboratory and stated that POC cTnT proved advantageous for rapid decision making. In the ED, optimal clinical sensitivity for ACS on first-draw specimens derives from myoglobin, a better adjunct test than CK-MB [76]. Although qualitative POC methods appear in routine and also several special settings (see Table 3), to expedite clinical assessment without missing cases of AMI, quantitative and highly sensitive POC assays are needed. POC assays also allow monitoring of release and clearance dynamics in the form of bedside changes ( $\Delta$ , “delta values”) [65]. A conservative approach, the evidence to date, and the guidelines above indicate a need for highly sensitive *and* quantitative cardiac biomarker POCT, and given a choice, chest pain centers should implement quantitative assays.

#### *Ischemia markers: critical need*

Any ischemia biomarker that works well clinically, that is, can detect ischemia in the absence of necrosis, would be an immediate success if used for POCT. Aggressive early triaging demands improved cardiac biomarkers for that purpose. A new biomarker, ischemia-modified albumin (IMA) (ACB, albumin Cobalt binding test; Ischemia Technologies, Denver, Colorado), has been approved and licensed by the Food and Drug Administration (FDA). Unfortunately, clinical data show that the current generation of the IMA assay lacks requisite specificity [77–87] like that possibly afforded, for example, by ultrahigh-sensitivity assays for troponins. In addition, IMA has not been implemented on any of the POC platforms listed in Table 1. Biomarkers of ischemia under evaluation include free fatty acid, glycogen phosphorylase isoenzyme BB, myeloperoxidase, nourin-1, pregnancy-associated plasma protein A, sphingosine-1-phosphate, soluble CD40L, and whole-blood choline. Future clinical studies of ischemia biomarkers should target low-risk patients in whom quick evaluation in the chest pain center can exclude AMI, and then attention can turn to the underlying cause of the chest pain.

#### **Therapeutic turnaround time**

Because it measures the *total* time from test ordering to treatment, TTAT (Fig. 1) represents an overall performance monitor (metric) useful for

identifying the “bottleneck” route, that is, the critical path of acute cardiac care in chest pain centers and EDs. Expedited treatment influences patient survival, and TTAT can assess efficiency. If blood specimens are obtained first or before verbal orders are documented, as may occur in critical situations, TTAT starts with collection. In the algorithmic evaluation and treatment of chest pain using critical pathways and in concepts recommended by the ACC/AHA [65,66,88] (also ESC [89,90]), the AMI and the UA/NSTEMI pathways call for rapid cTn testing but not necessarily at the point of care. POCT, however, eliminates preanalytic delays. Caragher and colleagues [91] showed that POCT for myoglobin, CK-MB, and cTnI expedited diagnosis in the ED by decreasing the time to test results by 55% (39 versus 87 minutes) compared with the clinical laboratory. Hsu and colleagues [33] found a reduction from 65 to 26 minutes with POCT. McCord and colleagues [6] reported a median time from sampling to reporting of 24 minutes, and others [92,93] reported results availability in about 20 minutes. Stubbs and Collinson [94,95] showed that POCT of cardiac biomarkers decreased turnaround time by 52 minutes (central laboratory, 72; POCT, 20) and shortened hospital stay. Altiner and colleagues [96] reported a turnaround time of 82.5 minutes (50<sup>th</sup> percentile) versus 17 minutes with POCT, which facilitated faster discharge for some patients in the ED. In a study of five hospitals, Gaze and colleagues [97] documented that bedside cTnT testing in ED produced results in 12 to 22 minutes, a gain in time of 65 minutes (range 34 to 135 minutes) compared with central laboratory measurements. Thus, these studies have established POCT as fast and capable of producing clinical results in time spans comparable to the analysis times shown in Table 1.

Lee-Lewandrowski and colleagues [98] showed that when POC cardiac biomarkers were combined with other POC tests (ie, pregnancy testing and urine dipstick), the integration decreased test turnaround time by 87% and ED length of stay by 41.3 minutes. Performed at a time when Boston ambulance diversion was an issue, this study found that implementation of a POCT satellite laboratory in the ED decreased divert hours by 27%. POCT increased physician satisfaction [68]. Integration of testing plus synthesis of test results and other clinical evidence represents an essential pivot for knowledge optimization and decision making [3]. Collinson [94] suggested that POCT must be used if cardiac biomarker

results are delayed more than 25% of the clinical decision time. In reality, POCT integrates decision making at the bedside. Widespread availability of POCT now makes fast TTAT an expectation in critical care management, the early recognition of life-threatening conditions, and the titration of commonly applied therapies [2,99–101]. Experience in United States legal deliberations has demonstrated that POCT may be deemed clinically necessary to achieve fast TTAT. Hence, well-conceived and mutually agreed upon goals for TTAT that are based on evidentiary needs [102] will improve cycles of individual patient care and overall performance in chest pain centers and emergency medicine.

## Timeliness

### *Perception versus performance*

Discordant viewpoints about how to measure the timeliness of diagnostic testing frustrate teamwork. Most clinicians measure response time as the interval starting with test ordering and ending with result reporting [103]. In contrast, laboratorians typically start the clock when they receive the sample in the laboratory and thereby discount preanalytic delays [103] that may degrade samples. Even for ED tests, such as potassium and hemoglobin, specimen transit times account for approximately one third of the total response time [104]. Active monitoring improves performance when the laboratory does not control the specimen handling process, but invariably, response time goals for EDs still are not met most of the time [105]. Significantly delayed outliers interrupt diagnostic-therapeutic processes. When finally reported, results from such delayed samples may no longer represent physiologically or medical relevant data, or they may sit in the laboratory information system unnoticed if the laboratory has not listed them as critical values. For enhanced clarity, communication, understanding, and teamwork, chest pain center physicians and laboratorians should agree on definitions of response time, jointly develop performance goals, and perpetually monitor key indicators.

In 2004, a College of American Pathologists (CAP) survey [106] of 159 hospital subscribers (mostly in the United States) to the Q-Probes program revealed critical deficiencies in the timeliness of cardiac biomarker services. Most (82%) laboratory participants deemed 1 hour or less a reasonable order-to-report response time for myocardial

injury markers (cTn or CK-MB), while most (75%) ED physicians wanted results within 45 minutes, in regards to patients presenting to the hospital ED with symptoms of AMI. Neither goal was met. Among the fastest performing 25% of laboratories, median order-to-report cTn and CK-MB response times equaled 50 and 48.3 minutes, respectively. On the average, 90% of results were reported in slightly more than 90 minutes measured from the time the tests were ordered. In about 50% of the hospitals, specimens were ordered by protocol before clinicians saw their patients. In 35.8% of participating hospitals, laboratory policies dictated that no results be reported until all results became available. In 10%, clinicians waited more than 2 hours for results. Shorter response times were associated with having specimens obtained by the laboratory rather than by nonlaboratory personnel and with performing marker assays in EDs or other peripheral laboratories compared with performing tests in central laboratories. For the CAP respondents, however, only 7.2% used an ED or other peripheral laboratory, and only 4.1% used POC instruments.

### *Evolution of guidelines and the standard of care for timeliness*

The discipline inherent in applying practice guidelines can improve teamwork and outcomes [107–109]. In 1993 over one decade ago, the National Institutes of Health (NIH) published, “Emergency Department: Rapid Identification and Treatment of Patients with Acute Myocardial Infarction” [110], a product of the “60 Minutes to Treatment Working Group” of the National Heart Attack Alert Program Coordinating Committee, which had nearly forty member organizations at the time. The working group proposed a goal of 60 minutes for laboratory test results “...in patients with questionable symptoms and ECG findings...”, and 30 minutes for algorithmic “door-to-drug” treatment of “patients with a clear diagnosis of AMI”. The document stated, however, that “the value of rapidly available assays... [CK isoforms, troponin, myoglobin] is unknown at this [1993] time” [110].

Five years ago the ACC/AHA 2000 guidelines [88] for the management of patients with UA and NSTEMI recommended a target of 60 minutes with 30 minutes preferred for completion of central laboratory test results, and stated further that, “Point-of-care systems, if implemented at

the bedside, have the advantage of reducing delays due to transportation and processing in a central laboratory and can eliminate delays due to the lack of availability of central laboratory assays at all hours” [88]. The guidelines also stated of POCT that “The evolution of technology that will provide quantitative assays of multimarkers that are simple to use will improve the diagnosis and management of patients with suspected ACS in the ED” [88]. The 2002 update reiterated [65] that “When a central laboratory is used, results should be available within 60 minutes, preferably within 30 minutes”.

The web-based draft of the National Academy of Clinical Biochemistry (NACB) guidelines [111] proposed that “The laboratory should perform cardiac marker testing with a turnaround time (TAT) of 1 hour, *optimally 30 minutes, or less*. The TAT is defined as the time from blood collection to the reporting of results.” “Institutions that cannot consistently deliver cardiac marker TATs of approximately 1 hour should implement POC testing devices.” The phrase, “...approximately 1 hour...” requires clarification to avoid misunderstandings. Nevertheless, over the past 12 years these NIH, ACC/AHA, and NACB guidelines have pointed consistently toward faster cardiac biomarker testing *within 30 minutes*. One must assess, therefore, whether POC technologies can meet or exceed expectations in these guidelines, positions tantamount to the standard of care. Additionally, the statistical distribution of performance times and outlier delays, and standards in critical care testing using WBA, must be considered to formulate cohesive rapid response criteria for chest pain centers. Lastly, the Society of Chest Pain Centers should consider adopting timeliness as a criterion for accreditation, as suggested in later discussion.

POCT has evolved substantially during the past decade, and so has the way it fits into clinical practice [112]. Now ubiquitous in the United States, POCT has established a new precedent for speed in *critical care testing*. Timeliness expectations for test results, such as electrolytes, blood gases, pH, and hematocrit or hemoglobin, in critical care medicine now have contracted to only 5 to 15 minutes, basically a little longer than WBA time [44,113]. This expectation for timeliness, a *de facto* legal requirement in the care of critically ill patients, prohibits diagnostic testing from prolonging TTAT and certainly from ever degrading efficiency in cases where AMI might be missed in an ED and patients

sent home prematurely. In chest pain centers, therefore, POCT should be approached not only from the perspective of cardiac biomarkers but also from the broader standpoint of garnering benefits that arise when integrating several test clusters. Delays could impede critical pathways, increase legal liability, aggravate risk exposure, and possibly also degrade medical and economic outcomes [3]. For some chest pain centers, fast TTAT and decision making will be achieved only by using POCT, in the form of bedside or near-patient testing.

The timeliness envelope (curve) in Fig. 2 traces progressive contraction of the time interval, test ordering → results receipt, the first of two intervals that make up TTAT (see Fig. 1), versus the year and conceptual evolution in POCT. To the right, standard-of-care milestones for cardiac biomarkers demarcate points that NIH and ACC/AHA published guidelines [88,110], practice standards, and chest pain centers have called for or actualized by virtue of published literature cited herein, faster response time. The performance (map) vector [2] consisting of POCT, focused multimarker innovations, faster immunotesting, and test cluster integration points to diagnostic-therapeutic (Dx-Rx) process optimization by which physicians in chest pain centers intuitively synthesize risk indices for individual patients. POCT provides not only immediate results but also acute awareness. The whole picture reflects a paradigm shift enabled by POCT and increasingly efficient solutions for the management of ACS patients. In the future, real-time in vivo and noninvasive function monitors, now embryonic or yet to be discovered, will supplant discrete in vitro diagnostic tests and lead to continuous knowledge optimization at the bedside, thus further improving the standard of care.

### **Cost-effectiveness, algorithmic strategies, and multimarkers**

Cardiac biomarkers, especially cTn and myoglobin [114,115], play a pivotal role in cost-effectively triaging patients, assessing damage, gauging risk, determining prognosis, and economizing length of stay [116–121]. Decision analysis modeling showed that in patients who presented with acute undifferentiated chest pain, biochemical testing, observation for 2 to 6 hours, and then repeat testing, had a low incremental cost per quality adjusted life year, and that strategies

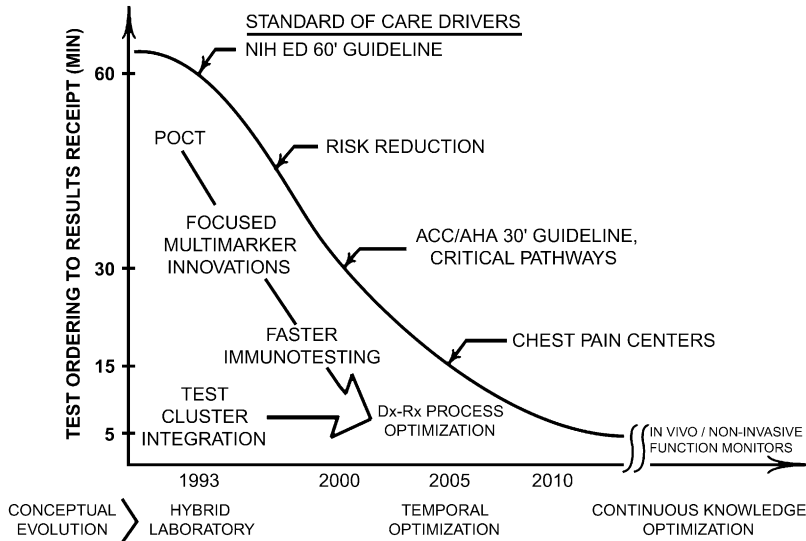


Fig. 2. The standard of care for timeliness of cardiac biomarker testing. Forceful clinical drivers mold the shape of the rapid response curve while the underlying performance vector enables it, aiming at optimization, first discrete, then in the future, continuous. Contemporary timeliness in critical care testing has set a continuum precedent for chest pain centers, which now can consider 15 minutes as reasonable criterion for accreditation. However, all cardiac biomarker results should be available within 30 minutes, the preference stated in ACC/AHA guidelines and the optimal stated in draft NACB guidelines.

requiring hospital admission had poor value [122]. Brogan and colleagues [26] recommended serial testing of CCU admissions to eliminate non-AMI causes and conserve resources. While serial testing of cardiac biomarkers, a hallmark for diagnosis of AMI, comes in at the low end of the cost spectrum of invasive procedures and hospitalization expenses [40], new POC multimarker approaches will redefine serial testing needs and temporal patterns. In the ED, cost and other issues, such as lack of connectivity or apparently modest value in STEMI, have slowed acceptance of POCT [123,124]. However, at a meeting in 2004, Kugelmass and colleagues [125] reported that in a broad group of four community-based hospitals, for 2248 consecutive admissions of patients who received a primary diagnosis of AMI, revascularization (PCI, CABG) rates increased significantly, and in-hospital mortality declined 24.7% ( $P = .049$ ) following 1 year of implementation of POCT.

In the context of ACS and chest pain evaluation, chest pain centers can provide the dual efficiencies of expediting definitive treatment while managing patients with accelerated diagnostic-therapeutic protocols that proved cost-effective and beneficial to patient care [6-9,126,127].

Algorithmic strategies, however, using cardiac biomarkers need to be adapted to local settings [40]. The relative efficacy of diverse testing strategies reported in the literature remains uncertain, in part because sensitivity and specificity for AMI depend on: biomarkers selected, decision levels, timing of testing after symptom onset, natural discordance, unique settings, risk and age strata of patients [128], infarct size [129], and random stochastic events encountered commonly during emergencies. Nonetheless, Mant and colleagues [130] used Monte Carlo statistical simulation of management strategies for suspected ACS and found that POCT with cardiac troponins proved cost-effective.

In the CHECKMATE study, Newby and colleagues [131] showed that rapid quantitative multimarker (myoglobin, CK-MB, and cTnI) NPT identified positive patients earlier and provided better risk stratification for mortality than a local laboratory-based, single-marker approach. NPT was used to facilitate early detection. The study related marker status with 30-day death or infarction. All three markers discriminated 30-day death better than just CK-MB and cTnI, and the report identified the effect of NPT with multimarkers, despite lack of standardization

and completion before guidelines suggested use of the 99<sup>th</sup> percentile of the normal interval and the 10% coefficient of variation precision level as the cutoff [132]. In 2001, McCord and colleagues [6] showed POC myoglobin and cTnI can help exclude AMI rapidly during the first 90 minutes after presentation to the ED. Using NPT in the CCU, Eggers and colleagues [133] showed that when a 10% coefficient of variation cutoff was used, POC multimarkers (cTnI + CK-MB + myoglobin) did not necessarily offer additional diagnostic value versus cTnI alone in the exclusion of MI. Thus, decision levels may affect the clinical efficiency of multivariate (multimarker) approaches, which need to be optimized mathematically and statistically.

Biomarkers of neurohormonal activation in heart failure include BNP and the N-terminal fragment of its prohormone (NT-proBNP), collectively called “BNP” here. In a recent University HealthSystem Consortium comprehensive review, Cummings and colleagues [134] cataloged the merits of BNP-facilitated decision making for early intervention, fewer echocardiograms, severity assessment, risk stratification, prognostic value, therapeutic monitoring, discharge decisions, post-surgical status, transplant rejection, sudden death, device alternatives, and so on. For example, a rapid bedside BNP assay recently was shown [135] cost-effective and efficient in accelerating hospital discharge for patients presenting to the ED with acute dyspnea. Outpatient reimbursement for BNP testing increased in 2003. BNP assays now reside, however, on several automated chemistry analyzers appropriate for main laboratories in hospitals where inpatient testing is covered under the capitated DRG reimbursement system. As noted earlier, the 2004 POCT survey [13] showed that institutions may move BNP to the main laboratory. Thus, the cost-effectiveness of future BNP testing depends on multiple dynamic factors that may change often. Chest pain centers are well advised to establish guidelines for BNP testing and its timeliness now and, with the aim of improving outcomes, reevaluate the guidelines periodically during the next 2 years.

BNP, other biomarkers, and POC test clusters (see Table 1) work synergistically. For example, although not POCT, Sabatine and colleagues [47] documented the value of including BNP and C-reactive protein (CRP) along with cTnI for risk stratification, “When patients were categorized on the basis of the number of elevated biomarkers at presentation, there was a near

doubling of the mortality risk for each additional biomarker that was elevated ( $P = .01$ )”. The investigators suggested using the number of elevated biomarkers at presentation to risk stratify patients for short- and long-term major cardiac events. Multimarker testing as historically configured [49,50] now embraces BNP, CRP, and other cardiac biomarkers to support patient evaluation and treatment. Speed, per se, can be achieved through efficient integration of all clinical pathology services, including the main laboratory (eg, using an automated transport system), NPT (eg, by placing a satellite laboratory in the emergency area), and bedside testing. The extent to which each of these modalities can be used conveniently for multimarker testing depends on individual health system facilities, organization, and priorities. However, to take advantage of multivariate analysis (eg, using cTnI, CK-MB, myoglobin, BNP, and CRP) and multimarker benefits—including improved triage, facilitated decision making, consistent ACS work-up of NSTEMI, enhanced communication, efficient cardiology consultation, shortened intervention wait times, scaling of treatment, decreased risk for inappropriate discharge, and reduced length of stay [47,133,136–140]—testing should be early, simultaneous, and quick, which can be accomplished conveniently with POCT.

#### **Chest pain centers, risk management, and customer satisfaction**

The largest dollar amount for liability recovery still involves chest pain with subsequent missed transmural MI [141]. Rather than treating patients in their offices, more physicians refer patients to EDs, and high-risk specialists progressively become unwilling to provide ED on-call coverage because of malpractice concerns and skyrocketing premiums [142]. Efficiency mandates that chest pain centers should use prompt rule-out schemes and that rapid cardiac biomarker testing should be performed (along with rapid EKG) to help physicians avoid missing patients who present with AMI, currently estimated to occur in 2% to 5% [109,143,144]. Chest pain centers that adopt a macroscopic viewpoint, aggressive leadership, and legal precautions generate excellent community relations and customer satisfaction [145]. Experience in legal case analysis has revealed patients were sent home before clinical laboratory results became available, only to discover too late an elevated cTnI or CK-MB. Also, physicians may

order cardiac biomarker tests for which blood collection is delayed, and attend to other patients or leave the area, thereby inadvertently overlooking important results. POCT and “physician capture” [2] can help alleviate these types of errors and simultaneously provide other critical test results necessary for patient evaluation and triaging.

To reduce risk exposure each institution should identify bottlenecks in cardiac critical pathways and then determine specifically if cardiac biomarker POCT can accelerate evaluation and therapy. TTAT actually achieved not only should meet ACS/AHA guidelines but also should satisfy the current standard of care for rapid response testing of patients with life-threatening conditions. Table 1 includes tests (other than cardiac biomarkers) that are available on the same platforms. These other tests can help physicians synthesize critical care solutions [2,3]. For example, clinicians evaluating acutely ill patients who present with chest pain can order electrolyte measurements, such as potassium ( $K^+$ ) and ionized calcium ( $Ca^{++}$ ), and these analytes, already available on several POC platforms (possibly the same ones that perform cardiac biomarker testing), can be integrated increasingly as market demand and manufacturing efficiencies drive instrument consolidation in the cardiac biomarker field.

### **Summary: planning and implementing point-of-care testing**

Table 4 presents 12 fundamental objectives and recommendations to consider when planning and implementing POCT in chest pain centers. If accurate, precise, safe, and cost-effective in the context of holistic cycles of patient care, no a priori reason exists to not use POCT. The discussion below highlights points from Table 4 and key considerations for chest pain centers.

#### *Timeliness accreditation and the Society of Chest Pain Centers*

For cardiac biomarkers, the evolution in clinical guidelines has shaped the standard-of-care envelope for timeliness (see Fig. 2). Response time is being decreased by minimizing the WBA time for on-site quantitative testing in vitro. Future ex vivo and in vivo techniques for assessing myocardial function can generate immediate real-time data. Needs assessment by leadership in individual chest pain centers will reveal how best to optimize

POCT, whether performed at the bedside or in near-patient satellite laboratories.

The 2004 United States survey of POCT [13] discussed earlier showed that some main laboratories may move tests, such as BNP, away from the point of care; however, timeliness must be preserved. The authors recommend, therefore, that the timeliness of cardiac biomarker testing and also the elimination of all delayed outlier results be adopted as criteria for accreditation by the Society of Chest Pain Centers. These criteria should be reassessed at least every 2 years as improved POC technologies for WBA grow progressively faster, more accurate, and better integrated.

#### *Therapeutic turnaround time and risk reduction*

POCT has set a general precedent for timeliness in the standard of care for critically ill patients. WBA facilitates that timeliness. TTAT (see Fig. 1) represents a common denominator for performance. Diagnostic testing must not compromise TTAT. Chest pain centers not using POCT or fast WBA of cardiac biomarkers eventually may have to prove, perhaps in a court of law if delayed test results lead to a missed diagnosis of AMI and adverse outcomes, that they consistently achieve requisite speed and TTAT without POCT.

Even if courier and pneumatic tube systems serve the ED, testing performed in a main laboratory may generate significantly and unpredictably delayed results that impair patient evaluation or treatment. Decision-makers must be cognizant of the medicolegal ramifications and reduce risk by optimizing performance, that is, by minimizing TTAT. TTAT represents an integrative performance indicator that can be applied to entire cycles of patient care. The time required to perform diagnostic testing should fit comfortably within the TTAT goals for different diagnoses in individual chest pain centers, so that testing does not delay the critical paths of care and increase risk exposure for patients.

#### *User-friendly new cardiac biomarkers and instruments*

In view of rapid growth, anticipate the appearance of several new cardiac biomarkers, some developed exclusively for POCT. For novel tests and new indices, chest pain centers should document clinical justification and assure cost-effectiveness. The benefits of on-site testing should outweigh the costs of innovating, implementing,

Table 4  
Planning and implementing future POCT in chest pain centers

Objective	Recommendation
• Algorithmic integrative strategies	Embedding POCT within diagnostic-therapeutic algorithms, care paths, and critical pathways improves the overall efficiency and effectiveness of cardiac biomarker testing.
• Connectivity	CPCs should use primarily POC devices that provide connectivity to the electronic medical record and other computerized information systems.
• Critical limits and urgent notification	Urgent notification of critical results assures physician awareness and may help prevent premature discharge to home of patients with evidence of AMI.
• Error prevention and biohazard control	Security of instrument operation, validation of personnel skills, and certification of qualified operators who perform POCT help prevent errors, decrease risk, and contain biohazards.
• Home testing and early detection	Since up to 50% of AMI patients die before reaching the hospital, future home testing with automated communication of cardiac biomarker results may facilitate early life-saving detection and transport.
• Integration of critical care test clusters	POC technologies that combine simultaneous measurements of blood gasses, pH, electrolytes (eg, K <sup>+</sup> and Ca <sup>++</sup> ), metabolites (eg, glucose), and other essential critical care test clusters along with cardiac multimarkers will streamline holistic evaluation, diagnosis, and treatment of critically ill patients.
• Minimum analysis time and critical path	CPCs can provide cardiac biomarker test results as expeditiously as permitted by newer, smaller, and faster analytical methods, which soon may provide quantitative results on fingerstick whole-blood samples in 2 to 3 minutes, thereby facilitating the critical path of patient care.
• Multimarker synthesis and indices	Multimarker synthesis will facilitate differential diagnosis and risk profiling through evidence-based joint probabilities and mathematical heuristics using indices that help decipher myocardial ischemia, NSTEMI, STEMI, heart failure, and inflammation.
• POCT coordinator and hybrid staff	POCT should be managed by POC Coordinators who work collaboratively with nurses and physicians to enhance performance through education, quality control, compliance monitoring, and proficiency testing.
• Quantitative assay performance	Quantitative POC assays should achieve equivalent or better performance (detection threshold, accuracy, and 10% coefficient of variation for precision at the 99th percentile of normals) and clinical performance (sensitivity, specificity, and predictive values) versus main laboratory counterparts.
• Standardization, continuity, and consistency	Use of identical POC assays in the CPC and critical care areas (eg, CCU, ICU, and OR) promotes local consistency, while for clinical continuity dissimilar assays, if used, should be referenced to the same comparison method or better, standardized, and all methods should have compatible reference intervals, decision levels, and critical limits.
• Timeliness and accreditation	Expanding numbers of CPCs in the US will lead to higher expectations for fast cardiac biomarker results and codification of timeliness, potentially a Society of CPCs accreditation requirement, here suggested as the analysis time of 15 minutes for POCT, with all results received by the clinical team within the ACC/AHA guidelines preferred time of 30 minutes (order-to-receipt, 24 h/d, 7 d/wk).

*Abbreviations:* ACC, American College of Cardiology; AHA, American Heart Association; CCU, cardiac/coronary care unit; CPC, chest pain center; ICU, intensive care unit; NSTEMI, non-ST-elevation myocardial infarction; OR, operating room; STEMI, ST-elevation myocardial infarction; TTAT, therapeutic turnaround time.



and operating POCT or proprietary multimarker indices. Economic analysis should assess the total benefits and costs of care episodes and determine the marginal effects of POCT alternatives. Analysis also should take into account hospital admissions that could have been prevented through timely cardiac biomarker POCT. Already valuable risk stratification will build as new POCT inventions and innovations appear, but lack of definitive biomarkers for myocardial ischemia represents an unmet need. Research should target discovery of highly sensitive and specific biochemical tests predictive for myocardial ischemia.

Because the 2004 POCT United States survey [13] showed hospitals evaluated but then rejected cardiac biomarker instrument platforms more frequently than other forms of POCT, user-friendly POC instrument designs also are needed badly. Solutions currently available will not satisfy the present or future needs of chest pain centers or busy EDs. Poorly integrated systems that lack connectivity to the electronic medical record threaten quality control monitoring and make the management tasks of the POC coordinator extremely difficult. Additionally, existing devices are poorly adapted for emergency field response and must be simplified substantially to garner waived status for home testing under federal regulations.

#### *Algorithmic practice and quantitative testing*

POCT can speed diagnostic synthesis in chest pain centers, and speed is essential in EDs overwhelmed with patients. For most cardiac biomarkers, accelerated algorithmic strategies will help position cardiac biomarkers temporally and optimally within the diagnostic decision tree and its treatment branches to take advantage of time-dependent kinetics, sensitivities, specificities, predictive values, and multivariate functions. The choice of test clusters, types of instruments, and sites, such as bedside or near-patient (eg, an ED satellite laboratory) and home or field (eg, ambulance, helicopter, ships, and airplanes), rests with collaborative care teams who must assure the continuity, efficiency, and efficacy of critical pathways in emergency situations.

Whether using cardiac biomarker POCT on-site or testing performed elsewhere, United States physicians (and physicians in United States jurisdictions abroad) must be aware of FDA-approved manufacturer claims to avoid clinical misuse of tests and unnecessary liability. Quantitative testing

is recommended by the ACC/AHA, ECS, and NACB guidelines discussed earlier, and also here. Qualitative testing remains beneficial in some cases to determine quickly whether a patient is “hot or not.” Highly sensitive quantitative testing with well-defined detection limits [146], however, has several advantages and better fits the multidimensional, multimarker, and multivariate algorithmic practice of the future in chest pain centers.

#### *Leadership vision and chest pain centers*

With more than 150 sites in the United States in 2005, chest pain centers now can pool professional resources to: (a) consolidate care algorithms, (b) write guidelines for POCT, (c) systematize bedside and NPT, (d) consider adopting timeliness accreditation criteria, (e) form purchasing groups to obtain POC devices and reagents inexpensively, (f) facilitate rapid discovery of evidence to avoid missing patients with AMI, (g) monitor performance indicators, such as TTAT, regularly, and (h) provide outreach programs to extend cardiac biomarker testing to field and home sites to help reduce unacceptably high mortality rates there.

POCT should be approached from the standpoint of the laboratory-clinical-community interface and optimized by physicians, nurses, POC coordinators, and laboratorians working collaboratively [2,147]. Professional leadership groups, such as the Society of Chest Pain Centers, can help guide the current rapid growth of cardiac biomarker POCT to fulfill important practice goals, including accurate diagnosis of myocardial ischemia, improved triage, administration of proven treatment (eg, glycoprotein IIb/IIIa inhibitors), quantitative risk stratification, early invasive strategies, and improved economic and medical outcomes.

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## Markers of Cardiac Ischemia and Inflammation

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Coronary artery disease (CAD) is one of the leading causes of death in the United States. The challenge is not only to diagnose acute coronary syndromes (ACSs) in patients who present with the traditional combination of anginal pain and electrocardiography (ECG) changes but also to recognize disease in patients who have atypical symptoms and initially nondiagnostic ECGs. Advances in the understanding of the pathophysiology of cellular injury and in analytical technology have made possible the development of molecular markers that can be measured in serum or plasma. This development has already made a tremendous impact on our clinical assessment of myocardial injury. In September 2000, a committee comprising members representing the American College of Cardiology and the European Society of Cardiology redefined acute myocardial infarction (MI), including the manner in which biomarkers of myocardial necrosis, preferentially cardiac troponins, are used in addition to ischemic symptoms and ECG changes [1].

Because current biomarkers of myocardial necrosis only become positive in the setting of MI and disruption of cellular integrity, the diagnosis of MI can only be made in retrospect. Ideally, one would like to identify patients at risk for complications before myocardial necrosis

occurs. Insights into the pathophysiology of atherothrombosis have allowed development of novel markers to detect not only early ischemia without myocyte death, but also early indicators of coronary inflammation in patients with pre-clinical atherosclerosis.

### Inflammation and atherothrombosis

There is extensive literature supporting the role of inflammation in CAD. Hemodynamic forces from hypertension and oxidative stressors, such as tobacco and hyperglycemia, result in vascular endothelial injury. The attachment of leukocytes, transformation of monocytes into macrophages, and subsequent uptake of cholesterol lipoproteins initiate the fatty streak. Cytokine release from the fatty streak recruits further inflammatory cells (macrophages, mast cells, activated T cells), with resulting uptake and oxidation of low-density lipoprotein (LDL). These cytokines also stimulate smooth muscle cell proliferation and development of a collagenous fibrous cap that covers this inflammatory mixture to form the mature atherosclerotic plaque [2].

Recent data show that the risk for an acute coronary event has less to do with the degree of angiographic luminal stenosis than with the underlying pathology of the atherosclerotic plaque that makes it susceptible to rupture [3]. Activated T cells within the atheromatous core secrete interferon gamma that decreases smooth muscle cell production of collagen [4]. Inflammatory cytokine-activated macrophages secrete matrix metalloproteinases that degrade the extracellular matrix, further weakening the fibrous cap and making it prone to rupture [5,6]. Disruption of

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the cap exposes the atheronecrotic core to blood, after which further inflammatory reactions lead to platelet activation, coagulation cascade, further vasomotor dysfunction [7,8], and ultimately luminal occlusion.

Thus, all stages of atherothrombosis implicate inflammation as a key pathogenic mechanism. Several clinical studies have therefore targeted inflammatory factors as potential markers for cardiovascular risk assessment.

### Markers of inflammation

Several inflammatory factors involved in the cascade described earlier have been studied in clinical trials in the last decade. These include the proinflammatory cytokines interleukin (IL)-1, IL-6, tumor necrosis factor  $\alpha$ , catalysts of the inflammatory reaction (CD40 ligand), cellular adhesion molecules (intercellular cell adhesion molecule [ICAM]-1, vascular cell adhesion molecule [VCAM]-1, selectins), and acute phase reactants (fibrinogen, white blood count, C-reactive protein [CRP], serum amyloid A).

#### *C-reactive protein*

CRP is the best studied of the inflammatory markers in cardiovascular disease. It is an acute-phase protein that has been shown to be a marker of systemic inflammation, elevated in response to acute injury, infection, and other inflammatory stimuli [9]. Hepatic production is directly related to IL-6 stimulation and, unlike other acute phase reactants, its levels remain stable over long periods of time in the absence of new stimuli [10]. Traditional CRP assays with limits of quantification of 3 to 8 mg/L lack adequate sensitivity to detect levels required for atherosclerotic risk prediction. The development of a standardized high-sensitivity CRP (hsCRP) assay has improved precision at low concentrations of CRP that permits its use in cardiovascular risk assessment.

In several studies of patients who have ACS (Chimeric c7E3 AntiPlatelet Therapy in Unstable angina REfractory to standard treatment, Thrombolysis In Myocardial Infarction [TIMI]-11a, and FRagmin during InStability in Coronary artery disease [FRISC] trials), elevated hsCRP at hospital admission independently predicted increased mortality [11–13]. In a Global Use of Strategies to open Occluded arteries IV substudy, hsCRP elevation during the acute stage of unstable CAD was associated with an increased 30-day mortality

independent of troponin levels; there was no association with recurrent MI [14]. However, in stable post-MI patients, elevated hsCRP predicted a significantly higher risk for recurrent nonfatal MI or fatal coronary events (75% higher in the highest versus lowest quintile of hsCRP), suggesting that it is not merely a marker for the extent of myocardial damage [15].

In the European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study, 2121 patients admitted with angina were followed over a 2-year period. A plasma concentration of CRP greater than 3.6 mg/L at study entry was associated with a 45% increase in the relative risk for nonfatal MI or sudden cardiac death (95% confidence interval [CI], 1.15–1.83) [16]. However, the usefulness of measuring hsCRP in patients who have ACS is limited because there is already sufficient evidence warranting maximal lipid-lowering, antiplatelet, and other cardioprotective drug therapies in these patients, so that measurement of hsCRP does not provide incremental information.

The setting in which hsCRP may be most useful is primary prevention. A population-based cross-sectional study in Great Britain showed that the prevalence of CAD increased 1.5 fold (95% CI, 1.25–1.92) for each doubling of hsCRP among men aged 50 to 69 years [17]. In the Multiple Risk Factor Intervention Trial cohort of middle-aged men who had traditional high cardiovascular risk factors, CRP was elevated more in smokers versus nonsmokers. Over 17 years of follow-up, an elevated baseline CRP was associated with a 2.8-fold increased risk for coronary heart disease mortality (95% CI, 1.4–5.4) [18].

Several prospective studies of hsCRP in apparently healthy individuals have also shown that elevated baseline levels of hsCRP are correlated with higher risk for future cardiovascular morbidity and mortality after adjustment for potential confounders. The Physicians Health Study, a prospective, nested case-control study of men who did not have prior history of CAD and had low rates of cigarette use, showed that men in the highest quartile of hsCRP ( $\geq 2.1$  mg/L) had a significant 2.9-fold increase in risk for MI that was independent of smoking status, lipid levels, and other traditional risk factors for CAD [19]. This finding was confirmed in the Monitoring Trends and Determinants of Cardiovascular Disease (MONICA)–Augsburg prospective study in Europe that followed 936 healthy, middle-aged men over 8 years and noted a 19% increase in risk for future coronary event for each standard deviation increase

in baseline hsCRP after adjustment for multiple risk factors [20].

This relationship also bears out in women. In a prospective nested case-control study involving postmenopausal women enrolled in the Women's Health Study, Ridker and colleagues [21] showed hsCRP to be the most powerful predictor of cardiovascular risk compared with other inflammatory markers, baseline lipid levels, and homocysteine. Women in the highest quartile had a relative risk of 4.4 (95% CI, 2.2–8.9,  $P < .001$ ) compared with those in the lowest quartile. Addition of hsCRP to cholesterol measurement increased the area under the receiver operating characteristic (ROC) curve from 0.59 to 0.66 ( $P < .001$ ). Furthermore, in women who had LDL levels less than 130 mg/dL (the target level recommended for primary prevention by the National Cholesterol Education Program), those who had elevated baseline CRP were still at increased risk for future events with a 3.1 relative risk in the highest quartile compared with the lowest (95% CI, 1.7–11.3,  $P = .002$ ) after adjustment for traditional risk factors and high-density lipoprotein (HDL) cholesterol levels.

Prospective data show that hsCRP levels minimally correlate with lipid levels and are a stronger predictor of risk than LDL cholesterol (area under the ROC curve 0.64 versus 0.60) [22]. Therefore, the role of CRP is adjunctive to lipid screening and the additive predictive value of hsCRP to the Framingham 10-year risk score, LDL, total, and HDL cholesterol measurements has been demonstrated in several studies [23,24]. However, there is not yet a consensus that the degree of hsCRP elevation correlates with atherosclerotic burden.

Tataru and colleagues [25] showed that in survivors of MI, there was a significant association of hsCRP level with angiographically detected degree of coronary artery stenosis. In addition, patients who had coronary disease who had sonographically detectable peripheral arterial disease had even higher levels of hsCRP compared with those who had CAD alone. In a small Denmark study of 269 patients referred for elective coronary angiography, hsCRP levels were significantly higher in patients who had coronary stenoses than those who did not, but no difference in hsCRP levels were found comparing groups with single, 2-, or 3-vessel disease [26]. In a nested case-control substudy of the Prospective Army Coronary Calcium trial that looked at healthy men between the age of 40 and 45 years who did not have coronary disease, the prevalence of coronary artery calcium as

assessed by electron-beam CT was similar across all hsCRP quartiles [27]. Therefore, although hsCRP has good risk assessment value, there is no definitive evidence supporting its role in selecting patients for coronary angiography.

The role of hsCRP in predicting CAD has been established. What remains uncertain at this time is whether CRP should be a target of therapy or used to guide therapy. In vitro and in vivo studies show that hsCRP contributes to plaque development by increasing monocyte adherence, inducing expression of cell surface adhesion molecules [28], and increasing LDL scavenger cell uptake of cholesterol [29]. Furthermore, high CRP is associated with decreased nitric oxide availability impacting vasomotor activity [30] and increased monocyte production of tissue factor [31]. CRP is also shown to activate complement and neutrophils [32] and decrease fibrinolytic capacity [33], thereby contributing to plaque instability and thrombus formation.

In the Physicians Health Study, use of aspirin was associated with a statistically significant, 55.7% risk reduction for first MI among men who had hsCRP levels in the highest quartile compared with a nonsignificant 13.9% reduction in those who had hsCRP levels in the lowest quartile [19]. No follow-up levels were drawn to deduce whether aspirin directly lowered hsCRP levels.

The anti-inflammatory effects of statins are still unclear; experimental evidence posits statin-mediated reduction in macrophage activation, antiproliferative effects on smooth muscle cells, improvements in endothelial function and vasomotion, and antithrombotic effects [34,35]. At 5-year follow-up of stable post-MI patients randomized in the Cholesterol and Recurrent Events trial, mean hsCRP levels decreased by 37.8% in those randomized to pravastatin therapy, whereas levels increased in the placebo patients [36]. This reduction in hsCRP was independent of the magnitude of changes in lipid levels. Furthermore, patients randomized to pravastatin therapy had a twofold reduction in risk for recurrent MI or fatal coronary event in the elevated hsCRP group compared with the group that did not have elevated hsCRP, even though baseline lipid levels were identical in both groups [15].

More recently, PRavastatin Or atorVastatin Evaluation and Infection Therapy (PROVE-IT) trial demonstrated that intensive statin therapy that lowered hsCRP levels to a mean of less than 2 mg/L resulted in a decreased risk for recurrent MI

or death from coronary causes, irrespective of the degree of LDL lowering [37]. In the PRavastatin Inflammation CRP Evaluation (PRINCE) study, pravastatin was shown to also reduce hsCRP levels in patients who did not have prior history of cardiovascular disease [38]. There is not yet evidence linking hsCRP reduction to a reduction in cardiovascular events in the primary prevention setting.

The Centers for Disease Control and Prevention/American Heart Association consensus statement advocates use of hsCRP for risk assessment in patients who are at intermediate risk for cardiovascular events (10% to 20% 10-year risk of coronary event) [39]. However, there is no prospective randomized clinical trial yet examining the benefits or harm of screening with hsCRP. Presently the guidelines rate a hsCRP level less than 1 mg/L as normal, 1 to 3 mg/L intermediate, and more than 3 mg/L as high. A level greater than 10 mg/L indicates a noncardiovascular source of inflammation and should prompt a search for a source of infection or other inflammation. For patients who have ACS, hsCRP may provide some prognostic information, and a cutoff level of more than 10 mg/L is most predictive of risk for adverse outcomes.

#### *Interleukin-6*

IL-6 is an inflammatory cytokine that induces hepatic synthesis of all the acute phase proteins and is the primary determinant of CRP levels. The presence of IL-6-expressing macrophages in coronary atherosclerotic plaques [40] suggests that increased IL-6 levels are not just a marker of inflammation but also play a direct role in increasing plaque vulnerability to fissuring and thrombosis. In addition to its proinflammatory effects, it also has procoagulant effects by modulating fibrinogen synthesis, enhancing platelet adhesion, and impairing endothelial vasodilation. High IL-6 levels in healthy men correlated with increased risk for future MI independently of hsCRP [41]. In patients who had ACS, IL-6 elevation (>5 ng/mL) was associated with 3.5-fold higher 1-year mortality than levels less than 5 ng/mL, independent of troponin and hsCRP [42]. Furthermore, in this study it appeared that patients who had inflammation as determined by IL-6 levels greater than 5 ng/mL had a greater response to an invasive versus conservative strategy than patients who had IL-6 levels less than 5 ng/mL.

#### *Lipoprotein-associated phospholipase A2*

Lipoprotein-associated phospholipase A2 (Lp-PLA<sub>2</sub>), previously described as platelet-activating factor acetylhydrolase, is a novel marker whose role in atherosclerosis has been heavily debated. Initially considered atheroprotective because of its ability to degrade platelet-activating factor, this enzyme has since been discovered to cleave oxidized phosphatidylcholine into lysophosphatidylcholine and oxidized free fatty acids which promote the inflammatory process of atherosclerosis. Lp-PLA<sub>2</sub> is produced by macrophages and T lymphocytes and can be detected in human atherosclerotic lesions [43]. In humans, Lp-PLA<sub>2</sub> is predominantly bound to LDL cholesterol particles and is activated once LDL particles undergo oxidative damage [44].

The West of Scotland Coronary Prevention Study first demonstrated that baseline Lp-PLA<sub>2</sub> elevation in hyperlipidemic men predicted risk for coronary events independently of other inflammatory markers, such as CRP and fibrinogen. There was a 60% statistically significant increase in risk between the highest and lowest quintile of Lp-PLA<sub>2</sub> [45]. However, in a lower risk population of women (in a nested case-control analysis of the Women's Health Study), the predictive ability of Lp-PLA<sub>2</sub> was not statistically significant after adjustment for traditional risk factors [46].

The Atherosclerosis Risk in Communities study enrolled men and women who had a wide range of LDL levels and found that in patients who had LDL levels below 130 mg/dL, Lp-PLA<sub>2</sub> was significantly and independently associated with CAD [47]. This finding suggests a role for Lp-PLA<sub>2</sub>, similar to CRP, in identifying high-risk patients who may benefit from drug therapy and are not targeted for statin use under the current Adult Treatment Panel (ATP) III guidelines. In the most recent study by Brilakis and colleagues [48], Lp-PLA<sub>2</sub> levels correlated with extent of angiographic CAD; however, this was not independently predictive after adjusting for CRP, lipid status, and other traditional risk factors. Inhibition of Lp-PLA<sub>2</sub> in animal models has been shown to be effective in reversing atherosclerosis in animal models [49], and phase II trials of SB-480848, a specific Lp-PLA<sub>2</sub> inhibitor, as a potential treatment of atherosclerosis are currently underway.

#### *CD40 ligand*

CD40 ligand (CD40L) is a transmembrane protein expressed on CD4+ T cells, macrophages,

and activated platelets. Its interaction with the CD40 receptor on endothelial cells, smooth muscle cells, and phagocytes has been shown to stimulate expression of proinflammatory cytokines, cellular adhesion molecules, matrix metalloproteinases, and procoagulant tissue factor [50]. Furthermore, CD40 ligand has a KGD sequence that is a known binding motif for platelet integrin  $\alpha$ IIb $\beta$ 3. T cells expressing CD40L are found in atherosclerotic plaques [51], and disruption of the CD40-CD40L interaction in vitro diminishes atheroma formation and promotes stabilization of the established plaque [52].

Biologically active soluble CD40L (sCD40L) released from stimulated lymphocytes can be measured in plasma. Healthy women who have high levels of sCD40L have been shown to be at increased risk for cardiovascular events [53]. In patients who have ACS, sCD40L elevation ( $>5 \mu\text{g/L}$ ) correlated with increased 6-month mortality (18.6% versus 7.1%,  $P < .001$ ) [54]. Treatment of these patients with abciximab before coronary angioplasty reduced risk for death or nonfatal MI (hazard ratio 0.12; 95% CI, 0.08–0.49;  $P < .001$ ). However, patients who had lower levels of sCD40L did not experience the same treatment benefit. Among troponin-negative patients, those who had elevated sCD40L had an increased risk for cardiac events (13.6%) similar to that of patients who were troponin-positive (14%). Treatment of these patients with abciximab also reduced risk for cardiac events (5.5% versus 13.6%,  $P = .03$ ).

### Selectins

Selectins (P-selectin, E-selectin) and cellular adhesion molecules (VCAM-1, ICAM-1) mediate the initial leukocyte rolling along the endothelium and attachment/subintimal transmigration, respectively, that are the initial steps of atherosclerosis. Immunohistochemical studies have demonstrated expression of these molecules, stimulated by oxidized LDL, in the endothelium overlying the atherosclerotic plaque. Circulating levels of VCAM-1, ICAM-1, and P- and E-selectin have been detected in plasma and are thought to arise from proteolytic cleavage from endothelial cells, particularly during inflammatory conditions [55]. In a nested case-control analysis of the Physicians Health Study, risk for future MI was 60% higher in patients who had soluble ICAM-1 elevation, and this increased risk was independent of smoking status or lipid levels [56]. Elevated baseline soluble

P-selectin levels in healthy women in the Women's Health Study were also associated with increased cardiovascular risk [57]. The levels of ICAM-1 and E-selectin, but not VCAM-1, have been shown to correlate with atherosclerotic burden as measured by carotid ultrasound, suggesting the usefulness of circulating adhesion molecules as indicators of subclinical disease [58]. Despite these intriguing data, the challenges of sample handling (samples are unstable unless frozen) currently limit the clinical usefulness of these markers.

### Serum amyloid A

Like CRP, serum amyloid A (SAA) is an acute-phase protein that is synthesized in the liver in response to stress, injury, or inflammation. During the acute phase, SAA becomes the predominant apolipoprotein on HDL cholesterol, thus altering HDL-mediated cholesterol delivery to cells [59]. In the Women's Ischemia Syndrome Evaluation study of women referred for coronary angiography for suspected myocardial ischemia, SAA level correlated with 3-year risk for cardiovascular events and with angiographic severity of CAD [60].

### Interleukin-10

IL-10 is a cytokine whose function is to limit the inflammatory reaction once the pathogen is eliminated. Its effects on macrophages include down-regulation of proinflammatory cytokine production and adhesion molecule expression. It also inhibits synthesis of matrix metalloproteinases implicated in plaque destabilization [61]. Overexpression of human IL-10 compensates for the rapid atherosclerosis of LDL-receptor knockout mice [62]. A small study in the United Kingdom showed higher IL-10 levels in patients who had stable versus unstable coronary syndrome [63].

### Markers of ischemia

Commonly used biomarkers such as creatine kinase (CK), CK-MB, and troponin are not detected in blood until several hours after symptom onset, and their presence is almost always correlated with myocardial necrosis. The challenge is to identify patients who develop symptoms of ischemia, such as plaque rupture with partial occlusion of the vessel lumen, before myocyte death. In this early stage of ACS, traditional

biomarkers are not yet detectable in blood. Recent efforts have focused on identifying new markers of ischemia. The main difficulty is the lack of a gold standard to diagnose myocardial ischemia, and many studies rely on clinical diagnosis with inconsistent objective data end points.

#### *Ischemia modified albumin*

Human serum albumin is a complex protein with an N-terminus capable of binding metals such as cobalt. During ischemic events, free radicals are released, resulting in acetylation of the N-terminus and alteration of the cobalt binding site. Therefore, ischemia-modified albumin (IMA) is unable to bind cobalt, and the free metal can be detected using a specific assay. The higher the amount of free cobalt detected, the greater the degree of ischemia [64]. The advantage of this test is that IMA becomes positive within a few minutes of the ischemic event. A positive test despite negative troponin places the patient at high risk for a cardiac event [65]. It has a sensitivity of 83%, specificity of 69%, negative predictive value (NPV) of 96%, and a positive predictive value (PPV) of 33%. Sensitivity increases to 92% when combined with positive ECG findings, and 95% when combined with positive troponin and ECG. Conversely, a combination of negative IMA, negative troponin, and negative ECG has 99% NPV of a cardiac event [66]. Rapid hepatic clearance (6 hours) allows specificity for an acute event, but the main disadvantage is that IMA is not specific for cardiac ischemia; any ischemia can result in a positive test [67]. It can also be elevated in patients who have cancer, acute infections, cirrhosis, and end-stage renal disease.

The Food and Drug Administration recently approved the Albumin-Cobalt Binding Test, which measures ischemia-modified albumin, for use in evaluating patients who have suspected myocardial ischemia. In its labeling, this test is intended to be used in conjunction with troponin testing and ECG evaluation to facilitate risk stratification of patients who have chest pain or other symptoms of suspected ischemic origin. Based on its sensitivity and specificity profile and excellent NPV, a negative ischemia-modified albumin level in conjunction with a negative troponin and nondiagnostic ECG can rule out ACS in low-risk patients. Thus, it is ideal for use in chest pain units. The results of an ongoing prospective study are expected to provide more information on the prognostic value of a positive IMA result.

#### *Unbound free fatty acid*

Unbound free fatty acid (u-FFA) is a new marker recently found to be elevated in patients who have ACS before more traditional biomarkers become positive. It is thought to be released as a marker of ischemia and plaque instability, with greater than 90% sensitivity [68]. In patients undergoing PCI, the elevation of u-FFA correlated with ST-segment changes and PCI-induced transient ischemic changes [69]. The clinical applicability of this test still needs to be determined and validated in a larger population.

#### *B-type (brain) natriuretic peptide*

B-type natriuretic peptide (BNP) is a peptide hormone released from cardiac ventricles in response to myocardial stretch or increased wall tension. Its actions include vasodilation, natriuresis, and inhibition of the renin-angiotensin aldosterone and sympathetic nervous systems [70]. BNP is produced as a prohormone, pro-BNP, which is enzymatically cleaved into BNP and N-terminal pro-BNP (NT-pro-BNP). Initially identified as highly sensitive diagnostic markers for congestive heart failure, BNP and NT-pro-BNP levels are highly correlated, although NT-pro-BNP may be slightly more sensitive for ventricular dysfunction. BNP and NT-pro-BNP have been found to predict increased mortality independently of left ventricular function when elevated in patients who have acute MI and unstable angina [71–73]. In patients who have unstable angina or non-ST-elevation MI, a BNP greater than 80 pg/mL was associated with angiographically tighter culprit lesions or left anterior descending coronary artery involvement, implicating more severe ischemia as a cause of increased mortality [74]. However, the role of BNP levels in terms of therapy decisions in ACS is still unclear. In the Treat Angina with Aggrastat and Determine Cost of Therapy with Invasive or Conservative Strategy (TACTICS-TIMI 18) population, an elevated baseline BNP did not predict significant benefit from an early invasive management strategy [75]. However, in the FRISC II study, baseline NT-pro-BNP in concert with IL-6 elevation were useful for identifying patients who derive survival benefit from an early invasive strategy [76].

Recent data have shown that BNP is elevated in the setting of myocardial ischemia even in the absence of necrosis. Plasma NT-pro-BNP levels are higher in patients who have unstable angina compared with age-matched controls who have

stable angina or no coronary disease [77]. Patients who have stable CAD and BNP elevation are more likely to have inducible ischemia on exercise treadmill testing [78]. BNP increases transiently after exercise in patients who have stable CAD and is correlated with size of ischemic territory as assessed by single-photon emission computed tomography [79]. In patients undergoing PCI, plasma BNP levels increase immediately after balloon inflation [80] and remain elevated 24 hours postintervention independent of intracardiac filling pressures [81].

Experimental studies confirm that acute cardiac hypoxia induces BNP expression in the ventricular myocardium [82] and BNP is released in the setting of coronary artery occlusion [83]. In the rat heart model, the degree of BNP elevation correlates with duration of ischemia (induced up to 20 minutes by reversible ligation of the left main coronary artery). Exogenous infusion of BNP limits infarct size in a dose-dependent manner, suggesting that BNP is released in response to ischemia such that its vasodilatory effect attenuates ischemic injury. These basic and clinical data suggest that plasma measurement of BNP and NT-pro-BNP can be useful in detecting myocardial ischemia. However, this finding still needs to be validated in larger studies.

### Markers of plaque instability or rupture

Recognition of the role of plaque rupture in the pathogenesis of cardiac ischemia has led to investigation of serum markers for plaque instability. These markers include whole blood choline levels, pregnancy-associated plasma protein-A (PAPP-A), and malondialdehyde-modified LDL.

#### *Whole blood choline*

Choline is thought to be released from leukocytes and platelets in response to activation of phospholipase D during plaque rupture. In patients presenting with symptoms of ACS and negative troponin levels on admission, an elevated choline level predicts higher risk for cardiac death, nonfatal cardiac arrest, life-threatening arrhythmias, heart failure, and future angioplasty within 30 days [84]. Furthermore, in the absence of MI, choline detects patients who have high-risk unstable angina (prolonged chest pain, ischemia-related pulmonary edema, rest pain with dynamic ECG changes, or hypotension) with a sensitivity and

specificity of 86%. Unlike troponin, choline is not a marker of myocardial cell necrosis. Its use as an early biomarker of MI is limited, with a sensitivity of 41%, specificity of 79%, PPV of 51%, and NPV of 71%. The weak association of choline with ST-elevation MI has been attributed to the possibility a different mechanism of plaque rupture, whereby rapid red thrombus formation leaves limited time for the injured endothelium and collagen tissue to activate phospholipase D [85]. Intermittent formation of nonoccluding white thrombi in the setting of unstable angina leads to phospholipase D activation in platelets and choline release. Therefore, choline may provide early detection of patients who have high-risk unstable angina, indicating subendocardial rather than transmural injury.

#### *Pregnancy-associated plasma protein-A*

Another emerging marker of plaque instability is PAPP-A, a zinc-binding matrix metalloproteinase that activates insulin-like growth factor I (IGF-I), a mediator of atherosclerosis. IGF-I induces migration of vascular smooth muscle cells, monocyte chemotaxis, and release of cytokines. Histologically, PAPP-A is abundantly expressed in ruptured or eroded plaques but not in stable plaques, suggesting a potential enzymatic role in extracellular matrix degradation and fibrous cap weakening that contributes to plaque rupture [86]. Circulating levels of PAPP-A were significantly higher in patients who had unstable angina or MI compared with patients who did not have an ACS; the areas under the receiver operating curve were 0.94 and 0.88, respectively, at the threshold level of 10 mIU/L. The sensitivity and specificity were 89.2% and 81.3%, respectively. PAPP-A levels did not correlate with markers of cardiac necrosis such as troponin and CK-MB, suggesting its role as a marker of early ischemia but not infarction [86]. In troponin-negative patients presenting with ACS, those who had elevated PAPP-A levels had a 4.6-fold higher risk for cardiovascular morbidity at 6 months compared with those who had low PAPP-A levels [87].

#### *Malondialdehyde-modified low-density lipoprotein*

During ischemic injury of the endothelium, a cascade of platelet adhesion and activation involving the prostaglandin pathway results in the release of aldehydes that bind to the apo-B100 moiety of LDL, forming malondialdehyde (MDA)-modified LDL [88]. Plasma levels of

MDA-modified LDL become elevated in patients who have ACS within the first 6 hours of symptom onset. In patients presenting with ACS, the sensitivity of admission MDA-modified LDL was 95% compared with 38% for troponin I in the diagnosis of unstable angina [89], and the specificity was 95%. The use of troponin I and MDA-modified LDL in combination achieved a sensitivity of 98%. MDA-modified LDL levels were threefold higher in patients who had unstable angina compared with those who had stable CAD. In acute MI, MDA-modified LDL is 95% sensitive when used alone, troponin I is 90% when used alone, and the combination had a sensitivity approaching 100% [89]. This evidence suggests that MDA-modified LDL, reflecting endothelial injury and plaque rupture, is useful in discriminating unstable from stable angina, in contradistinction to troponin, which helps to discriminate between unstable angina and myocardial infarction.

### Summary

Recent advances have identified many promising new molecular markers of ischemia and inflammation. Their clinical usefulness requires satisfaction of the following criteria: they must (1) be easily available, simple, and standardized assay, (2) have trial-based evidence of association with clinical end points, (3) be generalizable to various population groups, and (4) demonstrate adequate sensitivity and specificity.

There is a growing recognition of the role of hsCRP in further risk assessment, particularly in patients at intermediate cardiovascular risk and for risk stratification in patients who have ACS. However, it has limited diagnostic usefulness in chest pain patients. Ischemia-modified albumin is now available clinically to rule out acute coronary ischemia in conjunction with standard troponin and ECG evaluation, and whole blood choline and MDA-modified LDL are two markers of plaque instability that have been shown in small trials to diagnose unstable angina with good sensitivity and specificity. However, larger clinical trials will be needed to validate their clinical value.

As understanding of the pathophysiology of atherothrombosis evolves, the number of candidate markers meriting clinical consideration will increase exponentially. The hope is that these markers will permit earlier detection of disease, allowing time for interventions to circumvent

myocardial damage and other complications. The challenge for clinicians will be to integrate marker testing into practice without overwhelming, or substituting for, clinical judgment and rational decision making.

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## Exercise Testing in Chest Pain Units: Rationale, Implementation, and Results

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Although new diagnostic approaches have enhanced the evaluation of patients presenting to the emergency department (ED) with chest pain, this syndrome remains a major clinical challenge [1]. This symptom accounts for more than 8 million ED visits per year in this country, accounting for more than 2 million hospital admissions at a cost of \$8 billion for presumed acute coronary syndrome (ACS) [2]. However, a coronary event is actually confirmed in only a minority of these patients [3]. This population poses a dilemma to the clinician of inadvertent discharge of those with a life-threatening condition versus unnecessary admission for a benign process with its associated expense and the potential risks of further tests. A low threshold for admission of these patients was advocated early in the coronary care unit (CCU) era by the admonition that “patients should be admitted to the CCU solely on suspicion of having a myocardial infarction” [4]. This approach has persisted because of the focus on patient welfare as well as the litigation potential of missed ACS [5]. Inadvertent discharge of patients with ACS persists at a rate of 4% to 5% and the mortality and morbidity of this group are substantial [6]. However, a consequence of the low threshold for admission has been large numbers of unnecessary hospitalizations, suboptimal

patient management, and inefficient resource use. This problem is reflected by the recent demonstration that an appreciable number of patients with coronary artery disease (CAD) who present with acute chest pain respond to proton pump inhibitors, reflecting the gastrointestinal cause of their symptoms [7].

The development of chest pain units (CPUs) is a response to the need for a strategy to effect accurate, safe, and cost-effective management of patients presenting with possible ACS. Although their initial purpose was to facilitate rapid coronary reperfusion therapy, these units have evolved into centers for management of the lower risk population that composes the majority of patients presenting with chest pain. The latter include those without initial, objective evidence of myocardial ischemia/infarction in whom accelerated risk stratification can identify those requiring admission and those who can be safely discharged with outpatient follow-up [8–15]. A basic element of this accelerated diagnostic protocol (ADP) is stress testing after a negative initial assessment for myocardial infarction (MI) or unstable angina. The primary method of testing has been treadmill exercise electrocardiography (ECG) in the context of the ADP. Fundamental to this approach is the identification of patients with low clinical risk on presentation to the ED.

### Indicators of low clinical risk

There is abundant evidence that low risk in patients presenting with chest pain can be

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recognized on presentation and that this group neither requires nor benefits from traditional intensive care or extended observation in a monitoring unit. Lee and colleagues [16] reported that in patients admitted to rule out a coronary event, those with < 5% probability of acute MI could be identified by type of chest pain, past history, and initial ECG. Extension of this approach to over 4600 such patients demonstrated that the initial clinical assessment could distinguish those with < 1% probability of major complications [17]. The prognostic utility of the initial ECG alone in patients admitted to rule out MI was demonstrated by Brush and colleagues [18] in their report that a negative ECG on admission was associated with a 0.6% rate of serious complications during hospitalization compared with a 14% incidence in those with an abnormal ECG [18]. An earlier study indicated that a normal ECG in patients admitted for preinfarction angina predicted benign early and late outcomes in contrast to ECG evidence of ischemia, which correlated with markedly increased cardiac morbidity and mortality [19]. These findings were confirmed by Schroeder and colleagues [20] in their report that in patients in whom MI was ruled out, ECG evidence of ischemia was associated with a 1-year mortality similar to that of post-MI patients. An important concept to emerge from these studies is that although the cause of chest pain is frequently elusive, basic clinical tools provide powerful estimates of cardiac risk.

Recognition of low clinical risk stimulated alternative approaches to conventional coronary care, such as reduced time in the CCU [21,22], direct admission to a step-down unit [23], and observation in a short stay unit [24]. Recent innovations in the management of low-risk patients include guidelines, critical pathways, new serum markers of cardiac injury, novel ECG monitoring systems, early noninvasive cardiac imaging, early treadmill exercise testing, coronary calcium screening in the ED, noninvasive coronary angiography by CT and conventional coronary angiography [8–15,21].

### **Chest pain units**

Although risk is low in patients selected for admission to a CPU, it is not negligible. Contemporary CPUs (also known as chest pain observation units, chest pain emergency units, and chest pain evaluation units) provide an integrated approach to the patient with chest pain that

affords: (1) early identification of clinical risk and (2) further risk stratification of low-risk patients to identify those who require admission and those who can be discharged [8–15,21]. CPUs vary in form and may either occupy a designated structural area or function as virtual units comprising primarily personnel and process. Close coordination between ED physicians and cardiologists is an essential element for successful functioning of the unit. The strategy is based on a protocol-driven process that uses current standards of care for efficient and timely treatment in conformity with the guidelines of the American College of Cardiology (ACC) and American Heart Association (AHA) [25] as depicted in Fig. 1.

### **Accelerated diagnostic protocols**

ADPs have been increasingly used in low-risk patients, usually culminating in one of the methods of cardiac stress evaluation, depending on the results of the clinical assessment. This process usually entails 6 to 12 hours of clinical observation, serial 12-lead ECGs, continuous ECG monitoring, and measurement of serial serum markers of cardiac injury [11,13,15,21,25]. Positive findings indicate ACS (usually non-ST elevation ACS, rarely ST elevation ACS) and mandate admission for further management. Negative findings are consistent with absence of MI and no evidence of ischemia at rest. In these cases, the evaluation proceeds to a stress test to determine if the patient has inducible ischemia. Those with a positive test are admitted and those with a negative result are discharged to outpatient follow-up. Multiple methods are currently available to detect stress-induced ischemia, the most widely available and readily applicable of which is treadmill exercise testing. The utility of ADPs has been well demonstrated with this method, as indicated by its safety and the very low clinical risk in patients designated as appropriate for early discharge.

### **Development and evolution of early exercise testing**

#### *Initial recommendations*

Incorporation of treadmill exercise testing into current ADPs is a recent development based on ample data that has overcome initial concern regarding the possible hazards of this technique in potentially unstable patients. This early,

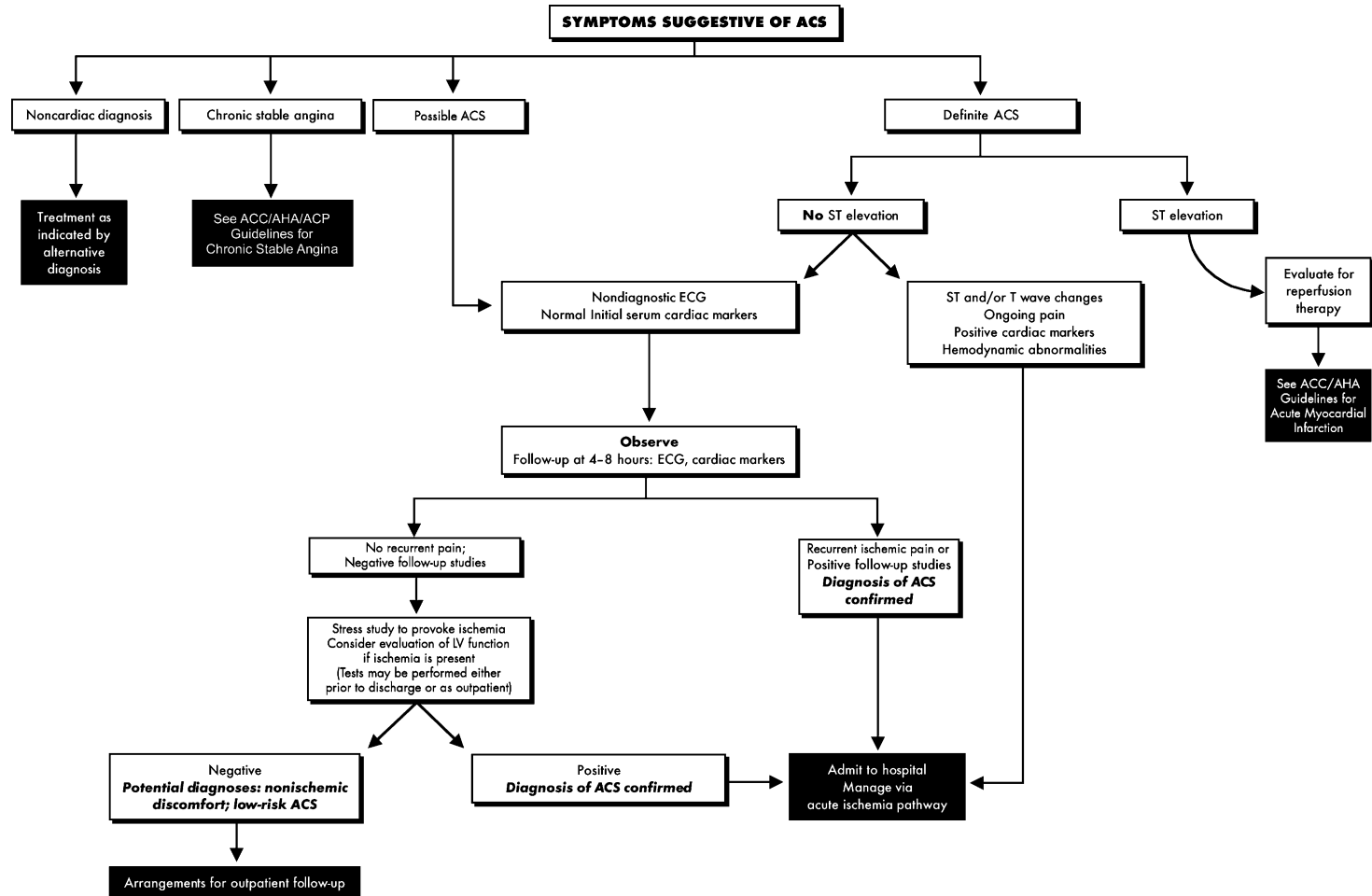


Fig. 1. Management of patients presenting with symptoms suggestive of an acute coronary syndrome (ACS). ACC, American College of Cardiology; AHA, American Heart Association. (Adapted from Braunwald E, Antman E, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST elevation myocardial infarction. <http://www.acc.org/clinical/guidelines/unstable/unstable.pdf>.)

cautionary approach and its evolution into current concepts is reflected in the progressive alteration of recommendations by expert panels that have considered exercise testing in patients presenting with possible ACS. Such caution is reflected in the Clinical Practice Guideline on Unstable Angina published in 1994 [26]. Noting that “In many cases, noninvasive stress testing provides a useful supplement to clinically based risk assessment,” this guideline recommended that “unless cardiac catheterization is indicated, stress testing should be performed in patients hospitalized with unstable angina who have been free of angina and congestive heart failure for a *minimum of 48 hours*.” The strength of the evidence for this recommendation was rated “B” (B = evidence from well conducted clinical studies but no randomized clinical trials). The report of the American College of Emergency Physicians in 1995 emphasized the efficacy of CPUs in reducing both missed ACS and unnecessary hospitalizations [27]. However, its only reference to stress testing as part of the patient evaluation was that “Many patients, upon discharge from the CPU, are scheduled for a form of testing that is reliable for identifying ischemic heart disease.” A year later, the Working Group Report of the National Heart Attack Alert Program published an extensive evaluation of technologies to detect ischemia in the ED [10]. This body concluded that “the expedited ECG exercise test may offer the benefit of an expedited workup and may reduce hospital admissions for chest pain. However, ECG exercise stress testing in the ED cannot be recommended in the absence of additional data demonstrating safety and effectiveness.” The quality of the evidence at the time of publication was rated “C,” indicating its basis in limited studies, and the test was viewed as modestly accurate with little or unknown clinical impact.

#### *Current guidelines*

Subsequent clinical studies demonstrating the safety and efficacy of exercise testing in ADPs have provided firm support for this approach. The 31<sup>st</sup> Bethesda Conference on Emergency Cardiac Care held in 1999 noted that “ADPs, including exercise testing as a key element, have been associated with reduced hospital stay and lower costs” [11]. The absence of adverse effects and the accurate identification of low post-discharge prognostic risk were also recognized. A subsequent Science Advisory of the AHA concluded that

contemporary studies “confirmed the safety of symptom-limited treadmill exercise ECG testing after 8 to 12 hours of evaluation in patients who have been identified as being at low to intermediate risk by a clinical algorithm that uses serum markers of myocardial necrosis and resting ECGs” [28]. This strategy is incorporated in the 2002 guidelines of the ACC/AHA for management of patients with non-ST elevation ACS in which it is recommended that exercise testing can be performed in stable, low risk patients if “a follow-up 12-lead ECG and cardiac marker measurements after 6 to 8 hours of observation are normal” [25]. Recent exercise testing guidelines are in accord with these recommendations [29,30]. These updated guidelines reflect evolution from earlier versions that advised exercise testing only after patients had been symptom-free for a “minimum of 48 hours” [31]. Thus, during the course of less than a decade, recommendations for exercise testing in low-risk patients progressed from admonitions for a pretest 48-hour period of clinical stability to expert consensus supporting its application after a much briefer interval.

#### *Initial studies of early exercise testing*

All studies of early exercise testing in patients presenting with chest pain have required that patients are clinically stable with no ECG evidence of ischemia/injury. The criteria for a positive test for myocardial ischemia are the standard indicators:  $\geq 1.0$  mm horizontal or downsloping ST segment shift. Other exercise-induced alterations that indicate an abnormal test and the need for further evaluation include angina, arrhythmias, and fall in blood pressure. Although the first two studies of this method included only small numbers of patients, they demonstrated the safety of exercise testing in low-risk patients in the ED setting, and the utility of this method was confirmed in multiple subsequent investigations (Table 1). There have been no reports of adverse events in any study of early exercise testing of low-risk patients.

Tsakonis and colleagues [32] evaluated 28 patients “several hours” after hospital arrival with treadmill ECG using a symptom-limited modified Bruce protocol (see Table 1). These patients had unexplained chest pain consistent with—but not diagnostic of—angina and normal baseline ECGs. The exercise test was negative in 23 patients and positive in 5. The latter group was admitted and the former was discharged. The

Table 1  
Studies of exercise electrocardiography (ECG) testing in chest pain centers<sup>a</sup>

Author	Number of patients	Percent positive tests <sup>b</sup>	Percent negative predictive value <sup>c</sup>	Percent positive predictive value <sup>c</sup>	Adverse exercise test events
Tsakonis et al [32]	28	17.8	100		0
Kerns et al [33]	32	0	100		0
Lewis and Amsterdam [34]	93	13.0	100	46	0
Gibler et al [35]	782	1.2	99	44	0
Gomez et al [37]	100	7	100	0	0
Zalenski et al [39]	224	8	98	16	0
Polanczyk et al [40]	276	24	98	15	0
Kirk et al [44]	212	12.5	100	57	0
Amsterdam et al [45]	1000 <sup>d</sup>	13	88.7	33	0

<sup>a</sup> Includes studies in which results of exercise ECG tests could be distinguished from those of other forms of stress testing.

<sup>b</sup> Positive exercise ECG.

<sup>c</sup> Based on clinical follow-up or further cardiac evaluation.

<sup>d</sup> Includes a small number of patients in Kirk and colleagues [44].

investigators reported no cardiac morbidity or mortality at 6 months in the patients with negative exercise tests. These findings were confirmed in the subsequent report of Kerns and colleagues [33] who performed exercise testing in 32 ED patients with atypical chest pain, normal ECGs, and cardiac risk factor stratification (see Table 1). Compared with similar patients admitted for evaluation of atypical chest pain, those with negative results during ED exercise testing had shorter length of stay (5.5 hours versus 2 days) and lower costs (\$467 versus \$2340). All patients in the accelerated protocol had negative exercise tests and no evidence of CAD at 6 months follow-up. In addition to their small numbers, limitations of these two studies include the very low risk of the patients (none had been designated for admission), the lack of any positive tests in Kerns' patients, and no further evaluation for CAD in Tsakanosis's patients with positive tests.

The first study of exercise testing in patients with the clinical profile of those currently included in CPU ADPs was published from the authors' institution in 1994. In this investigational protocol, selected patients presenting with chest pain who were designated for admission by ED physicians to rule out ACS underwent immediate treadmill testing (see Table 1) [34]. The study group comprised 93 patients in whom ED symptom-limited exercise testing was performed by a cardiologist using a modified Bruce protocol without prior measurement of any markers. The test was performed within a median time of less

than 1 hour from the decision to admit and in less than 24 hours in all patients. Positive tests occurred in 13% of patients, negative in 64%, and nondiagnostic (no ischemia but peak heart rate < 85% of age-predicted maximum) in 13%. Ischemic ECG changes occurred at a significantly lower percentage of age-predicted maximal heart rate (70%) in patients with true-positive tests compared with those with false-positives (>90%) (Fig. 2). No complications were associated with exercise testing. Coronary angiography revealed significant CAD in 6 of the 13 patients with positive tests, 5 of whom had multivessel involvement. A majority (54%) of the 81 patients with negative or nondiagnostic results was discharged immediately after the exercise test. At 6 months follow-up, there were no coronary events in patients with negative or nondiagnostic exercise tests. Several unique aspects of this study demonstrated the utility of early exercise testing in low-risk patients and provided the basis for the authors' current approach of "immediate" exercise testing in low-risk patients without excluding MI by a traditional series of negative cardiac serum markers. In contrast to the preceding studies, it included only patients who were assigned to admission for a traditional rule out MI protocol. In these patients, exercise testing was performed before the latter process, there were no adverse effects of testing, true and false positive tests were related to the heart rate at ST-segment depression, the majority of patients were discharged immediately after a negative or nondiagnostic test, and there were

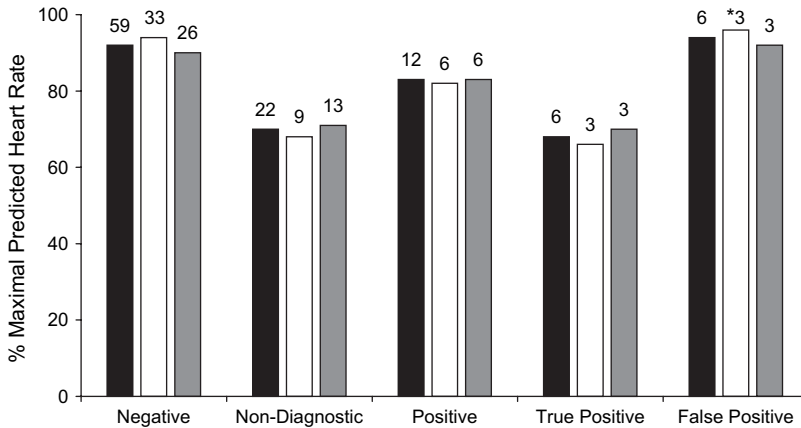


Fig. 2. Treadmill exercise results. Percent maximal predicted heart rate attained versus exercise electrocardiographic result for all patients (solid bars), men (open bars), women (shaded bars). Numbers above bars represent number of patients. \*Percent maximal predicted heart rate for patients with true-positive tests versus false-positive tests,  $P < .01$ .

no coronary events during the posthospital course. One patient with a positive test was found to have non-ST elevation MI by subsequent serial serum enzymes. Coronary angiography revealed right coronary artery disease, coronary angioplasty was performed, and the clinical course was uncomplicated.

#### Exercise testing in chest pain units

Gibler and associates [34] demonstrated the utility of early exercise testing in 782 patients in whom low risk was by an ADP (see Table 1) [35]. Their protocol included serial ECGs and serum CK-MB, 9 hours of continuous ST-segment monitoring, and a resting echocardiogram followed by symptom-limited exercise testing in those with negative findings. There were no adverse effects and no mortality at 30-day follow-up in the patients with negative tests. The negative predictive value of the exercise test was 99%. Although the positive predictive value was less than 50%, only 9 of 782 patients (<2%) had positive exercise tests, which was lower than in the authors' initial investigation [34].

Emerging from these studies [32–35] is recognition of the safety and excellent predictive value of negative exercise tests in patients identified as low risk (see Table 1). Further, a large majority of patients selected for exercise testing by an ADP had negative findings and, although the positive predictive value was modest, positive tests were infrequent and resulted in the need for further

evaluation in only small numbers of patients (see Table 1). The utility of this strategy was confirmed in its ability to safely and efficiently reduce unnecessary admissions in low-risk patients. Indeed, the relative frequency of patients with true- and false-positive exercise tests in this setting is actually similar to that seen in asymptomatic individuals [36], confirming the value of clinical indicators in identifying the probability of disease in patients presenting to the ED with chest pain [12,16,17,21,34,35].

The Rapid Rule-Out of Myocardial Ischemia Observation (ROMIO) study of Gomez and co-workers [37] was the first prospective, controlled investigation of ADP-exercise testing (see Table 1). It evaluated 100 patients with chest pain, half of whom were randomly assigned to admission for regular care and half to a chest pain center protocol consisting of a 12-hour observation period with standard ECGs, continuous ST-segment monitoring, and serial CK-MBs. Observation and monitoring were negative in 44 patients in the accelerated protocol in whom symptom-limited exercise testing was performed without adverse effects, demonstrating normal tests in 93% and positive results in 7%. The latter were all false-positives based on coronary angiography. All patients with negative tests were discharged after the exercise evaluation, and there were no coronary events at 30-day follow-up. However, compared with regular care, the observation protocol was associated with substantial reductions in length of stay (11.0 versus 22.8 hours) and total cost (\$624 per patient at 30 days). This was the first



study to document the anticipated cost savings by an observation unit protocol.

By the latter part of the last decade, the efficacy of ADP-exercise test protocols was evident for low-risk patients. However, although the potential for cost savings was suggested, this advantage had not been firmly established. Additionally, there was also the possibility, as suggested by Roberts and co-workers [38], that this strategy could actually lead to higher costs by capturing very low-risk patients who would previously have been discharged directly from the ED. These investigators addressed this issue in a prospective, randomized trial in which the primary outcomes were length of stay and total cost [38]. The study group comprised 165 low-risk chest pain patients enrolled in a 12-hour ADP followed by an exercise test in appropriate subjects. There were no deaths or serious complications associated with the ADP, which also resulted in fewer indeterminate evaluations than standard care (16% versus 54%,  $P < .001$ ). Length of stay and cost were significantly less for ADP patients than those receiving standard care (33 versus 45 hours,  $P < .01$ ; and \$1528 versus \$2095,  $P < .001$ ) (Table 2). Extrapolation of this cost benefit by the authors indicated a potential annual national saving of over \$238 million.

In a prospective, cross-sectional study, Zaleski and colleagues [39] evaluated 317 patients by a 12-hour ADP followed by exercise testing (see Table 1). A unique aspect of this trial was admission of all patients to obtain a diagnosis to which the ADP evaluation could be compared. Exercise testing was performed in 224 patients with negative observation data and was negative in 66%, positive in 8%, and inconclusive in 26% because of failure of patients to reach 85% of age-predicted maximal heart rate. There were no adverse effects of exercise testing. There were no follow-up data in this study, in which the accuracy of the ADP-exercise strategy was based on diagnoses obtained during admission. In combination with the

CK-MB data and serial ECGs, the exercise test had a high sensitivity (90%) and excellent negative predictive value (98%); as in prior studies, specificity and positive predictive value were low (51% and 16%, respectively). Cost analysis demonstrated a savings of \$567 per patient managed by the ADP-exercise test strategy.

The report of Polanczyk and colleagues [40] evaluated the prognostic significance of the exercise test performed within 48 hours of presentation in 276 low-risk patients admitted for chest pain (see Table 1). Twenty-six percent of these patients had a prior history of CAD. The test was performed within 12 hours in 7% of patients, at 12 to 24 hours in 45%, and after 24 hours in 48%. The Bruce treadmill protocol was used in 84% of the patients, and the modified version was used in 12%. A negative test was defined by achievement of at least 3 METs (one stage of the Bruce protocol) without evidence of ischemia. Positive tests were "those in which the results were interpreted as highly predictive of significant coronary disease or strongly positive" and "inconclusive tests were those consistent with but not diagnostic of ischemia" or without evidence of ischemia at a peak work of  $< 3$  METs. There were no adverse effects of exercise testing. The test was negative in 71% of patients, positive in 24%, and inconclusive in 5%. Outcome data were available at 6 months for 92% of the study group. Events during the follow-up period were defined as cardiac death, MI, or myocardial revascularization. During this interval, there was no mortality and the event rate in the negative exercise test cohort was 2% compared with 15% in those with positive or equivocal tests. In the negative test group, compared with those with positive/equivocal tests, there were also fewer repeat ED visits (17% versus 21%,  $P < .05$ ) and fewer readmissions (12% versus 17%,  $P < .01$ ). The negative predictive value of the exercise test was 98%; sensitivity and specificity were 73% and 74%, respectively. In addition to the documented prognostic utility of the exercise test, this study afforded other noteworthy features. The investigators demonstrated the safety of the early exercise test in patients with a history of CAD and their definition of test results yielded a low rate of inconclusive diagnoses, increasing the clinical utility of the test in clinical decision-making.

Mandatory stress testing in a chest pain center was evaluated by Mikhail and co-workers [41] for its safety, utility, and cost-effectiveness. After negative findings for myocardial ischemia/infarction,

Table 2  
Primary outcomes

Outcome	ADP (n = 82)	Control (n = 83)	P
Hospitalized, %	45.1	100	$< .001$
Total cost, mean	1528	2095	$< .001$
LOS, mean, h	33.1	44.8	$< .01$

Abbreviations: ADP, accelerated diagnostic protocol; CI, confidence interval; LOS, length of stay.

a total of 424 patients underwent cardiac stress evaluation, which included 247 exercise treadmill tests. The remainder of the tests included stress imaging studies; no data are given on the results of the separate test modalities. The tests were negative in 392 (92.6%) patients, and average stay in the CPU was 12.8 hours. At 5 months follow-up, there was no mortality or MI in any of the patients discharged after a negative evaluation. A final diagnosis of ischemic heart disease was made in 44 patients admitted from the chest pain center, 24 (55%) of whom were identified only on stress testing with which there were no adverse effects. Evaluation in the CPU with mandatory stress testing was associated with a cost-per-case saving of 62% for each patient who would otherwise have been admitted to the inpatient service.

The largest and most recent prospective, randomized trial comparing management by an ADP-stress test with regular inpatient care is that of Farkouh and co-investigators [42]. They studied 424 patients with a diagnosis of unstable angina based on symptoms and considered to be at intermediate risk. Patients with ECG evidence of ischemia were excluded. The observation protocol, which included ECGs, ST-segment monitoring, and serial serum creatine kinase-MB measurements, differed from prior studies in its duration of only 6 hours. Patients with negative ADP findings who were sufficiently ambulatory underwent exercise testing while pharmacologic stress imaging was performed in the others. No adverse events occurred with the stress tests but the proportion of patients receiving the various tests is not specified. Patients with negative tests were discharged and those with positive or equivocal results were admitted. Forty-six percent of patients in the ADP-stress test group had a negative overall evaluation and were directly discharged after a median stay of 9.2 hours. At 6 months, there was no significant difference in cardiac events in the ADP-stress test group versus the regular care patients (6.6% versus 8.5%, respectively). Events were broadly defined (primary: death, MI, heart failure, stroke, cardiac arrest; secondary: any revisit to the ED or hospitalization for cardiac diagnosis or care). There were no primary events in the ADP-stress patients with negative evaluations and early discharge. The investigators emphasized that this group represented 46% of patients who ordinarily would have been admitted but in whom the accelerated protocol avoided admission. Finally, the use of cardiac procedures and hospitalization for cardiac

care during the follow-up period was significantly higher in the hospital admission patients ( $P = .003$ ), amounting to an estimated 61% increase in costs.

The impact of CPUs compared with regular hospital care was analyzed by Graff and colleagues [27] in the report of the Chest Pain Evaluation Registry (CHEPER) Study. Results were assessed in terms of the proportion of patients undergoing a complete "rule out MI" investigation, the number of missed MIs, and costs. Outcomes in over 23,000 patients managed in eight chest pain observation units were compared with results in over 12,000 patients in five studies from hospitals without these units. Although data on exercise testing were not provided in the report, the investigators note that all CPUs complied with standards of the American College of Emergency Physicians [8,43] and the Clinical Practice Guidelines for Management of Unstable Angina [26], which include recommendations on exercise testing in their management algorithms. CPUs were associated with an increase in evaluations to rule out MI (67% versus 57%,  $P < .001$ ), a lower rate of missed MIs (0.4% versus 4.5%,  $P < .001$ ) and a lower admission rate (47% versus 57%,  $P < .001$ ). The latter effect equated to a potential for 2314 admissions avoided and more than \$4 million saved.

The foregoing studies of the last decade reflect the parallel and interdependent development of chest pain centers, ADPs, and early exercise testing in low-risk patients presenting to the ED with chest pain. Integration of these methods into a protocol-driven process has firmly established the contemporary chest pain center and its capacity for safe, accurate, and rapid patient management. After a negative observation period of 12 hours or less to exclude MI and ischemia at rest, exercise testing has been feasible to detect or exclude inducible ischemia. The negative predictive accuracy of this strategy is very high (~98%) and the low positive predictive accuracy is not problematic because the frequency of positive exercise tests is low, resulting in a small number of patients requiring admission for further inpatient evaluation. Additionally, the exercise test avoids inappropriate discharge of patients not identified by the observation process. Estimates of cost-effectiveness indicate the potential for substantial savings by chest pain centers through reduction of unnecessary admissions and decrease of inadvertent discharges of ACS patients. The chest pain center is a relatively recent

development, and investigation is ongoing to determine optimal implementation of this concept, which will vary with the resources of individual institutions and the expertise and experience of the responsible physicians. In this regard, as previously noted [12–15,34], the authors have used a unique approach to the management of low-risk patients at their institution.

### Immediate exercise testing

The authors' evaluation of low-risk patients in the University of California (Davis) CPU differs from that of the previous studies in that they apply exercise testing "immediately" after identification of low-risk patients on presentation. Serial cardiac injury markers are not obtained in this selected group, as described in their first study 10 years ago [34]. Since then, more than 3000 patients have been assessed by this strategy with no adverse effects. The current approach embodies several modifications based on their continuing experience, as documented in their second study (see Table 1) [44]. In this investigation of 212 patients, those with a history of CAD were not excluded, exercise testing was performed by internists trained in this technique, who serve as attending physicians on the CPU, and cardiac injury markers were not obtained before testing. Strict selection criteria for exercise testing included, as before, absence of hemodynamic dysfunction or cardiac arrhythmias, normal or near-normal ECGs, and no evidence of a noncardiac cause of chest pain on screening examination (Box 1). Symptom-limited treadmill exercise was performed by a modified Bruce protocol with the following endpoints: ischemic ST-segment shift (1.00 mm horizontal or downsloping depression 60 to 80 msec after the J point), symptoms, or arrhythmias, any of which is an indication for immediate termination of the test (Box 2). Negative exercise tests were obtained in 59% of patients, positive in 13%, and nondiagnostic in 28% (negative exercise ECG but failure to reach  $\geq 85\%$  of age-predicted maximum heart rate). Patients with positive tests were admitted and all patients with negative exercise tests and 93% with nondiagnostic results were discharged directly from the ED. In the latter group, the decision to discharge was based on achievement of adequate functional capacity (eg,  $\geq 2$  stages of the Bruce protocol or  $\geq 75\%$  of maximum predicted heart rate). Further evaluation

#### Box 1. Selection criteria for immediate exercise test

Chest pain suspicious for myocardial ischemia  
 Able to exercise  
 ECG normal, minor ST-T changes, or no change from previous abnormal ECG  
 Hemodynamically stable, no arrhythmia  
 A single negative serum marker is measured in selected patients

demonstrated CAD in 57% of those with a positive test and 30-day follow-up revealed no mortality or morbidity in the negative or nondiagnostic groups. This study demonstrated the safety of proceeding to exercise testing in carefully selected patients on the basis of the initial presentation without serial ECGs or cardiac injury markers. However, its limited numbers required a larger patient population for confirmation of the feasibility of this strategy.

In the largest single center study of exercise testing in low-risk patients, the authors reported results in 1000 patients (see Table 1) [45]. This study incorporated their current approach, which includes confirmation of a single negative cardiac

#### Box 2. Immediate exercise test procedure and end-points

Modified Bruce treadmill protocol<sup>a</sup>  
 Symptom-limited  
 Other end-points  
 Ischemia ( $\geq 1.0$  mm ST segment shift for 80 msec after the J point)  
 ↓ Blood pressure ( $\geq 10$  mm Hg systolic)  
 Significant arrhythmia (sustained supraventricular tachyarrhythmia; high-grade ventricular ectopy [ $\geq 2$  consecutive beats, sustained bigeminy])  
 Positive result:  $\geq 1.0$  mm horizontal ST segment shift  
 Nondiagnostic result:  $< 85\%$  maximum predicted heart rate with no ST shift

<sup>a</sup> Includes two initial 3-minute states (1.7 mph, 0% grade and 1.7 mph, 5% grade) before the standard Bruce protocol.

injury marker before exercise testing. Almost two-thirds of the patients had negative immediate exercise tests, approximately 13% were positive and less than 25% were nondiagnostic (Fig. 3). There was no mortality during the 30-day follow-up interval. The negative predictive value for a cardiac event was 99.7% at 30 days. In the nondiagnostic group, all events were accounted for by revascularization in 32% of the 79 patients who had further evaluation. The positive predictive value of the exercise test was 33% for a cardiac event (four non-Q MIs detected after admission, 12 myocardial revascularizations) or a confirmatory imaging test for CAD (two patients). These results extended the authors' previous findings to a large, heterogeneous population in that testing was uncomplicated, the bulk of patients had negative tests and could be released directly from the ED, negative predictive value was excellent, and the low positive predictive value involved a relatively small group with positive exercise tests. The safety and accuracy of this method has been confirmed in patients with known CAD by a specific study of immediate exercise testing of 100 consecutive patients with this disease [46]. Although exercise testing is considered to have limited value in women, the authors' experience has confirmed the reliability of a negative immediate exercise test in this group. The negative predictive value of the test was 99% in 661 women with a mean age of 54 years studied in the CPU [47].

#### Comparison of exercise testing and myocardial scintigraphy

The utility of myocardial scintigraphy has been well established in patients presenting with chest pain [48]. However, the cost and logistics of this

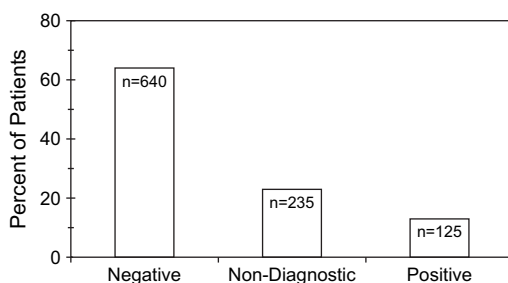


Fig. 3. Proportion of 1000 patients with negative, positive, and nondiagnostic immediate exercise tests. Numbers in bars indicate number of patients.

method are prohibitive for many institutions. In this regard, the authors have shown that > 70% of low-risk patients presenting with chest pain qualify for immediate exercise testing and that more complex and expensive stress imaging techniques can be appropriately reserved for the remainder of patients [49]. Moreover, a comparative study of 239 low risk patients by Senaratne and colleagues [50] revealed that early treadmill testing was as informative and more cost-effective than scintigraphy in identifying low-risk patients who did not require hospitalization. In this study, in which the follow-up period was 20 months, exercise testing was applicable in all but 9.6% of patients. These investigators report that, compared with scintigraphy as the initial cardiac study, exercise testing yielded a savings of more than \$86,000 in this group of patients. In contrast to our strategy in which noncardiologists assess patients and perform immediate exercise testing, with cardiology consultation available as required, Senaratne and colleagues [50] emphasize the essential role of cardiologists in these processes. In this regard, the expertise of the authors' noncardiology CPU physicians in performing exercise testing has been confirmed by their accuracy in test interpretation and the complete absence of complications [51]. Analysis of 645 immediate exercise ECGs revealed a concordance of greater than 98% between the interpretations of these physicians and the authors' staff cardiologists.

#### Immediate exercise testing in special groups

The authors have recently explored a number of other issues presented by early exercise testing in patients presenting with chest pain. The use of beta-blockers or rate-limiting calcium channel-blockers often precludes diagnostic exercise testing because of attenuation of exertional heart rate by these agents. These drugs are associated with reduction of peak exercise heart rate and rate-pressure product, resulting in an increased frequency of nondiagnostic tests compared with patients not receiving these agents [52]. However, a majority (>60%) of patients taking these medications did have a diagnostic test. Therefore, it is our experience that use of these drugs should not preclude early exercise testing.

Recent trials of non-STE ACS have demonstrated the prognostic importance of multiple clinical factors in patients presenting with this diagnosis, including elevated cardiac injury markers, ST-segment deviation, age  $\geq$  65 years,

$\geq$  three coronary risk factors, known CAD,  $\geq$  two anginal episodes in the previous 24 hours and aspirin use in the previous 7 days. These factors comprise the TIMI risk score for prediction of fatal and nonfatal coronary events, which increase directly with the number of these risk factors [53]. However, in patients presenting to their CPU, the authors have found that, with the exception of elevated cardiac injury markers and ST-segment deviation, both of which preclude exercise testing, the test can be safely performed for reliable risk stratification regardless of the presence of the other TIMI risk factors [54]. Because it has recently been reported that augmenting the standard exercise ECG with additional leads enhances its sensitivity for detecting ischemia [55], the authors evaluated this innovation in their CPU patients. In this setting, the addition of four leads (two posterior and two right-sided) to the standard 12-lead ECG enhanced the sensitivity of the test minimally without altering specificity [56]: sensitivity rose only minimally from 7.6% to 8.0% based on detection of two patients who were positive only in the additional leads compared with 37 patients with positive findings in the standard exercise ECG. These additional leads were also not useful in detecting ischemia or injury in the resting ECG in patients admitted to the CPU [57]. In a study of 2021 patients referred for elective outpatient treadmill testing, the authors also found that the 16-lead exercise ECG did not afford increased sensitivity in this setting [58], thereby failing to confirm the prior study of Michaelides and colleagues [55].

A notable aspect of the authors' CPU experience has been the high recidivism rate of patients discharged from the unit with a negative evaluation. During a 7.5-year period, 13% of 1960 patients had  $\geq$  two or more negative immediate exercise tests and accounted for 26% of the CPU visits [59]. Further, of the latter group, almost 10% had  $\geq$  four negative exercise tests during this period. The multi-exercise test patients were relatively young (mean age 52 years) and most of them were women. Beyond the traditional differential diagnosis of multiple somatic causes of chest pain [60], common and underdiagnosed conditions responsible for this symptom include anxiety syndromes and somatoform disorders [11,60–62].

#### *Further issues*

Several aspects of the authors' application of immediate exercise testing in CPU patients

warrant comment. As previously noted, patients in whom this method is used are carefully screened to confirm their low-risk status, as outlined in Box 1. The test is terminated at the initial appearance of any abnormality (see Box 2). Although noncardiologists perform the clinical assessment and exercise tests in CPU patients, these specially trained physicians have ready availability of consultation by staff cardiologists. In regard to the relatively large proportion ( $>20\%$ ) of patients with nondiagnostic tests (negative but peak heart rate  $< 85\%$  of predicted maximum), the authors have found that those with negative tests at  $\geq 80\%$  of maximum predicted heart rate had uneventful outcomes on follow-up [45]. Therefore, use of this lower heart rate for a diagnostic test for the purpose of risk stratification appears prudent and would reduce the nondiagnostic group by 25% [45]. Although follow-up is only 30 days, the purpose of this approach is to determine short-term risk. This strategy is predicated on timely follow-up and further outpatient evaluation. Finally, although clinical assessment is basically reliable in identifying low-risk patients, it is imperfect and can result in inadvertent exercise testing in patients with ACS. This possibility is minimized by physician expertise and experience together with continued caution in the selection of patients for testing and in the indications for test termination.

A recurrent question concerns the necessity of performing exercise testing before discharge after a negative ADP rather than a short time after discharge. The former approach provides the most efficient completion of the evaluation and obviates concern regarding lack of return of patients for the outpatient test, which would contribute to the hazard of incomplete assessment and missed ACS [6]. However, where testing is not feasible and the system and patient characteristics are conducive to early return for testing (within 48 hours), it is reasonable to consider this approach. The authors have discharged selected very low-risk patients from their CPU without a pre-discharge exercise test. They have specifically studied this approach in a group of very low-risk women presenting to the ED with chest pain who were less than 50 years old, nondiabetic, and nonsmokers [63]. Of the entire group of 346 women, 175 were discharged from the CPU without exercise testing. At 30 days follow-up, none of these patients had confirmatory evidence of CAD or ACS. The results suggest that the risk of ACS is very minimal in women with low-risk profiles

who present with chest pain and that stress testing in the CPU may not be necessary to determine disposition in these patients. These findings have implications for optimal use of limited resources.

### Summary

CPUs are now established centers for assessment of low-risk patients presenting to the ED with symptoms suggestive of ACS. ADPs, of which treadmill testing is a key component, have been developed within these units for efficient evaluation of these patients. Studies of the last decade have established the utility of early exercise testing, which has been safe, accurate, and cost-effective in this setting. Specific diagnostic protocols vary, but most require 6 to 12 hours of observation by serial ECGs and cardiac injury markers to exclude infarction and high-risk unstable angina before proceeding to exercise testing. However, in the CPU at UC Davis Medical Center, the approach includes "immediate" treadmill testing without a traditional process to rule out MI. Extensive experience has validated this approach in a large, heterogeneous population. The optimal strategy for evaluating low-risk patients presenting to the ED with chest pain will continue to evolve based on current research and the development of new methods.

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## Imaging in the Evaluation of the Patient with Suspected Acute Coronary Syndrome

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Over the last decade, major advances have been made in the treatment of acute coronary syndromes (ACSs). However, effective implementation of these treatments requires timely and accurate identification of the high-risk patient among all those presenting to the emergency department (ED) with symptoms suggestive of ACS. In the patient population presenting with a diagnostic ECG or those who have typical chest pain and a history of coronary disease, the initial triage and treatment strategies are straight-forward and guideline driven. However, for most patients the diagnosis is not clear-cut and further evaluation is required. The population of patients considered low risk after the initial evaluation accounts for nearly two thirds of ED chest pain patients [1,2], representing as many as 4 million patients a year in the United States. An additional consideration is that the opportunity for improving outcomes is time-dependent, so that early identification of the patient who has true ACS is essential. This necessity further increases the need for rapid triage tools, especially in the current setting of ED and hospital overcrowding that has become the norm in large urban centers.

In an effort to better identify patients who do not have myocardial ischemia, ED physicians have increasingly relied on technological advances, such as new bedside biomarkers and advanced imaging techniques. As these tools have become more available in the ED, triage decisions can

be made with more rapid and comprehensive information. Advantages of rapid, accurate diagnosis are obvious and include early initiation of appropriate therapy for those who have myocardial infarction (MI) or unstable angina; reduction in the inadvertent discharge of patients who have ongoing ischemia; and shortened length of stay and reduced admissions for patients who have noncardiac chest pain.

Before implementing a new diagnostic tool or test, several questions require an affirmative answer, including whether it is accurate (ie, sensitive and specific), if it adds incremental diagnostic information to that which is already available, and if it is cost-effective. Over the last 15 years, numerous studies examining the usefulness of acute ED myocardial perfusion imaging (MPI) have confirmed that the answer to these questions is “yes.”

### Acute myocardial perfusion imaging

Knowledge of the ischemic cascade presupposes that “in vivo” noninvasive imaging of myocardial perfusion should provide an optimal technique for not only detecting (diagnosis) but also grading (risk stratification) ACS. This presumption is confirmed by studies dating back over 3 decades. Wackers and colleagues [3] and others used planar myocardial perfusion imaging with thallium in the 1970s to demonstrate that acute imaging had significant incremental diagnostic power in patients who had non-ST-elevation ACS [4]. However, the intrinsic characteristics of thallium as a radiotracer and the inherent

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limitations of planar imaging prevented widespread adoption of the technique in the clinical management of ACS. Although some of the issues related to the radionuclide could be mitigated by performing imaging immediately in the ED [5,6], the limitations of planar imaging required improvements in technology to overcome the low sensitivity for detecting small areas of ischemia and for detecting ischemia in the posterior distribution. The development of single-photon emission computed tomography (SPECT) in combination with the superior image quality provided by technetium-labeled myocardial perfusion agents led to observational studies followed by clinical trials demonstrating the usefulness of acute ED MPI. Technetium 99m (Tc-99m) sestamibi and tetrofosmin are taken up by the myocardium in proportion to blood flow, similar to thallium, but do not undergo significant redistribution [7]. Therefore, patients can be injected while experiencing symptoms and imaged up to several hours later, making it possible to perform high-quality SPECT imaging outside of the ED setting in the absence of dedicated equipment.

The favorable energy and dosimetry of Tc-99m also allow gated acquisition and reconstruction of dynamic functional images, thereby providing simultaneous assessment of regional and global ventricular function that can be correlated with perfusion defects [8]. In the setting of acute infarction or ischemia, wall motion is typically abnormal; in contrast, an apparent perfusion defect in the presence of normal wall motion and thickening on gated SPECT usually indicates an artifact such as tissue attenuation. The ability to perform simultaneous wall motion and perfusion significantly improves specificity [9,10] and is particularly valuable in the acute setting where serial images are not available.

In the presence of significant ischemia, the concomitant presence of a wall motion abnormality in conjunction with perfusion defects on acute imaging not only adds specificity but is an additional prognostic indicator. Recent data indicate this is true. A recent multicenter study by Kaul and colleagues [11] found that perfusion plus regional function provided substantially greater diagnostic and prognostic value for predicting outcomes in 163 patients who had possible ACS. In our study of 2286 consecutive patients who were admitted for exclusion of ischemia following acute rest MPI, we found that among the patients who had Troponin-I (TnI) elevations (4.0% versus 3.5%), creatine kinase-myocardial band (CK-MB) MI (1.7% versus 1.5%), or who underwent revascularization (5.6% versus 5.1%), there was no difference in the proportion of patients who had perfusion defects but had normal wall motion in that area and those who had normal perfusion and function. In contrast, those who had perfusion defects associated with abnormal wall motion were significantly more likely to have TnI elevations (15%), CK-MB MI (10%), and undergo revascularization (16%).

### Diagnostic value

#### *Sensitivity: acute myocardial infarction*

Several studies to assess the diagnostic accuracy of acute ED MPI have found a high sensitivity for identifying patients who have MI (Table 1) [3,12–18]. However, because acute MPI is performed predominantly in low-risk patients, the absolute numbers of patients who have MI in any individual study is small, resulting in an imprecise measurement of sensitivity. In a study that included 141 patients who had CK-MB MI, we found that sensitivity was 89% (95%

Table 1

Diagnostic accuracy of rest myocardial perfusion imaging in patients who have acute chest pain syndrome and normal or nonischemic rest electrocardiograms

	Year	N	Tracer	Sensitivity	Specificity	NPV	End point
Wackers et al [3]	1979	203	Tl-201	100%	72%	100%	AMI
Varetto et al [12]	1993	64	Tc-mibi	100%	92%	100%	CAD
Hilton et al [13]	1994	102	Tc-mibi	94%	83%	99%	CAD/AMI
Tatum et al [14]	1997	438	Tc-mibi	100%	78%	100%	AMI
Kontos et al [15]	1997	532	Tc-mibi	93%	71%	99%	AMI
Heller et al [16]	1998	357	Tc-tetro	90%	60%	99%	AMI
Kontos et al [17]	1999	620	Tc-mibi	92%	67%	99%	AMI
Udelson et al [18]	2002	1215	Tc-mibi	96%	NR	99%	AMI

*Abbreviations:* AMI, acute myocardial infarction; CAD, angiographic coronary artery disease; NPV, negative predictive value; NR, not reported; Tc-mibi, Tc-99m-sestamibi; Tc-tetro, Tc-99m-tetrofosmin; Tl-201, thallium 201.

confidence interval, 83%–94%), similar to prior reported studies. As would be expected, patients who had negative MPI had small MIs as estimated by peak creatine kinase (CK) values, with an average CK of  $313 \pm 227$  U/L, compared with  $590 \pm 620$  U/L ( $P < .001$ ) in those who had positive MPI [19].

Another confounding issue with these studies is that most used elevations in either CK or CK-MB as the diagnostic standard for MI. However, because of its high sensitivity and specificity for detecting myocardial necrosis [20,21], current guidelines recommend that cardiac troponin be the diagnostic standard for MI [22]. Because approximately 3% to 4% of the left ventricle must be ischemic to allow detection by MPI [23], the number of patients who have troponin elevations and negative MPI would be expected to be higher than the previous standard. This assumption has been supported by several small studies that reported that, although the sensitivity of MPI was high, it was significantly lower than that of TnI or Troponin-T [17,24]. In a larger study, we analyzed outcomes in 319 patients who were initially considered low risk for MI and underwent acute rest MPI as part of standard chest pain evaluation protocol and were subsequently found to have elevated TnI values [25], thus meeting the ACC/ESC definition for MI [22]. Seventy-seven patients had negative MPI, giving a sensitivity of only 76%; much lower than when CK or CK-MB was used as the diagnostic standard for MI. However, among the 77 patients who had negative MPI, more than half ( $n = 47$ , 61%) had a peak CK-MB of more than 8 ng/mL and therefore would not previously have been diagnosed with MI (Fig. 1). Patients who had negative MPI had significantly lower peak CK-MB values ( $15 \pm 25$  ng/mL versus  $45 \pm 78$  ng/mL,  $P < .001$ ), had higher ejection fractions ( $56\% \pm 15\%$  versus  $47\% \pm 13\%$ ,  $P < .01$ ), and were more likely to have nonsignificant disease (60% versus 85%,  $P < .001$ ) than those who had positive MPI. These findings demonstrate that acute MPI continues to provide additional risk/prognostic information even with the introduction of a newer generation of biomarkers.

#### *Acute coronary syndrome without myocardial infarction*

In the past 15 years, a large body of evidence has demonstrated that acute MPI using Tc-99m myocardial perfusion agents can accurately

identify patients who have unstable angina. In one of the first studies, Bilodeau and colleagues [9] imaged 45 patients who did not have a previous history of MI and had been admitted for unstable angina. The presence of a perfusion defect had a sensitivity of 96% and specificity of 79% for predicting angiographic coronary disease in patients injected during an episode of pain, compared with a sensitivity of only 65% for the ECG. Although specificity of acute MPI appears low when MI is used as the end point, an important advantage is to remember that the entire continuum of ACS remains a diagnostic dilemma. Using revascularization or significant disease as a surrogate for unstable angina, abnormal images are found in a high proportion, and overall specificity and predictive value are increased. For example, we found that in 532 patients admitted after acute rest MPI in the ED, acute MI as assessed by CK-MB elevations was present in only 15% of patients who had positive MPI (Fig. 2) [15]. However, most patients who have positive MPI had an end point consistent with ACS, including acute infarction, subsequent revascularization, or significant coronary disease (>70% stenosis) on coronary angiography.

#### **Negative predictive value and prognosis**

A high negative predictive value is critical for the value of acute MPI to serve as a risk stratification tool. The ability to exclude significant ischemia in more than 99% of patients allows effective identification of those who can be placed in lower-intensity settings other than the coronary care unit (CCU) or can be discharged home (see Table 1). The predictive value of a negative acute MPI also extends beyond the immediate setting in identifying patients at low risk for short- and long-term cardiac complications. For example, Hilton and colleagues [26] found that patients who had normal perfusion imaging had an excellent prognosis, with no late events at 90-day follow-up. Similarly, we reported that patients who had negative acute MPI had a cardiac event rate of only 3% during the subsequent year [14]. In our experience over the last 9 years, low-risk patients discharged from the ED after undergoing acute ED rest MPI ( $n = 10,775$ ) demonstrated a 30-day cardiac mortality of only 0.08%, with only nine cardiac deaths during the follow-up period.

An important prognostic parameter provided by acute MPI is that it not only identifies patients

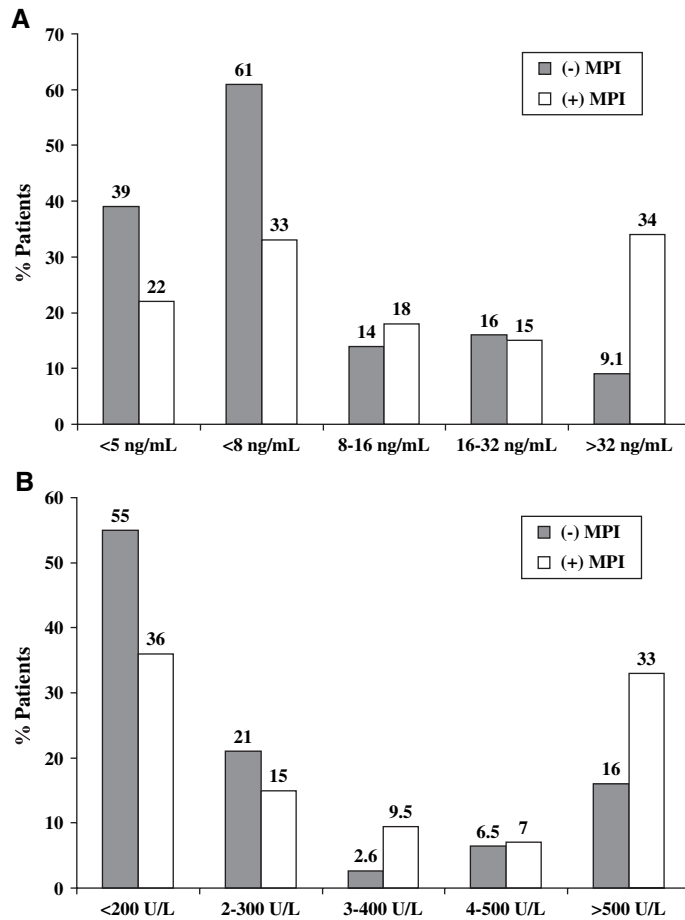


Fig. 1. Proportion of patients who had positive (*black bars*) and negative (*white bars*) rest MPI and levels of (A) CK-MB and (B) CK elevations. Of 104 patients who had creatine kinase myocardial band (CK-MB) level  $<8$  ng/mL, 61% had negative images, whereas of 192 patients who had CK-MB  $\geq 8$  ng/mL, only 27% had negative images (sensitivity 83%). (Modified from Kontos MC, Fratkin MJ, Jesse RL, et al. Sensitivity of acute rest myocardial perfusion imaging for identifying patients with myocardial infarction based on a troponin definition. *J Nucl Cardiol* 2004;11:12-9; with permission.)

who have ACS but also provides a validated measurement of the ischemic risk area. The size of a perfusion defect is of significant clinical importance, as patients who have larger defects have a worse long-term prognosis [27,28]. The most important determinant of infarct size is the ischemic risk zone or the amount of myocardium in jeopardy [29]. MPI is the only technique among those commonly available that can determine the ischemic risk zone [30,31]. In studies in which post-MI patients had MPI before discharge, defect size correlated well with other outcome predictors, including left ventricular ejection fraction [32,33], regional wall motion index [32], end-systolic volume [33], and peak CK levels [34].

Even in the absence of ischemic ECG changes, the ischemic risk area can be large. We found that the ischemic risk area ranged from 0% to 62% of the left ventricle, with a mean risk area of  $18\% \pm 11\%$ . Even patients who had normal ECGs at the time of presentation had risk areas similar to those of patients who had abnormal but non-ischemic ECGs ( $16\% \pm 12\%$  versus  $19\% \pm 12\%$ ,  $P = .25$ ) (Fig. 3) [35]. One explanation for this finding is that MI in these patients is often caused by occlusion of the left circumflex coronary artery, and the myocardial territory supplied by it is "silent" on a surface ECG [36]. In a small study that included patients who had ST-segment depression, Christian and colleagues [37] performed

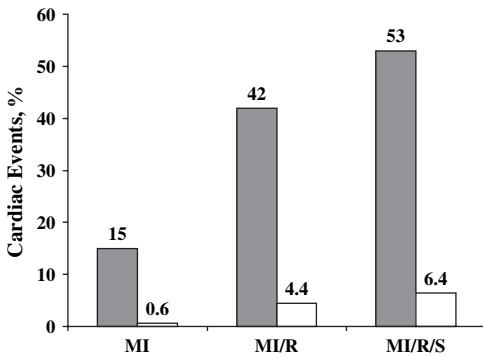


Fig. 2. Outcomes associated with results of acute rest MPI. Patients who had positive rest MPI (dark bars) had significantly ( $P < .0001$ ) more MI; MI or revascularization (MI/R); and MI, revascularization, or significant coronary artery disease ( $>70\%$  stenosis) (MI/R) or significant disease than patients who had negative rest myocardial perfusion imaging (white bars). (Modified from Kontos MC, Jesse RL, Schmidt KL, et al. Value of acute rest sestamibi perfusion imaging for evaluation of patients admitted to the emergency department with chest pain. *J Am Coll Cardiol* 1997;30:976–82; with permission.)

early MPI in 14 patients who did not have ST-segment elevation and later underwent coronary angiography. The culprit vessel was the circumflex coronary artery in six (43%) patients. In another study of 79 patients presenting with a nonischemic ECG and acute MI, we found that the left circumflex coronary artery was the infarct-related artery in 42% of the cases [35].

In patients who have left circumflex occlusions, the absence of ischemic ECG changes does not

predict small MIs [36]. O’Keefe and colleagues [38] reported that the risk area was not significantly different in patients who had left circumflex occlusion associated with ST-segment elevation, left circumflex occlusion without ST-elevation, and right coronary artery occlusion. Consistent with these results, we found that the ischemic area at risk was similar in patients in whom the infarct-related artery was the left circumflex ( $18\% \pm 10\%$ , median 19%), the right coronary ( $18\% \pm 13\%$ , median 17%), or the left anterior descending artery ( $18\% \pm 10\%$ , median 19%) [35].

### Incremental diagnostic value

Although a new test may offer high diagnostic accuracy, it may have limited value unless it provides significant incremental value over the current standard of care. Because the existing standard usually includes testing that is readily available and less expensive, the barrier to inclusion of techniques such as acute MPI is that they must demonstrate a clear benefit.

Studies performed in lower-risk patients have demonstrated that acute ED MPI does offer incremental value. In one of the first studies, Hilton and colleagues [13] used Tc-99m sestamibi SPECT imaging to study 102 patients presenting to the ED with typical angina and either a normal or nondiagnostic ECG. Seventy patients had a normal perfusion scan, only one of whom had a cardiac event. In comparison, 2 of the 15 (13%) patients who had equivocal scans and 12 of the 17 (71%) patients who had perfusion defects had cardiac events. When equivocal scans were classified as

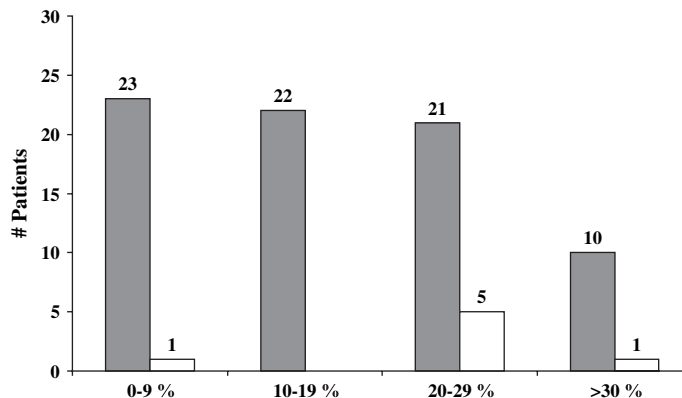


Fig. 3. Distribution of the risk area sizes as a percent of the left ventricle. Dark bars represents patients who had ECG evidence of prior infarction. (Modified from Kontos MC, Kurdziel KA, Ornato JP, et al. A nonischemic electrocardiogram does not always predict a small myocardial infarction: Results with acute myocardial perfusion imaging. *Am Heart J* 2001;141:360–66; with permission.)

abnormal, the sensitivity and specificity of an abnormal study for predicting adverse cardiac events were 94% and 83%, respectively.

Similarly, we found that abnormal MPI was the most important independent predictor of MI or revascularization in 532 patients who underwent acute ED MPI [15]. Finally, Heller and colleagues [16] found that that abnormal SPECT was the most important multivariate predictor of MI in 357 patients who underwent acute MPI. In addition, acute MPI added significant incremental diagnostic value after consideration of demographic, clinical, and ECG variables (Fig. 4).

In an interesting intent-to-treat survey study, Knott and colleagues [39] performed acute MPI on 120 patients in the ED. The requesting physician completed a questionnaire before imaging, asking what the proposed management would be had the test not been available. They found a 34% reduction in overall hospital admissions and a 59% reduction in planned CCU admissions. Overall, CCU admissions were not reduced because 17 patients initially considered low risk were admitted to the CCU after MPI was found to be abnormal.

Data from several observational studies were confirmed in the Emergency Room Assessment of Sestamibi for Evaluating Chest Pain (ERASE) study, a large prospective randomized controlled study. This study demonstrated that acute MPI was effective when compared with standard management of low-risk chest pain patients [18]. In this study, 2475 patients were randomized to

routine care or ED MPI, in which patients were injected with sestamibi in the ED and subsequently underwent acute imaging, with the results called back to the ED physician [18]. All patients, whether admitted or discharged, underwent marker analysis and diagnostic evaluation. There was no difference in the percentage of patients who had ACS and either MI (97% versus 96%) or unstable angina (83% versus 81%) who were admitted, with one patient who had MI from each group discharged from the ED. However, there was a significantly lower admission rate and a higher rate of direct discharge from the ED in the ED MPI arm compared with the standardized care arm.

## Other issues

### Radiopharmaceutical

Although most studies were performed with sestamibi, comparable results have been obtained with tetrofosmin. In a multicenter study, Heller and colleagues [16] found a sensitivity of 90% in 357 patients who underwent acute MPI. Negative predictive value (NPV) was equally high at 99%, with only two patients who had small non-Q-wave MIs having negative acute MPI. In our study in which 319 patients had TnI elevations, sensitivity of those who had acute MPI with sestamibi (75%) and tetrofosmin (80%) were similar, as was the proportion who had CK-MB MI (84% versus 87%) [16].

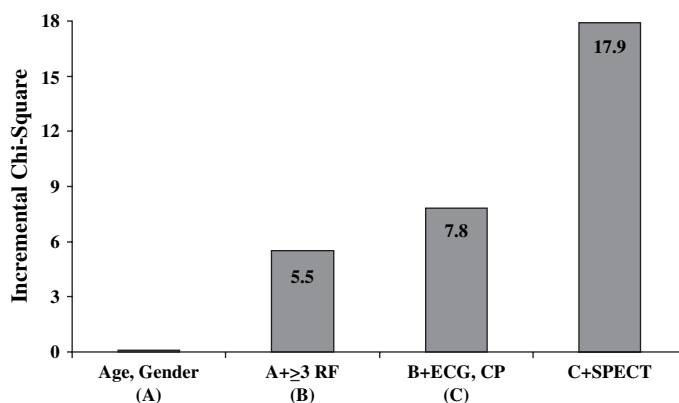


Fig. 4. Incremental prognostic value of rest tetrofosmin SPECT imaging over clinical variables. Model A: clinical variables; Model B: A plus three or more risk factors (RF); Model C: B plus admission ECG and chest pain (CP) at the time of tetrofosmin injection. (Modified from Heller GV, Stowers SA, Hendel RC, et al. Clinical value of acute rest technetium-99m tetrofosmin tomographic myocardial perfusion imaging in patients with acute chest pain and nondiagnostic electrocardiograms. *J Am Coll Cardiol* 1998;31:1011-17; with permission.)

### Comparison with troponin

Although markers of necrosis, such as troponin, are considered the gold standard for identifying MI, rest MPI does have some important advantages over using markers alone. First, myocardial markers are by definition abnormal only in patients who have necrosis, and therefore are negative in patients who have ischemia alone. Also, given the time required for imaging and processing, acute MPI results can be available within 1 to 2 hours after injection. In contrast, markers of necrosis are not detectable in the blood until several hours after the damage has occurred. To achieve a high sensitivity, sampling must be performed over an 8- to 9-hour period [40]. Thus, the sensitivity of MPI is significantly higher than that of the initial troponin (Fig. 5).

A second advantage of acute MPI is that it can identify risk area, and therefore better quantitate overall cardiac risk. For example, two patients who have similar low-peak TnI values—one secondary to occlusion of a small branch vessel and the other resulting from a brief occlusion of the proximal portion of a major vessel—have markedly different areas at risk and the potential for markedly different outcomes, which can be readily determined using MPI.

Acute MPI has some limitations when used to assess patients who have chest pain. Acute MI, acute ischemia, and prior MI all cause perfusion defects, and differentiation is not possible based on the images alone. However, patients who have

prior MI are at higher risk for acute events and are usually not candidates for primary triage to a subsequent outpatient evaluation. Sensitivity for identifying necrosis is imperfect for MPI, as at least 3% to 5% of the left ventricle must be ischemic for a defect to be detected. However, the many patients who have negative rest MPI despite marker elevations have nonsignificant disease on coronary angiography [25], and therefore are at low risk for short-term adverse outcomes, although aggressive risk factor modification would still be indicated. Therefore, rather than being seen as competitive diagnostic tools for evaluating patients presenting to the ED with chest pain, markers and MPI should be considered complementary.

### Timing of tracer injection

Although it appears that sensitivity of acute MPI decreases as the symptom-free interval increases, the reduction is highly variable. In the case of thallium, Wackers and colleagues [3] performed thallium-201 scintigraphy in 98 patients admitted with chest pain who had MI excluded. When imaged within 6 hours of the last anginal symptoms, 57% of the patients had abnormal studies; however, when imaged after 12 hours, only 8% had abnormal studies. Similar results have been reported by Van der Wicken and colleagues [4].

Studies using technetium agents also demonstrate higher sensitivity when injection is

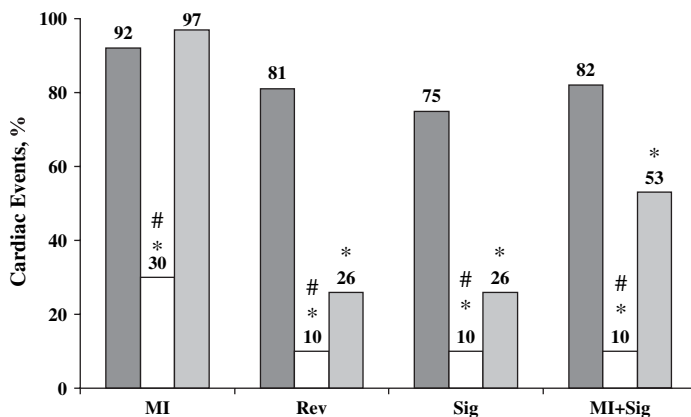


Fig. 5. Sensitivity of MPI (dark bars), the initial troponin I (open bars), and troponin I (light bars) for identifying end points. Asterisk denotes  $P < .001$  compared with perfusion imaging; # denotes  $P < .001$  compared with serial troponin. Rev, revascularization; Sig, significant disease ( $>70\%$  stenosis). (Data from Kontos MC, Jesse RL, Anderson FP, et al. Comparison of myocardial perfusion imaging and cardiac troponin I in patients admitted to the emergency department with chest pain. *Circulation* 1999;99:2073–8.)

performed during or soon after pain. Bilodeau and colleagues [9] found that the sensitivity of MPI for detection of coronary artery disease was 96% in 45 patients injected with tracer during chest pain. When the same patients were reinjected later while pain-free, the sensitivity had decreased to 65%. However, in both cases the sensitivity was significantly higher than that of the initial ECG. In contrast, we found that when patients were injected within 6 hours of symptoms, sensitivity was similar for identifying patients who had MI, revascularization, or significant coronary disease between those who were injected with and without symptoms [15]. Others have also reported high sensitivity despite the absence of symptoms during injection [12].

One explanation relates to the difference in the underlying mechanisms causing perfusion defects in patients who have ACS as compared with those undergoing stress testing. Rather than causing true ischemia, stress perfusion defects result from flow heterogeneity between areas supplied by coronary arteries with and without significant stenoses. The perfusion tracer is injected at the time of maximal flow imbalance, with a rapid return of coronary flow to baseline once the patient stops exercising. In contrast, in patients who have ACS, perfusion defects result from the combination of intermittent thrombotic occlusion and vasoconstriction in the setting of complex coronary morphology [41], resulting in marked decreased coronary blood flow [42] and persistently decreased regional myocardial perfusion [41]. Because regional hypoperfusion is one of the first steps in the ischemic cascade, symptoms of chest discomfort are often a late clinical manifestation, so that regional hypoperfusion will frequently be present even in the absence of symptoms. Suboptimal flow frequently persists despite prolonged treatment with newer pharmacologic treatments, such as glycoprotein IIb/IIIa antagonists [43,44].

Perfusion defects may also result from distal embolization of a proximal thrombus leading to downstream microvascular obstruction [45]. In a study of 75 patients who underwent sestamibi injection during rotational atherectomy, a procedure in which distal embolization of microparticles is frequent, perfusion defects were present in 65% of patients [45].

Finally, a third potential mechanism was reported in an interesting study of 40 patients who had a percutaneous intervention. Fram and colleagues [46] found that perfusion abnormalities persisted in patients injected with Tc-99m

sestamibi at varying intervals after balloon inflation, although the size of the perfusion defect decreased as the interval after the procedure increased. One explanation is that the pharmacodynamics of sestamibi are dependent on membrane and mitochondrial functional integrity, which may be depressed as a result of lingering metabolic alterations, especially in high-energy metabolites that occur after transient ischemia.

All of these findings strongly support the conclusion that the sensitivity of acute MPI will be dependent on the extent, duration, severity, and reperfusion status of the ischemic insult. It must be kept in mind that chest pain is not the gold standard for myocardial ischemia and that silent ischemia is common. In patients who have been pain-free for prolonged periods, acute MPI will have a lower sensitivity for detection of the presence of coronary disease, but persistent abnormality suggests a more complex and possibly unstable condition associated with higher risk.

### Special populations

Although not normally considered candidates for acute MPI because of their higher pretest likelihood of ischemia, rest MPIs can provide useful additional diagnostic information in selected subgroups of patients who have known coronary artery disease. This group includes patients who have a nonischemic ECG and atypical symptoms (particularly if they are different from their typical angina), those who have had a recent negative cardiac evaluation, or those in whom the risk for coronary angiography is increased, such as patients who have significant renal disease. In patients who have multivessel disease, such as those who have had prior bypass surgery, the ability to determine risk area can be used to delineate the culprit lesion.

It should be recognized that patients who have prior MI, especially those who have Q waves, are likely to have perfusion defects, and that subsequent repeat rest-imaging after a pain-free period is required to differentiate new ischemia from old infarction. Alternatively, if prior images are available, they can be used for comparison to determine the significance of perfusion defects. When deciding whether to pursue further invasive or noninvasive treatment, it has been our experience that minor differences in images when compared with prior studies are unlikely to be of clinical significance.



Another group of patients in whom ED rest MPI can be useful are those presenting with cocaine-associated chest pain. In the absence of ischemic ECG changes or known coronary disease, the risk for ACS is low [47]. Rather than admitting the patient, an alternative evaluation process is to perform rest MPI, with discharge if images are negative. We found that in 216 consecutive patients who had chest pain after recent cocaine use who underwent ED MPI, only five (2.3%) patients had abnormal studies, including two who had acute MI [48]. None of the 38 patients who had normal MPI had subsequently acute MI by biomarkers after admission to the CCU, and only 7% of the 67 patients undergoing subsequent stress MPI had reversible myocardial perfusion defects. At 30-day follow-up there were no cardiac events in patients who had normal rest MPI. This finding indicates that hospital admission can be avoided in this subgroup of patients who have a history of cocaine use if rest MPI is negative.

#### *Cost-effectiveness*

The ability to discharge patients directly from the ED has obvious cost implications. Despite the application of complex and expensive technology, ED MPI can be cost-effective if the number of patients admitted is decreased [16,49–51]. Several observational studies have confirmed that cost reductions occur when rest MPI is used as an integral part of patient management. Costs are reduced in two ways. One obvious mechanism is by discharging more patients directly from the ED, with an increase in the admission of more appropriate patients. A second mechanism is by more appropriate selection of diagnostic procedures, as the rate of coronary angiography in low-risk patients is reduced [39,49]. A preliminary analysis from the ERASE study confirms that using ED MPI as a key part of the initial diagnostic strategy was cost-effective, with costs reduced to an average of \$70 per patient [52].

#### *Incorporation into chest pain evaluation*

Recent updated guidelines for the clinical use of cardiac radionuclide imaging indicate that acute ED MPI has a Class IA indication for assessing myocardial risk in patients who have possible ACS and have nondiagnostic ECGs and negative initial serum markers and enzymes, if available [53].

In addition, recommendations for using MPI in the ED have been published [54]. The recommended patient selection criteria are similar to those used for admission to a chest pain evaluation unit. Patients should be low risk (no ischemic ECG changes or history of coronary disease) and hemodynamically stable. The optimal use of MPI as a triage tool is in patients who will be discharged home and have stress testing as an outpatient if imaging is negative.

One of the first programs to incorporate rest MPI as a strategy was at Virginia Commonwealth University Medical Center (formerly Medical College of Virginia). In contrast to most chest pain programs, the systematic chest pain protocol developed and implemented is designed for all chest pain patients, with MPI used for evaluation of lower-risk patients (Table 2) [14]. All patients presenting to the ED with chest pain or other symptoms consistent with myocardial ischemia undergo rapid evaluation with assignment to a triage level, which is based on the probability of having MI or myocardial ischemia derived from clinical and ECG variables. After the initial evaluation, patients thought to be at high risk (those who have ischemic ECG changes and those who have known coronary disease experiencing typical symptoms) and characterized as levels 1 and 2 are admitted directly to the CCU. Patients considered low to moderate risk for ACS (eg, absence of ischemic ECG changes or history of coronary disease) undergo further risk stratification using acute rest MPI [14]. Level 3 patients are admitted as observation patients and undergo a rapid rule-in protocol. Level 4 patients are evaluated in the ED. If images are either negative or unchanged from previous studies, patients are discharged home and scheduled for outpatient stress testing. If MPI is positive, they are admitted and advanced to the level 2 treatment protocol.

It is important to appreciate the difference in the role of acute rest MPI between level 3 and level 4 patients. In level 3 patients, the presence of a significant perfusion defect identifies a high-risk patient in whom early initiation of aggressive treatment is indicated, with the potential for early intervention. Negative MPI and negative markers, on the other hand, identify patients who can safely undergo early stress testing and discharge. Although the identification of higher-risk patients is the focus of much interest, the ability to better risk-stratify intermediate-risk patients into low-risk who can be stressed safely is an important advantage. In contrast, the role of MPI in patients

Table 2  
Acute chest pain diagnostic treatment pathways at Medical College of Virginia/Virginia Commonwealth University Medical Center

Primary risk assignment	Probability of AMI	Probability of ischemia	Diagnostic criteria	Disposition	Secondary risk stratification	Treatment strategy
Level 1: AMI	Very high (>95%)	Very high (>95%)	Ischemic ST elevation Acute posterior MI	Admit CCU	Serial ECGs Cardiac markers every 6–8 h until peak	Fibrinolytics within 30 min Primary PCI within 90 min
Level 2: Definite or highly probable ACS	Moderate (10%–50%)	High (20%–50%)	Ischemic ECG Acute CHF Known CAD with typical symptoms	Admit CCU Fast track rule-in protocol	Serial ECGs Cardiac Markers at 0, 3, 6, and 8 h If rule-in for AMI (markers positive) continue every 6–8 h until peak	ASA IV UFH or SC LMWH IV and/or topical NTG IV and/or PO Beta Blocker Clopidogrel GP IIb/IIIa inhibitor if TnI positive Cath/PCI
Level 3: Probable ACS	Low (1%–10%)	Moderate (5%–20%)	Nonischemic ECG and either: Typical symptoms > 30 min, no CAD, or Atypical symptoms > 30 min, known CAD,	Observation Fast track rule-in protocol	MPI Cardiac Markers at 0, 3, 6, and 8 h Serial ECGs	ASA If cardiac markers or MPI positive: treat per level 2 protocol If negative: stress
Level 4: Possible UA	Very low (<1%)	Low (<5%)	Nonischemic ECG and either: Typical symptoms <30 min, or Atypical symptoms,	ED evaluation	MPI	MPI positive: admit to level 2 treatment protocol MPI negative: discharge; schedule out patient stress
Level 5: Very low suspicion for AMI or UA	Very low (<1%)	Very low (<1%)	Evaluation must clearly document a noncardiac etiology for the symptoms	ED evaluation as deemed necessary	As appropriate for the clinical condition	As appropriate for the clinical condition

*Abbreviations:* ACS, acute coronary syndrome; AMI, acute myocardial infarction; ASA, aspirin; CAD, coronary artery disease; CCU, coronary care unit; CHF, congestive heart failure; ED, emergency department; GP, glycoprotein; IV, intravenous; LMWH, low molecular weight heparin; MPI, myocardial perfusion imaging; NTG, nitroglycerin; PCI, percutaneous intervention; TnI, troponin I; UA, unstable angina; UFH, unfractionated heparin.

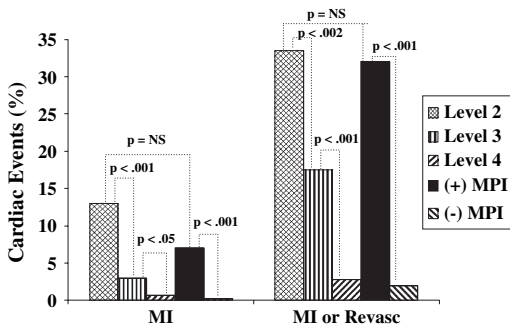


Fig. 6. Cardiac outcomes compared with the initial triage level assignment and the MPI results. The incidence of MI or MI or revascularization was significantly different among level 2 (hatched bars), level 3 (vertical bars), and level 4 (diagonal bars) patients. Patients who had positive imaging (dark bars) had an incidence of MI or MI or revascularization similar to the level 2 patients. (Adapted from Tatum JL, Jesse RL, Kontos MC, et al. Comprehensive strategy for the evaluation and triage of the chest pain patient. *Ann Emerg Med* 1997; 29:116–23; with permission.)

who are considered level 4 is to diagnose unsuspected ACS and prevent the inadvertent discharge of these patients from the ED. Follow-up stress testing is used to exclude significant coronary disease.

This simple risk stratification scheme accurately separates patients into high-, intermediate-, and low-risk groups. The ability of MPI to further risk stratify lower-risk patients is also obvious, as outcomes in patients who have positive MPI are similar to those in the patients considered high-risk level 2 (Fig. 6) [14]. Close collaboration of the CCU and nuclear medicine staff has resulted in the ability to successfully triage patients who do not have known coronary disease and have large perfusion defects at the time of imaging directly to coronary angiography and revascularization.

Patients presenting with chest pain are evaluated similarly to the Medical College of Virginia protocol. Patients who present without chest pain undergo rest SPECT thallium imaging. If images are negative, subsequent stress SPECT Tc-99m sestamibi imaging is immediately performed. If rest images are abnormal, the patient is re-evaluated for possible ACS before stress testing.

## Summary

The rapid triage of the patient who has suspected ACS continues to be a challenge. Chest

pain and other symptoms suggestive of ischemia remain nonspecific and frequent presentations to the ED. The ECG appropriately remains the first triage tool and is essential for identifying the patient who requires admission; however, numerous studies have demonstrated that it is inadequate for triaging most of the remaining patients. Acute MPI has been shown to have a high NPV and is a powerful risk stratification tool. When MPI is used in conjunction with the newer biomarkers such as troponin, the combination provides an impressive risk profile.

The inherent success of acute MPI in the ACS population is not serendipitous but rather based on the knowledge of the pathophysiology of ACS and the ischemic cascade that has been elucidated through the work of many investigators. The fact that one of the earliest events in the cascade is a marked reduction in absolute blood flow, leading to metabolic ischemia and its functional consequences, led researchers decades ago to attempt to noninvasively detect this early signature of ACS. However, as is often the case, these early investigators were limited by available technology. With the development of technological advances such as SPECT imaging and the introduction of Tc-99m-labeled MPI agents, it became possible to translate basic science observations into meeting a recognized patient need. Importantly, the ability to noninvasively assess perfusion acutely in combination with a quantitative measurement of function has important prognostic power. The studies that followed have confirmed that when this information is applied to the appropriate population in a timely manner it has significant clinical impact. A key aspect of the clinical success of nuclear cardiology techniques in this and other settings has been the ability to standardize all aspects of this process, from image acquisition to computer-assisted diagnosis. As new techniques are applied to the ACS population, the same questions posed earlier will need to be answered for each new technique.

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## Echocardiography in the Evaluation of Patients in Chest Pain Units

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In experimental models, impairment of left ventricular segmental wall motion is apparent almost immediately after the onset of myocardial ischemia, preceding symptoms and ST-segment alterations (Fig. 1). Using percutaneous angioplasty to induce the ischemic cascade in the cardiac catheterization laboratory, echocardiographic wall motion abnormalities have been documented to precede electrocardiographic abnormalities and angina [1]. Therefore, detection of cardiac wall motion abnormalities is potentially more sensitive than the history, physical examination, and ECG for identification of myocardial ischemia. Echocardiography is highly reliable for assessing cardiac wall motion and, thus, it has been used for diagnosis and risk assessment in patients presenting to the emergency department (ED) with symptoms suggestive of myocardial ischemia. In patients who have acute ST-elevation myocardial infarction (MI), echocardiography is comparable to invasive left ventriculography for detecting wall motion abnormalities [2]. However, the usefulness of echocardiography in the low-risk population that has chest pain of uncertain origin and a nondiagnostic initial presentation is less well established.

Table 1 depicts the results of nine studies in patients presenting to the ED with chest pain in which resting echocardiography was used to predict cardiac events during the initial presentation by detection of resting wall motion abnormalities [3–11]. The events defined by the authors ranged from hard events, such as MI [4], to a combination of hard and soft end points, such as MI, revascularization, angiographic coronary disease, and abnormal perfusion imaging studies [11]. Although

six of these reports indicated a high positive predictive value (PPV) for this technique, the overall event rate in these studies was approximately 51%. In these high-risk populations, the positive predictive value of a test for ischemia/infarction will be augmented compared with that in typical low-risk, rule-out MI (ROMI) patients. Thus, in the study of Sabia and colleagues [4] in which the cardiac event rate was 17%, the PPV of a resting wall motion abnormality was only 31%. When comparing resting ECG with resting echocardiography in a similarly low-risk population, Kontos and colleagues [5] demonstrated similar positive and negative predictive values for predicting cardiac events: 60% and 88% for ECG versus 44% and 98% for echocardiography. In another report with a similarly low cardiac event rate, echocardiography did not add to a 3-hour evaluation consisting of clinical assessment and cardiac serum enzymes [12]. Furthermore, in all the aforementioned investigations, the patients who had false-negative echocardiographic findings had non-ST elevation MI (NSTEMI) or unstable angina, reflecting the limited sensitivity of wall motion abnormalities for identification of this population. Unstable angina (with or without small troponin elevation) is the more common event in the low-risk patients who have ischemic events.

Typical of a high-risk ST-elevation MI population, Mohler and colleagues [11] studied 92 patients who had a 60% cardiac event rate. The echocardiogram was abnormal in 15 of the 18 patients who had MI, and in 12 of the 37 patients who had unstable angina. Five patients who had unstable angina had wall motion abnormalities unchanged from prior echocardiographic studies, and they were therefore considered to be echocardiographically negative. Two of the three patients

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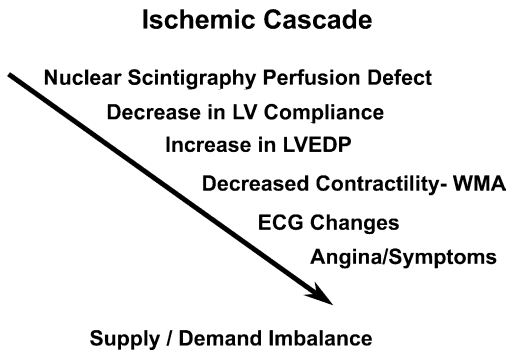


Fig. 1. The ischemic cascade as seen in the cardiac catheterization laboratory during controlled coronary occlusion. LV, left ventricle; LVEDP, left ventricular end-diastolic pressure; WMA, wall motion abnormality.

who had MI that were not detected by echocardiography had been given thrombolytic therapy. All patients who had a new wall motion abnormality had an event, leading to a PPV of 100%. The negative predictive value was 57%, demonstrating that MIs in 43% of patients who had events were not detected by echocardiography. These events were predominantly unstable angina diagnosed by typical chest pain lasting more than 30 minutes without ECG or enzymatic changes.

All of these studies were performed in the 1980s and 1990s using older echocardiographic machinery. For example, the study by Kontos and colleagues [11] used Hewlett-Packard 500, 1000, and 1500 machines (Hewlett-Packard, Palo Alto, California). Newer equipment with improved imaging techniques could improve wall motion imaging and improve the predictive value of resting echocardiography for detecting ischemia. Fundamental echocardiography receives echocardiographic signals at the same frequency at which they were transmitted, usually in the 2- to 3-MHz range for adult imaging. Fundamental echocardiography has difficulty imaging structures nearest the transducer because of artifact generated by the chest wall. Artifacts can also be generated from the side of the transducer, causing "side lobes." As echocardiographic sound waves travel through the heart, the tissues start to oscillate and can produce harmonics. Tissue harmonic echocardiography sends signals at the 2- to 3-MHz fundamental, but uses the 4- to 6-MHz harmonic signals received for imaging. This technique reduces the near-field artifact, as near-field signals don't usually produce harmonic signals. Harmonic signals also travel in a narrower beam, reducing the side lobe artifact.

Table 1

Predictive accuracy of echocardiography in patients presenting with acute chest pain

	N	Event+	Event-	PPV (%)	NPV (%)
Kontos et al [3]	130	RWA+ 15	29	34	
		RWA- 6	80		93
Sabia et al [4]	169	RWA+ 27	60	31	
		RWA- 2	80		98
Kontos et al [5]	260	RWA+ 41	53	44	
		RWA- 4	162		98
Korosoglou et al [6]	98	RWA+ 19	2	90	
		RWA- 18	59		77
Saeian et al [7]	60	RWA+ 22	3	88	
		RWA+ 2	33		94
Sasaki et al [8]	46	RWA+ 17	1	94	
		RWA- 6	22		79
Horowitz et al [9]	65	RWA+ 34	2	94	
		RWA- 2	27		93
Peels et al [10]	35	RWA+ 22	4	85	
		RWA- 3	14		82
Mohler et al [11]	92	RWA+ 27	0	100	
		RWA- 28	37		57

*Abbreviations:* N, number of patients; RWA+, regional wall motion abnormality present; RWA-, no regional wall motion abnormality; Event+, Coronary event present; Event-, no coronary event; PPV, positive predictive value; NPV, negative predictive value.

*Adapted from* Lewis W. Evaluation of the patient with "rule out myocardial infarction". Arch Intern Med 1996;156:41-5; with permission.

Hickman and colleagues [13] studied 80 patients presenting to the ED with chest pain of suspected cardiac origin that lasted at least 30 minutes within the previous 6 hours. The population studied was typical of the ROMI population in that 13 of the 80 patients (16%) were subsequently diagnosed as having had an event. An HDI 3000 (ATL, Bothell, Washington) machine with tissue harmonics was used for echocardiographic imaging. Tissue harmonic imaging was significantly better than fundamental imaging and allowed for adequate visualization of all segments in all patients, compared with fundamental imaging in which 11% of segments could not be visualized (Fig. 2). The positive and negative



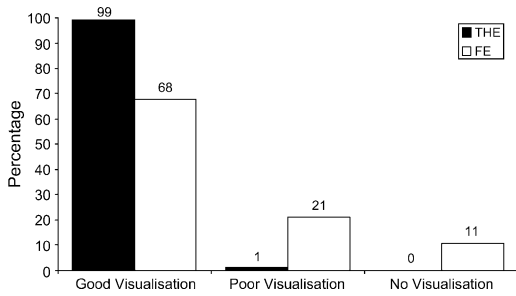


Fig. 2. Bar graph comparing quality of segmental visualization with echocardiography using fundamental (FE) and tissue harmonics (THE) imaging. (Adapted from Hickman M. Wall thickening assessment with tissue harmonic echocardiography results in improved risk stratification for patients with non-ST-segment elevation acute chest pain. Eur J Echocardiogr 2004;5(2):142-8; with permission.)

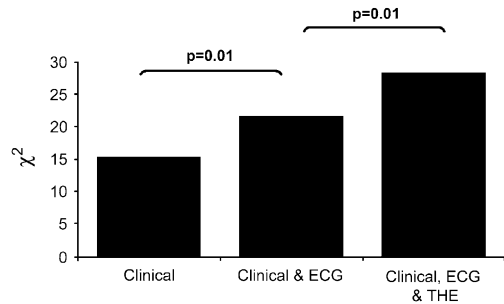


Fig. 3. Bar graph showing incremental value of clinical, ECG, and echocardiographic (THE) variables for the prediction index acute MI or a subsequent cardiac event. (Adapted from Hickman M. Wall thickening assessment with tissue harmonic echocardiography results in improved risk stratification for patients with non-ST-segment elevation acute chest pain. Eur J Echocardiogr 2004;5(2):142-8; with permission.)

predictive value of fundamental echocardiography for an event (elevated creatine kinase-myocardial band [CK-MB], coronary revascularization, and cardiac death) was 21% and 90%, respectively. Using tissue harmonic echocardiography, the positive and negative predictive values improved to 26% and 97%, respectively. This predictive accuracy was nearly identical to electrocardiography with a positive and negative predictive value of 24% and 97%, respectively (Table 2). However, tissue harmonic echocardiography provided added ability to predict future cardiac events when compared with clinical history and the electrocardiogram (Fig. 3). This added benefit was not seen using fundamental echocardiography.

There are several factors that limit the value of echocardiography for detecting patients in the

Table 2

Accuracy of clinical, ECG and echocardiographic variables for prediction of myocardial infarction as the presenting event

	PPV (%)	NPV (%)	P
Diabetes	5	80	.09
Abnormal ECG	24	97	>.1
Abnormal fundamental ECG	21	90	>.1
Abnormal tissue harmonic ECG	26	97	.007

Abbreviations: PPV, positive predictive value. NPV, negative predictive value. P, probability.

Adapted from Hickman M. Wall thickening assessment with tissue harmonic echocardiography results in improved risk stratification for patients with non-ST-segment elevation acute chest pain. Eur J Echocardiogr 2004;5(2):142-8; with permission.

ROMI population who are at risk for a cardiac event. The examination is highly dependent on skilled, experienced personnel for adequate data acquisition and reliable interpretation. According to the Task Force on Echocardiography in Emergency Medicine of the American Society of Echocardiography and Technology and Practice Executive Committees of the American College of Cardiology, a minimum of 6 months of training and performance of 300 echocardiographic studies are required to become a competent reader [14]. Therefore, highly specialized physicians, technical personnel, and equipment are required for dedicated use in the ED. Furthermore, although ventricular wall motion abnormalities associated with ischemia may persist for prolonged periods, they may also resolve in as little as 2 hours [15]. Studies in animals have demonstrated that wall motion abnormalities may not be detected when infarction involves less than 20% of ventricular wall thickness [16] or less than 12% of left ventricular circumference [17]. Therefore, patients who have NSTEMI and unstable angina may have no discernible abnormalities of wall motion. Echocardiography provides no information on the age of a wall motion abnormality, reducing its usefulness in patients who have known CAD or other cardiac disease. Finally, wall motion abnormalities may be seen in patients who have left bundle branch block and right ventricular volume or pressure overload that complicate interpretation of the echocardiogram for ischemic wall motion abnormalities.

Newer echocardiographic approaches may overcome some of these limitations. A technique

under investigation is analysis of variation in the scatter of acoustic signals during ischemia (ultrasonic tissue characterization). Acute myocardial ischemia results in increased integrated backscatter of ultrasound signals and decreased variability of scatter during systole and diastole. When compared with wall motion analysis for the detection of MI in the coronary care unit, Saeian and colleagues [7] found ultrasonic tissue characterization had comparable sensitivity, specificity, and accuracy. Ultrasonic tissue characterization had difficulty detecting apical infarcts, whereas wall motion analysis had difficulty detecting ischemia in the presence of left bundle branch block. It is possible that a combination of the two techniques would be complementary.

A second strategy that may be useful for identification of myocardial ischemia is contrast echocardiography [18]. In standard contrast imaging, the ultrasonic properties of the myocardium and ventricular cavity can be enhanced by intravenous injection of myocardial contrast agents. The current agents used are microbubbles formed by encapsulated gases that are small enough to traverse the pulmonary capillary bed, access the systemic circulation, and perfuse not only the left ventricular cavity but also the myocardium. When echocardiographic ultrasound strikes these microbubbles, the bubbles vibrate in a nonlinear fashion and give off enhanced echocardiographic signals. When using these agents to assess myocardial perfusion, a pulse of high-intensity ultrasound is given that is strong enough to burst the bubbles in the myocardium. The myocardium is visualized over the next 10 to 15 cycles and analyzed for wash-in of myocardial contrast agent (Table 3). Normally, the myocardium reperfuses within five to ten cardiac cycles. The intensity of the signal in the myocardium at steady state is

related to blood volume in the myocardium and can be normalized to the ventricular cavity. Variability in steady state opacification is related to myocardial viability. Delay in regional myocardial reperfusion is related to coronary flow rates and coronary disease (Fig. 4) [19].

Korosoglou and colleagues, [6] studied myocardial contrast echocardiography in 100 patients presenting to the ED with chest pain. Of these patients, 37 were ultimately given the diagnosis of acute coronary syndrome, resulting in a high event rate of 37%; 12 were diagnosed with unstable angina by Braunwald criteria and found to have greater than 70% stenosis in a coronary artery at arteriography; and 25 were diagnosed as having NSTEMI with troponin T elevation. Two patients were excluded from analysis because of poor echocardiographic images. Of the remaining 61 patients diagnosed as having noncardiac chest pain, 21 underwent angiography that showed no high-grade ( $\geq 75\%$ ) lesions and 40 patients underwent stress testing that resulted in normal findings. As shown in Table 3, the presence of resting echocardiographic wall motion abnormalities had a 90% PPV and a 77% negative predictive value (NPV) for acute coronary syndrome. Myocardial contrast echocardiography had an 89% PPV and a 91% NPV for acute coronary event. Using resting wall motion abnormalities plus myocardial contrast echocardiography yielded an 89% PPV and a 93% NPV. Because troponin assays can be rapidly performed in the ED, the group of patients that remain a diagnostic dilemma are those who have unstable angina without troponin elevation or electrocardiographic abnormalities. Focusing on the group diagnosed as having unstable angina without troponin elevation in this current study, the sensitivity of resting wall motion abnormality was 17% and the sensitivity of myocardial contrast

Table 3

Detection of unstable angina and non-ST-elevation myocardial infarction by myocardial contrast echocardiography

Visual assessment	Sensitivity	Specificity	PPV	NPV	Accuracy
Wall motion (2D-echo)	51%	97%	90%	77%	80%
Perfusion (MCE)	84%	93%	89%	91%	90%
Perfusion (MCE), single-vessel CAD	71%	93%	71%	93%	89%
Perfusion (MCE), multivessel CAD	92%	93%	85%	93%	93%
Wall motion and perfusion	89%	93%	89%	93%	92%

*Abbreviations:* 2D-Echo, two-dimensional echocardiography; CAD, coronary artery disease; MCE, myocardial contrast echocardiography; NPV, negative predictive value; PPV, positive predictive value;  $P < .05$ , myocardial perfusion versus wall motion.

*From* Korosoglou G. Usefulness of real-time myocardial perfusion imaging in the evaluation of patients with first time chest pain. *Am J Cardiol* 2004;94(10):1225–31; with permission.

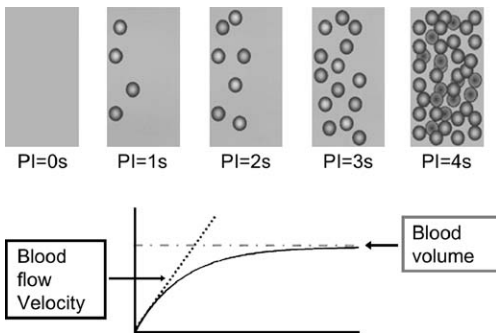


Fig. 4. Method of assessing mean blood flow velocity and myocardial blood volume using myocardial contrast echocardiography. (From Lepper W, Belcik T, Wei K, et al. Myocardial contrast echocardiography. *Circulation* 2004;109:3132–5; with permission.)

echocardiography was 66%. This means that one of three patients who has unstable angina without troponin elevation will go undetected using myocardial contrast echocardiography, compared with five out of six patients undetected using only resting wall motion as the detection criterion.

From the above data, it is clear that myocardial contrast echocardiography yields greater diagnostic accuracy compared with wall motion analysis in the detection of acute coronary syndromes. Kaul and colleagues [20] compared myocardial contrast echocardiography to resting single photon emission computed tomography (SPECT) in 203 patients. All patients underwent myocardial contrast echocardiography, but only 163 patients underwent SPECT. Thirty-eight patients (19%) had an event, consistent with this being a moderate risk group for a coronary event. When comparing myocardial contrast echocardiography to SPECT, myocardial contrast echocardiography perfusion was superior to SPECT myocardial perfusion in predicting events. However, SPECT myocardial regional function was superior to echocardiographic regional function in predicting events, resulting in SPECT having a greater overall predictive value compared with myocardial contrast echocardiography. The incremental value of tests performed in hierarchical order after clinical, demographic, and electrocardiographic variables are known is shown in Fig. 5.

All of the studies reviewed to this point used resting echocardiographic studies. As with the ECG, resting echocardiographic studies provide information regarding only the presence of resting ischemia within a narrow time frame. When the resting study is normal, then a stress study may

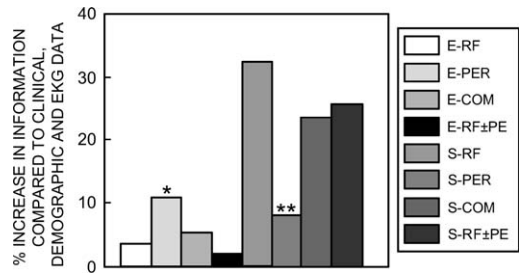


Fig. 5. Percent incremental value of tests performed in hierarchical order after clinical, demographic, and electrocardiographic variables are known. Values were significantly higher (\*) ( $P < .05$ ) compared with other CE variables, and significantly lower (\*\*) compared with other SPECT variables. E-RF, echocardiographic regional function; E-PER, echocardiographic perfusion; E-COM, combination of echocardiographic perfusion and function; S-RF, regional function by SPECT; S-PER, perfusion by SPECT; S-COM, combination of perfusion and function by SPECT. (From Kaul S. Incremental value of cardiac imaging in patients with chest pain and without ST-segment elevation: a multicenter study. *Am Heart J* 2004;148(1):129–36; with permission.)

yield further diagnostic information regarding the presence of significant coronary disease that is not producing active ischemia at the time of examination. Geleijnse and colleagues [21] studied dobutamine stress echocardiography in 102 patients presenting to the ED with chest pain of suspected cardiac origin. Of these patients, 59 had known coronary artery disease and 43 did not. The patients who did not have known coronary artery disease underwent stress testing after a minimum 12-hour observation period, whereas patients who had known coronary artery disease underwent a minimum 24-hour observation period. As a result, 13 patients were diagnosed as having events based on abnormal resting electrocardiograms and serum cardiac enzymes, and 89 patients were then referred for dobutamine stress testing. Patients who had resting wall motion abnormalities were not excluded from stress testing. Dobutamine was administered in 10  $\mu\text{g}/\text{kg}/\text{min}$  increments at 3-minute intervals up to a maximum of 40  $\mu\text{g}/\text{kg}/\text{min}$ . Atropine, up to 1 mg, was administered to patients failing to reach 85% maximal predicted heart rate with dobutamine infusion alone. The test was terminated for the usual end points of attaining target heart rate, stress-induced wall motion abnormalities, electrocardiographic changes, arrhythmias, severe chest pain, hypertension, or intolerable side effects. The echocardiograms were

interpreted using the standard 16-segment model [22]. Three patients had poor acoustic windows precluding stress testing, and six patients failed to reach 85% maximal predicted heart rate. Of the 80 remaining patients, 44 had normal stress echocardiograms and 36 had stress-induced wall motion abnormalities. Results of the stress test were conveyed to the attending physician and could be used to manage the patient. Seven patients who had positive stress echocardiograms underwent coronary revascularization during the index event, and seven patients had unstable angina during the 6-month follow-up period, with three of these patients having coronary revascularization procedures. Two patients who had normal stress studies had events (one MI and one unstable angina). The positive and negative predictive accuracy for dobutamine stress echocardiography was 25% and 95.5% (Table 4). Seven patients had significant dobutamine stress testing–related adverse events. Two patients had stress-induced nonsustained ventricular tachycardia, four patients had stress-induced supraventricular tachycardia, and one patient had stress-induced atrial flutter.

In the largest study to date, Bholasingh and colleagues [23] studied 577 patients admitted to the ED who had suspected acute coronary disease. During a 12-hour observation period, 119 patients were diagnosed with acute coronary syndrome and 34 were given other diagnoses, such as aortic stenosis or atrial fibrillation. Following this period, 404 patients were then referred for dobutamine stress

echocardiography using 3-minute stages and dobutamine at 10  $\mu\text{g}/\text{kg}/\text{min}$  increments to a maximum of 40  $\mu\text{g}/\text{kg}/\text{min}$ . Atropine, 1 mg, was given for patients failing to reach 85% maximal predicted heart rate. The test was terminated for the usual end points. This testing determined that 23 patients had poor acoustic windows precluding stress testing, 4 patients had resting wall motion abnormalities and did not undergo stress testing, 377 patients completed the dobutamine stress protocol, and 26 patients had stress-induced wall motion abnormalities in at least one segment of a 16-segment model. The attending physicians were blinded to the results of the dobutamine stress tests and patient management was determined by use of other diagnostic protocols. Over the 6-month follow-up period, eight patients who had positive dobutamine stress echocardiography had events, including one cardiac death (Table 5). Of the 351 patients who had negative dobutamine stress echocardiography studies, 14 patients had events during the follow-up period, including one cardiac death (see Table 5). The PPV for stress-induced wall motion abnormalities was 31% and the NPV was 96% (see Table 4). In 75 (19.9%) patients, the protocol was not completed because of the prespecified criteria: extensive new wall motion abnormality (1 patient), electrocardiographic changes (7 patients), chest pain (28 patients), and intolerable

Table 4  
Predictive accuracy of dobutamine stress echocardiography in patients presenting with acute chest pain and good quality images

	N	Event+	Event–	PPV (%)	NPV (%)
Geleijnse et al [21]	80 RWA+	9	27	25	
	RWA–	2	42		95.5
Bholasingh et al [23]	377 RWA+	8	18	31	
	RWA–	14	337		96
Trippi et al [24]	137 RWA+	7	0	100	
	RWA–	2	128		98.5

*Abbreviations:* N, number of patients; RWA+, regional wall motion abnormality present; RWA–, no regional wall motion abnormality; Event+, coronary event present; Event–, no coronary event; PPV, positive predictive value; NPV, negative predictive value.

Table 5  
Clinical outcomes at 6 months according to dobutamine stress echocardiography results

	Positive DSE (n = 26)	Negative DSE (n = 351)
Cardiac death	1	1
Nonfatal AMI	2	0
Rehosp UA	2	6
Primary end point	5	7
PTCA	2	4
CABG	1	3
Combined end point	8	14

*Abbreviations:* AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; DSE, dobutamine stress echocardiography; PTCA, percutaneous transluminal coronary angioplasty; Rehosp-UA, rehospitalization for unstable angina. Primary end point, cardiac death, AMI + rehosp-UA. Combined end point, primary end point + PTCA + CABG.

From Bholasingh R, Cornel JH, Kamp O, et al. Prognostic value of predischARGE obutamine stress echocardiography in chest pain patients with a negative cardiac troponin T. *J Am Coll Cardiol* 2003;41(4):596–602; with permission.

side effects (39 patients) such as arrhythmia and severe hypertension or hypotension.

Stress echocardiography requires experienced personnel to perform and interpret the test results. Cardiologists may not be available at off hours for the performance or interpretation of dobutamine stress testing. To circumvent these limitations, Trippi and colleagues [24] developed a protocol in which dobutamine stress echocardiography was performed by trained nurses and sonography technicians and then transmitted through telemedicine for interpretation by cardiologists. The authors studied 163 patients admitted to the hospital for chest pain with negative cardiac enzymes and electrocardiogram. Overall, 57% of the studies were performed after regular hours or on weekends. Of this population, 26 patients had resting wall motion abnormalities and were excluded from stress testing. Dobutamine was administered in 3-minute stages of 5, 10, 20, 30, 40, and 50  $\mu\text{g}/\text{kg}/\text{min}$  infusions. Stress testing was terminated prematurely in 9 patients because of chest pain or arrhythmias. The symptoms resolved in less than 10 minutes and required no specific therapy. There were no major complications of dobutamine stress testing. The study showed that 7 patients had stress-induced wall motion abnormalities and were found to have greater than 50% coronary stenoses on arteriography (100% PPV), 130 patients had normal dobutamine stress tests, and 2 patients were subsequently found to have coronary disease during the 3-month follow-up period (one inferior wall MI and one unstable angina, 98.5% NPV). Two patients were not described as either positive or negative by the authors. In patients who had normal resting echocardiograms, overall PPV and NPV for combined rest and subsequent dobutamine stress echocardiography was 51.5% and 98.5%, respectively (see Table 4). The authors have subsequently reported over 4 years of experience in 734 patients being managed by this protocol [25]. In this larger group of patients, the test was discontinued prematurely in only 3.1% of patients, 12.5% of patients had abnormal stress echocardiograms, and 70% of patients were discharged after negative stress echocardiograms.

Although none of the patients suffered an MI with dobutamine stress testing in these papers, MI has been reported with dobutamine stress echocardiography in outpatients [26]. Dobutamine has also been shown to tremendously activate platelets, independent of circulating catecholamines [27]. Platelet activation was not seen with exercise

testing. Caution is therefore warranted when using dobutamine stress echocardiography in evaluating these patients, and none of the published guidelines yet include dobutamine stress testing as part of the evaluation of patients who have chest pain in the ED.

The NPV is uniformly good when comparing the three dobutamine stress studies, whereas the PPV varies greatly. The low PPV seen in the study by Geleijnse and colleagues [21] may be caused by the inclusion of a large number of patients who have pre-existing disease and resting wall motion abnormalities. A true positive study was also defined as one in which the patient had a hard event. One could argue that in patients who have known coronary disease, a positive stress echocardiogram is by definition a true positive. This assertion would result in a greatly increased PPV in this study. In the study by Bholasingh and colleagues [23], the attending physicians were blinded to the results of the dobutamine stress test and therefore not all patients underwent coronary arteriography. Again, a true positive test was defined as one with a hard event in the follow-up period. The true predictive value may be much greater and the other diagnostic modalities, which were unreported by the authors, may not have detected the disease in these patients. In the study by Trippi and colleagues [24], all patients who had abnormal stress echocardiograms underwent coronary arteriography and the true PPV was known and found to be 100% for the detection of more than 50% coronary stenoses.

In summary, resting echocardiography may lack sufficient sensitivity to be of clinical usefulness in the patient who has low-risk chest pain in the ED, and the role of resting echocardiography is debatable. The National Heart Attack Alert Program Working Group concluded that “false negative rates in the prospective studies are too high to be safe” [28]. In addition, the American College of Cardiology/American Heart Association 2002 Guideline Update for the Management of Patients with Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction does not include echocardiography in the initial evaluation and management of patients [29]. In contrast, another viewpoint is offered by the American College of Cardiology/American Heart Association/American Society of Echocardiography that states that “early echocardiography is particularly useful in patients with a high clinical suspicion of acute myocardial infarction but a non diagnostic ECG” [30].

One of the aims in evaluating patients in the ED who have suspected acute coronary syndrome is to identify patients who are at low enough risk to be discharged home and those who are at high risk and require admission. Inclusion of myocardial contrast echocardiography or stress echocardiography can significantly improve the diagnostic accuracy of echocardiography in the detection of ischemia. Therefore, a rational use of echocardiography in this schema would be to evaluate patients for resting wall motion abnormalities in whom serial electrocardiograms and serum cardiac markers were negative. Patients who have resting wall motion abnormalities could be admitted to the hospital for further evaluation. Patients who do not have resting wall motion abnormalities could be scheduled for exercise or dobutamine stress testing, myocardial perfusion imaging, or other diagnostic modalities as part of their accelerated diagnostic protocol.

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## Newer Imaging Methods for Triageing Patients Presenting to the Emergency Department with Chest Pain

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Electron beam computed tomography (EBCT), also known as ultrafast CT, is highly sensitive for detecting and quantifying coronary artery calcium. Coronary artery calcium is absent in the normal vessel and occurs almost exclusively in the arteries with atherosclerosis [1–3]. The degree of coronary calcium is strongly associated with the total atherosclerotic burden [4–6]. Patients who have more coronary artery calcium are more likely to have significant angiographic obstructions and, more importantly, are known to suffer more adverse cardiac events [7–13]. These findings, and the procedure's noninvasive methodology and low cost, have provided the rationale for the use of EBCT for risk stratification of patients in the emergency department (ED) who have possible acute coronary syndrome (ACS) [14–16].

### Technology considerations

EBCT involves an electron emitter rather than a standard radiograph that allows for rapid screening times. Transaxial images are obtained at 100 ms with 3-mm to 6-mm slices during one to two breath holds. Scanning is triggered near end-diastole to minimize motion artifact. No intravenous or oral contrast is required and the entire scan can be completed in 10 to 15 minutes. Multislice CT (MSCT) is another CT modality

that can assess coronary calcium, and studies have shown that this technology correlates well with EBCT for the detection of coronary calcium [17,18]. Many institutions employ MSCT for coronary calcium scoring as this CT modality can also be used for scanning other organs, and EBCT is only useful for coronary calcium quantification. However, most clinical studies have employed EBCT for cardiac risk stratification. The cost of an EBCT is approximately \$400.

Histologic studies have shown that tissue densities greater than 130 Hounsfield units (a measurement that characterizes the relative density of a substance) are associated with calcified plaque. A coronary calcium score, also called the Agatston score, is calculated as a product of the area of calcification and a factor based on the maximal calcium density. A composite score to indicate the quantity of calcium detected in the entire coronary artery system is typically used: a score of 0 is considered normal, 1 to 99 is mild, 100 to 400 is moderate, and more than 400 is severe. Coronary calcium scores have also been age- and sex-adjusted as coronary calcium is more extensive in older and male patients [19]. A more recently developed calcium volume score may offer more precision as compared with the traditional Agatston score [20,21].

### *Coronary calcium score and cardiac risk assessment*

Numerous studies have shown that the coronary calcium score has prognostic value

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significance in symptomatic and asymptomatic individuals [22–31]. A study of 5365 asymptomatic individuals demonstrated 224 adverse events (death, nonfatal myocardial infarction (MI), coronary bypass surgery, or percutaneous intervention) over 3 years [23]. Individuals who have a score of more than zero had a significantly higher event rate compared with those who do not have calcium (6.1% versus 0.4% in men; 3.3% versus 1.0% in women). The magnitude of cardiac risk is directly related to the extent of calcification [24]. However, controversy has arisen concerning the additional prognostic significance of coronary calcium after accounting for traditional risk factors. In 2000, the American College of Cardiology/American Heart Association published a consensus document concerning EBCT that states, “Importantly, the incremental value of EBCT over traditional multivariate risk assessment models has yet to be established” [32].

Some early studies suggest that coronary calcium scores do not offer additional prognostic information after accounting for the Framingham risk score [9], which predicts cardiac risk based on age; sex; low-density lipoprotein and high-density lipoprotein cholesterol; hypertension; cigarette smoking; and diabetes mellitus [33]. The consensus document published in 2000 was written after a literature review through 1998. However, since that time publications have shown that coronary calcium scores give additional independent prognostic information. A recent meta-analysis of four studies demonstrated that an elevated coronary calcium score was associated with an increased risk for adverse cardiac events after accounting for classic cardiac risk factors [26]. Across the categories of the Framingham risk score, a study of 1461 asymptomatic individuals showed at a median of 7 years at follow-up that coronary calcium was predictive of cardiac risk among patients who had a Framingham risk score higher than 10%, but not among patients who had a score less than 10% [34]. Thus, more recent studies suggest that coronary calcium scores are independently predictive of cardiac risk even after accounting for traditional risk factors.

#### *Electron beam CT in patients who present to the emergency department with chest pain*

Between 1999 and 2001, there have been three published studies evaluating the diagnostic usefulness of EBCT in patients evaluated in the ED who had chest pain [14–16]. The first study by

McLaughlin and colleagues [14] evaluated 181 patients who were admitted to the hospital from the ED with chest pain of presumed cardiac origin. Patients were included if they had a normal or nondiagnostic ECG at presentation. Exclusion criteria were history of coronary artery disease (CAD) (MI, coronary bypass surgery, or percutaneous intervention), diagnostic ST changes or Q waves on electrocardiogram, weight more than 250 lb, initial elevated creatine kinase-myocardial band (CK-MB), and known or suspected pregnancy. Among those evaluated, 44 patients did not meet entry criteria and 4 patients did not give consent, yielding 133 patients in the final analysis. An EBCT was considered positive if the score was more than one; the results of the scan were blinded to the responsible clinician.

Patients had 30-day follow-up by phone call for adverse events such as MI (as defined by World Health Organization criteria), coronary artery bypass surgery, percutaneous intervention, or sudden cardiac death. The population was 71% African-American, Hispanic 19%, 19% White, and 1% Asian, and comprised 84 (63%) women and 50 (37%) men. The mean age was  $53 \pm 2$  years. There were 86 (64%) patients who had a positive scan and 48 (36%) patients who had a negative scan. In the entire group there were seven (5%) adverse cardiac events, including four MIs, two coronary artery bypass surgeries, and one percutaneous intervention. Among the 48 patients who had normal coronary calcium scores, there was one (2%) adverse event. This patient was a 45-year-old man who suffered a MI after cocaine use. Of the patients who had an abnormal coronary calcium scan, there were six (12%) adverse events. These findings indicated the low event rate associated with the absence of elevated coronary calcium, and the higher adverse event rate in patients who had elevated coronary calcium. However, most patients who had increased coronary calcium did not experience an adverse cardiac event.

The second study by Laudon and colleagues [15] evaluated 105 patients who had chest pain in the ED. Inclusion criteria were women between 40 and 65 years and men between 30 and 55 years; normal initial cardiac marker; and a normal or indeterminate ECG. Exclusion criteria included history of CAD; ECG with ST-segment elevation, Q waves, or left bundle-branch pattern; elevated cardiac marker at presentation, hemodynamic instability; and pregnancy. Patients had follow-up at 4 months and a coronary calcium score more

than zero was considered abnormal. The need and type of stress testing was left to the discretion of the physicians who were blinded to the results of the scan.

Of these 105 patients, 54 (51%) were admitted to an inpatient cardiology service and 51 (49%) were admitted to the ED chest pain observation unit. The patient population consisted of 98 Whites, 4 African-Americans, 1 Southeast Asian, 1 Arab, and 1 Hispanic. There were 57 (54%) men and 48 (46%) women. Mean age for men was 45 years and for women 51 years. All patients underwent EBCT and 100 underwent other cardiac testing, including 58 who underwent regular stress testing; 19 who underwent exercise or pharmacologic radionuclide testing; 25 who underwent coronary angiography; and 11 who underwent rest, exercise, or pharmacologic echocardiography. Of the 100 patients who had EBCT and other cardiac testing, 46 patients had an abnormal EBCT and 54 patients had a normal EBCT. There were no patients who had a normal EBCT and abnormal other cardiac test. EBCT had 100% sensitivity, 63% specificity, 100% negative predictive value, and 30% positive predictive value for an abnormal cardiac test. At 4 months there were no adverse events in patients who had a normal EBCT.

The third study by Georgiou and colleagues [16] considered 192 patients who were evaluated in the ED and were believed to require admission to exclude MI. Patients were included if they were aged 30 years or older, had chest pain lasting at least 20 minutes in the last 12 hours, and had a nondiagnostic ECG. Patients were excluded if they had a history of CAD (coronary artery bypass surgery or percutaneous intervention), ECG findings of Q waves, ST-segment elevation more than 1 mm in two consecutive leads, T-wave inversion of 5 mm or more, hemodynamic instability, or pregnancy. There were 221 patients screened. Of these, 13 patients were excluded because of an acute cardiac event at presentation and 16 were excluded because of lack of follow-up data, yielding 192 patients for final analysis.

Of the 192 patients, 69 (36%) were White, 49 (26%) were Hispanic, 48 (25%) were African-American, and 26 (14%) were Asian-American. Prevalence of coronary calcium was significantly lower in Hispanics compared with Whites (47% versus 73%,  $P = .004$ ). There were 104 (54%) men and 88 (46%) women. The average follow-up was 50 months  $\pm$  10. Of the total group, 116 (60%) had some level of calcium detected. There were 58 (30%) patients who had an adverse cardiac

event, 30 (16%) who had "hard" events (11 cardiac deaths and 19 nonfatal MIs), and 28 (15%) who had other cardiac events, including nine coronary artery bypass surgeries, four percutaneous interventions, 11 hospitalizations for angina, and four ischemic strokes. Patients who had higher coronary artery calcium scores had significantly more adverse cardiovascular events (Fig. 1). Dividing patients into quartiles of coronary calcium scores, there were no "hard" cardiac events in the first quartile, one in the second quartile, ten in the third quartile, and 19 in the fourth quartile. In a multivariate analysis, coronary calcium scores were more predictive of adverse cardiac events as compared with traditional cardiac risk factors.

#### *Considerations regarding the potential role of electron beam CT in the emergency department*

Are we ready to start using EBCT in the ED for the routine evaluation of patients who have possible ACS? Use of an ECG, followed by serial cardiac markers and then a rapid, easily performed, and inexpensive EBCT is an attractive strategy for risk stratification in this setting. For many institutions it is a major logistic challenge to provide timely stress tests, which may include imaging modalities, before discharge of low- to intermediate-risk patients from chest pain observation units. However, there are certain patients who should not have an EBCT in this setting. Patients who have known CAD, which was rightly an exclusion criterion for all three studies, are known to have high coronary calcium scores and therefore EBCT would be unlikely to aid in risk stratification. This exception is a relevant issue as

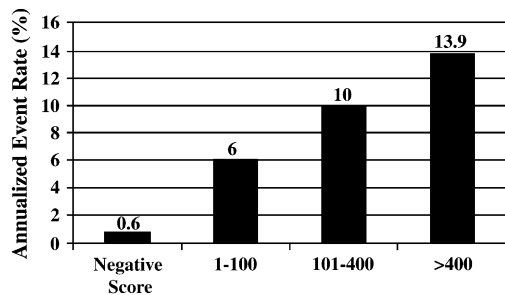


Fig. 1. Patients who have chest pain screened using electron beam tomography in the emergency department. (Adapted from Georgiou D, Budoff MJ, Kaufer E, et al. Screening patients with chest pain in the emergency department using electron beam tomography: a follow-up study. *J Am Coll Cardiol* 2001;38:105-10; with permission.)

more patients who have atypical symptoms and a history of CAD are being managed in chest pain units [35]. One study demonstrated that 38% of patients evaluated in a chest pain unit had known CAD (history of MI, percutaneous intervention, or coronary artery bypass surgery) [36]. In addition, older patients are known to have a higher degree of coronary calcium even without known coronary disease. Thus, if EBCT is to have some role in risk stratification of patients in the ED who have chest pain, it would likely involve a younger population.

Although the low adverse event rates in patients who have normal EBCT scans in these three studies are impressive (Laudon, 0%; McLaughlin, 0% [excluding the one patient who had cocaine-induced MI]; Georgiou, 0.6% per year), these studies do have some significant limitations. These studies include a small number of patients. More unusual cases of adverse cardiac events, such as the patient who has MI secondary to cocaine, may become apparent if a larger number of patients were studied. Also, all three of these studies only involved a single center. Moreover, in two of the studies, the patients who were entered represented a convenience sample that may have led to selection bias. In the study by Georgiou and colleagues [16], the EBCT scanner was available 5 days per week from 7 AM to 11 PM, whereas the study by Laudon and colleagues was "limited at times in the enrollment of patients by the availability of the EBCT scanner" [14]. The thought-provoking results of these small studies will hopefully lead the way to a larger multicenter study of consecutive patients.

A further concern of these three studies is the large proportion of positive EBCT scans: 49%, 64%, and 60% (Table 1). If an EBCT is positive, what should the next step be in patient

management? All of these patients likely would not benefit from coronary angiography, as many patients would not have obstructive coronary disease as a cause of their symptoms. These patients would at least require some form of stress testing, which would make the difficult process of risk stratification even more cumbersome. In addition, the need for "double-testing" would likely make the strategy less cost-effective. Instead of using any degree of calcium as defining an abnormal EBCT, certain levels of calcium may be used to assist in risk stratification that may obviate the need for holding the patient for stress testing in the chest pain unit. However, the extent of coronary calcium is affected by age, sex, and race. The optimal degrees of calcium distinguished by age and gender would need to be determined to discriminate a low-risk patient who has chest pain in the ED. The ongoing Multi-Ethnic Study of Atherosclerosis (MESA) is following 6500 individuals over 10 years and will provide additional data concerning EBCT and cardiac risk assessment in a large diverse population.

Finally, although coronary artery calcium is associated with atherosclerosis, EBCT does not detect vulnerable plaques that are the most likely to lead to ACS. In fact, some vulnerable plaques may contain no calcium. A large degree of coronary calcium is associated with more extensive overall atherosclerotic burden, and therefore more stable and unstable plaques. Although more coronary calcium makes developing ACS more likely, the absence of coronary calcium does not preclude the possibility of ACS. In a study of 118 patients who had ACS (101 who had acute MI and 17 who had unstable angina), 12 (10%) had no coronary calcium detected by EBCT [37]. Patients who had ACS and a normal EBCT were significantly younger and more likely to be active

Table 1

Electron beam CT for risk-stratification in patients who have chest pain in the emergency department

Study	Number of patients	Age inclusion criteria in years	Number (%) positive test	Number (%) negative test	Follow-up	Number (%) adverse events in patients who have negative test
Laudon et al 1999 [14]	105	Men aged 30–55 Women aged 40–65	51 (49)	54 (51)	4 m	0 (0)
McLaughlin et al 1999 [15]	134	All ages	86 (64)	48 (36)	30 d	0 (0)
Georgiou et al 2001 [16]	192	≥30	116 (60)	76 (40)	50 m	1 (2)

cigarette smokers. Thus, there may be certain groups of patients that are more prone to developing ACS in the setting of a normal EBCT.

### *Cardiac MRI*

Cardiac MRI has diagnostic usefulness for myocardial perfusion and regional wall motion abnormalities. Wall motion abnormalities may not only be detected in MI, but transient ischemia in unstable angina may lead to stunning, which in turn can be detected by MRI. An MRI scan may be more sensitive for stunning as compared with radionuclide imaging. Kwong and colleagues [38] studied 161 consecutive patients who were evaluated in the ED for possible ACS. Inclusion criteria were 30 minutes or more of chest pain within 12 hours of presentation, age over 21 years, and weight less than 270 lb. Exclusion criteria were ST-segment elevation MI, pregnancy, significant heart failure such that patient could not lie flat, and metal prosthesis precluding MRI. Of the 161 patients, 25 (16%) had ACS, 10 had NSTEMI, and 15 had unstable angina. The sensitivity and specificity of MRI for ACS were 84% and 85%, respectively. In a multivariate regression analysis, MRI was independently associated with the diagnosis of ACS and was of greater diagnostic usefulness when compared with ECG and peak troponin-I. Considerable research is presently in progress with MRI in identifying coronary atherosclerotic lesions, including vulnerable plaques, which may prove to be of diagnostic value for patients in the ED who have chest pain of unclear origin [39].

### *CT coronary angiography*

Major advances in noninvasive imaging of the coronary arteries by contrast-enhanced CT have stimulated considerable interest in the potential of this technique to rapidly confirm or exclude CAD in low-intermediate risk patients presenting to the ED with chest pain. Contemporary 64 slice CT scanners [40–42] have overcome many of the limitations of earlier 16 slice devices [43], resulting in recently cited gantry rotation times of 330 msec, spatial resolution of 0.4 mm and temporal resolution of 83–165 msec. Although these values are less than those of conventional coronary angiography (~0.15 mm and 0.33 sec), they are sufficient to yield diagnostic data in a large proportion of patients (Fig. 2). The accuracy of CT coronary angiography with 64 slice scanners is based on limited comparative studies with invasive coronary

angiography in elective patients. In their evaluation of 59 patients, Leber et al reported the following sensitivities of CT angiography for detecting coronary stenoses of various degrees: stenosis <50%, sensitivity 79%; stenosis >50%, sensitivity 73%; stenosis >75%, sensitivity 80% [41]. Specificity was 97%, indicating the utility of the method in identifying absence of CAD. Raff and colleagues compared invasive and CT coronary angiography in 70 patients in whom they analyzed 1,065 coronary artery segments and found a mean difference in percent stenosis of  $1.3 \pm 14.2\%$  [42]. Specificity, sensitivity, positive and negative predictive values of CT angiography for significant stenoses were: 86%, 95%, 66% and 98%, respectively. The latter value again indicates the reliability of a negative CT coronary angiogram in excluding CAD. However, there have been no reports of CT coronary angiography in the ED setting in patients presenting with chest pain.

Visualization of the coronary arteries by CT has important advantages that include its non-invasive methodology, rapidity, reliability in excluding severe CAD and simultaneous acquisition of other chest structures such as the aorta and pulmonary arteries. However, limitations of the technique are significant. A low heart rate (optimally, <70/min) is required to avert blurring of the images of the moving coronary arteries. Administration of a beta blocker or rate-limiting calcium channel blocker is often necessary for this purpose. Regular rhythm is also necessary precluding CT angiography in patients with atrial fibrillation or frequent ectopic beats. Even with the currently enhanced resolution, the method cannot precisely assess the severity of coronary stenoses, which has resulted in diagnostic categories such as no CAD, <50% stenosis, >50% stenosis and uninterpretable due to calcification or artifact. A dose of 60–100 cc of iodinated contrast is required, which may be a relative contraindication in patients with renal insufficiency. Finally, the radiation dose is higher than that with invasive coronary angiography and has led to methods for reducing the exposure of the patient [43].

### **Summary**

Three small single-center studies using EBCT in the ED to risk stratify patients who have chest pain and nondiagnostic ECGs show promising results, but limitations of this approach are apparent. Although patients who did not have

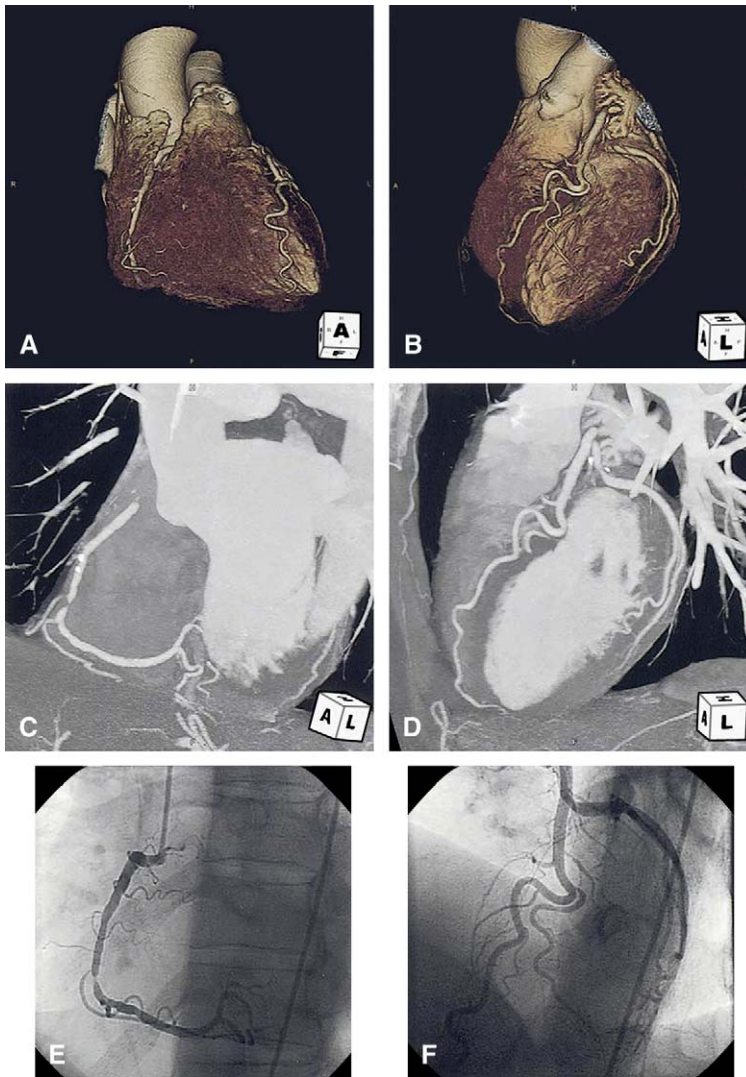


Fig. 2. Noninvasive visualization of coronary artery anatomy by 64-slice multislice computed tomography (CT). (A,B) Volume rendering technique depicts a severe stenosis of the right coronary artery (RCA) distal to the marginal branch, nodular coronary calcifications mainly extrinsic to the RCA lumen and normal left coronary artery. (C,D) Maximum-intensity projection demonstrates severe soft plaque of the RCA and superficial calcific plaques of the RCA and proximal left circumflex artery. (E,F) Invasive coronary angiography confirms the major stenosis of the RCA and absence of significant lesions in the left coronary artery. (From Raff GL, Gallagher MJ, O'Neill WW, et al. Diagnostic accuracy of noninvasive coronary angiography using 64-slice spiral computed tomography. *J Am Coll Cardiol* 2005;46:552-7; with permission.)

coronary calcium detected by EBCT had very low adverse event rates, EBCT in this setting can be associated with poor positive predictive value that would lead to at least the need for another cardiac test, such as stress testing, or even unnecessary hospital admission. Before EBCT is adopted as routine practice in this patient population, a large multicenter study of consecutive patients is

required to better ascertain for which subset of patients this would be an effective strategy. This subset would likely include a younger population that does not have a history of CAD. Ideally this would lead to a randomized diagnostic trial comparing EBCT in this population with some form of stress testing. Other imaging technologies, including cardiac MRI and MSCT, are even less

well studied in this patient population, but may prove to be of value in this setting in the future.

Limited data with 64 slice scanners indicate diagnostic quality coronary imaging in many patients and a high degree of reliability of a negative study. However, although the technique has important potential, significant limitations remain and there are currently no reported studies of its utility in the ED setting.

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## Chest Pain Units: Management of Special Populations

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Chest pain evaluation units provide a safe and cost-effective means for risk stratification of patients who present to the emergency department (ED) with chest pain and no evidence of myocardial infarction (MI) or ischemia on initial evaluation. A standardized protocol is often used that combines serial measurements of cardiac injury markers, repeat electrocardiograms (ECG), and telemetry monitoring followed by secondary risk stratification by additional diagnostic testing for coronary artery disease (CAD). The latter usually comprises provocative testing with exercise or pharmacologic stress. Although these units rely heavily on a protocol-driven approach, appreciation of the limitations of this method in certain patient populations is essential. In particular, the inclusion of women, diabetics, patients with a history of CAD, and those with chest pain after stimulant use (eg, cocaine, methamphetamine) may necessitate additional consideration in the choice of diagnostic testing. Some would suggest that these patients should be excluded from chest pain unit evaluation based solely on their presumed high risk of cardiac disease and adverse events. Additionally, exercise stress, the most common provocative test used in chest pain units, has important limitations in these patients. However, the clinical presentations of many of these patients often lack high-risk features associated with adverse cardiac events, making them appropriate candidates for a chest pain unit. This article reviews the evaluation of these special populations

by accelerated diagnostic protocols, focusing on the value and limitations of this strategy for assessment of these unique patients.

### Women

Cardiovascular disease is the leading cause of death in women, accounting for nearly half of all deaths in this population. Timely diagnosis early in the course of the disease is essential. Thirty-eight percent of women who have MI die within a year, compared with 25% of men. This staggering variation is in part because MI occurs at a significantly older age in women than in men. In addition, within 6 years of MI, as many as one third of women will have another heart attack, 15% will develop angina, 13% will have a stroke, and 30% will be disabled with heart failure [1]. These alarming numbers have led to an increased interest in cardiovascular health in women. Recent studies have revealed unique aspects of pathophysiology, diagnosis, prognosis, and treatment of CAD in women. The lower age-specific risk of CAD and prevalence of acute coronary syndrome (ACS) in women leads to decreased accuracy of diagnostic tools commonly used in a chest pain unit (Box 1).

In addition, there are important gender-specific physiologic responses to exercise stress [2]. Challenges to diagnostic testing in women include variable ability to reach target heart rate and baseline ECG changes that may decrease accuracy of treadmill testing [3–5]. Women also have labile ST-segment alterations and body habitus attributes that may result in false-positive exercise ECG interpretation. Despite these unique

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**Box 1. Unique factors in women affecting exercise test results**

Decreased exercise capacity  
 Baseline electrocardiographic abnormalities  
 Body habitus  
 Lower age-specific risk of coronary artery disease  
 High rate of single vessel disease

physiologic issues, the chest pain unit provides an important option for the evaluation of women. Their exclusion would result in the costly use of traditional hospital beds to evaluate these patients with a low rate of CAD, especially those of premenopausal age, no diabetes, and absence of a smoking history. Nevertheless, understanding these limitations is important for the prudent selection of diagnostic modalities when evaluating women in a chest pain unit.

Several approaches to risk stratification in women in the nonacute setting have been published. A recent review of the evaluation of chest pain in women suggests that it is possible to risk stratify them into low, moderate, and high likelihood of CAD solely by the presence or absence of traditional cardiac risk factors. Based on this scheme, recommendations for diagnostic testing were presented to improve the cost-effectiveness of the evaluation [6]. However, these recommendations have not been validated in any published clinical trials. Wilson and colleagues [7,8] developed a risk prediction model based on blood pressure, cholesterol level, history of diabetes or smoking, and age. This model was derived from Framingham data; information on estrogen use was not available. The risk score was very effective in stratifying remaining lifetime risk for coronary heart disease in women, with 1.5- to 3-fold higher absolute risk in the highest versus lowest tertile of risk score at all ages. Despite initial promise, risk stratification based on simple tools such as these has not gained general clinical use and outcome data are limited. In part, this may be due to the lack of utility of such models in the acute setting.

Exercise stress testing, a cornerstone of the evaluation of patients with chest pain, has a diagnostic accuracy as low as 52% in women, with a false-positive rate as high as 40% [9,10]. Thus, its utility in women has been questioned, especially in those considered low risk for CAD. Despite

these criticisms, the ED-based exercise stress test has provided useful prognostic information for adverse cardiac events in low- to moderate-risk chest pain patients that have included women [10,11]. Diercks and colleagues have evaluated the use of treadmill exercise testing in 666 women who underwent evaluation in our chest pain unit. Using Agency for Health Care Policy and Research classification, 38 (5.7%) women were retrospectively identified as high risk, 136 (20.4%) were intermediate risk and 492 (73.9%) were low risk for CAD. Of these, 465 (70%) had negative exercise testing, 145 (22%) had nondiagnostic tests, and 56 (8%) had positive tests. Thirty-day clinical follow-up or confirmatory cardiac evaluation was achieved in 512 of 666 (77%) patients. The sensitivity, specificity, and negative and positive predictive values of the treadmill test are shown for patients with a positive or abnormal test result (positive or nondiagnostic) in Table 1. Compared with a negative exercise test, the relative risk of CAD for a positive test was 19 (95% CI 6–56) and for a nondiagnostic test it was 8 (95% CI 3–22) [12]. Despite the poor positive predictive value of exercise testing in the women, positive tests were relatively infrequent and the negative predictive value affords excellent accuracy in identifying those patients who do not require hospital admission. As recommended in the American College of Cardiology/American Heart Association guidelines, treadmill testing should be applied as a first-line diagnostic method only in those women with a normal baseline ECG and ability to exercise [13].

Imaging techniques such as myocardial stress perfusion scintigraphy have higher sensitivity and specificity than treadmill testing, but gender-

Table 1  
 Diagnostic accuracy of positive or abnormal exercise treadmill testing in women evaluated in a chest pain observation unit

	Sensitivity	Specificity	Negative predictive value	Positive predictive value
Positive exercise treadmill testing (N = 56)	41%	91%	96%	22%
Abnormal exercise treadmill testing (N = 201)	82%	70%	99%	14%

specific confounders still exist. Breast attenuation, small left ventricular size, and a high rate of single vessel disease may affect the diagnostic utility of this modality [14]. Despite these limitations, myocardial perfusion imaging has been established as a safe, noninvasive, cost-effective and accurate method to identify CAD in women [15]. After injection of thallium-201, areas of decreased uptake by the myocardium are seen as a negative scintigraphic image, indicating regions of ischemic or infarcted myocardium. Gated single photon emission CT radionuclide imaging with thallium or technetium-99m sestamibi has been used in the ED to improve the diagnostic accuracy and risk stratification of patients presenting with chest pain and a nondiagnostic ECG [16–18].

Cardiac stress imaging methods provide several advantages in women. They allow for pharmacologic stress, which alleviates the problem of decreased exercise capacity and failure to reach target heart rate that limits the value of traditional exercise stress testing. In addition, the use of gated images allows differentiation of breast tissue attenuation from a true perfusion defect. Studies that have evaluated the benefit of gated images, which included 170 women, report an improved specificity for the detection of CAD from 67% to 91% [19,20].

The prognostic value of myocardial perfusion imaging has also been evaluated in women. Pooled data from more than 7500 women demonstrated an annual cardiac event rate of < 1% in those with a normal perfusion scan [14]. These results were also found in women with a high pretest probability of CAD [21]. Hachamovitch and colleagues [22] evaluated the determinants of risk and prognosis in patients with a normal myocardial perfusion scan. Diabetic women had the highest rate of cardiac-related death or MI at 1 year after adjusting for confounders. The lowest 1-year event rate was in nondiabetic women (< 1%). The results of these trials have led the American Society of Nuclear Cardiology Task Force on Women and Heart Disease to incorporate the use of myocardial scintigraphy into an algorithm for the initial evaluation of women with chest pain. These guidelines recommend the use of exercise or pharmacologic gated single photon emission CT as a first line test in intermediate- to high-risk women with diabetes, an abnormal resting ECG, or inability to exercise. In addition, they recommend this modality as a second-line diagnostic adjunct or confirmatory test in patients who have an intermediate risk exercise ECG.

These recommendations are based on the high sensitivity and specificity and prognostic utility of scintigraphy [23].

### History of coronary artery disease

Patients with a history of CAD compose a high-risk subgroup whose inclusion in the standard chest pain unit strategy is controversial. These patients are often complex and frequently have undergone prior myocardial revascularization. In general, their suitability for chest pain unit management should primarily depend on the immediate risk of ACS based on symptoms, ECG features, and cardiac serum markers rather than their past history and risk factors (Box 2) [24,25]. Other considerations should include review of prior evaluations and management goals of the patient's cardiologist.

The Chest Pain Evaluation in the Emergency Room (CHEER) trial examined the utility of a chest pain observation unit in a group of patients with suspected unstable angina and intermediate risk for adverse cardiac events based on AHCPR guidelines [26]. This cohort of patients included 27% with known CAD, defined by history of prior MI or prior percutaneous coronary intervention. After adjustment for comorbid conditions, the investigators observed no difference in cardiac events at 6 months in those patients randomized to the chest pain unit and those receiving traditional hospital admission [26]. Our group evaluated the use of immediate exercise testing of 100 patients with a history of CAD evaluated in a chest pain unit. These patients had a normal or nondiagnostic ECG at presentation and were pain free at the time of evaluation. A negative exercise treadmill test was found in 38% of patients and 39% had nondiagnostic tests, with two-thirds discharged home immediately from the ED. An additional 19

#### **Box 2. Unique factors in patients with a history of coronary artery disease that affect stress test results**

- Multiple co-morbidities
- Prior myocardial revascularization
- Baseline left ventricular wall motion abnormalities
- Baseline fixed myocardial perfusion deficits
- Use of anti-anginal medications

patients were discharged within 24 hours of presentation. Of the 23% who had a positive exercise test, uncomplicated non-ST segment elevation MI was diagnosed in two patients. No adverse events occurred during the 6-month follow-up period. Despite a slightly higher incidence of abnormal tests and adverse events than the typical chest pain unit patient population, this strategy was quite effective in risk stratification and prompt disposition of patients [27].

Diercks and colleagues [28] have also evaluated the utility of an accelerated diagnostic protocol in patients with a history of CAD evaluated in their chest pain unit from 1/94 to 10/01. A diagnosis of ACS was based on clinical presentation and cardiac testing consistent with myocardial ischemia, MI, or the need for revascularization within 30 days of presentation. Of the 6839 patients evaluated, 1153 (17%) had a history of CAD. MI was detected in 12 patients (1%) during their chest pain unit evaluation. Initial diagnostic testing was performed in 639/1153 (55%), yielding positive results in 191. Testing included 371 (58%) exercise treadmill tests, 208 (32%) myocardial scintigrams, 54 (8%) exercise echocardiograms, and 51 (7%) cardiac catheterizations. Subsequent testing was done in 77 patients who had no initial diagnostic test during their chest pain unit stay. During the follow-up period there were two deaths, three MIs, and revascularization was performed in 46 patients. A final diagnosis of ACS was made in 238 patients (22%). The data indicate that although the frequency of ACS in patients with a history of CAD is higher than that in typical low-risk patients presenting with chest pain, evaluation in a chest pain unit is appropriate.

Studies using myocardial scintigraphy in patients with a history of CAD have reported satisfactory diagnostic and prognostic ability. Zellweger and colleagues [29] evaluated the prognostic value of stress radionuclide imaging in patients with prior MI. In 1143 patients, they reported 118 adverse events during follow-up. The annual rate of adverse events was proportional to the size of the perfusion abnormality. In addition, the size of the infarction was also an independent predictor of adverse events. Elhendy and colleagues [30] studied the use of stress technetium 99 sestamibi in patients with a history of prior MI. In the 383 patients evaluated, there were 48 cardiac events during follow-up. The frequency of events was again directly proportional to the size of the perfusion defect with an event rate of 0.4%, 2.4%, and 4% in patients with

normal perfusion, perfusion deficit consistent with single vessel disease, and that consistent with multi-vessel disease, respectively. Although these studies were not performed in patients in a chest pain unit, they support the use of scintigraphy in this setting for risk stratification of patients with history of CAD.

A further issue complicating chest pain unit management of patients with a history of CAD is the high prevalence of anti-ischemic medications in this group, which may confound the diagnostic utility of stress testing. Beta-blockers and calcium channel-blockers limit the heart rate and blood pressure response during exercise testing and they can avert angina in patients with CAD [31–33]. There are conflicting data regarding the effect of these drugs on the sensitivity of the exercise test in detection of CAD, and patients are often considered ineligible for diagnostic exercise testing if they are taking these agents [31–38]. This potential problem may exclude patients from an accelerated assessment in a chest pain unit, cause a delay in diagnosis, or require hospital admission for further management.

Diercks and colleagues [39] have evaluated the use of beta-blockers and calcium channel-blockers in patients undergoing immediate stress testing in their chest pain unit. Of 176 patients on one of these agents who underwent exercise testing, 50 (28.6%) were taking a beta-blocker only, 116 (66.6%) a calcium channel-blocker only, and 10 (5.7%) were being treated with both classes of drugs. After adjusting for age, gender, cardiac risk factors, and presenting complaint, those patients on beta-blockers or calcium channel-blockers (study group) were more likely to have nondiagnostic tests 69 of 176 (39%) (OR 2.1, 95% CI 1.5–3.1) compared with patients in the cohort who were not taking these agents. The proportion of patients with a nondiagnostic exercise test was higher in the group on antianginal drugs, and beta-blockers were more problematic in this regard than calcium channel-blockers. However, the majority of patients on one or both of these drugs had a diagnostic test 107 of 176 (61%) (negative or positive), confirming the utility of exercise testing in these patients. Thus, despite a higher rate of nondiagnostic tests, inclusion of these patients in a chest pain unit protocol did afford timely disposition of a substantial proportion that would have otherwise been admitted to the hospital [39].

Taillefer and colleagues [40] evaluated the influence of beta-blockers in patients undergoing

dypridamole Tc-99 sestamibi myocardial scintigraphy. They randomly assigned patients with known CAD to receive placebo, low-dose metoprolol, or high-dose metoprolol. Of the 21 patients completing the study, the sensitivity for detection of CAD was 85.7% in the placebo group versus approximately 71.0% in both the low- and high-dose beta-blocker group. In addition, the beta-blocker appeared to decrease the ability to assess severity of CAD based on the size of the perfusion deficit compared with placebo [39]. Although the rate of nondiagnostic tests is higher and sensitivity lower for detecting CAD in patients on beta-blockers, these medications should not be considered an absolute contraindication to chest pain unit management. Although patients with a history of CAD, including those on anti-anginal medications, pose a challenge to traditional chest pain unit protocols, their inclusion in this diagnostic strategy appears to be safe and effective if appropriate selection criteria are used.

### Diabetics

Diabetic patients represent a group with increased risk and a high rate of atypical symptoms for CAD. Cardiovascular disease is the leading cause of death in diabetic patients, and the prevalence of CAD in some diabetic populations is over 50% [23]. Detection of CAD and risk stratification is often confounded by several unique features, including the markedly increased risk in female diabetics, lower predictive value of LDL cholesterol, and high rate of silent myocardial ischemia. In addition, diabetic patients often have poor exercise tolerance and nonspecific ST segment alterations that can result in nondiagnostic or false-positive exercise testing (Box 3) [41].

Despite the foregoing confounders, the value of exercise testing for detection of CAD in asymptomatic patients with type 2 diabetes was demonstrated by Bacci and colleagues [42]. They studied 141 patients who also had peripheral arterial disease or atherogenic risk factors, 71 of whom underwent coronary angiography. The diagnostic accuracy of exercise treadmill testing was 79%. In patients with a positive exercise test, 20 of 27 (74%) had a stenotic lesion  $> 70\%$ . Marwick and colleagues [41] evaluated the use of stress echocardiography in 937 patients with diabetes and confirmed CAD or symptoms of CAD and observed that a positive stress echocardiogram was an independent predictor of death. Elective stress myocardial perfusion imaging has

#### **Box 3. Unique factors in diabetics that affect stress test results**

Increased risk of cardiac events in females with diabetes  
 Lower predictability of traditional cardiac risk factors  
 High rate of silent myocardial ischemia  
 Limited exercise capacity  
 Nonspecific baseline ST segment alterations

also been an acceptable tool for detection of CAD in diabetic patients. A retrospective review of diabetic patients who underwent myocardial perfusion imaging followed by cardiac catheterization reported a sensitivity of 97% and positive predictive value of 88% for CAD [43]. Kang and colleagues [44] reported a similarly high sensitivity (86%) but a specificity of 56% in a similar patient population. These studies support a detection rate for CAD by stress scintigraphy, but specificity of the method may be limited in diabetic patients.

Myocardial stress scintigraphy has also provided prognostic information. Berman and colleagues [45] evaluated 2826 patients who underwent adenosine myocardial perfusion imaging. They noted that diabetics who had an abnormal perfusion scan were at a significantly increased risk of death compared with nondiabetics and that perfusion imaging data was an independent predictor of events. Including diabetic patients in an accelerated protocol that involves stress scintigraphy is a potentially important tool for safe, expedient diagnosis and risk stratification in these often difficult to manage patients.

The studies in diabetics cited previously were performed largely in stable outpatients. Diabetic patients are frequently excluded from chest pain unit evaluation due to their presumed high risk [7]. As in patients with a prior history of CAD, the suitability of diabetics for chest pain unit management is controversial, but it should primarily depend on the immediate risk of ACS rather than the likelihood of underlying CAD. However, the safety and efficacy of including diabetics in a rapid diagnostic protocol are not well documented in the literature. Diercks and colleagues [46] have assessed the use of immediate exercise treadmill testing in diabetic patients evaluated in a chest pain unit. Their findings demonstrated that, whereas

diabetics had more frequent evidence of CAD at 30-day follow-up than nondiabetics (12% versus 5%, RR 2.6, CI 1.7–4.1,  $P < .0001$ ) and required more subsequent diagnostic studies (26% versus 14%, RR 2.0, CI 1.5–2.6,  $P < .001$ ), there was no significant difference in acute cardiac events or length of stay in the chest pain unit between the two populations. Immediate exercise treadmill testing was also equally sensitive in detecting CAD in diabetics as in nondiabetics. Hence, exercise testing in diabetics with a normal baseline ECG and negative cardiac injury markers is a safe, efficacious, and cost-effective method for risk stratification and improves quality of care in this patient population.

Further evidence in support of the safety of this strategy was presented by Sanchez and colleagues [47] who evaluated the 30-day outcomes, resource use, and severity of CAD in patients with and without diabetes admitted to a chest pain unit, who comprised a subgroup of the Chest pain Evaluation and Creatinine Kinase-MB, Myoglobin, and Troponin I (CHECK-MATE) study. The study included 772 patients, of whom 109 had diabetes. All patients were assigned to a chest pain unit or evaluated in the ED for more than 6 hours. In accord with the author's aforementioned findings, the investigators reported an increase in adverse cardiac events (death/MI) in the diabetic patients (8.3% versus 3.2%,  $P = .027$ ). In addition, they reported higher rates of the following events in the diabetic group: admission from the chest pain unit, incidence of elevated cardiac markers, and rate of multivessel disease, especially in patients with  $> 2$  cardiac risk factors. However, there were no safety issues related to assignment to the accelerated diagnostic protocol. Indeed, even the higher adverse event rate in the diabetic group was well within that expected in a typical chest pain unit population.

These studies indicate that chest pain unit observation is appropriate in the foregoing populations if it is predicated on recognition of the higher prevalence of CAD in these patients and appreciation of the limitations of the diagnostic tools. Rigorous patient selection and firm adherence to protocol standards cannot be overemphasized to enhance safe evaluation of in the chest pain unit.

### **Chest pain related to stimulant use**

The use of stimulants such as cocaine and methamphetamines is of epidemic proportions.

According to recent data, 25 million people in the United States have reported using cocaine [48,49], and it is likely that these numbers are similar for methamphetamine. The cardiovascular complications of cocaine have been well studied. It has been reported that the risk of MI is 24 times baseline risk in the hour after cocaine use [50]. In patients under the age of 45 years with acute MI, approximately 25% are cocaine related [51]. Of patients who present to the ED with cocaine-related chest pain, 6% have MI and the rate of cardiac arrhythmia has been reported to be over 2% [52]. Because there are no prospective studies in the methamphetamine patient population, data for cocaine are often extrapolated to the methamphetamine patients. A small study of patients admitted to the hospital with a positive screen for methamphetamine reported an in-hospital event rate of 8%, and in this selected group of patients ACS was diagnosed in 25% [53]. Because this rate of ACS is similar to that in the typical chest pain unit population, it is important to examine the potential utility of this strategy in patients with chest pain during stimulant use. Important considerations include defining the optimal time of observation and the need for specific diagnostic testing after an initial negative evaluation that included cardiac injury markers and ECG on presentation to ED.

Weber and colleagues [48] performed a prospective study to determine the safety of a 9- to 12-hour period of observation in patients who were at low to moderate risk for coronary events. The patient cohort consisted of 347 patients presenting with acute chest pain associated with cocaine use. A total of 42 patients (12%) were admitted to the hospital, of whom 20 had a final diagnosis of ACS, three had congestive heart failure, and two had ventricular tachycardia. Of the remaining 305 patients discharged home after a negative 9- to 12-hour observation period, including exercise testing, there were four nonfatal MIs (1.6%) in patients who continued to use cocaine. The investigators concluded that a 9- to 12-hour period of observation that included cardiac monitoring, serial cardiac biomarkers, and stress testing based on physician discretion was safe.

These results support prior retrospective studies that evaluated the use of an observation unit for the management of cocaine related chest pain. Kushman and colleagues [54] reported a similarly low rate of complications in a retrospective study of 197 consecutive patients admitted to a chest

pain unit. Their protocol included cardiac biomarkers at hours 0, 3, and 6 and consultation by a cardiology fellow with selective use of stress evaluation by treadmill testing. Of the entire group, 22 (11.2%) were admitted to the hospital from the observation unit, one of whom had MI. In the remaining patients who were discharged, there was one (0.6%) cardiac complication during follow-up. However, the implications of provocative testing could not be assessed, because it was performed in only 40.6% of patients.

Current studies on the inclusion of patients with cocaine-related chest pain in a chest pain unit have concluded that a 6- to 12-hour observation period is safe. In both studies mentioned previously, approximately 10% of patients were admitted to the hospital from the observation unit. This result substantiates the utility of inclusion of these patients in a chest pain unit, despite the overall low risk of ACS and arrhythmia. Because of the general lack of provocative testing in these studies, it is difficult to determine the overall cardiac risk of these patients and therefore difficult to compare the prevalence of CAD in these patients with that in a more typical chest pain unit population.

## Summary

Chest pain units provide an important alternative to traditional hospital admission for patients who present to the ED with symptoms compatible with ACS and a normal or inconclusive initial evaluation. Although patient subgroups such as women, diabetics, those with established CAD, and those with symptoms related to stimulant use present unique challenges, management in a chest pain unit appears to be appropriate in these populations. Judicious application of accelerated diagnostic protocols and current testing methods can promote safe, accurate, and cost-effective risk stratification of special populations to identify patients who can be safely discharged and patients who require hospital admission for further evaluation.

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# Management of the Patient with Chest Pain and a Normal Coronary Angiogram

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Approximately 20% to 30% of patients undergoing coronary angiography for symptomatic chest pain are found to have normal epicardial coronary arteries [1,2]. When compared with patients who present with obstructive coronary artery disease, these patients are more likely to be women and tend to be younger [3,4]. Several conditions can result in chest pain with a normal coronary angiogram (NOCAD) and a proper diagnosis of the etiology is essential in managing these patients. This article discusses the pathophysiology of NOCAD and provides a systematic diagnostic approach to these patients. Potential therapeutic options and prognosis are also reviewed.

## Pathophysiology

Angina occurs when there is a mismatch between myocardial oxygen supply and demand. In the absence of significant coronary artery stenosis, coronary blood flow (CBF) is regulated and limited by two main factors: coronary endothelial function and microvascular function.

### *Endothelial function*

Traditionally, the coronary endothelium has been thought of as a monolayer of endothelial cells that line the lumen of the vascular bed; however, it is now known that the endothelium also extends into the vascular wall and adventitia

[5]. The endothelium plays an important role in the regulation of vasomotor tone and CBF. This regulation occurs by way of the production and release of vasoactive factors. The important vasodilators are:

1. *Nitric oxide*: Nitric oxide (NO) is a potent vasodilator. Its effects are mediated by the secondary messenger cyclic 3'5'-guanosine monophosphate [6]. It has a short half-life and is synthesized from the oxidation of the N'-terminal of arginine [7]. This reaction is catalyzed by the enzyme endothelial nitric oxide synthase, which is produced by endothelial cells [7].
2. *Prostacyclin I<sub>2</sub>*: Prostacyclin I<sub>2</sub> causes coronary vasodilation by increasing the production of cyclic 3'5'-adenosine monophosphate in platelets and smooth muscle cells [8]. It is derived from arachidonic acid by the sequential reactions of cyclooxygenase and prostacyclin synthase [9].

The most potent vasoconstricting agents produced by the endothelium are:

1. *Endothelin-1*: Endothelin-1 is produced in endothelial cells from the cleavage of a propeptide by endothelin converting enzymes I and II [10–12]. Vasoconstriction occurs when endothelin-1 binds to the ETA-receptor located on smooth muscle cells [13].
2. *Thromboxane A<sub>2</sub>*: Thromboxane A<sub>2</sub> is derived from arachidonic acid by way of a cyclooxygenase catalyzed reaction. It stimulates vasoconstriction by binding to the thromboxane receptor located on vascular smooth muscle cells [14].

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If the endothelium does not function properly, NOCAD may occur as a result of a mismatch between myocardial oxygen supply and demand. In addition to NOCAD, endothelial dysfunction also promotes atherosclerosis and the eventual development of coronary artery stenosis.

### Microvascular function

The coronary microcirculation consists of the small arteriolar vessels that are less than 300  $\mu\text{m}$  in diameter. These vessels determine 80% of the coronary resistance and therefore play an important role in the regulation of CBF. Four factors regulate the microcirculation:

1. *Myogenic control*: The pressure exerted from the surrounding myocardium influences the intraluminal area of the microcirculation. Myogenic control of the microcirculation allows for the optimal transport of metabolic substances across capillary membranes by maintaining intraluminal pressure within a physiologic range [15].
2. *Flow-mediated control*: This process is endothelium-dependent allowing for auto-regulation of microvascular blood flow [16]. Flow-mediated control helps to maintain intracoronary pressure and prevent shear stress-mediated injury.
3. *Metabolic control*: The metabolic state of the myocardium plays an important role in the regulation of blood flow. Oxygen consumption is the main regulating factor and mediators, such as adenosine, prostacyclin, norepinephrine, and carbon dioxide are involved [17].
4. *Neurohormonal control*: Sympathetic and parasympathetic innervation of the microcirculation allows for neural regulation of CBF. Neurotransmitters, such as acetylcholine, norepinephrine, and neuropeptide Y, help mediate the response [17].

If these control mechanisms do not function properly, microvascular dysfunction occurs. A reduction in the coronary flow reserve (CFR) in the absence of epicardial coronary artery stenosis indicates the presence of endothelial-independent microvascular dysfunction. CFR is the ratio of the average peak velocity (APV) during maximal hyperemia to the APV at baseline. Intracoronary or intravenous adenosine can be used to achieve hyperemia, and APV can be measured with an

intracoronary Doppler wire or by way of transthoracic echocardiography. Patients who present with endothelial-independent microvascular dysfunction have a CFR less than or equal to 2.5.

### Differential diagnosis

The differential diagnosis of NOCAD can be classified anatomically into three categories: (1) epicardial disease, (2) coronary microvascular dysfunction, and (3) noncoronary disease (Table 1). Epicardial disease resulting in NOCAD includes endothelial dysfunction, coronary artery spasm, and coronary artery bridging. Microvascular dysfunction may be secondary to endothelial dysfunction, hypertension, cardiomyopathy, infiltrative disease, valvular disease, or idiopathic. Noncoronary artery disease involving other organ systems, such as the pulmonary, gastrointestinal, or musculoskeletal systems, can also result in NOCAD.

### Epicardial disease

#### *Endothelial dysfunction*

Proper endothelial function is necessary to insure that CBF is adequate to meet myocardial oxygen demand and endothelial dysfunction can result in NOCAD. Intracoronary acetylcholine can be used to assess endothelial function [18,19]. In patients who have normal endothelial function, the smooth muscle contraction mediated by acetylcholine is counterbalanced by its stimulation

Table 1  
Differential diagnosis of chest pain in the setting of a normal coronary angiogram

I. Coronary disease
A. Epicardial disease
1. Endothelial dysfunction
2. Coronary spasm
3. Coronary bridging
B. Microvascular dysfunction
1. Microvascular endothelial dysfunction
2. Hypertension
3. Cardiomyopathy
4. Infiltrative disease
5. Valvular disease
6. Idiopathic
II. Noncoronary disease
A. Gastrointestinal
B. Pulmonary
C. Musculoskeletal
D. Psychologic

of NO production in endothelial cells. According to previous studies, epicardial endothelial dysfunction is defined as a reduction in coronary artery diameter greater than 20% in response to acetylcholine [20,21].

#### *Coronary spasm*

Angina caused by coronary spasm was first described in 1959 by Prinzmetal and colleagues [22]. The chest pain induced by coronary spasm is similar to the pain caused by coronary artery disease but tends to occur at rest and between midnight and 8:00 AM [23]. Each episode can last from 30 to 60 minutes and may be associated with ischemic changes on the ECG. Although the mechanism of disease is not completely known, it seems to involve endothelial dysfunction and an increased response to vasoconstrictor agents, such as catecholamines and thromboxane A<sub>2</sub> [24,25]. Evidence also exists that an increase in autonomic tone may play a role in coronary spasm [26].

Intracoronary acetylcholine can be used as a provocative test for the diagnosis of coronary spasm [27]. Other direct vasoconstricting agents, such as ergonovine maleate, also can be used [28]. Although many patients have some degree of vasoconstriction to these agents, spasm is defined as a greater than 50% focal reduction in lumen caliber that is reversed with intracoronary nitroglycerin [29].

#### *Myocardial bridging*

Systolic compression of a coronary artery by the surrounding myocardium is referred to as myocardial bridging. It was first described in 1737 by Reyman [30] and occurs when a segment of the coronary artery is tunneled in the myocardium. Bridging most frequently occurs in the left anterior descending artery, but reports have shown that it may involve any of the major epicardial coronary arteries. The prevalence of myocardial bridging in autopsy studies has varied from 5% to 86%, but angiographic studies have shown a lower rate of 0.5% to 33% [31]. Although the mechanism is not clear, myocardial bridging can cause NOCAD. Intravascular ultrasound studies have shown that compression can extend into early diastole and reduce CBF [32]. Intracoronary hemodynamic studies have also shown that bridging results in a greater dependence on diastolic CBF [32]. Tachycardia can therefore decrease the diastolic time period and cause a decrease in CBF and ischemia. Endothelial dysfunction and coronary artery

spasm also can occur at the site of myocardial bridging and may result in myocardial ischemia and coronary artery thrombosis [33].

### **Microvascular disease**

#### *Microvascular endothelial dysfunction*

Impaired microvascular endothelial function can result in NOCAD by disrupting autoregulation of CBF. Previous studies have defined microvascular endothelial dysfunction as an increase in CBF less than 50% in response to acetylcholine [20,21].

#### *Hypertension and microvascular dysfunction*

Patients who present with hypertension can present with NOCAD. The mechanism of chest pain in these patients may involve a decrease in CBF caused by an increase in microvascular resistance [34,35]. The increase in resistance may be a result of an increase in myogenic tone caused by elevated diastolic pressures or compression of the microcirculation by the hypertrophied myocardium. A previous study suggests that ventricular hypertrophy plays an important role in microvascular dysfunction because hypertensive patients without ventricular hypertrophy did not have a reduction in CFR [36].

#### *Cardiomyopathy and microvascular dysfunction*

NOCAD occurs in approximately 50% of patients who present with dilated cardiomyopathy [37] and studies have shown that these patients have microvascular dysfunction and a reduced CFR [38,39]. The mechanism of microvascular dysfunction most likely involves myogenic compression secondary to elevated filling pressures or microvascular endothelial dysfunction. Patients who present with hypertrophic cardiomyopathy may also have a reduced CFR and NOCAD [40,41]. Histologic studies suggest that microvascular dysfunction in these patients may be caused by a reduction in the number of small arterioles and a narrowing of the luminal area of the microcirculation [42,43]. An alternative mechanism for the reduction in CFR may be that the microcirculation is already near maximally dilated in the basal state to meet the increase in oxygen demand [44]. Because the vessels are already dilated, their ability to further dilate is limited and the CFR is reduced.

### *Infiltrative disease and microvascular dysfunction*

Patients who present with cardiac amyloidosis can present with NOCAD [45] caused by endothelial dysfunction [46] and amyloid deposits in the tunica media [47]. These deposits cause a reduction in the luminal area of the microcirculation [48–50] and the subsequent ischemia may be one of the factors responsible for the sudden cardiac death that occurs in cardiac amyloidosis.

### *Valvular disease and microvascular dysfunction*

NOCAD can occur in patients who develop aortic stenosis, aortic regurgitation, and mitral regurgitation [51–54]. Previous studies have shown that these patients have a reduction in CFR that may be caused by an increase in filling pressures and wall stress [52,55–57]. These factors increase the myogenic tone and the amount of microvascular compression. Surgical treatment of the underlying valvular disease seems to correct the microvascular dysfunction in these patients [52,58,59].

### *Idiopathic microvascular dysfunction*

Patients who present with no apparent etiology for microvascular dysfunction have idiopathic disease. Syndrome X has been used to describe these patients, but the term is not specific and probably should not be used. The mechanism of disease is not known but may involve an impaired vasodilator response as a result of smooth muscle cell dysfunction and primary microvascular endothelial dysfunction [60]. Increased activity of the sodium-hydrogen ion channel also may play a role in idiopathic microvascular disease [61].

### **Noncoronary etiologies**

The noncoronary etiologies of NOCAD are shown in Table 1. Although these causes of NOCAD are not discussed in this review, the clinician should be aware of noncardiac disease when evaluating patients who present with NOCAD.

### **Systematic approach to diagnosing the etiology of normal coronary angiogram**

#### *Functional angiogram*

Determination of the etiology of NOCAD is essential in its management. A “functional angiogram” (Fig. 1) involving the invasive assessment of coronary physiology allows for a systematic diagnostic approach to these patients. The protocol

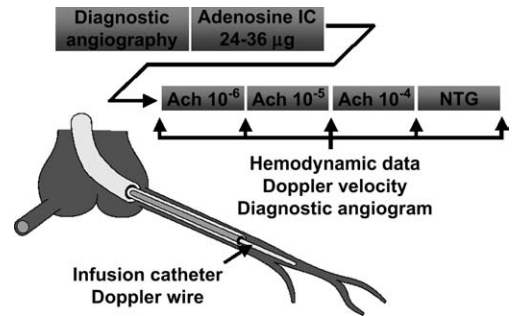


Fig. 1. Functional angiogram protocol to assess coronary endothelial and microvascular function. Ach, acetylcholine; IC, intracoronary; NTG, nitroglycerin.

has been described previously [20,62–64] and a summary is as follows:

After coronary angiography, a guiding catheter is placed into the left main coronary artery. A 0.014-inch Doppler guide wire is placed within a 2.2-F coronary infusion catheter and the system is advanced through the guiding catheter into the middle portion of the left anterior descending coronary artery. The Doppler wire is then positioned 2 to 3 mm distal to the tip of the infusion catheter, and a baseline APV is obtained. Coronary artery diameter is measured 5 mm distal to the tip of the Doppler wire and baseline CBF is calculated with the following equation:  $CBF = \pi (\text{coronary artery diameter}/2)^2 \times (\text{APV}/2)$ . Microvascular function is assessed with the use of an intracoronary adenosine (18–42 µg) bolus. CFR is calculated as the ratio of the APV during maximal hyperemia to the APV at baseline. The authors define a normal CFR as greater than 2.5. Endothelial function is then assessed with the use of acetylcholine. Intracoronary acetylcholine is infused through the infusion catheter at three different doses:  $10^{-6}$ ,  $10^{-5}$ , and  $10^{-4}$  M for 3 minutes each to achieve intracoronary concentrations of  $10^{-8}$ ,  $10^{-7}$ , and  $10^{-6}$  respectively. Two hundred micrograms of intracoronary nitroglycerin is then given at the end of the procedure. APV and coronary diameter is measured before and after each infusion. Based on prior studies, an abnormal response to acetylcholine is an increase in CBF less than or equal to 50% or a reduction in epicardial coronary artery diameter greater than or equal to 20% [20,62].

#### *Interpretation of results*

Epicardial stenosis and myocardial bridging can be ruled out by carefully reviewing the diagnostic angiogram. The functional angiogram then can be

used to classify patients into one of four groups (Fig. 2). Those patients who experience an abnormal response to acetylcholine but a normal CFR have abnormal endothelial function. If there is a focal greater than 50% reduction in luminal caliber during the infusion of acetylcholine then coronary spasm is present. Patients who present with a normal response to acetylcholine but an abnormal CFR have endothelial-independent microvascular dysfunction. These patients probably should undergo echocardiography to help determine the etiology of their microvascular dysfunction. An abnormal response to acetylcholine and a reduced CFR indicates the presence of endothelial dysfunction and endothelial-independent microvascular dysfunction. Finally, those patients who experience a normal response to acetylcholine and a normal CFR are most likely to have a noncoronary etiology of NOCAD. These patients should be evaluated for other etiologies of chest pain, such as gastrointestinal, pulmonary, or musculoskeletal disease. The distribution of findings from 820 functional angiograms performed at the Mayo Clinic are summarized in Fig. 3.

### Prognosis and treatment

#### Endothelial dysfunction

Coronary endothelial dysfunction is a marker of early coronary atherosclerosis and has been

shown to be associated with an increase in myocardial infarction, coronary revascularization, and cardiac death [20]. Fortunately, endothelial dysfunction is reversible if the proper therapy is initiated. Risk factor modification is the cornerstone of therapy and previous studies have shown improvement in endothelial function with exercise, weight loss, and smoking cessation [65,66]. Blood pressure and cholesterol control are also essential. Angiotensin-converting enzyme inhibitors (Table 2) have been shown to improve endothelial function [67–70]. The mechanisms are unknown but seem to be independent of their blood pressure effects. The benefits of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) on endothelial function seem to be independent of their cholesterol lowering effects and may involve their antioxidant and anti-inflammatory properties [71]. Initial studies with peroxisome-activated receptor- $\gamma$  agonists, such as rosiglitazone, have shown some beneficial effects on endothelial function [72]. Finally, other therapies, such as L-arginine and folic acid, have also been shown to improve endothelial function [73,74].

#### Coronary spasm

During the initial active phase (first 6 months) patients experience frequent episodes of angina and are at increased risk for adverse cardiac events; however, long-term studies have shown

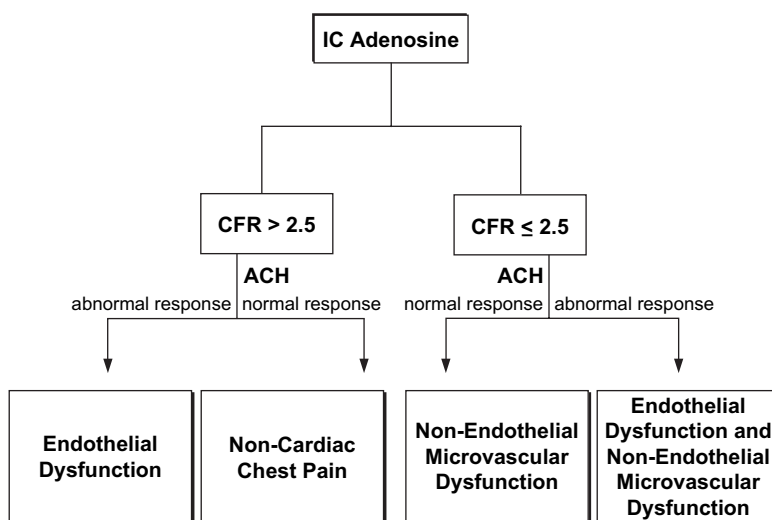


Fig. 2. Algorithm for a systematic diagnostic approach to patients who present with chest pain and NOCAD. An abnormal response to acetylcholine is defined as an increase in CBF less than 50% (microvascular endothelial dysfunction) or less than a 20% increase in coronary artery diameter (epicardial endothelial dysfunction). Ach, acetylcholine; CFR, coronary flow reserve; IC, intracoronary. (Data from Al Suwaidi J, Higano ST, Holmes DR Jr, et al. Pathophysiology, diagnosis, and current management strategies for chest pain in patients with normal findings on angiography. *Mayo Clin Proc* 2001;76:813.)

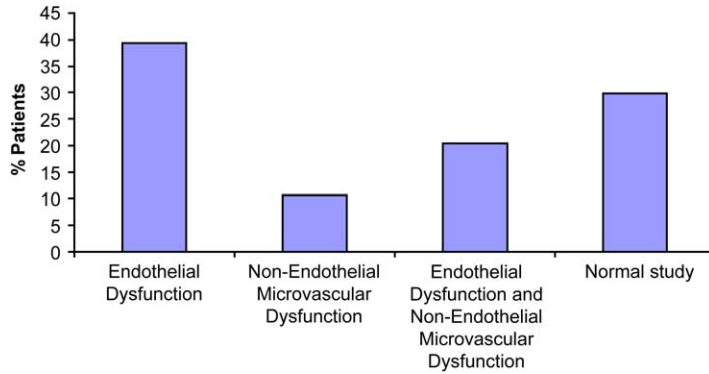


Fig. 3. Distribution of results from 820 functional angiograms performed at the Mayo Clinic.

that after the active phase, the 5-year survival is excellent and there is no increase in cardiac events [75,76]. The first line of therapy for patients who present with coronary spasm (see Table 2) is nondihydropyridine calcium channel blockers and long-acting nitrates [77]. Nonselective beta-blocking agents, such as propranolol, should be avoided because of their potential to exacerbate spasm by way of unopposed alpha-1 action [78]. Aspirin also should be used with caution because of its potential to inhibit the production of vasodilating prostacyclin derivatives [79]. Additional therapy with nifedipine and alpha-blocking agents can be used in patients refractory to first-line therapy [80,81]. Finally, when medical therapy becomes unsuccessful, placement of coronary artery stents or bypass surgery can be considered [82].

*Myocardial bridging*

Patients who present with myocardial bridging have been shown to have a good long-term prognosis [83]. Pediatric patients who present with hypertrophic obstructive cardiomyopathy and myocardial bridging, however, may have an increased risk for death and adverse cardiac events [84]. This increased risk does not seem to occur in adult patients who have developed hypertrophic obstructive cardiomyopathy and myocardial bridging [85].

All patients who develop NOCAD as a result of myocardial bridging should be treated with beta-blockers [86]. Those patients who do not improve with medical therapy can be treated with more invasive procedures, such as surgical

Table 2  
Treatment strategies for patients with chest pain and a normal coronary angiogram

Etiology	First Line Therapy	Second Line Therapy	Comments
Endothelial Dysfunction	Life style modification, ACEI, Statins	L-arginine, folate	PPAR-γ agents may offer benefit
Coronary Spasm	Non-dihydropyridine calcium channel blockers, long-acting nitrates	Nifedipine, alpha-blockers, coronary artery stenting, bypass surgery	Non-selective beta blockers should be avoided, aspirin may exacerbate spasm
Myocardial Bridging	Beta-blockers	Coronary artery stenting, surgical myotomy, bypass surgery	Higher rates of in-stent restenosis occurs in bridging segment
Endothelial-Independent Microvascular Dysfunction	Treatment of underlying etiology of microvascular dysfunction	Beta-blockers, Statins	Imipramine may offer benefits in idiopathic microvascular dysfunction

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; PPAR-γ, peroxisome-activated receptor-γ agonist.

myotomy, coronary artery stenting, and bypass surgery [87–89]. Stents placed in coronary segments with bridging have a higher restenosis rate than those placed in segments without bridging [90].

### *Microvascular dysfunction*

Little is known about the long-term prognosis of patients who experience microvascular dysfunction and otherwise normal coronary arteries. Patients who develop hypertrophic cardiomyopathy and microvascular dysfunction seem to have an increase in adverse clinical events [91]. The interaction between microvascular dysfunction and dilated cardiomyopathy is not known. Treatment of the underlying etiology of microvascular dysfunction is the focus of therapy. Blood pressure control in those with hypertension and reduction of filling pressures and wall stress in patients who present with dilated cardiomyopathy improves microvascular function. Valvular replacement or repair has been shown to improve microvascular function in patients who have valvular disease [52,58,59]. In patients who develop hypertrophic obstructive cardiomyopathy, the effect of myectomy and septal ablation on microvascular function is not known.

Numerous therapies have been investigated for the treatment of patients who present with idiopathic microvascular dysfunction (see Table 2). The efficacy of these therapies is difficult to determine because of the heterogeneous population of patients. Beta-blockade seems to reduce angina symptoms, but no large randomized studies have been performed. Treatment with angiotensin converting enzyme inhibitors and HMG-CoA reductase inhibitors also result in some benefit [92,93]. Imipramine, a tricyclic antidepressant, has been shown to reduce anginal pain in patients who develop idiopathic microvascular dysfunction [94]. The mechanism is not understood completely but may involve inhibition of pain-modulating neurons by blockade of norepinephrine reuptake [95].

### **Summary**

Approximately 20% to 30% of patients who experience chest pain who undergo coronary angiography are found to have normal epicardial coronary arteries. The management of these patients can be challenging and a correct diagnosis of the etiology is essential. A systematic approach to diagnosing the cause of chest pain can be accomplished with a functional angiogram

to assess endothelial and microvascular function. Once the etiology of chest pain is determined, the appropriate therapy can be initiated.

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# Using the Emergency Department Clinical Decision Unit for Acute Decompensated Heart Failure

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In the United States, heart failure (HF) management costs exceed all other single pathologic entities. Because HF is predominately a disease of the elderly, and demographic trends are expected to double the at-risk cohort over the next 30 years, the consequences of HF will only increase. More efficacious strategies for early diagnosis, better treatment options, and improved clinical outcomes are urgently needed. This article reviews the newest options for HF management with particular emphasis on care in the emergency department (ED) observation unit (OU).

## Epidemiology and economics

Disproportionately affecting the elderly, HF is the only cardiovascular pathology that is increasing in both incidence and prevalence [1,2]. If under 50 years of age, less than 1% of the U.S. population is diagnosed with HF, but by age 80, this number rises to 10%. This has huge cost implications for our national health system. Inpatient HF costs are estimated as high as \$23.1 billion and outpatient costs at \$14.7 billion, annually. Annual HF hospitalization costs exceed the combination of costs for breast and lung cancer [3].

In the United States, patients older than 65 have health insurance provided by the Centers for Medical Studies (CMS). Because most HF patients are elderly, statistics from the CMS drive many of HF management decisions. According to CMS, HF is the most common cause of hospitalization, and it is the most common reason for hospital readmission in patients over 65 years of age [3]. Unfortunately, HF has an extremely poor

prognosis. After becoming symptomatic, 2-year mortality is about 35%, and rises to 80% in men and 65% for women over the next 6 years. After a diagnosis of pulmonary edema, only 50% survive at 1 year. Up to 85% of those with cardiogenic shock are dead within 1 week. Unless new strategies are devised, the HF epidemic will markedly worsen. Management in an OU represents an opportunity to improve the quality of care for HF patients.

HF is a disease of recidivism, characterized by frequent clinical exacerbations that prompt ED visits. Although it may have a pattern of deterioration and improvement, the overall course is that of a steadily deteriorating clinical pattern. As HF slowly progresses, quality of life is eroded by frequent ED visits, hospitalizations, and increasing disability until death. The frequency of recidivism is reflected in the ED HF population: only 21% of patients represent a de novo presentation. The majority of the ED HF population already carries the HF diagnosis when they arrive with acute dyspnea.

Once a patient presents to the ED with acute decompensated HF (ADHF), inpatient admission is the rule, rather than the exception. An ED visit is indicative of either severe disease or the consequence of inadequate social support. In the best of situations, definitive resolution of either is difficult, particularly in the ED environment. Consequently, 80% of HF presentations result in hospitalization.

As discussed previously, CMS provides health insurance to patients older than 65 in the United States. Because most HF patients are older than 65, this creates an unusual economic situation where a specific disease is predominately covered by a single third-party payor, and a hospital's

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economic health may be greatly impacted by their reimbursement rules. Inpatient care of HF falls within the diagnostic related group (DRG) system, with DRG 127 (HF) as the single most expensive diagnosis. In this year alone, there will be more than 1 million HF hospital discharges in the United States.

CMS affects care by reimbursement inducements, where three main parameters drive HF management. These include length of stay (LOS), revisit frequency, and intensity of service. By this method, when a hospital submits patient data, a diagnosis-based algorithm is used to calculate reimbursement and a regionally standardized sum of money is paid. The actual amount received by the hospital is determined by the diagnosis and is independent of the actual cost of care. Therefore, the financial margin on which the hospital must survive is the difference between reimbursement and the true cost of providing care.

The single greatest contributor to cost is LOS. Therefore, significant pressure exists for the institution to control LOS so that costs do not exceed the CMS payment. Ultimately, an excessive average LOS results in an institutional loss. With regard to HF, the breakeven point occurs at approximately 5 days. The average LOS must be maintained closer to 4 days to ensure that a profit margin exists to cover the losses incurred by outliers. In reality, the average hospital in the United States is unable to control cost and sustains a net loss of \$1,288 for every HF admission [3].

If the only economic incentive were to shorten LOS, undue discharge pressure on hospitals could adversely impact care. Theoretically, patients could be sent home from the hospital every 3 days, only to immediately return for readmission. Therefore, to balance the early discharge incentive, the 30-day revisit penalty was created. After an initial hospitalization, readmission within 30 days for the same DRG may be considered part of the original visit. In this situation, there is no additional reimbursement, and the hospital receives no additional money for the second admission. This creates an economic pressure to prevent premature discharge and eliminate readmissions within 30 days.

The third pressure impacting HF care comes from the resources required to manage the patient. This represents the true cost of care and is proportionate to the intensity of service provided. Therefore, the more staff or physical resources required to manage a patient, the greater the rate

of consumption of the DRG payment. In this manner, the areas with the greatest cost of care (eg, the ICU) must be carefully used to prevent economic loss.

When global resource use is considered, diagnostic and therapeutic interventions represent a small percentage of the cost of HF management. Rather, LOS, 30-day revisit frequency, and the intensity of service occurring within the hospital are the main determinants of institutional financial success.

### **Role of the observation unit**

In 2002 CMS began an ambulatory patient classification (APC) code for the OU. The OU is defined as an outpatient environment providing a longer period of management, far exceeding the usual capabilities of the ED, but not considered hospitalization. This new code allows a non-DRG reimbursement, independent of the 30-day revisit penalty, for treatment with a length of stay up to 48 hours. OU admissions may occur as many times as is required, and the hospital is reimbursed for each individual event. Not only is this economically beneficial to the hospital, but by avoiding inpatient hospitalization, limited intensive management could provide quality-of-life improvements.

The OU is an option for HF care in an environment where a period of short intensive therapy, monitoring, and aggressive management can occur. This definition is important for its success. The OU is not a preadmission testing unit, nor is it a holding area for patients with unclear treatment goals, undefined diagnostic endpoints, or vague disposition plans. Successful HF management is complicated and difficult. Physician involvement, and a dedicated nursing staff armed with clear management protocols, can significantly improve the care in the HF patient. A well-orchestrated OU HF management plan has been shown to decrease revisits, hospitalizations, and LOS [4]. Even if subsequent hospitalization is required, overall LOS, inclusive of the OU visit, decreases [4].

To qualify for the APC code, there are several requirements. First, care must be given for at least 8 hours in the OU environment. Second, there are several clinical parameters that must be met; these include the documentation of pulse oximetry measurement, the performance of a chest radiograph, and obtaining an electrocardiogram (ECG). Finally, the APC allows for care that

may not exceed 48 hours. However, the length of stay rule is tempered by an important caveat: although the APC structure allows for hospitalization for up to 48 hours, CMS ceases reimbursement at 24 hours. Therefore, most units plan for disposition within 1 day at which time patients are either admitted to the hospital and converted to a DRG or discharged home.

Although the APC thresholds are easily met, it is important that the OU does not admit every ED patient with HF. Because the requirement of the OU is discharge within 24 hours, populating the unit with patients who exceed the LOS parameter results in decreasing its efficiency. Furthermore, nurse-to-patient ratios are usually lower in the OU than in the ICU (three to four patients per nurse), so that admissions to an OU environment should match its ability to manage appropriately selected patients.

An OU HF management program can provide benefit to the institution and the patient. The hospital benefit is two-fold: (1) by providing care outside of the DRG revisit rule, the average per patient reimbursement rate is higher, and (2) the intensity of service costs are lower, compared with the inpatient unit. For the patient, the OU is able to provide short, intensive therapy without the necessity of several days of hospitalization and allows early return to the home environment. Additionally, the OU can facilitate the performance of procedures that may be difficult. For instance, ejection fraction (EF) measurement is a standard for HF treatment and is requirement of the JCAHO [5]. Transportation limitations in nonambulatory patients (eg, a nursing home resident) can delay or prevent this evaluation. Likewise, multiple outpatient visits required for initiation and optimization of HF medication (eg, beta-blockers or angiotensin-converting enzyme inhibitors) can be accomplished.

As a last point of discussion regarding the fiduciary structure options for a hospital, an institution may benefit financially to a greater extent by the admission of all short-stay HF patients to the higher reimbursed inpatient DRG. Although this is accurate in the short-term, in the long-term this behavior is penalized by the case mix multiplier. The case mix multiplier is the tool by which CMS adjusts DRG reimbursements at the local level. It is based on the average acuity for a given DRG. When a hospital's average acuity of illness is decreased, the case mix multiplier is decreased proportionally so that the hospital receives less average DRG payment per

patient. If the average acuity increases, the case mix multiplier is increased proportionally. By admitting short-stay HF patients to the hospital and claiming the DRG, the hospital will realize a short-term gain as they receive the higher acuity DRG, up until time for the case mix multiplier adjustment. After their case mix multiplier is decreased, they will receive a decreased DRG reimbursement for all their DRG 127 (HF) patients. This becomes trading short-term gain for long-term loss and provides the incentive for accurate DRG and APC coding.

### Pathophysiology

Wall tension is a product of pressure (after-load) and ventricular radius. Increasing wall tension is a stimulus for cardiac remodeling. With increasing tension, cardiac myocytes either hypertrophy or die (apoptosis) to form scar tissue. The dominant response determines HF type. Many different pathologies may ultimately lead to the clinical presentation of HF (Box 1). The dominating pathway determines the type of HF that results.

HF is divided into systolic dysfunction or preserved systolic function (PSF) types by the EF. A normal EF is defined as 60%, with systolic

#### Box 1. Causes of heart failure

- Acute mitral regurgitation (papillary rupture)
- Acute pulmonary embolus
- Anemia
- Arteriovenous fistula (eg, dialysis)
- Cardiac free wall rupture
- Constrictive pericarditis
- Complications of MI
- Coronary artery disease
- Hyperkinetic states
- Idiopathic cardiomyopathy
- Myocarditis
- Pericardial disease/tamponade/effusion
- Poorly controlled hypertension
- Postpartum cardiomyopathy
- Sustained cardiac arrhythmia/tachycardia
- Thyrotoxicosis
- Valvular rupture or disease

dysfunction defined as an EF < 40%. Systolic dysfunction is most commonly the result of ischemic heart disease, although many other causes exist. The pathologic feature of systolic dysfunction is a ventricle that has difficulty ejecting blood. Impaired contractility leads to increased intracardiac volumes and pressure, and increasing afterload sensitivity. Consequently, these patients are sensitive to hypertension, and maintaining blood pressure (BP) to as low as is tolerated becomes an important management goal.

PSF HF is defined by preserved mechanical contractile function. When measured, the EF is normal or higher. The pathologic deficit is a ventricle with impaired relaxation, which results in an abnormal diastolic pressure-volume relationship. In this situation, the left ventricle (LV) has difficulty in receiving blood. Decreased LV compliance necessitates higher atrial pressures to ensure adequate diastolic LV filling. The hemodynamic consequence of a stiffened noncompliant ventricle is preload sensitivity, where excessively lowered preload may result in hypotension because of a lack of ventricular filling. The frequency of diastolic dysfunction increases with age. Chronic hypertension and LV hypertrophy are often responsible for this syndrome. Coronary artery disease (CAD) also contributes, and diastolic dysfunction is an early event in the ischemic cascade. It has been reported that as many as 30% to 50% [6] of HF patients have circulatory congestion on the basis of diastolic dysfunction.

The pathologic distinctions based on EF are less important in the acute care setting of the ED and OU. In these environments, volume overload with excessive filling pressures are the most common ED presentation. Irrespective of the EF, the treatment approach is therefore similar. However, once hemodynamics are stabilized, and volume status approaches euvolemia, recognition of the underlying EF and the etiology of HF should be considered. In patients with PSF, excessive diuresis or venodilation may exacerbate the underlying deficit in ventricular filling and result in hypotension.

Determining HF type is difficult using the history and physical examination; consequently, an ECG becomes necessary. Some differentiate between left- and right-sided HF. Left-sided HF has dyspnea, fatigue, weakness, cough, paroxysmal nocturnal dyspnea, and orthopnea in the absence of peripheral edema, jugular venous distention (JVD), or hepatojugular reflux (HJR). Right-sided HF has peripheral edema, JVD, right

upper quadrant pain, and HJR, without pulmonary symptoms. Because the cardiovascular system is mechanically closed and abnormal pressure and chamber volumes are eventually reflected to the contralateral side, this distinction has greatest applicability when there is suspicion of valvular heart disease.

#### *Role of neurohormones*

Before the natriuretic peptides (NPs) were identified, extracellular fluid regulation was believed to be controlled by the kidneys, adrenal glands, and sympathetic nervous system via the renin-angiotensin system and other neuroendocrine mechanisms [7]. When arterial BP declines, renin is released by the kidneys. Renin splits hepatically synthesized angiotensinogen to form angiotensin I. Angiotensin I is a biologically inactive decapeptide that is cleaved by angiotensin-converting enzyme (ACE) to form active angiotensin II (AII). AII, a potent vasoconstrictor, increases peripheral vascular resistance and causes an increase in systolic BP. AII also has direct kidney effects that result in salt and water retention and stimulates adrenal aldosterone release. Increased aldosterone causes renal tubular absorption of sodium and results in water retention. Ultimately, extracellular volume and BP increase [7].

Natriuretic peptides are important in both BP and fluid balance. Physiologically, atrial NP (ANP) and B-type NP (BNP) function as a counter-regulatory arm to the renin-angiotensin system in regard to BP and volume maintenance. Three types of natriuretic peptides are recognized. ANP is primarily secreted from the atria. BNP is secreted mainly from the cardiac ventricle. Finally, C-type natriuretic peptide (CNP) is localized in the endothelium. The clinical effects of NPs are vasodilation, natriuresis, decreasing levels of endothelin, and inhibition of both the renin-angiotensin-aldosterone system and the sympathetic nervous system. BNP is synthesized as a prohormone, which is cleaved to inactive N-terminal pro-BNP, with a half-life of approximately 2 hours, and physiologically active BNP with a half-life of about 20 minutes [8].

Although BNP was named "brain natriuretic peptide" because it was first identified in porcine brain [9], in humans the dominant source is myocardial. BNP is secreted and stored in cardiac ventricular membrane granule [9]. BNP is continuously released from the heart in response to both volume expansion and pressure overload [10].

BNP is cleared by three pathways: a protein receptor, neutral endopeptidases, and to a lesser extent, the kidney [11]. Both ANP and BNP have natriuretic and diuretic characteristics that increase sodium and water excretion by increasing glomerular filtration rate and inhibiting renal sodium resorption [12]. They also decrease aldosterone and renin secretion, causing both a reduction in blood pressure and extracellular fluid volume [8–12]. Circulating BNP levels increase in direct proportion to HF severity, as based on the New York Heart Association (NYHA) classification, and BNP is detectable even with minimal clinical symptoms. Physiologically, there is a correlation between BNP concentrations and LV end diastolic pressure (LVEDP). This suggests that the natriuretic effects, coupled with neurohormonal antagonism, serve to counterbalance fluid overload and elevated ventricular wall tension [12]. There is also an inverse correlation between BNP and LV function after acute MI. Elevated BNP occurs in the setting of raised atrial or pulmonary wedge pressures, or MI [12]. Ultimately, BNP measurement offers an independent assessment of ventricular function without the use of intravascular pressure monitoring.

### Clinical features of decompensated heart failure

HF may present after myocardial infarction as the result of acute pump dysfunction. This is the result of the loss of a critical amount of myocardial contractile ability, the consequence of which is immediate symptoms. If there is symptomatic hypotension accompanied by findings of symptoms of inadequate perfusion (eg, mental status change, decreased urine output), cardiogenic shock is diagnosed. Patients with cardiogenic shock require hemodynamic monitoring and arrangements for emergency revascularization. They are therefore inappropriate OU candidates.

HF can present precipitously, as acute pulmonary edema (APE), and also insidiously as the final consequence of a cascade of pathologic events initiated by myocardial injury or stress. After a threat to cardiac output, a cascade of neurohormonally mediated reflexes occurs. These include activation of both the renin–angiotensin–aldosterone system and the sympathetic nervous system. Consequently, the levels of these neurohormones increase and include norepinephrine, vasopressin, endothelin (the most potent vasoconstrictor known), and TNF-alpha. Although not available in routine clinical practice, these

hormone elevations are critical and correlate directly with mortality in HF patients.

Neurohormonal activation results in both sodium and water retention and an increase in systemic vascular resistance. Although these reflexes are initially compensatory and function to maintain systemic BP and perfusion, they occur at a cost of increased myocardial workload and cardiac wall tension. HF can be asymptomatic through these initial neurohormonal and hemodynamic perturbations. However, these reflexes establish the mechanism that initiates the secondary pathologic process of cardiac remodeling. Neurohormonal activation portends a worse prognosis in HF. Its attenuation forms the theoretical basis for nearly all treatments that decrease morbidity and mortality. This includes ACE inhibitors, angiotensin-receptor blockers, aldosterone antagonists, beta-blockers, and nesiritide.

### Differential diagnosis

Many diseases mimic HF (Box 2). Because treatment omissions prevent optimal response, and misdirected therapy may have adverse consequences, an accurate diagnosis is important. Acute MI must always be considered as the cause of a HF visit. As many as 14% of ED HF presentations will have a troponin diagnostic for MI [13]. Furthermore, ADHF patients with elevations in troponin have markedly worse acute outcomes [14].

Additionally, because shortness of breath is the most common presenting symptom, other dyspneic conditions must be considered. A common confounder is coexisting chronic obstructive

#### Box 2. Differential diagnosis of acute heart failure

- Acute MI or myocardial ischemia
- Aortic dissection
- Chronic obstructive pulmonary disease exacerbation
- Hypoproteinemias (nephrotic syndrome, liver failure)
- Pericardial effusion
- Pneumonia
- Pneumothorax
- Pulmonary embolism
- Renal failure
- Superior vena cava syndrome
- Thyroid disease

pulmonary disease. Severe hypertension and peripheral vasoconstriction may suggest acute HF, even with audible wheezing. Pneumonia or pulmonary embolus can mimic or exacerbate HF. Finally, edema is common in HF, but is nonspecific because it is found in many hypoproteinemic states, including hepatic or renal failure, and vascular diseases.

### Diagnostic evaluation

Effective HF care must begin with accurate diagnosis and be followed by expeditious treatment. Failure with either aspect will have adverse effects on outcome. Despite being common in the ED, HF is frequently misdiagnosed. This is due to the fact that the history and physical, ECG, and radiograph findings are either nonspecific or insensitive [6,15–25]. The ED misdiagnosis rate has been reported as 12%. Of these, half are patients diagnosed with HF, although their symptoms are actually the result of other pathology, and the remainder are HF patients given a different diagnosis (eg, chronic obstructive pulmonary disease) [26]. This occurs not only because of the limitations noted previously but also because the differential diagnosis of the at-risk population is complicated by many other conditions. In individual patients, even experienced physicians disagree on the diagnosis of HF, especially if the patient presents early in the disease course [10].

HF has historically been defined as a syndrome, but even with the advent of the BNP assay, clinical data are still required for an accurate diagnosis. This presents a diagnostic challenge, and various strategies have been constructed to improve diagnostic accuracy. Diagnostic criteria, such as the Framingham HF scoring systems [27], help address the challenge. However, they depend on the presence of symptoms, and so they are insensitive if the patient is asymptomatic. Consequently, the severity of illness is important when attempting to determine the presence of an HF diagnosis. In a study of patients presenting to a primary care environment, the first diagnosis of HF was falsely positive in more than 50% of cases. This misdiagnosis rate was attributed to obesity, unsuspected cardiac ischemia, and pulmonary disease [15]. Diagnostic accuracy was also affected by gender, and the rate of a correct HF diagnosis was surprisingly low at the first encounter—18% for women and 36% for men [15].

With regard to the physical diagnosis of HF, the clinical examination is poor. The best physical

findings are jugular venous distention and abdominal jugular reflux (AJR), but their overall accuracy is only 81% for predicting a pulmonary capillary wedge pressure (PCWP) > 18 mm Hg. Alone, AJR has a specificity of 94%, but its sensitivity is only 24% [24]. Rales are common, but their negative predictive value is only 35% [23]. Lung sounds, peripheral edema, jugular venous distention, AJR, and the presence of extra heart sounds help to detect fluid overload, but they are either insensitive or nonspecific in those at risk for HF. Unfortunately, the easily available diagnostic tests (laboratory studies, ECG, and radiographs) are not sufficiently accurate to reliably make a correct diagnosis [16,17].

Many physicians rely on the chest radiograph (CXR) for diagnosis; however, it is an insensitive tool. In chronic HF, CXR signs of congestion have poor sensitivity and specificity for detecting a high PCWP [19]. A radiographically enlarged cardiac silhouette can help, but 20% of echocardiographically proven cardiomegaly is undetectable on radiograph [20]. Pleural effusions can also be missed by CXR, especially if the patient is intubated and the radiograph performed supine. The sensitivity, specificity, and accuracy of the supine CXR are reported as 67%, 70%, and 67%, respectively [21], with the portable CXR having even less sensitivity [22].

The determination of EF has been termed the “single most important measurement in HF” [1] and represents the standard for noninvasive ventricular function assessment. It is indicated in those without an established diagnosis of systolic dysfunction, unless performed within the previous year [1,28–30]. Although defining HF cause and type is important, there is no correlation between symptoms and EF. Consequently, EF measurement is usually unnecessary in the ED. EF may be useful in the OU to help determine treatment strategies at discharge.

### B-type natriuretic peptide assays

Although a number of companies manufacture central lab BNP assay, and Roche Diagnostics produces a central lab NT-pro-BNP assay, there is currently only one point-of-care BNP assay available (Triage BNP, Biosite Diagnostics, San Diego, California). This has ramifications in the ED, where time to diagnosis has consequences for disposition decisions, as well as general ED operational efficiency. The only point-of-care



assay is a fluorescent immunoassay that quantitatively measures whole blood BNP, or plasma specimens in which EDTA is the anticoagulant. It is rated as a moderately complex assay per Clinical Laboratory Improvement Amendment (1988) regulations. To perform the assay, a sample of whole blood is placed in the device, and within 15 minutes it displays the BNP concentration. Testing should not be delayed more than 30 minutes after the blood has been placed in the device. The analytic sensitivity is 5 pg/mL (95% CI 0.2 to 4.8 pg/mL) (per package insert). When this system was tested against more than 50 commonly used cardiac medications (eg, digoxin, warfarin, nitroglycerin, furosemide) and cardiac neurohormones (eg, renin, aldosterone, angiotensin I, and II, ANP), the assay demonstrated no significant measurement interference or cross-reactivity (per package insert).

#### *B-type natriuretic peptide versus filling pressures*

In a study of 72 symptomatic LV dysfunction patients with EF < 50%, BNP was an independent predictor of increased LVEDP, and BNP varied directly with changes in LVEDP [31]. In a second study, the sensitivity and specificity for predicting LVEDP > 18 mm Hg were 81% and 85%, respectively [32]. Others support that an elevated BNP is predictive of elevated end-diastolic pressures [31,33]. In decompensated HF patients, with BNP levels obtained every 2 hours during treatment, there was a correlation between PCWP and BNP changes ( $r = 0.79$ ,  $P < .05$ ). BNP levels dropped in parallel with a falling PCWP in response to treatment [34]. These studies suggest that BNP is an indicator of elevated intracardiac pressures and responds dynamically to ventricular volume and pressure changes.

#### *B-type natriuretic peptide confounders*

If the BNP assay is construed as only a test for HF, a number of confounders exist. In one report, approximate median BNP levels were increased two-fold in medically treated essential hypertension, three-fold in cirrhosis, and 25-fold in dialysis patients, although all measurements included significant ranges around the median [35]. Although some describe increased BNP with hypertension [36], others have not duplicated this finding unless there was coexistent LV hypertrophy [37]. Therefore, isolated hypertension is probably not associated with elevated BNP unless

there is coexistent LV hypertrophy. BNP is also elevated in a number of other conditions. The elderly can have elevated BNP, and there is good correlation between BNP, age, and LV mass index [38]. In a study of 72 healthy 85 year olds [37], compared with 105 healthy 40-year-old men, the older cohort had a mean BNP level of 24.8 pg/mL, compared with a level of 4 pg/mL in the younger group ( $P < .05$ ). BNP may be elevated in the elderly because of greater ventricular mass as compared with the young [39].

BNP is also elevated in renal failure. It is unclear if this results from volume overload-related BNP elevation or a decrease in BNP clearance. In a study of 32 hemodialysis patients without overt HF, BNP was markedly increased. The predialysis BNP was 688 pg/mL, decreasing to 617 pg/mL after dialysis, although mean BNP levels were higher if the EF was less than 60% [40]. Studies controlling for creatinine clearance have shown that BNP has predictive utility for the diagnosis of HF, and some have suggested using a higher cutpoint of 200 pg/mL for BNP indicating HF [41].

Other causes of non-HF BNP elevation include conditions that result from predominately right ventricular dysfunction. In these situations, BNP can be elevated and may be helpful for determining both diagnosis and prognosis. BNP appears to be elevated in ventricular dysfunction, irrespective if left or right, and independent of the cause of the dysfunction. Although there are limited data to date, this also suggests that BNP may be elevated in other causes of right-sided heart strain (eg, a large pulmonary embolus).

Recent literature has addressed the potential for false-negative BNP levels. Some have reported a negative relationship between body mass index and BNP levels [42]. In the ambulatory care setting, both symptomatic and asymptomatic patients with chronic, stable systolic HF may present with a wide range of plasma BNP levels [43]. Clinical impression, in addition to confirmatory testing, is necessary to interpret the results of BNP testing accurately.

#### *Diagnosis*

BNP is markedly elevated over baseline in symptomatic HF. Data from several studies [10,44,45] indicate that its sensitivity for diagnosing HF is from 85% to 97%, with a specificity of 84% to 92%. The positive predictive value is 70% to 95% [10,26], and the negative predictive

value consistently exceeds 90% [26,46]. In 250 Veterans Administration dyspneic urgent care patients, BNP was an accurate predictor of the presence of HF. In this trial, the mean BNP in HF was  $1076 \pm 138$  pg/mL, versus  $38 \pm 4$  pg/mL among non-HF patients. Using a cut point of 100 pg/mL, BNP provided sensitivity, specificity, and positive and negative predictive values of 94%, 94%, 92%, and 96%, respectively [26]. In this study, 30 patients were misdiagnosed clinically. In 15 patients diagnosed as having HF, although later proven to have another diagnosis, the mean BNP was  $46 \pm 13$  pg/mL. In the 15 erroneously given non-HF diagnoses, their mean BNP was  $732 \pm 337$  pg/mL. BNP levels also were indicative of being hospitalized; those requiring hospitalization had a mean levels of 700 pg/mL, compared with those who were discharged who had a mean BNP of 254 pg/mL [26].

Similar results were found in the larger Breathing Not Proper trial, which studied 1586 ED patients short of breath. Using a cut point of 100 pg/mL, BNP had a diagnostic accuracy for HF of 83.4%, and the negative predictive value was 96.0% at a cut point of 50 pg/mL [47].

Although excellent for excluding the diagnosis of HF, BNP is only moderately accurate at determining HF type. It predicts systolic dysfunction with a sensitivity and specificity of 83% and 77%, respectively, compared with PSF, for which the sensitivity and specificity were 85% and 70%, respectively [32]. Compared with PSF, systolic HF had higher levels; 362 pg/mL, as compared with 137 pg/mL ( $P = .03$ ) [48]. The receiver operating characteristic (ROC) AUC for BNP detecting HF was 0.92, ( $P < .0001$ ). Although BNP is a good predictor of the presence of HF, it does not accurately predict EF.

Once a baseline BNP is established, serial measures may suggest therapeutic response. In a study of HF patients receiving carvedilol, there was a correlation ( $r = 0.698$ ,  $P < .01$ ) between improving EF and a declining BNP [49]. In a report of malignant hypertension, therapy-associated LV hypertrophy regression was associated with decreasing BNP levels [50]. Sequential BNP measurements may have an application for monitoring therapeutic response.

### Prognosis

In decompensated HF, serial BNP measurement may predict outcomes. In a group who died or was readmitted to the hospital within 30 days

after receiving inpatient treatment for HF, 52% had an increasing BNP during hospitalization. This compares to the group without readmission or death, in which 84% had a declining BNP during hospitalization [42]. This suggests that therapy-induced BNP changes can predict outcome in decompensated HF.

In the outpatient setting, BNP can reflect HF severity and prognosis [51]. In 290 NYHA class I or II HF patients, with a mean EF of 37%, followed for 812 days, an initial BNP  $> 56$  pg/mL was an independent predictor of HF progression and mortality [52]. Others corroborate BNP predicting cardiovascular mortality. In a 1-year study, an elevated BNP was a better predictor of cardiovascular mortality than age, ANP, EF, PCWP, gender, HF etiology, or NYHA class [53]. An elevated BNP predicts greater mortality and morbidity for HF patients, and this relation is independent of underlying CAD.

### *N-terminal pro-B-type natriuretic peptide*

N-terminal pro-BNP (pro-BNP) is a synthetic BNP precursor. Like BNP, pro-BNP originates primarily from the ventricular myocardium and is released as a result of ventricular stress from either pressure or volume overload. On a molecular basis, pro-BNP is about twice the size of BNP and has a half-life of 1 to 2 hours. According to manufacturer (Roche Diagnostics, San Diego, California) recommendations, the pro-BNP assay has two diagnostic cut points based on age, 125 pg/mL if  $< 75$  years and 450 pg/mL if  $> 75$  years of age. Only recently available, there are relatively few data guiding the clinician in the clinical use of pro-BNP. One trial directly compared pro-BNP and BNP for predicting EF [54]. They found that while both assays had similar performance, neither was adequately sensitive or specific for clinical EF prediction. In evaluating the development of HF in post-MI patients, pro-BNP had a 97% sensitivity for predicting an EF  $< 45\%$ , if levels were determined between 3 and 5 days post-MI. Accuracy of predicting post-MI ventricular dysfunction is similar between pro-BNP and BNP, but the level must be obtained later after presentation if using pro-BNP.

Differences between the two assays include that, unlike BNP, biologically inert pro-BNP is not confounded by concurrent nesiritide infusion and, therefore, pro-BNP measurement can be performed accurately during its infusion. Because four half-lives are needed to reach steady state,

pro-BNP levels reflect hemodynamics from 6 to 8 hours prior. To make the same determination with BNP, because of its much shorter half-life, a nesiritide infusion must be withheld for 90 minutes so that endogenous BNP levels reflect the hemodynamic state rather than infused BNP. Finally, while BNP is available on a point-of-care platform, pro-BNP is only currently available on a central lab platform.

#### *Clinical use of B-type natriuretic peptide assays*

In ED HF patients, an elevated BNP suggests future adverse cardiac events [55] and, when considered with clinical impression, may help in selecting candidates for OU HF therapy. BNP is most useful for excluding HF in those conditions where the differential would normally suggest HF. This includes undiagnosed patients with any of the classic signs or symptoms of HF (shortness of breath dyspnea on exertion, orthopnea, dependent edema, and physical examination findings of a cardiac S3, jugular venous distention, or basilar rales). In this scenario, a normal BNP should prompt the consideration of an alternative diagnosis.

Because non-HF conditions can result in an elevated BNP, the clinical context of a positive BNP must be considered. A positive BNP suggests the need for routine tests to confirm the diagnosis, as well as evaluation of the cause and definition of the type of HF (eg, ECG, CXR, and echocardiogram). See **Box 3** for suggested approach to the use of the BNP assay.

BNP is also used to monitor chronic HF, because levels correlate with treatment efficacy. After HF exacerbation, a declining BNP indicates a good response to therapy and portends a more favorable outcome. A rising BNP suggests a greater risk of adverse outcome, and a more aggressive treatment strategy may be warranted.

### **Emergency department management**

#### *General support*

The initial approach is based on the acuity of presentation, volume status, and systemic perfusion. In critical patients, airway management overrides all other interventions. This is in contrast to minimally symptomatic patient whose evaluation may occur in lieu of stabilization procedures. Initial stabilization is aimed at maintaining airway control and adequate ventilation.

#### **Box 3. Interpretation of B-type natriuretic peptide (BNP) assays**

- Low BNP (< 100 pg/mL)
  - Presenting symptoms are unlikely the result of HF, an alternative diagnosis should be considered (eg, chronic obstructive pulmonary disease).
- Intermediate BNP (100 to 500 pg/mL)
  - Consider other diagnoses (Cor pulmonale, pulmonary embolism, primary pulmonary hypertension).
  - Compare with prior baseline BNP levels.
- High BNP (> 500 pg/mL)
  - HF is the likely diagnosis, although confounders should be considered.

Supplemental oxygen can be given based on pulse oximetry. As the consequences of hypoxia are of greater significance than the potential for hypercarbia, O<sub>2</sub> is not withheld based on CO<sub>2</sub> retention concerns. Arterial blood gases may be helpful in the critically ill or if CO<sub>2</sub> retention is likely.

Because patients with HF do not hemodynamically tolerate hypertension, it is desirable to maintain the BP as low as is consistent with the ability to mentate, urinate, and ambulate. Chronic systolic BPs in the 90 mm Hg range are usually well tolerated by the HF patient. In the hypertensive acute pulmonary edema patient, a controlled lowering of BP may result in a profound improvement of symptoms and dyspnea.

Noninvasive positive pressure ventilation (NPPV) is controversial. Some report it may be used to prevent endotracheal intubation in the properly selected patient while awaiting hemodynamic interventions to become effective. Biphase positive pressure ventilation (BiPAP) requires the delivery of separately controlled inspiratory and expiratory pressures via facemask. Continuous positive airway pressure (CPAP) provides constant pressure throughout the respiratory cycle. For a trial of NPPV, close cardiac monitoring, relative hemodynamic stability, and patient cooperation are needed. NPPV may provide mortality benefit over invasive mechanical ventilation in chronic obstructive pulmonary disease, but the data are controversial in APE. In APE the use of NPPV may decrease the rate of endotracheal intubation, but mortality is unchanged and CPAP patients may have higher rates of MI

than those treated with BiPAP [56]. Patients requiring PPV or more than 2 L per nasal cannula supplemental oxygen are not good OU candidates.

Intravenous (IV) access is needed in all with HF exacerbation. This is because electrolyte abnormalities may occur from aggressive diuretic therapy, and HF patients are at risk for ventricular arrhythmia. In both scenarios, prompt therapy can be needed. Limitations notwithstanding, all suspected HF patients should have a chest radiograph to help exclude other confounding diagnoses and provide confirmatory evidence of HF. Underlying coronary artery disease is the most common cause of HF in the United States; therefore, until stability is determined, all suspected HF patients need initial continuous ECG monitoring, a 12-lead ECG, and cardiac biomarker testing. Additionally, a search for the other HF precipitants is needed (Box 4).

Diuresis causes abnormalities in K<sup>+</sup>, Na<sup>+</sup>, blood urea nitrogen, and creatinine, undetectable by history or examination, so these should be evaluated. A complete blood count is needed to check for anemia. With hepatomegaly resulting from passive congestion, liver enzymes can exclude other pathologies. Elevated lactate levels may identify unsuspected cardiogenic shock, and testing for drug levels (eg, digoxin) is guided by presentation. Occasionally ethanol and drug screening may be needed. Assessment of the Mg<sup>2+</sup> level is considered when there is cardiac arrhythmia and if severe or treatment-resistant hypokalemia occurs. Finally, selective foley catheterization

may be used to monitor fluid status or if urine output is sufficient to interfere with the patient's ability to rest.

#### *Benefits of early therapy*

All patients not being discharged from the ED should receive therapy while still in the ED. The reasons for this are two-fold. Treatments delayed until inpatient arrival are not received by the patient for many hours. Second, optimal ED HF outcomes are directly related to time to treatment.

The Acute Decompensated HF National Registry (ADHERE) is a multicenter database that records data from episodes of hospitalizations in patients discharged after an inpatient stay for acutely decompensated HF. Using data from 46,599 hospitalizations from this registry [57], patients were stratified as to where IV vasoactive therapy was started. Vasoactive therapy was defined as the receipt of an intravenous agent that would be administered to effect a change in hemodynamics (eg, dopamine, dobutamine, nitroglycerin, nesiritide). Of the cohort receiving vasoactives, 4096 received them in the ED, compared with 3499 whose treatment was delayed until arrival on the inpatient unit. Patients treated in the ED received the vasoactive agent much sooner (1.1 versus 22.2 hrs), had reduced lengths of stay (4.5 versus 7.0 days), and lower mortality (4.3 versus 10.9%) than those whose treatment was delayed until arrival on the inpatient unit.

An experienced emergency physician usually knows within minutes which patients will need inpatient admission. When the requirement for HF admission is identified, the early use of vasoactive therapy is indicated. In the minority of HF patients for whom ED treatment may result in discharge home, a limited trial (2 to 3 hours) of intermittent diuretic bolus therapy may be appropriate.

#### *Identifying candidates for the observation unit*

The OU is an effective treatment option for many diseases requiring a short period of intensive therapy or diagnostic evaluation. Patients with a HF exacerbation usually require longer than the short treatment course possible in the ED; consequently, many are OU candidates for additional therapy. Relief of congestion is the most common rate-limiting step preventing discharge. In the past, most HF patients were simply admitted for inpatient therapy. Because most will

#### **Box 4. Common causes of heart failure decompensation**

- Atrial fibrillation
- Acute MI
- Chronic nonsteroidal anti-inflammatory drug use
- Excessive alcohol
- Endocrine abnormalities (eg, diabetes, hyperthyroidism)
- Infection
- Negative inotropic medications
- Noncompliance (diet, medication)
- Suboptimal pharmacologic management
- Obesity
- Uncontrolled hypertension

have insufficient diuresis for relief of congestion in the ED, the OU offers an opportunity for longer therapies and may prevent the necessity of an inpatient admission [58].

The OU provides safe and effective therapy for the appropriately selected HF patients. In a retrospective study of decompensated HF [59], post-discharge revisit rates for OU patients treated for 24 hours, compared with inpatients discharged within 24 hours, were superior in the OU cohort. In the OU group, there were no return visits within 1 week of admission compared with a revisit rate of 8% in the hospitalized group. By 1 month, only 8% of the OU patients had a revisit, versus 16% of the inpatient group. There were no mortality differences between the groups ( $P > .05$ ). This study suggested that OU treatment is at least as safe and effective as a similar period of inpatient hospitalization.

Patient selection before OU consideration is important. If a patient has a high likelihood of HF, with pulmonary or systemic congestion, and meets the entry criteria listed in Box 5, OU admission may be appropriate. Because OU treatment is temporally restricted, with lower nursing-patient staffing ratios, and has limited invasive monitoring capability, careful patient selection is necessary to ensure that admissions are appropriate for the available level of care. Exclusion criteria, designed to prevent admissions in those with needs exceeding OU resources, are listed in Box 6 [58]. Patients with airway instability, a high probability of adverse outcome (eg, acute MI), and those with hemodynamics suggestive of critical underlying pathology should be excluded.

**Box 5. Heart failure observation unit: inclusion criteria**

- Adequate systemic perfusion
- Evidence of hemodynamic stability
  - Heart rate  $> 50$  and  $< 130$  beats/min
  - Systolic BP  $> 90$  and  $< 175$  mm Hg
  - Oxygen saturation  $> 90\%$
- No evidence of acute ischemia/infarction by electrocardiogram or cardiac markers
- Chest radiograph findings compatible with the diagnosis of HF
- B-type natriuretic peptide  $> 100$  pg/mL

Like acute coronary syndromes, patients with decompensated HF represent a spectrum of presentation that must be sorted to determine appropriate OU admission. Although there are very few analyses to define the best OU candidate, the exclusion of patients with excess risk is important. An analysis of the ADHERE registry [60] provides several mortality predictors that should exclude patients from consideration of OU admission. The most of important of these predictors is the BUN. Patients with a BUN exceeding 43 mg/dL have markedly increased inpatient mortality (8.98%) compared with those with a lower BUN (2.68%). Further refining the risk stratification process, in the cohort of patients

**Box 6. Heart failure observation unit: exclusion criteria<sup>a</sup>**

- Unstable vital signs (despite emergency department therapy):
  - Systolic BP  $> 220$ , Diastolic BP  $> 120$  mm Hg
  - Respiratory rate  $> 25$  /min
  - Heart rate  $> 130$  beats/min
  - Temperature  $> 38.5^{\circ}\text{C}$
- Electrocardiogram or serum markers diagnostic of myocardial ischemia or infarction
- Unstable airway or oxygen requirement  $> 4$  L/min by nasal cannula
- Evidence of cardiogenic shock or signs of end-organ hypoperfusion
- Require continuous titration of vasoactive medication (eg, nitroglycerin)
- Clinically significant cardiac arrhythmia
- Altered mental status
- Severe electrolyte imbalances
- Chronic renal failure requiring dialysis
- Peak expiratory flow rate  $< 50\%$  of predicted
- Chest radiograph suggestive of pneumonia

<sup>a</sup> These criteria are meant to discourage entry by patients not likely to benefit from an aggressive diuresis and vasodilation management protocol.

with a BUN less than 43, adding systolic BP provides additional prognostic data. In this group, the addition of a systolic BP < 115 mm Hg was associated with a mortality rate of 5.49% compared with those with a higher BP whose mortality was 2.89%.

OU admission candidates should have a BUN < 43 and careful consideration if admitted with a systolic BP < 115 mm Hg.

Other studies have specifically examined OU outcome predictors for HF. In 499 patients, Diercks and colleagues [61] reported that a negative troponin and an initial systolic BP > 160 mm Hg identified a cohort who were successfully discharged within 24 hours of admission and had no death or re-hospitalization within the subsequent 30 days. Burkhardt and colleagues [62] reported in 385 OU patients that successful discharge from the OU within 24 hours of an admission for decompensated HF was predicted by an admission BUN < 30 mg/dL. These parameters may also be considered to assist in the selection of the appropriate OU candidate.

Once admitted to the OU, many different aspects of medical management are needed to assure optimal outcomes and discharge rates. Attention to the many details required for HF management [63,64] can be daunting for a physician already running a busy ED. This not only includes medication intervention and titration, but the diagnostic evaluation, patient education, and the discharge planning required by regulatory agencies. HF protocols drive treatment algorithms and provide superior outcomes, as compared with standard therapy, and ensure that required interventions are accomplished [4,58].

ED OU protocol-driven management has been shown to result in a significant improvement in outcomes, as compared with independent physician-driven care. In a before and after study of 154 decompensated OU HF patients, a prespecified management protocol resulted in significant outcome improvements [4]. Use of the protocol resulted in 90-day ED HF revisit rates declining by 56% (0.90 to 0.51,  $P = .0000$ ) compared with pre-protocol management. Similarly, 90-day HF rehospitalizations decreased by 64% (0.77 to 0.50,  $P = .007$ ). Lastly, 90-day mortality and OU HF readmissions decreased from 4% to 1% ( $P = .096$ ), and 18% to 11% ( $P = .099$ ), respectively. From a cost perspective, during the same time period, annualized hospital costs declined by nearly \$100,000, predominately the result of 30-day readmission avoidance [65].

The only validated OU HF protocol published to date includes an aggressive diuretic algorithm, initiated in the ED, and continued throughout the OU stay [4,58]. In this protocol, additional diuretic use was driven by the patient's urine output. If the urine output was inadequate, inpatient admission for invasive monitoring was suggested. Additionally, ACE inhibitor algorithms encouraged physician initiation and up-titration toward target levels, provided there were no renal function contraindications, systolic blood pressure was adequate, and there was no history of ACE inhibitor intolerance. Unless there are significant contraindications (eg, anaphylaxis), all HF patients should be discharged on an ACE inhibitor [1].

The OU provides an opportunity for more extensive evaluation than can be performed in most EDs. EF measurement may be determined in those without an established diagnosis of systolic HF. This should be repeated if PSF HF was previously diagnosed, and it has been more than 1 year since the last assessment of ventricular function. The OU environment also offers the option of elective multidisciplinary consultations, not available in a busy ED, for those who may have transportation difficulties in getting to an outpatient appointment. While in the OU, the option of HF cardiology specialist consultation may help to evaluate discharge medication dosages, and screen candidates for heart transplantation listing. Other ancillary care staff may consult also. This includes dietetics and home health care. Social workers can ensure that all patients have the ability to obtain their medicines and can arrange a home environment assessment to assess the potential of other psychosocial, cultural, or economic factors that could prevent therapeutic compliance. A home health care consultation serves to ensure post-discharge follow-up care and can help arrange visiting nurse services for home bound or nonambulatory patients.

Because noncompliance causes up to 50% of HF rehospitalizations [63,64,66], patient education is a critical facet in the treatment program. Bedside teaching videotapes on HF may provide detailed education during a teachable moment for the patient. Finally, patients should be provided with HF literature, medication information, and lifestyle modification suggestions at discharge.

OU HF management not only impacts the OU, it results in changes in the inpatient HF population as well. By treating selected patients in the

OU, rather than the inpatient unit, patients are diverted to less intensive levels of care. After implementation of an OU HF management protocol, inpatient acuity as indexed by the mean number of billable procedures per HF patient, increased by 11% [65]. This provides improved resource matching between patients requiring intensive monitoring environments and those who could benefit from less costly OU care.

### *Therapeutic agents*

HF management is a complicated task. It requires the successful interaction of many different medications, individual titration regimens, patient factors (eg, education and compliance issues), and multidisciplinary services. Clearly defined patient care management programs addressing these issues have demonstrated clinical and financial success in both the OU and outpatient environment [4,58,63–67]. A validated management protocol is provided in **Box 7**.

Very large trials provide evidence-based data for managing stable, systolic HF. The principal drugs are beta-blockers, ACE inhibitors, angiotensin-receptor blockers (ARBs), hydralazine/nitrates, diuretics, digoxin, and spironolactone. In general, the strategy focuses on maintaining the lowest possible BP that allows mentation, ambulation, and urination [1]. All HF patients without contraindications should be on an ACE inhibitor and beta-blocker, even in the setting of stable disease with minimal symptoms. In most diseases, therapy is driven by continuing symptoms; this is not the situation in HF because of the unique neurohormonal antagonism requirements for the treatment of HF.

The emphasis on neurohormonal antagonism in HF represents a major management shift. The relief of congestion by the use of diuretics has been the main thrust of ED therapy. Although diuretics are important for acute symptomatic congestion relief, they do not improve mortality. Very large studies evaluating the role of ACE inhibitors, beta-blockers, and other agents show neurohormonal antagonism is required for the greatest mortality improvement.

### *Diuretics*

Initial OU HF therapeutic goals are directed at the relief of congestion by the use of IV diuretics. Recommended dosing strategies are to use up to twice the daily dose of furosemide (or its equivalent) administered as an IV bolus, to a maximum

### **Box 7. Heart failure observation unit: management protocol**

- Standardized orders (algorithm)
  - Diuretics
  - Neurohormonal antagonist (angiotensin-converting enzyme inhibitors or nesiritide)
- Aggressive fluid management monitoring
  - Admission weights, input/output
  - Fluid restriction, low-sodium diet
- Diagnostic testing
  - Standing orders for measurement and correction of potassium and magnesium
  - Electrocardiogram and cardiac injury markers
  - Echocardiography
- Patient education
  - Educational videos (living with HF, smoking cessation)
  - Personalized educational material
  - Nursing and physician bedside teaching
  - Dietetic consultations
- Discharge planning
  - Social worker, home health nurse consultation
  - HF specialist consultation

of 180 mg to promote urine output. If a patient is not currently on a diuretic, 40 mg of furosemide is usually adequate [4,58,59,65,68]. Urine output and serum electrolytes are monitored to track diuresis volume and to screen for treatment-induced hypokalemia. If target urine outputs are not met, the diuretic dose is doubled and repeated at 2 hours. Adequate output should exceed 500 cc within 2 hours, unless the creatinine exceeds 2.5 mg/dL. With elevated creatinine, 2-hour urine output goals are halved. Failure to meet output goals suggests inpatient hospitalization may be needed [4,58,59,65,68].

Diuretics prevent hospitalization and provide symptomatic relief. They are indicated for all patients with congestive findings, but not as

chronic monotherapy (diuretics should be combined with ACE inhibitors and beta-blockers) because alone they provide no mortality benefit [1,5,27,29]. With aggressive diuresis, potassium supplementation is frequently required. However, if loop diuretics are used in concert with nesiritide, potassium supplements are less often needed. Standing orders for oral or IV potassium supplementation with the goal of maintaining a  $K^+$  between 4.0 and 5.0 meq/dL may be useful.

Magnesium is an important cofactor for myocardial function and should be supplemented if the patient is deficient. Give magnesium if the creatinine is  $< 1.5$  mg/dL; otherwise, therapy should be individualized. Magnesium may be given as 140 mg magnesium oxide orally once.

Limited data suggest that combining loop diuretics treatment with IV vasoactive agents has benefit. In 1442 patients from 42 hospitals, patients receiving intermittent IV bolus therapy (eg, furosemide bolus) of any type while in the ED had a mean hospitalization LOS of 9.9 days. This compared with an LOS of 6.6 days ( $P = .004$ ) for those treated with IV infusion therapy (eg, nesiritide or nitroglycerin) while still in the ED. In this registry analysis, early infusion therapy with a vasoactive agent, as opposed to intermittent bolus therapy, was associated with a significantly shorter hospital LOS [57].

### *Vasodilators*

Certain vasodilators have the potential to provide both symptomatic improvement and mortality reduction in HF. Although hemodynamic improvements are the direct result of the effect on the vascular tree, mortality improvements in long-term outcomes are not a universal feature of all vasodilators. For mortality reduction to occur, the vasodilator must also have the characteristic of neurohormonal antagonism directed at the pathologic hormonal excesses of HF [69–72]. With regard to specific agents, ACE inhibitors, with both vasodilation and neurohormonal antagonistic effects, represent a class of medications with a mortality reduction benefit of such magnitude that all HF patients deserve a therapeutic trial [1,29,5,69–72]. ARBs, predicted to have similar physiologic effects as ACE inhibitors, may have fewer side effects than ACE inhibitors. However, as the preponderance of the current mortality reduction data uses ACEI, they should be replaced by ARBs only if

significant intolerance or a contraindication to the ACE inhibitor exists [1,29].

Improvement of hemodynamic parameters in the acutely decompensated HF patient, reflected by improvements in vital signs and in the clinical presentation of dyspnea, may be obtained with the use of intravenous vasodilators. The appropriate candidate usually has a blood pressure in excess of 90 mm Hg and no contraindications to vasodilation. Vasodilation can result in hypotension in selected populations, including those conditions where there is either an impediment to outflow (eg, aortic stenosis), situations where cardiac output depends on adequate or elevated pre-load (eg, right ventricular infarct, pericardial tamponade), or when preload is already abnormally decreased (eg, volume depletion).

Because their optimal use in HF requires invasive monitoring, nitroprusside and nitroglycerin are generally discouraged from use in the OU environment. Conversely, nesiritide, which can be used safely and efficaciously without invasive hemodynamic monitoring, is permissible in the OU.

Nesiritide is an IV medication for the treatment of decompensated HF. It provides hemodynamic [73,74] and clinical benefits [75–77] from the combination of vasodilation [78], natriuresis, and neurohormonal antagonism [78]. It has been shown to decrease costs and hospital readmissions [79] and lower 6-month mortality as compared with dobutamine [75,76]. Compared with nitroglycerin, nesiritide improves dyspnea and hemodynamics more rapidly and to a greater extent [77]. Nesiritide is appropriate for use in the ED OU. Once stabilized in the ED, patients on the recommended fixed dose of nesiritide (2  $\mu$ g/kg IV bolus, then a 0.01  $\mu$ g/kg infusion) are candidates for OU admission.

The Proaction Trial was a multicenter, double-blind, randomized, placebo-controlled safety and efficacy trial of standard OU therapy, with and without nesiritide [80]. In this trial, OU patients with acute decompensated HF and receiving standard therapy were treated with at least 12 hours of either standard dose-blinded nesiritide or placebo. In the safety analysis, there were no differences in adverse outcomes between the standard care and nesiritide cohorts. NYHA class III or IV HF patients receiving nesiritide had a 29% decrease in revisit rates ( $P = .057$ ). Days in the hospital in the month after study entry were markedly lower in patients receiving nesiritide compared with standard therapy (2.5 versus 6.5, respectively;  $P = .03$ ).



*Digoxin*

Similar to diuretics, digoxin decreases hospitalizations but does not alter mortality. It is recommended for LV systolic dysfunction and rate control in atrial fibrillation [1,5,29]. Toxicity manifests as cardiac arrhythmia (heart block, ectopy, or re-entrant rhythms), gastrointestinal symptoms, or neurologic complaints (eg, visual disturbances and confusion). Serum levels can suggest toxicity if they exceed 2.0 ng/mL, but toxicity can also occur at lower levels if there is coexistent hypokalemia or hypomagnesemia. Digoxin should be used at a dose of 0.125 to 0.250 mg daily [1,5,29].

*Beta-blockers*

Beta-blockers prolong life in HF patients [81–85] but should only be initiated if the patient is hemodynamically stable [1,29]. They should not be started in decompensated HF; consequently, this generally precludes OU initiation. Conversely, abruptly stopping a beta-blocker has the potential to worsen hemodynamics. Recommended therapy for decompensated HF patients presenting to the ED while on a beta-blocker is to hold the dose or continue it at one dosing level lower than the maintenance dose. If inotropes are required, the beta-blocker may be withheld [1,29]. Patients at this stage of their disease are not usually ideal OU candidates.

*Aldosterone antagonists*

The aldosterone antagonist spironolactone decreases the relative risk of mortality in end stage HF [86]. These patients should receive 12.5 to 25.0 mg qid [1,29]. It is not recommended if the creatinine exceeds 2.5 mg/dL or the  $K^+$  is  $> 5.0$  mEq/L. If a patient is already on an aldosterone antagonist, it should be continued in OU patients.

*Anticoagulants*

The risk of thromboembolism in the clinically stable HF outpatient is low, estimated at 1% to 3% per year, and is greatest in patients with the lowest EF [87,88]. However, hospitalized HF patients are at significant risk for sustaining deep vein thrombosis (DVT) and its complications. In the MEDENOX (prophylaxis in MEDical patients with ENOXaparin) study of hospitalized patients, subcutaneous enoxaparin decreased venographically documented DVT, from 14.9% in the placebo group to 5.5% in the 40-mg every day enoxaparin prophylaxis group [89]. Empiric

DVT prevention in hospitalized, bedridden HF patients must be balanced against the relatively low risk of complications associated with anticoagulant prophylaxis. The precise value of prophylactic anticoagulation has never been reported in ED OU HF management. However, as it is anticipated that this cohort of patients will be discharged in a relatively limited time frame, anticoagulation is usually not performed.

*Other agents*

Calcium channel blockers (CCBs) are not routinely recommended in HF [1,90]. This is because short-term use may result in pulmonary edema and cardiogenic shock, whereas in the long-term, they may increase the risk of worsening HF and death [91–94]. These adverse effects have been attributed to the negative inotropic effects of CCBs. If necessary, amlodipine, the CCB with no clear adverse mortality effect, may be used for compelling clinical reasons (eg, as an anti-anginal agent despite maximal therapy with nitrates and beta-blockers).

Nonsteroidal anti-inflammatory drugs should be avoided in HF [1,90]. They inhibit the effects of diuretics and ACE inhibitors and can worsen cardiac and renal function [1].

HF is an important risk factor for sudden cardiac death, and its likelihood increases in proportion to the decrease in EF and HF severity [95]. Premature ventricular contractions occur in 95% of dilated cardiomyopathy patients, and nonsustained VT may be seen in up to 30% to 40% of cases. Prophylactic administration of anti-arrhythmics is not effective and may actually increase mortality [96]. Therefore, their routine use to suppress asymptomatic ventricular arrhythmias is not warranted.

**Observation unit disposition**

OU patients may be discharged at any time, once there has been a good therapeutic response. Although there are very few studies that have determined predictors of successful ED discharge, a net volume output of greater than 1 L is associated with a higher rate of successful discharge from the ED OU [68].

Discharge criteria may aid in selecting candidates who may be sent home (Box 8). Most important in the disposition determination is the clinical assessment, but a post-treatment BNP level can help to guide this decision. If nesiritide

**Box 8. Heart failure observation unit: discharge guidelines<sup>a</sup>**

- Patient reports subjective improvement.
- If normally ambulatory, able to do so without significant orthostasis.
- Resting heart rate < 100 beats/min; Systolic BP > 80 mm Hg.
- Total urine output > 1 L, and urine output > 30 cc/h (or > 0.5 cc/kg/h).
- Room air oxygen saturation > 90% (unless on home oxygen).
- No angina.
- No electrocardiogram or cardiac marker evidence of myocardial ischemia/infarction.
- No new clinically significant arrhythmia.
- Normal electrolyte profile without increasing azotemia.

<sup>a</sup> Patients not meeting all of the guidelines should be considered for inpatient treatment (except as appropriate in the end-stage palliative care cohort).

has been used, it will be necessary to stop its infusion at least 4 half-lives (90 minutes) before its measurement.

Successful discharge of HF patients after an OU treatment course requires the coordination of a multimедication regimen that includes diuretics, digoxin, ACE inhibitors (or ARBs), and possibly spironolactone, and beta-blockers. Optimally, medications are adjusted to meet target-dosing recommendations [1,5,29]. Therefore, close consultation with the physician who will ultimately manage the outpatient course is necessary to provide the best outcomes. An aggressive management protocol may anticipate the discharge of approximately 75% of OU HF patients [4,58,59,65].

Discharge planning is critical in HF. A multidisciplinary team approach can produce significant improvements in HF outcomes by decreasing revisit rates, lowering inpatient length of stay, and reducing hospitalization costs [4,58,59,65,67,97–100]. The team approach should provide the option of outpatient consultations with social work, dietetics, cardiology, and advance practice

nurses. Because noncompliance is estimated to cause 50% of HF re-hospitalizations [60,63,64,66], patient education is a critical facet to be addressed during OU treatment.

Disposition from the OU is predicated on the relief of dyspnea, improvement of congestion without long-suffering orthostasis, and discharge to an adequate outpatient environment. If these goals cannot be met, inpatient hospitalization or placement in an assisted-living facility should be considered. Approximately 25% [4,58,59,65] of HF patients will require inpatient hospitalization after a 24-hour OU admission. Patients not meeting discharge criteria by the 24-hour OU LOS limit require inpatient admission. A lower threshold for admission is appropriate in the very elderly, those with poor social situations, and those with multiple co-morbidities. Even patients requiring admission after an OU stay derive a measurable benefit from its use. In patients admitted from the OU after failure of therapy, the mean hospitalization LOS, inclusive of their OU time, was 0.8 days less than patients admitted directly from the ED to the inpatient unit [4].

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## Cost Effectiveness of Chest Pain Units

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Health care is undergoing unprecedented change resulting from increasing pressures to deliver quality care to greater numbers of people in a resource-constrained environment. Although all providers of care are affected, the acute hospital facility bears an inordinate amount of this pressure, often caught between decreasing global reimbursements and the need to care for sicker and more complex patients. The Chest Pain Unit (CPU) represents a venue that effectively merges the clinical needs of a segment of acute cardiac patients with the economic needs of the acute care facility.

### Origin of the chest pain unit

Historically, the outpatient CPU concept was developed to heighten community awareness on the early warning signs of a heart attack and create an ease of hospital entry for the chest pain patient. CPUs experienced exponential growth from 1980 to 1998 but offered little more than successful marketing strategies to increase hospital admissions, a factor that often contributed to overcrowding in many community hospitals [1].

After, the CPU served as a temporary holding area, sorting out patients who were at low risk for developing a myocardial infarction. This “triage role” allowed for reduced use of acute inpatient stays by those patients who did not require a high level of care. This triaging allowed appropriate care to be provided to the low-risk chest pain patient while maintaining open bed availability in the intensive care unit (ICU) for patients requiring a higher level of service.

CPUs have continued to evolve to better meet the needs of the health care system and the acute cardiac patient. More recently, as a result of changing reimbursement patterns, CPUs also have been able to address some of the financial pressures placed on the acute care facility by third-party payers.

### *Financial pressures on acute care facilities*

The Balanced Budget Act (BBA) of 1997 made sweeping changes to Medicare, generating savings that were critical to extending the life of the Medicare Trust Fund [2]. In the health care arena, most of these changes impacted the acute care facility most directly. Lacking a complete understanding of the impact of the BBA; however, many facilities failed to make the necessary changes to offset the new plan, resulting in overall decreased reimbursements in 1997. The fixed reimbursements of the diagnosis-related group (DRG) program began to adversely affect hospitals' revenues and profit margins.

In an effort to maintain economic viability, hospitals targeted two key areas for cost reduction efforts: bed days and staffing. Intense efforts were made at reducing average length of stay (LOS) and reducing the number of hospital employees. Although this strategy resulted in initial cost benefits, savings plateaued, and margins eroded further. By 1999, DRG reimbursement increased only 0.6%, and hospitals' overall average-operating margins had decreased to 2.76% [3]. These eroding profit margins, and a reduction in the number of acute care facilities as a result of mergers and acquisitions, created an unstable environment in which hospitals were struggling to remain solvent [3].

As revenues were held in check, another factor added to the burdens on the acute care facility: health care use continued to increase. During the

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decade leading to 2003, inpatient admissions increased nearly 10% while outpatient visits increased approximately 61% [3]. The number of emergency department (ED) visits increased steadily from 1997 to 2002, from 99.6 million to 114.2 million [3]. This immense growth and demand on emergency services led to an overwhelming reduction in the availability of these services and is considered a major contributor to the process and economic changes that are now occurring.

The ED is acknowledged as the most common point of entry into the health care system. As facilities begin to factor in the expected 8 million annual ED visits for chest pain predicted in the upcoming years, the emergence of the CPU—often termed ED Observation Unit—and other specialized short stay units are now under reconsideration to help alleviate some of the hospital system burdens, such as ED overcrowding, reduction of unnecessary admissions, and the opportunity to optimize revenue.

#### *Acute coronary syndrome*

Current bottlenecks in the ED are caused by the large, challenging group of patients who present with chest pain of possible cardiac origin, or “low-probability” patients as categorized by the America Heart Association and the American College of Cardiology (ACC/AHA) guidelines.

The ED itself is not the cause of overcrowding; rather, it is simply the unit most vulnerable to gridlock (Fig. 1) [4]. The lack of inpatient beds is the most commonly cited reason for crowding in the ED [4,5]. Although most chest pain patients are unlikely to have sustained a myocardial infarction or need treatment in an ICU, the high rate of acute hospital admission adds to the bed-day burden of the acute care facility.

Acute coronary syndrome (ACS) is a potentially lethal condition that affects approximately 2 million people in the United States. Most ACS patients seek care through an ED, and this patient volume is saturating these departments. Treatment delays, medical errors, poor outcomes, against medical advice, higher re-admissions, diversions, increasing costs, and threatened quality all play a role in the health care crisis.

ACS patients use a tremendous amount of resources initially in the ED, only to be admitted into an inpatient bed later for a 2- to 3-day LOS in the acute facility. From a DRG reimbursement perspective, all testing done in the ED arena is now debited from the total DRG payment for which the patient was admitted. If the admitting diagnosis DRG is not changed from DRG 143 (chest pain) to a higher acuity DRG 140 (unstable angina), it will most likely contribute negatively to the hospital bottom line (opportunity revenue loss of \$1500–\$2000).

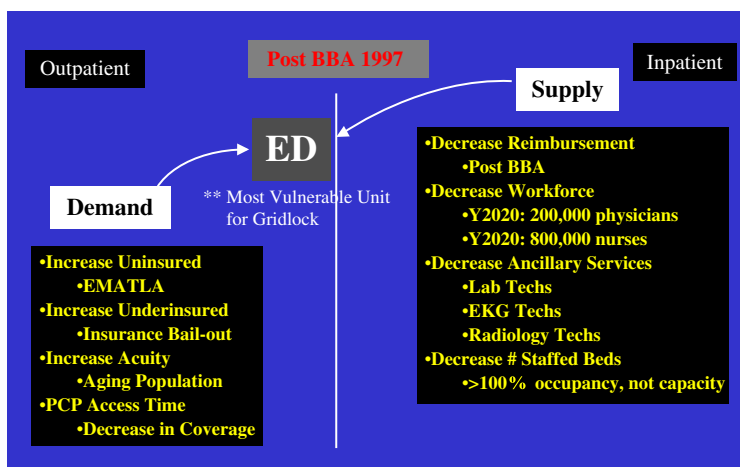


Fig. 1. Comparison between supply and demand affecting the health care systems access to care, hospital overcrowding and efficiency demands. Hospital overcrowding was considered a unit phenomenon tied to the emergency department. Issues surrounding the causes and solutions, overcrowding is increasingly perceived as a system problem. (Adapted from Joint Commission Resources. Managing patient flow: strategies and solutions for addressing hospital overcrowding. 2004. p. 11.)



### *Emergence of the “new” chest pain unit*

The CPU is no longer merely a holding area for low-risk cardiac patients or a conduit to the inpatient service for the higher-risk group. A new CPU concept is emerging as a venue for addressing some of the previously mentioned clinical and economic pressures that face the acute care facility.

Use of a CPU can show resource advantages over the typical acute hospital admission. The typical chest pain patient spends an average of 2.1 days in the hospital; when seen and treated only in the CPU, this same patient can be discharged safely in 6 to 12 hours. Each outpatient bed frees 2.2 to 3.5 inpatient beds that can be allocated to high-acuity patients who require admission [6]. Additionally, quality measures can be improved also. For instance, the Impact on the Care of the Emergency Department Chest Pain Patient from the Chest Pain Evaluation Registry (CHEPER) study reported a significant reduction in missed myocardial infarctions from 4.5% to 0.4%, a change that enhances quality and directly impacts the high-cost medical/legal payouts and re-admissions from erroneous diagnoses [7].

Observation units for heart failure recently have shown a positive impact on reducing after-health-care use in patients who present with acute decompensated heart failure. Table 1 summarizes data from the Cleveland Clinic experience [8].

### *Future directions in acute coronary syndrome*

Non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA) patients represent the next challenging focus for optimizing cost-efficient acute cardiac care. These patients present to facilities earlier in the thrombosis progression model of the disease than STEMI patients, making them more difficult to

diagnose and treat, and essentially all are admitted to the acute care facility. They are often difficult to distinguish from non-ACS patients who present with chest pain.

The ACC/AHA guidelines highlight the role of CPUs and “short-stay ED coronary care units” to facilitate a more definitive evaluation while avoiding the unnecessary hospital admission of patients who have not developed ACS. Such evaluation also helps to avoid the inappropriate discharge of patients who develop active myocardial ischemia without ST-segment elevation. Personnel in these units use critical pathways or protocols designed to arrive at a decision about the presence or absence of myocardial ischemia and, if present, to characterize it further as UA or NSTEMI and to define the optimal next step in the care of the patient (eg, admission, acute intervention). The goal is to arrive at such a decision after a finite amount of time, which usually falls between 6 and 12 hours but may extend up to 24 hours, depending on the policies in individual hospitals. The time spent shifts from days of care to hours of care.

The difference between NSTEMI and UA also brings to light an important economic factor. If a physician diagnoses a patient who presents with elevated biomarkers with ST depression but fails to document the elevation of these cardiac markers, the facility is reimbursed as a UA payment. The difference in reimbursement for the NSTEMI and UA patients is approximately \$4000 to \$6000. Physician documentation can thus play a vital role in how the facilities and office practice coders submit for reimbursement.

CPUs are able to advance the STEMI and NSTEMI/UA patients through the system quickly and consistently while promptly facilitating safe discharge of the low-probability chest pain patients. The ultimate goal of the CPU is to transition many of the services now performed in the ICU setting to the CPU for earlier diagnosis and management—the true “short-stay coronary care unit.”

### *Reimbursement issues*

Centers for Medicare and Medicaid Services (CMS) is the third-party payer for most of the acute cardiac patients who are largely of Medicare age. CMS is now trying to shift unnecessary inpatient volume back to the point of entry for more efficient risk stratification, assessment, and more intense treatment. This approach

Table 1  
Observation unit results for patients with heart failure

Utilization parameter	Change after OU	Percent change
Revisits	90%–51%	44% decrease
ED observation discharges	9%	
HF rehospitalizations	77%–50%	36% decrease
Observation hospitalizations	23% decreased LOS	

*Abbreviations:* HF, heart failure; OU, observation unit.

emphasizes the integration of observation unit services as a viable alternative to inpatient health care delivery and is being accomplished by shifting resources—or reimbursement—to the outpatient setting, most commonly the ED in a CPU or observation unit.

The facility payment for a CPU service is paid under a new observation code, the Ambulatory Patient Classification (APC) 0339. APC 0339 is a separate observation carve-out payment that CMS has agreed to pay as a third door opportunity for acute care facilities. One intention of APC 0339 is to offer an alternative pathway to diagnose, treat, and admit or discharge patients rapidly who are diagnosed with chest pain, congestive heart failure, and asthma. CMS selected these three medical conditions to focus on four main areas of concern: (1) morbidity, (2) mortality, (3) appropriateness of admissions, and (4) reduction in inappropriate discharges. The current shift of this large class of patients from their traditional inpatient treatment protocol to a more efficient plan of care initiated in the CPU or ED observation unit has resulted in a significant economic impact on the acute care facility [9].

The CPU is shown to impact economics and clinical outcomes in several studies. One multicenter study demonstrated that observation in a CPU resulted in a lower incidence of missed myocardial infarction (0.4% versus 4.5%,  $P <$

0.001) and lower final rate of hospital admission (47% versus 57%,  $P < 0.001$ ) [7]. These clinical benefits were accompanied by an average saving of more than \$120 per patient (almost \$2.9 million reduction in true costs for 23,407 patients seen in the ED for chest pain) [7]. In a prospective, randomized trial of patients seen at a CPU, no cases existed of missed primary cardiac events and no erroneous discharges, and use of resources was more efficient when ACS patients were seen at the CPU than when they were admitted by way of the ED to a cardiac care unit [10]. Practice standards specific to the institution represent another method of improving quality of care while controlling cost. Practice standards can promote adherence to regulatory directives, cost-containment measures, and evidence-based guidelines for diagnosis and treatment.

Hospitals have also reduced costs of treatment for inpatient stays for low-risk chest pain. Fig. 2 shows the effect of a quality-improvement initiative in fiscal year (FY) 2000 related to ACS patients. As part of the initiative, the acute care facility modified treatment protocols to adhere to the AHA/ACC guidelines for the management of ACS. From FY 2000 to 2002, in-hospital mortality of ACS patients decreased from 4.8% to 1.9%, and LOS decreased from 5.9 days to 4.6 days. The average cost per case dropped from \$11,777 to \$10,623, saving \$1,154 per ACS

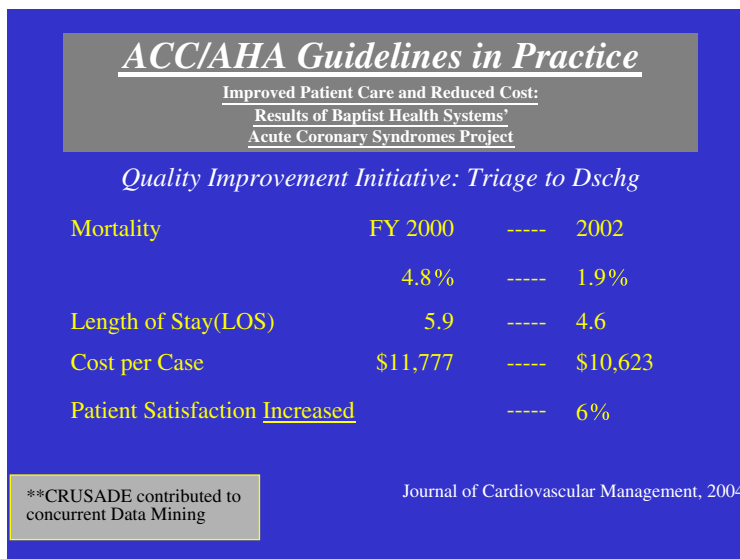


Fig. 2. Healthcare facilities increasing must provide high quality medicine at reasonable cost. (Adapted from Jackson S, Sistrunk H, Staman K, et al. Improved patient care and reduced costs: results of Baptist Heal Systems' acute coronary syndromes project. J Cardiovasc Manag 2003;14:4.)

patient. These results demonstrate that institutions can examine care patterns, change them, and maintain quality clinical outcomes [11].

Despite these cost savings, the DRG reimbursement system does not always result in full coverage of costs of care for an inpatient stay (Fig. 3). The following example demonstrates the full impact of reimbursement differences between DRG and APC coding for chest pain evaluation and treatment in a hospital.

The hospital analysis is based on 4000 chest pain patients, 289 of which qualified for APC 0339 outpatient observation versus an inpatient admission using DRG 143. In a 12-month retrospective analysis, the patients who were routed through the CPU generated a profit of \$32,000 for the hospital, whereas the patients admitted under DRG 143 resulted in a loss, “costing” the system \$188,000. By merely “transferring to observation” and at the time meeting minimal testing to meet the APC 0339 payment requirements, whereas in the outpatient CPU versus “admitting” to the inpatient system, a \$220,000 variance was created. Fixed cost and variable cost was factored into these calculations to give a more accurate representation of the results.

Although this scenario does not reflect every hospital’s situation, it underscores the potential adverse financial implications of providing higher-intensity care than is medically necessary. An evidence-based, protocol-driven CPU has the ability to route patients rapidly through rapid

risk-stratification protocols to appropriate inpatient admissions while reducing missed myocardial infarctions and providing safe discharges with fewer returns. Careful up-front risk stratification not only results in increased efficiency of care, but also in cost advantages through a more favorable reimbursement situation.

Services, such as CPUs, can be structured to provide the resources necessary at the point-of-entry to diagnose and treat ACS patients efficiently, directing them into the proper service lines at maximum efficiency. High-acuity and moderate-risk patients are now admitted, and low-probability patients, who in the past would have been admitted, are diagnosed and released safely after only hours versus the past pattern of days. The study performed by Ross on the impact of an ED observation bed on inpatient bed availability [12] indicates that 1 patient treated in an observation unit bed equals 2.2 to 3.5 inpatient beds. This equation is one of the variables that contributes to the economic feasibility of CPUs. This 3:1 ratio increases the physician’s productivity while driving down fixed and variable costs allocated to the outpatient services.

*Federal regulations and the effect on chest pain units in 2005*

The federal regulations continue to change to accommodate the shift in acuity to the outpatient setting. These regulations do not specify bricks

APC 0339 Chest Pain			DRG 143 Chest Pain		
Level III/IV < 8 hours.....		\$177	Average Reimbursement		\$1997
APC 0339 > 8 hours.....		\$350	ALOS __2.1 days__		
Billable (UB92)		Reimbursable	Billable (UB92)		Reimbursable
EKG	yes	yes	EKG	yes	bundled in DRG
Enzymes	yes	yes	Enzymes	yes	bundled in DRG
Nuclear Studies	yes	yes	Nuclear Studies	yes	bundled in DRG
Stress Test	yes	yes	Stress Test	yes	bundled in DRG
Total.....		\$900/\$1000	Fixed Cost (FC).....		(\$1498)
Fixed Cost (FC).....		(\$570)	FC varies per institution, usually 3 times OP		
FC varies per institution			Mean Variable Cost (VC).....		(\$1168)
Mean Variable Cost (VC).....		(\$252)	All diagnostics are bundled under corresponding DRG		
OP diagnostic testing enhancing bottom line					
<b>**PROFITABLE \$32,000</b>			<b>**LOSER (\$-188,000)</b>		

Fig. 3. Comparison of inpatient DRG 143 (chest pain) coverage versus outpatient APC 0339 (chest pain). DRG, diagnosis-related group; APC, ambulatory patient classification; FC, fixed cost; VC, viable cost; OP, outpatient.

and mortar as part of the reimbursement criteria for APC 0339. A CPU or observation unit can be located within or near an ED or be a free-standing unit. It is not the location of a CPU that distinguishes its services from an ED but the type of care it provides.

These regulations are particularly influential from a reimbursement standpoint. Financial incentives have been put into play to ensure efficient care is provided in the CPU. These changes are more economically favorable to the hospitals that employ CPUs.

Specific excerpts from the Federal Register on the recent changes in the APC reimbursement as of January 2005 are summarized in Table 2 [13].

The main impacts of the regulatory changes are

- The duration of the CPU stay must be 8 to 48 hours.
- If an admission occurs after the CPU stay, the hospital is not financially disadvantaged.
- Previously required laboratory tests have been eliminated as part of the APC requirement (requires medical necessity).
- Any tests performed (medically necessary) as part of a CPU stay can be billed for in addition to the APC 0339 charge.

#### *Quality implications of chest pain units*

In an effort to support the dramatic restructuring of health care delivery, CMS has also revamped its image from an institution of strictly financial reimbursement to include a healthy plan of quality mixed into its evolving plan of health care delivery. CMS is crafting new aggressive approaches to facilitate implementation of a proactive strategy to provide resources for care aimed at earlier detection and treatment of acute cardiac conditions. In recent years, however, leaders and policy-makers have directed increased attention to strategies for achieving system-wide improvements in health care quality and patient safety that will lead to larger-scale, more rapid changes in professional and provider behavior than have been experienced to date.

Protocols designed around the ACC/AHA guidelines will allow facilities to meet or exceed certain quality indicators developed for these ACS patients, also creating greater patient satisfaction. CMS is developing pay-for-performance programs and a bonus reimbursement for meeting quality standards in certain clinical areas;

reducing reimbursement for those who do not meet the defined indicators; participating in the CMS/Premier Quality Demonstration Project initiative; and experimenting with a sliding scale concept that pays based on the number of quality indicators facilities meet (Fig. 4).

The pay-for-performance approach acknowledges the reality that financial rewards are among the most powerful tools for bringing about behavior change [1]. Also, the alignment of payment program incentives to support the provision of safe, high-quality care is a complex undertaking because it must simultaneously achieve fair reimbursement for necessary services, promote desired behavior change, and avoid unintended consequences. In the end, new payment policies and programs must work to the advantage of the patient and support the provision of patient-centered care.

In the near future, hospital reimbursement likely will be directly proportional to quality performances. CMS also has several efforts in progress to provide hospital quality information to consumers and others to improve the care provided by the nation's hospitals. These initiatives build on previous CMS and quality initiative strategies to identify illnesses or clinical conditions that affect Medicare beneficiaries to promote the best medical practice associated with the targeted clinical disorders; prevent or reduce further instances of these selected clinical disorders; and prevent related complications [2].

#### *Trans-theoretic Y model application*

The separation of quality and finance is no longer a viable plan of operation and must be redesigned to create an efficient plan focused on process to optimize clinical and financial outcomes. The business world has long recognized this tenet and has created models by which business units are aligned efficiently and strategically toward achieving a well-defined end product or service.

A new approach to understanding the entire concept of health care delivery from point-of-entry to discharge is the trans-theoretic Y-model (Fig. 5). This model emphasizes a multidisciplinary team approach to align the "care units" that affect a cardiac patient's progress through the current system (Fig. 6). By understanding how each care unit's operational strategies affect each subsequent care unit from point of entry to discharge, a seamless transfer of patient care in outpatient and inpatient settings can optimize quality

Table 2  
Summary of federal regulation changes in 2005 [12]

Excerpts	Analysis/Comments
<p>1. Beginning in early 2001, the APC Panel began discussing the topic of separate payment for observation services. In its deliberations, the APC Panel asserted that observation services following clinical and emergency room visits should be paid separately, and that observation following surgery should be packaged into the payment for the surgical procedure. For CY 2002, separate payment for observation services (APC 0339) was implemented under the OPPTS for three medical conditions: chest pain, CHF, and asthma. A number of accompanying requirements were established: the billing of an evaluation and management visit in conjunction with the presence of certain specified diagnosis codes on the claim; hourly billing of observation care for a minimum of 8 hours up to a maximum of 48 hours; timing of observation beginning with the clock time on the nurse's admission note and ending at the clock time on the physician's discharge orders; a medical record documenting that the beneficiary was under the care of a physician who specifically assessed patient risk to determine that the beneficiary would benefit from observation care; and provision of specific diagnostic tests to beneficiaries based on their diagnoses.</p>	<p>APC 0339, outpatient observation, was developed in 2001 and implemented in April 2002 as a clinical and financial opportunity for facilities. This new outpatient observation differs from the traditional inpatient observation. Criteria, such as the inclusion of an E&amp;M level code, must be billed with one of three conditions (chest pain, CHF, and asthma). Once the patient has been in observation for minimum of 8 hours up to a maximum of 48, beginning with the nurse's admission note and ending at the time on the physician's discharge orders. Physician must document progress notes during beneficiary's stay in observation. Diagnostic testing requirements have changed from 2002 to 2005 and are discussed later in Analysis # 2.</p>
<p>2. CMS received comments from the community and the APC Panel asserting that the requirements for diagnostic testing are overly prescriptive and administratively burdensome, and that hospitals may perform tests to comply with the CMS requirements, rather than based on clinical need.</p>	<p>Specifying which diagnostic tests must be performed as a prerequisite for payment of APC 0339 may be imposing an unreasonable reporting burden on hospitals and may, in some cases, result in unnecessary tests being performed.</p> <p>Therefore, beginning in CY 2005, the authors are proposing removal of the current requirements for specific diagnostic testing, and reliance on clinical judgment in combination with internal and external quality review processes to ensure that appropriate diagnostic testing (which the authors expect would include some of the currently required diagnostic tests) is provided for patients receiving high-quality, medically necessary observation care.</p> <p><b>Accordingly, beginning in CY 2005, the following tests should no longer be required to receive payment for APC 0339 (observation):</b></p> <p>For congestive heart failure, a chest radiograph (71010, 71020, 71030), and ECG (93005), and pulse oximetry (94760, 94761, 94762).</p> <p>For asthma, a breathing capacity test (94010) or pulse oximetry (94760, 94761, 94762).</p> <p>For chest pain, two sets of cardiac enzyme tests, two CPK (82550, 82552, 82553) or two troponins (84484, 84512), and two sequential ECGs (93005).</p>

(continued on next page)

Table 2 (continued)

Excerpts	Analysis/Comments
3. Hospitals and the APC panel further suggested that the method for accounting for the beneficiary's time in observation care be modified.	In an effort to reduce hospitals' administrative burden related to accurate billing, counting time in observation care should end at the time the outpatient is actually discharged from the hospital or admitted as an inpatient. Twentyfour hours is adequate for the clinical staff to determine what further care the patient needs. In CY 2005, separate payment should continue to be made for observation care based on claims meeting the requirement for payment of HCPCS code G0244 (observation care provided by a facility to a patient with CHF, chest pain, or asthma, minimum 8 hours, maximum 48 hours). However, do not include claims reporting more than 48 hours of observation care in calculating the final payment rate for APC 0339. In CY 2005, OPSS payments for observation care should increase over CY 2004 levels for two reasons. First, the proposal to eliminate the requirement that specific diagnostic tests be performed to receive separate payment for observation care will result in more observation stays being paid for under APC 0339. Several CY 2003 claims with packaged observation services reported for CHF, asthma, and chest pains would qualify for separate payment. Adopting the proposed changes, the volume of claims for payment under APC 0339 should increase in CY 2005. This volume increase, combined with the slightly higher median cost calculated for APC 0339 based on CY 2003 claims, would likely result in higher aggregate Medicare payments to hospitals for observation care in CY 2005 than in previous years. The payment is approximately \$403.93, which translates into a 12% increase over 2004.
4. The beneficiary must be in the care of a physician during the period of observation, as documented in the medical record by admission, discharge, and other appropriate progress notes that are timed, written, and signed by the physician.	The medical record must include documentation that the physician explicitly assessed patient risk to determine that the beneficiary would benefit from observation care.

*Abbreviations:* CHF, congestive heart failure; CY, calendar year; OPSS, outpatient prospective payment system; E&M, evolution and management; CPK, creatine phosphokinase; HCPCS, healthcare common procedure coding system.

improvement and positive economic value. Without each care unit providing vital information to others in this holistic approach, moving patients efficiently through the system is challenged.

The trans-theoretic Y-model places an emphasis on process improvement while targeting two end points: quality and contribution margin (Fig. 7). This concept begins at the point of entry and ends at discharge and marries a clinical and financial strategy that meets quality indicators while producing desirable profit margins. This

plan can be implemented on any disease state, particularly chest pain or ACS patients. Beginning in the ED, this concept emphasizes an efficient, rapid assessment and action centered on a seamless integration of ancillary services, such as the laboratory, diagnostic imaging, and skilled nursing while understanding the economic impacts on decisions made as the patient is directed through the system. The failure of any one of these services could bring the ED to a halt, thus supporting the notion that the ED is not

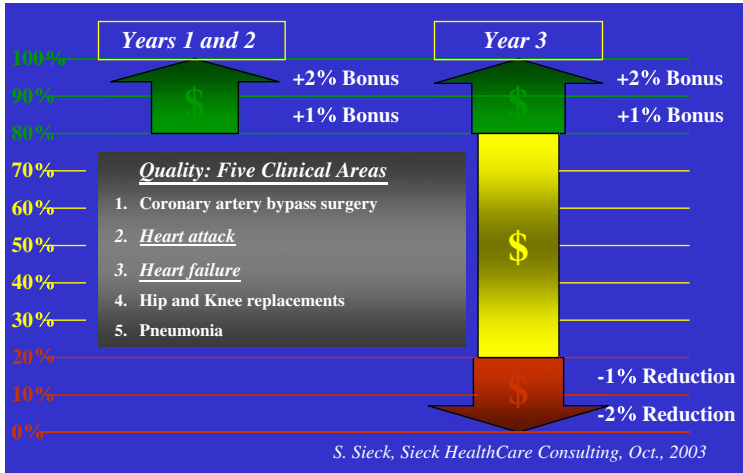


Fig. 4. Principles for the construct of pay-for-performance.

necessarily the cause of the gridlock; rather, it is the unit that becomes most vulnerable to it [4].

Compare the hospital setting to an industrial setting. Without uncertainty industrial facilities can detail the route from raw material to finished product with pinpoint accuracy. Checks and balances and alternative plans for the unexpected exist throughout the process. At every opportunity, dollars and time are being shaved—cost-avoidance. The end product is priced to the market based on the operating costs within the process. If the process varies and these costs or resource use climb, actions are taken to control the variances. If not, the contribution margin is eroded and eventually

could become negative. The objective is to keep the contribution margin at its maximum without compromising quality. If the quality team does not communicate its concerns to the profitability team, then major issues of conflict arise and the system does not operate at optimal efficiency (see Fig. 6). Without question, the top industry leaders can pick a point randomly within their process and report on the variables within.

Until health care delivery systems take an internal look at their plan of operation and the economic plan that coincides, reimbursement will continue its current path. The Joint Commission on Accreditation of Health care Organizations

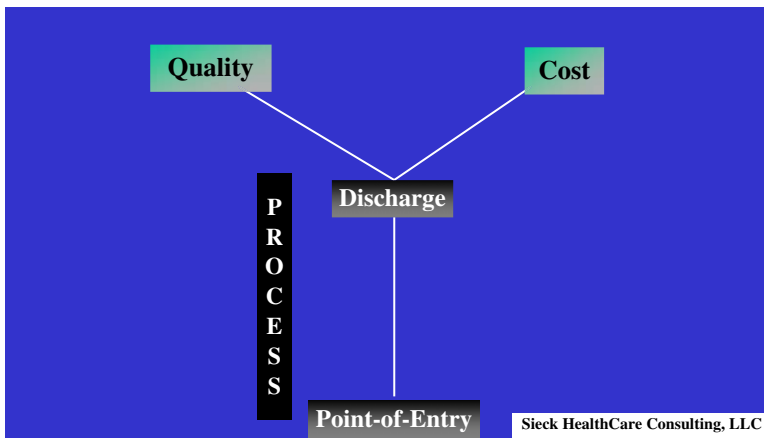


Fig. 5. Trans-theoretical Y Model: a new approach to understanding the entire concept of health care delivery from point-of-entry to discharge.

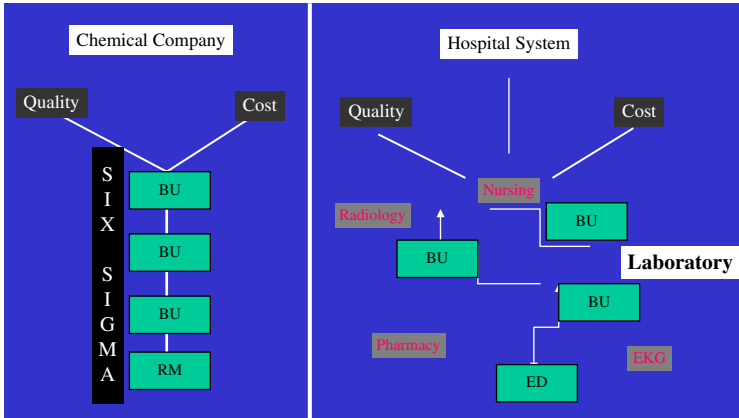


Fig. 6. Comparison of hospital system, Zig-Zag model to industry leaders, Vertical model.

(JCAHO) is looking for efficiency from point-of-entry to discharge, and CPUs can assist in this process because the ED is the most common point of entry into the system. JCAHO has developed a new standard, LD.3.15, to monitor the management of patient flow, attempting to alleviate overcrowding, effective January 1, 2005. Its main focus is identifying and mitigating impediments to efficient patient flow throughout the hospital [4].

Health care is a service industry and is learning to operate like an efficient and quality-driven business. The CPU represents an early step in this learning that can be applied throughout the point-of-care continuum. The Institute of Medicine in its recent report *Crossing the Quality Chasm* [14], concluded that in order for the health system to meet the future demands of the population of the United States and provide quality care, drastic reinvention is required; trying to “fix” the

current system is insufficient. The principles used in the redesign of the CPU and the overall shift of care to the outpatient setting represent initial stages in that direction.

**Summary**

Acute care facilities are struggling to maintain economic viability in an environment of cost-constraints, declining reimbursements, and increasingly expensive technology. Two-thirds of facilities are operating at 1% or less, and one third of all hospitals have reported operating margins in the negative [15]. To survive, hospitals are being challenged to reinvent the way acute care is delivered. The experience and evolution of CPUs for the treatment of certain segments of the acute cardiac patient offer insight into the

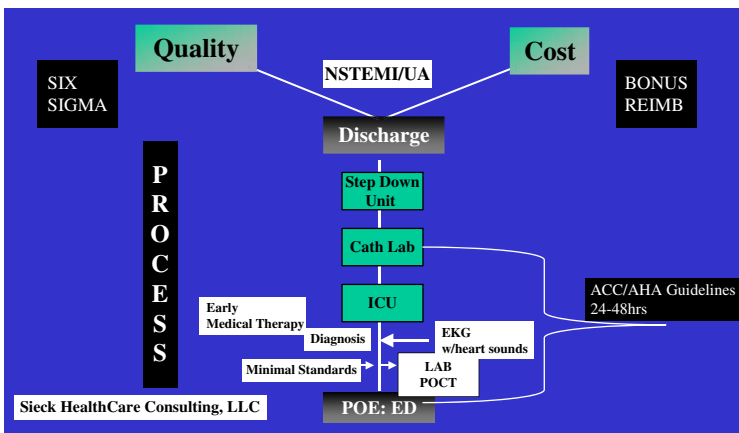


Fig. 7. Applying disease management to Trans-Theoretical Y model.



development of new models of acute care that can blend cost-efficiency with quality.

CPU has taken on a new role with clinical outcomes and quality improvement at their core. The new federal regulations and APC coding provide re-allocation of resources and dollars to outpatient services to identify and treat patients rapidly, thus enhancing the role of the CPU as a cost-efficient entry for acute cardiac patients.

The CPU offers an alternative clinical and financial strategy to hospitals and physicians in the emerging health care reform model. Third-party payers will continue to assess the impact on morbidity and mortality as the transition to outpatient services progresses. In order for hospitals to take advantage of outcomes-based financial incentives offered by the government, realignment of the business units must occur to maximize efficiency by including all departments, such as ancillary services.

Strategies that emphasize focused care-process improvement initiatives while targeting quality and economic margins are the wave of the future. The CPU represents the first wave of the new model for patients who experience chest pain and heart failure. As this model is refined and shown to impact cost and quality favorably, this experience is likely to extend to other cardiac conditions.

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# Medical Error Prevention in ED Triage for ACS: Use of Cardiac Care Decision Support and Quality Improvement Feedback

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Acute coronary syndromes (ACS) is the most common serious condition requiring emergency and acute care. Among the 8 million patients who present to emergency departments (EDs) in the United States each year with symptoms consistent with a cardiac problem, about 25% prove to have actual ACS. About one third (8%) of the presenting group prove to have acute myocardial infarction (AMI), of whom approximately 40%, or 3% of the overall group, have early-stage AMI deserving reperfusion treatment. The problem for the ED physician, therefore, is to identify, triage, and treat promptly and accurately the small proportion of patients who require immediate emergency care while efficiently dealing with the great majority who do not have ACS. This issue has been a focus of the time-insensitive predictive instrument (TIPI) approach to improving ED triage and treatment decision-making [1–5] and the TIPI Information System (TIPI-IS) feedback reporting system.

In the care of such patients, errors are made; thus, important opportunities exist for improvement in these ED triage and treatment decisions.

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In ED *triage* in the United States each year, about 12,000 patients who present with AMI and 14,000 who present with unstable angina (UA) are mistakenly sent home from the ED [6], which nearly doubles their expected mortality rates [6]. Reflecting this problem is that ED cases of missed ACS perennially represent one of the largest cost categories of adult malpractice claims in the United States. In ED *treatment* of patients who present with AMI, the lifesaving impact of coronary reperfusion therapy is directly related to the timeliness of implementation [7,8], yet many are not treated promptly and about 90,000 per year are not treated at all. These errors in triage and treatment for ACS are critical to the patient and occur on a scale that makes them a public health issue. Thus, they present important opportunities to reduce medical errors.

Reducing these medical errors requires innovative changes to patient care processes, existing equipment, and performance improvement activities that can be achieved through the use of information technology (IT).

Computerized physician order entry systems and electronic medical error reporting software are patient safety systems that require changes to, or additional layers in, the patient care workflow. These systems prove challenging to introduce effectively and without disruption to patient care. More easily introduced is IT that is seamlessly built into workflow and that enhances existing patient care and performance improvement activities. Representing this approach, the conventional computerized electrocardiograph is

an IT tool that can be adapted to improve patient safety by providing clinical decision support in real-time, without changing the patient care process. The device also provides workflow tools to prevent medical error and identifies patients for inclusion in performance and outcome measurement systems.

### **Development of real-time decision support, concurrent event alerts, and retrospective feedback reporting**

A series of decision support and risk reduction tools for real-time use in the ED have been developed in addition to an information system to provide concurrent missed AMI event alerting and retrospective feedback reports for improvement of the management of ACS patients. The core of this approach is the ability of a "time-insensitive predictive instrument" (TIPI) to compute, for every ED patient on presentation, a 0% to 100% probability that a patient truly has acute cardiac ischemia (ACI), and if having an AMI, the likely outcome benefits of thrombolytic therapy. A key feature of this prediction is the "time-insensitive" aspect of TIPIs, which refers to the fact that they compute, for a given ED patient, the same probability of value when used in the real-time ED setting or when used retrospectively for review of medical care. As now available in conventional electrocardiographs, besides printed on the ECG header as a decision aid for the physician the computed TIPI probabilities are stored in the electrocardiograph's computer, can be saved in a database, and then used to trigger concurrent flags about ongoing care and to generate retrospective reports and feedback for clinicians.

### **Real-time decision support for emergency department triage: the original acute coronary ischemia predictive instrument**

The original ACI predictive instrument [1] was developed to be an easy-to-use method to improve ED physician triage decisions so that fewer patients without ACI would be admitted to cardiac care units (CCUs), but without decreasing proper admission of those with ACI. Reasoning that a 0% to 100% probability value might be incorporated easily into physicians' clinical decision-making, based on prospectively collected data on 2801 patients seen in six divergent hospitals' EDs for 1 year, a logistic regression equation was developed that used seven variables and was

applicable to all six hospitals. Using a programmed calculator, a patient's 0% to 100% probability of having ACI could be computed in 20 seconds. In a 2320-patient 11-month prospective controlled trial of the predictive instrument's impact on ED care, its use markedly improved physicians' diagnostic specificity ( $P = .002$ ), with no significant change in sensitivity. The false positive diagnosis rate improved significantly ( $P = .004$ ), whereas the false negative diagnosis rate did not change. Accordingly, ED triage dispositions for patients who proved to have ACI were not changed from the appropriately high CCU admission rates, but for patients without ACI, CCU admission rates dropped from 24% during the control periods to 17%, and their ED discharge rates to home increased from 44% during the control periods to 51% ( $P = .003$ ), a 30% reduction in CCU admissions for patients without ACI. The predictive instrument's need for a calculator, however, was cumbersome. Thus, for better ease of use and attractiveness to clinicians, the authors designed the ACI-TIPI, its revised version, to be programmed into conventional computerized electrocardiographs.

### **Development of the acute coronary ischemia time-insensitive predictive instrument for real-time and retrospective decision support**

Although improvement of CCU use might be done by real-time and retrospective interventions, the latter has had little formal evaluation. Use of real-time test results and decision aids are more familiar to clinicians than feedback systems. Attractive and clinically relevant reports on triage and treatment decisions, however, should facilitate continuous quality improvement by emergency medical services (EMS), physicians and institutions self-assessment. (Also, payors and organizations responsible for hospital and CCU use for coronary disease need a fair and accurate retrospective tool by which the appropriateness of CCU use can be measured.) Thus, there is a need for a clinically valid attractive measure for feedback on ACI/AMI care.

Ideally, a single tool should be able to serve prospective and retrospective purposes. Generally, however, tools designed for real-time use, such as our original ACI predictive instrument, have not been validated for retrospective medical record review, and tools for retrospective review of care have not been applicable to real-time use, limiting clinicians' interest and confidence in

their use. Thus, the authors developed a “*time-insensitive* predictive instrument” for ACI (ACI-TIPI), valid for prospective real-time clinical use *and* retrospective medical record review, that accurately computes a patient’s likelihood of having ACI at the time of presentation [2]. Not only theoretically desirable as a tool usable by clinicians, administrators, and payors, the ACI-TIPI might have the added benefit of promoting cooperation between these groups. This ACI-TIPI was tested on the 2320 patients seen at the six study hospitals’ EDs during the second year, along with the original instrument, and both were compared with ED physician diagnostic performance [2]. Calculation of the receiver-operating characteristic (ROC) curve areas, which simultaneously evaluate sensitivity and specificity of a continuous scale test, yielded values of 0.88–0.89 for the ACI-TIPI and the original instrument, demonstrating excellent and similar diagnostic performance by both. Besides the ACI-TIPI, all subsequent predictive instruments, for mortality from ACI/AMI [3], for mortality from congestive failure [4], and the TPI [5] (see later discussion) meet TIPI criteria.

#### **Incorporating acute coronary ischemia time-insensitive predictive instrument into electrocardiographs to support real-time emergency department/emergency medical services care**

Convinced that the predictive instrument’s probability would be used more were it automatically printed in the text header on ECGs (Fig. 1), the ACI-TIPI was programmed into a computerized electrocardiograph [9]. To do this, an ACI-TIPI was written using Hewlett-Packard (now Philips) ElectroCardiographic Language [9,10]. This activity was done in repeating iterative cycles of programming ECG waveform-based measurement criteria and then comparing the program’s performance on sample ECGs to readings by the ECG reader who designed the original ACI-TIPI ECG variables (HPS).

Because it was felt that the ACI-TIPI and the approach of incorporating a predictive instrument into a computerized electrocardiograph would not benefit a maximal number of patients if restricted, we published all details of the ACI-TIPI’s formula and the incorporation of a TIPI into an electrocardiograph was put into the public domain. Marketed or prototype ACI-TIPI/TPI electrocardiographs

exist by all United States EMS electrocardiograph manufacturers.

Besides enabling presentation of the ACI-TIPI on the ECG, its incorporation into a computerized electrocardiograph allows transfer of patients’ ACI probabilities into a database, which is central to the development of a performance measurement and feedback system, the TIPI information system (TIPI-IS). Thus, the probability, ECG, and data entered into the electrocardiograph in clinical use (age, sex, presenting symptoms, physician, location) can be combined with other data and used for reports and analyses. This information allows clinicians and operations personnel of EMS and hospital organizations to use the same clinically valid risk-adjusted outcome predictions/measures (without medical record review).

#### **The multicenter acute coronary ischemia time-insensitive predictive instrument clinical trial**

In our 10-hospital, 10,689-patient clinical trial of the ACI-TIPI electrocardiograph’s impact on ED triage of patients with symptoms suggestive of ACI conducted in public, private, community, and tertiary hospitals in urban, suburban, and semi-rural areas, the ACI-TIPI improved ED triage [11]. In doing so, it demonstrated differential impact depending on whether patients had ACI or not, whether the hospital had high or low cardiac telemetry unit capacity, and whether the triaging ED physician was an unsupervised resident or not. Even as the ACI-TIPI reduced unnecessary admissions, it did not reduce appropriate hospital and cardiac unit admission for patients with true ACI, either UA or AMI. This result further confirmed the ACI-TIPI’s safety and effectiveness in ED use. Given that about 6% of ED patients presenting with symptoms suggesting ACI prove to have stable angina, such reductions would correspond yearly in the United States to approximately 30,000 fewer hospitalizations and 20,000 fewer CCU admissions, and about \$728 million saved [11].

#### **Studies of failure to hospitalize emergency department patients with acute coronary ischemia**

Among our studies of factors contributing to ED triage and treatment errors [12–24], the authors have sought the causes for failing to hospitalize ED patients who have ACI [6,25,26]. In the authors’ first such study, based on the care at the hospitals that participated in the original

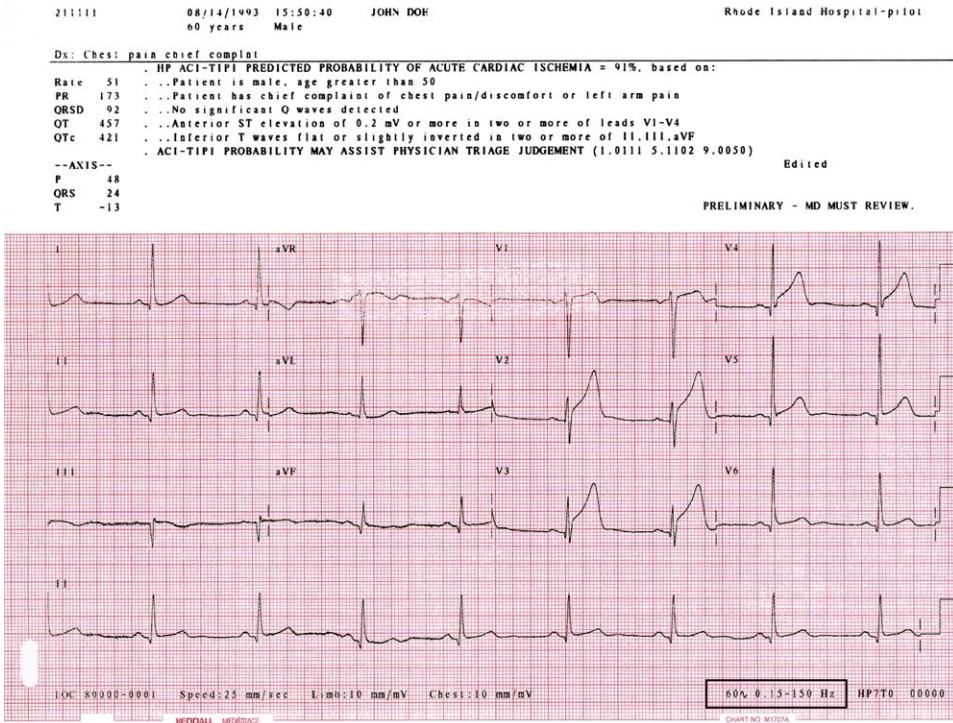


Fig. 1. ACI-TIPI ECG header.

ACI predictive instrument trial, approximately 2% of ED patients with AMI were sent home mistakenly [25], most commonly related to problems in physician use of the ECG [6,25]. Among ED patients sent home with AMI, 35% had ECG abnormalities consistent with ACI noted by the physician but not given sufficient weight in the triage decision [25]. Additionally, 25% had ECG abnormalities suggesting AMI (ST elevation) that were missed by the ED physician [25]. Analyses showing errors in physician ECG reading of ST segments and T waves contributing to suboptimal ED triage supported these findings [26].

In the authors' study of failure to hospitalize ED patients with ACI (AMI or UAP) in the ACI-TIPI Trial hospitals, the results were consistent with earlier findings [6]. Among the 10,689 ED patients studied, of those with AMI ( $n = 889$ ), 2.1% were sent home, and of those with UAP ( $n = 966$ ), 2.3% were not hospitalized. Yearly in the United States, this corresponds to 26,000 ED patients with ACI mistakenly not hospitalized: 12,000 with AMI and 14,000 with UAP. Of note, failure to hospitalize for ACI was more likely if the patient was nonwhite (2.2 times more likely, and 4.5 times more likely if having an AMI), a woman

under age 55 (6.7 times more likely) had a primary symptom of shortness of breath rather than chest pain (2.7 times more likely), or a normal or non-diagnostic ECG (3.3 times more likely, and 7.7 times more likely if having an AMI). These failures to hospitalize showed a statistical trend for greater mortality: nonhospitalized patients with AMI were 1.9 times more likely to die than similar patients who were hospitalized, and nonhospitalized patients with UAP were 1.7 times more likely to die than similar patients who were hospitalized.

These findings possibly reflected physicians' overdependence on generalities. Among ED patients, it is true that ACI is less likely in younger women, African-Americans, those without chest pain, and those with normal ECGs; but some such patients do have ACI. Physicians must be careful not to over-generalize about certain groups, and for these patients, the ACI-TIPI and TPI may help (see later discussion of TPI Trial on use of coronary reperfusion therapy for women). The wide range in hospitals' rates of failure to hospitalize (0%–11%) suggests that hospitals should monitor, and continually improve, their ED performance. Of note, "chest pain centers" did not have better performance; it seems that what is

important is not the ED label, but that its physicians fully evaluate the entire patient, and understand the proper use of diagnostic technologies and receive feedback about diagnostic performance [27,28].

**Acute coronary ischemia time-insensitive predictive instrument risk management tool: an ECG-based form for avoiding medical errors**

Based on these studies, cases of patients who presented with AMI and mistakenly sent home were reviewed to devise a way to reduce such errors. A “risk management form” was developed and integrated into ACI-TIPI software so the form is generated and partially filled-out automatically by the electrocardiograph at the time of the patient’s initial ECG (Fig. 2) [29]. The intent was that the form prompt consideration and documentation of the key clinical factors for such cases, be immediately and conveniently available for real-time use, and include the electrocardiograph’s computerized interpretation in its text, along with the ACI-TIPI probability of ACI, to lessen the likelihood that ECG abnormalities and high-risk patients would be missed.

To assess the potential impact of the risk management form, the form was retrospectively applied to 20 cases that came to malpractice litigation. This information was also compared with what the impact would be were the form not automatically generated by the electrocardiograph, to see whether this approach was warranted. With the electrocardiograph-generated version, 61% of cases were seen as much less likely or certain to not come to malpractice litigation, versus 37% for the nonautomatic version ( $P = .001$ ). Moreover, for those that would have come to litigation, had the automatic electrocardiograph-generated version been used, 80% would have had a significantly better outcome, including 59% who were judged to be likely to have a better outcome ( $P = .001$ ). The provision of the ACI-TIPI probability should help the clinician appreciate the importance of such ECG abnormalities as contributors to the patient’s likelihood of having ACI. The clinical information needed to fill out the rest of the form should provide the kind of documentation that better reveals appropriate care, and the process of filling-in the items was created in the hopes that it deter suboptimal care in the process of such documentation. Based

CHEST PAIN / POSSIBLE MYOCARDIAL INFARCTION  
EMERGENCY MEDICAL RECORD SUPPLEMENTAL FORM

Name: JOHN DOE  
ID: \_\_\_\_\_ Age: 56 years Male  
Dept: 12/03/2004 03:07  
NEW ENGLAND MEDICAL CENTER

CHEST PAIN/DISCOMFORT: Yes, chief complaint (MD Agree:  YES  NO, CORRECT: \_\_\_\_\_)

CHARACTER OF CHEST PAIN OR CHIEF COMPLAINT: \_\_\_\_\_ DURATION: \_\_\_\_\_

MADE WORSE BY: \_\_\_\_\_ RELIEVED BY: \_\_\_\_\_

SUGGESTIVE OF ISCHEMIA?  YES  SOMEWHAT  NO

PATIENT REPORTS PRIOR HEART ATTACK:  YES  NO PRIOR NITROGLYCERIN USE:  YES  NO

ECG ISCHEMIA-RELATED Q, ST, & T WAVE FINDINGS: (ECG DONE: 12/03/2004 03:07:59 )

CHEST PAIN AT TIME OF THIS ECG?  YES  YES, BUT IMPROVED  NO. COMMENT: \_\_\_\_\_

Anterior significant Q waves in two or more of leads V1-V4: MD Agree:  YES  NO\*

Anterior ST depression of 0.1 mV or more in two or more of leads V1-V4: MD Agree:  YES  NO\*

Anterior T wave inversion of 0.1 mV or more in two or more of leads V1-V4: MD Agree:  YES  NO\*

\*ADDITIONAL ECG FINDINGS/CORRECTIONS TO ABOVE: \_\_\_\_\_

COMPARED TO PRIOR ECG:  NO CHANGES. CHANGES: \_\_\_\_\_

NO PRIOR ECG DONE  PRIOR ECG NOT AVAILABLE  PRIOR ECG NOT REQUESTED

HP ACI-TIPI PREDICTED PROBABILITY OF ACUTE ISCHEMIA = 83%, based on this information collected at the time of the ECG.  
Patient is male, age greater than 50  
Patient has chief complaint of chest pain/discomfort or left arm pain  
Patient's ECG Q, ST, & T wave findings as noted above (1.0111 5.1110 9.1011)

TRIAGE DECISION:  CCU/ICU  INTERMEDIATE CARE  WARD  HOME  OTHER: \_\_\_\_\_

IF SENT HOME, SPECIFIC FOLLOW-UP INSTRUCTIONS GIVEN TO PATIENT:  YES  NO  COPY IN ED MEDICAL RECORD

ADDITIONAL COMMENTS: \_\_\_\_\_

PHYSICIAN SIGNATURE: \_\_\_\_\_ DATE: \_\_\_\_\_ TIME: \_\_\_\_\_

MERRILL MEDTRAC CHART NO. 01107A

Fig. 2. ECG risk management form.

on this, the authors worked with Hewlett-Packard (now Philips) to incorporate the automatic form into their electrocardiograph.

Financial implications of the impact of the form exist. For the 12 case records for which complete financial data were available, the legal and processing expenses averaged \$45,000 and settlements averaged \$337,000 [29]. With the form automatically generated by the electrocardiograph, the mean projected savings per case was \$382,000, corresponding to \$1.2 billion yearly savings in the United States. These savings should serve to make the ACI-TIPI approach attractive to hospitals, especially those with their own "captive" malpractice companies.

### **Development of the thrombolytic predictive instrument to assist recognition and treatment of ST-elevation myocardial infarction**

Emergent coronary reperfusion therapy, used promptly, can be lifesaving for patients with ST-elevation myocardial infarction (STEMI) [7,30–32]. In emergency settings, however, this can be difficult, especially for less obvious candidates, and when key physician decision-makers are not on-site. Intensive efforts by physician leaders, the National Heart Attack Alert Program, organizations interested in quality of care, and others [32–41], have helped increase use and promptness of coronary reperfusion therapy [42]. Further improvement is needed [42,43], especially for other than anterior STEMI, the category of AMI for which thrombolytic therapy was first recognized as effective [7,30] and for women, who have received less coronary reperfusion therapy than men [43,44]. Also, a need remains for ways to support prompt and accurate coronary reperfusion therapy decisions in hospitals and prehospital EMS settings where consultation with off-site physicians is required.

To assist treatment decisions, the TPI was developed, a collection of five component predictive instruments designed to accurately assess the likely patient-specific benefits and risks from the use of thrombolytic therapy for STEMI. This tool helps clinicians identify patients for coronary reperfusion therapy based on their probabilities of benefits and complications and facilitates earliest possible use of coronary reperfusion therapy [5,45]. With manufacturers, programs were developed for conventional computerized electrocardiographs, so that when significant ST-segment elevation of STEMI is detected, TPI predictions

are automatically computed and printed on the ECG header. These predictions include probabilities for acute (30-day) mortality if and if not treated with thrombolytic therapy; 1-year mortality rates if and if not treated with thrombolytic therapy; cardiac arrest if and if not treated with thrombolytic therapy; thrombolytic therapy-related stroke and major bleeding requiring transfusion.

The TPI database, on which the TPI's five component models were developed and tested, include the original data on patients who presented with AMI from 13 clinical trials and registries, including 107 hospitals of all types throughout the United States, totaling 4911 patients [1,45–57]. Separate logistic regression predictive instruments were developed for each outcome. For each, clinically important and statistically significant variables were selected for preliminary models, alternative forms and combinations of these variables were investigated, and models reformulated to optimize performance while preserving parsimony. This included creating two special ECG variables to reflect two determinants of the impact of thrombolytic therapy: a measure of AMI size and an indicator of "earliness" in the AMI's course [56]. In addition, to satisfy the need for a regression method that could accommodate the rapidly changing influence of ECG-based infarct size, QT interval, and coronary reperfusion therapy use in the first hours of ACI/AMI, a new method of regression was devised [58].

### **Thrombolytic predictive instrument clinical effectiveness trial: impact on use and promptness of coronary reperfusion therapy**

To test whether the electrocardiograph-based TPI improves ED selection of patients for coronary reperfusion therapy and promptness of treatment, a 22-month randomized controlled clinical effectiveness trial was run on the use and impact of thrombolytic therapy and overall coronary reperfusion therapy. Given our interest and the demonstrated need for improvement in the use of coronary reperfusion therapy [42,43], especially for other than anterior AMI [7,30] and for women [43,44], our study hypotheses focused on these groups, and also on hospitals where consultation with off-site physicians was required. Study endpoints were percentages of patients receiving (a) thrombolytic therapy; (b) thrombolytic therapy within 1 hour of ED presentation; and (c) all coronary reperfusion therapy, either by thrombolytic therapy or percutaneous transluminal coronary

angioplasty (PTCA). The trial ran in EDs at 28 urban, suburban, and rural hospitals across the United States, from major cardiac centers to small community hospitals.

Included in the trial were all consenting patients at least 35 years old presenting to any study hospital with STEMI. At participating hospitals, software-generating TPI predictions was installed on conventional computerized electrocardiographs. When a significant ST-elevation characteristic of STEMI was automatically detected, the electrocardiograph randomly assigned the patient to the control or intervention group. If assigned to the intervention group, the electrocardiograph automatically prompted the user to enter information needed to compute the TPI predictions: age, sex, history of hypertension or of diabetes, blood pressure, and time since ischemic symptom onset. The remaining variables, based on ECG waveform measurements, were automatically acquired by the electrocardiograph. Then the ECG was printed with TPI predictions on its header (Fig. 3). If variables were missing, TPI predictions were not calculated, but an alert listing missing variables was printed, allowing entry of missing data, if available. For patients in the control

group, the ECG had only the header text customarily used in that ED.

Collected data included: sociodemographic data; initial and follow-up clinical features; ECGs and cardiac biomarker test results; triaging physician training level, specialty, and whether ED-based; whether on-site or off-site (telephone) consultation was used for the coronary reperfusion therapy decision; whether the patient received thrombolytic therapy or PTCA; and how long after chest pain onset was the therapy received. TPI software automatically acquired clinical variables required for TPI calculations and ECG Q-wave, ST-segment, and T-wave measurements. Site physicians, blinded to study group, assigned confirmed diagnoses based on presentation, clinical course, initial and follow-up ECGs, and biomarker tests, using the World Health Organization criteria [59]. Patients' ED care was classified by whether consultation with an off-site physician was used in making the treatment decision. Hospital size, type, whether having on-site ED staff, and physician type were used as potential explanatory variables.

Of 2875 patients who presented with AMI at the participating hospitals, 1243 (43%) had

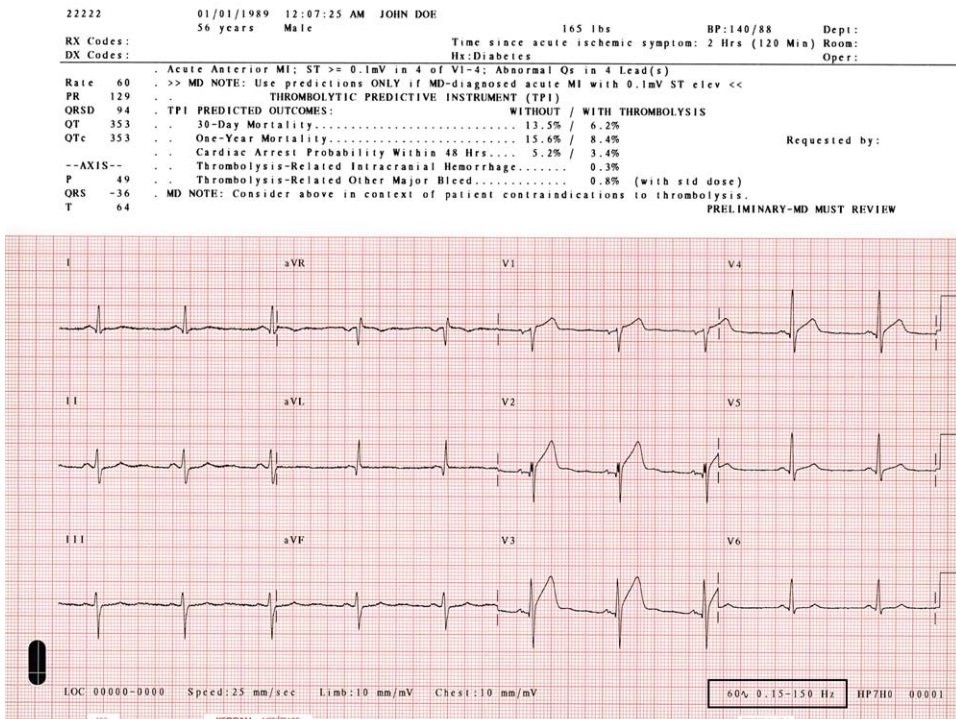


Fig. 3. TPI ECG header.



ST-segment elevation. Of these, 1197 were randomly assigned to study groups; 732 (61%) had inferior STEMI, and 465 (39%) had anterior STEMI. Of patients with inferior STEMI in the control group, compared with the TPI group, 61% compared with 68% ( $P = .03$ ) received thrombolytic therapy; 53% compared with 59% ( $P = .08$ ) received thrombolytic therapy within 1 hour; and 68% compared with 75% ( $P = .03$ ) received coronary reperfusion therapy overall, either as thrombolytic therapy or primary PTCA. Of patients with anterior STEMI in the control group compared with the TPI group, 60% compared with 54% ( $P > .2$ ) received thrombolytic therapy; 51% compared with 45% ( $P > .2$ ) received thrombolytic therapy within 1 hour; and 68% compared with 64% of TPI patients ( $P > .2$ ) received overall coronary reperfusion therapy. Among women ( $n = 398$ ) in the control group compared with the TPI group, 48% compared with 58% ( $P = .03$ ) received thrombolytic therapy; 41% compared with 48% ( $P = .10$ ) received thrombolytic therapy within 1 hour; and 56% compared with 66% ( $P = .04$ ) received overall coronary reperfusion therapy. Of patients who required physician consultation by telephone ( $n = 271$ ) in the control group compared with the TPI group, 47% compared with 63% ( $P = .01$ ) received thrombolytic therapy; 41% compared with 54% ( $P = .04$ ) received thrombolytic therapy within 1 hour; and 51% compared with 66% ( $P = .01$ ) received overall coronary reperfusion therapy. Thus, the trial showed that the TPI increased use of thrombolytic therapy, use of thrombolytic therapy within 1 hour, and use of overall coronary reperfusion therapy by 11% to 12% for patients with inferior STEMI, 18% to 22% for women, and 30% to 34% for patients with an off-site physician. The TPI's effect was minimal on patients who exhibited high baseline coronary reperfusion therapy rates, such as for men who presented with anterior STEMIs. For the targeted groups (those more often missed, women and those with less obvious STEMIs, and situations in which physicians were off-site), however, the TPI increased recognition of STEMI and use and timeliness of coronary reperfusion therapy.

In the TPI Trial, it is of interest that the TPI's impact was not seen among patients with anterior STEMI, and when combining STEMI locations, it was not seen among men. This is thought to be because anterior STEMIs have received longer-standing emphasis for coronary reperfusion

therapy and are more easily recognized in the pre-cordial leads of the conventional ECG, and thus physicians already do a good job of detecting them as appropriate candidates for coronary reperfusion therapy, and treat them. Similarly, AMI presents more "classically" in men and is already better recognized (and treated) in men than women [6,60,61]. The high rates of coronary reperfusion therapy for anterior STEMI and men when seen in experienced centers may require little improvement. Less than 5% of the TPI Trial's patients, however, were seen in hospitals without on-site ED physicians, and no patients were included while in transit by way of EMS (when all physician input would be remote). Thus, it is important that the TPI did improve the speed and use of coronary reperfusion therapy among all patients who presented with AMI (including anterior and men) when the ED physician or needed physician consultants are off-site. Because many hospitals' EDs still are not staffed 24 hours daily, and, especially in rural settings, long transport times may mandate EMS use of thrombolytic therapy or a decision for direct transport to one of the 20% of United States hospitals that are primary PTCA-capable [62], it seems likely that the TPI may improve coronary reperfusion therapy use for patients with anterior STEMI in these settings.

The TPI is particularly attractive for EMS use. Prehospital thrombolytic therapy is indicated for situations in which transport times are long [63–66], and the recent availability of single bolus thrombolytic therapy [67–69] and the increasing use of 12-lead ECGs in ambulances [70–74] provide a foundation for this approach [75–77]. The provision of TPI predictions for patients with STEMI in the field can support EMS use of thrombolytic therapy. Also, for patients who present with contraindications to thrombolytic therapy, prehospital identification as a reperfusion candidate by the TPI can help avoid transport to a facility lacking primary PTCA capability, avoiding the need for re-transport to a PTCA-capable center. Clarifying reperfusion needs and options in the field, especially in rural areas, can save time, and improve patient outcomes [78]. That the TPI increased overall coronary reperfusion therapy use suggests it should facilitate decision-making for both types of reperfusion in prehospital EMS use. Also, even with hospital-based coronary reperfusion therapy, advance notice by EMS, as in the MITI Trial [63], prompted by the TPI, should reduce delays after arrival.

**Time-insensitive predictive instrument information system cardiac error reduction system based on acute coronary ischemia time-insensitive predictive instrument demonstration project**

Having shown that ACI-TIPI's predictions on ECGs provide effective real-time decision support, the TIPI-IS demonstration project was undertaken. An ACI-TIPI-IS was created to measure the impact of real-time, concurrent, and retrospective ACI-TIPI interventions on medical errors in ED triage. Also, through a series of user tests, the system's attractiveness and use for various users was evaluated, and its reports were modified to improve their usefulness in identifying and addressing medical error.

In the ACI-TIPI-IS demonstration project [79], the TIPI-IS provided concurrent and retrospective reporting and feedback for ED physicians and their hospitals. Implemented and used at five hospitals, the project provided a range of concurrent alerts and feedback reports to over 70 physicians at these facilities. This project has been successful in demonstrating the use of the ACI-TIPI probabilities within an information system providing concurrent alerting and retrospective feedback reports.

A prototype TIPI-IS database and web server-based user interface was created to (1) aggregate

the ECG Management System data, ADT, Lab and ICD9 diagnostic coding data into a data warehouse database; and (2) create a TIPI-IS web server to distribute TIPI-IS reports and allow physicians (using a standard web browser) to explore the underlying patient data (Fig. 4). The web-based user interface was fully redesigned after repeated usability testing and enhanced with additional outcome information, including confirmed diagnoses of ACI after inpatient evaluation and whether patients had cardiac catheterization, PTCA or coronary bypass surgery. The system evaluation process included an iterative review with ED physicians leading to the redesign of screens and reports. Reports for comparison and benchmarking across groups of hospitals and for drill-down within a hospital were created and were additionally reviewed and revised by health plans and malpractice insurers to ensure that the reports met the requirements for risk reduction and medical error prevention programs (Fig. 5).

Implementation of the TIPI-IS had five major components: (1) preparation of the ECG equipment and ECG computerized management system; (2) installation of the TIPI-IS server within each hospital's intranet; (3) linking and integrating each

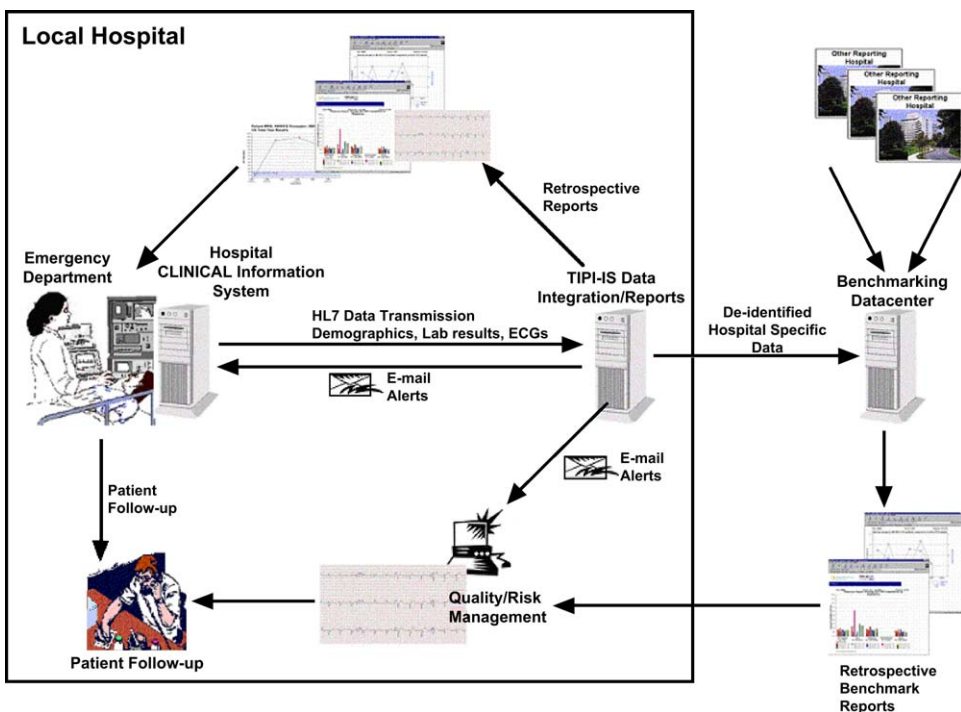


Fig. 4. TIPI-IS diagram. (Courtesy of Clinical Care Systems, Inc., Bedford, MA.)

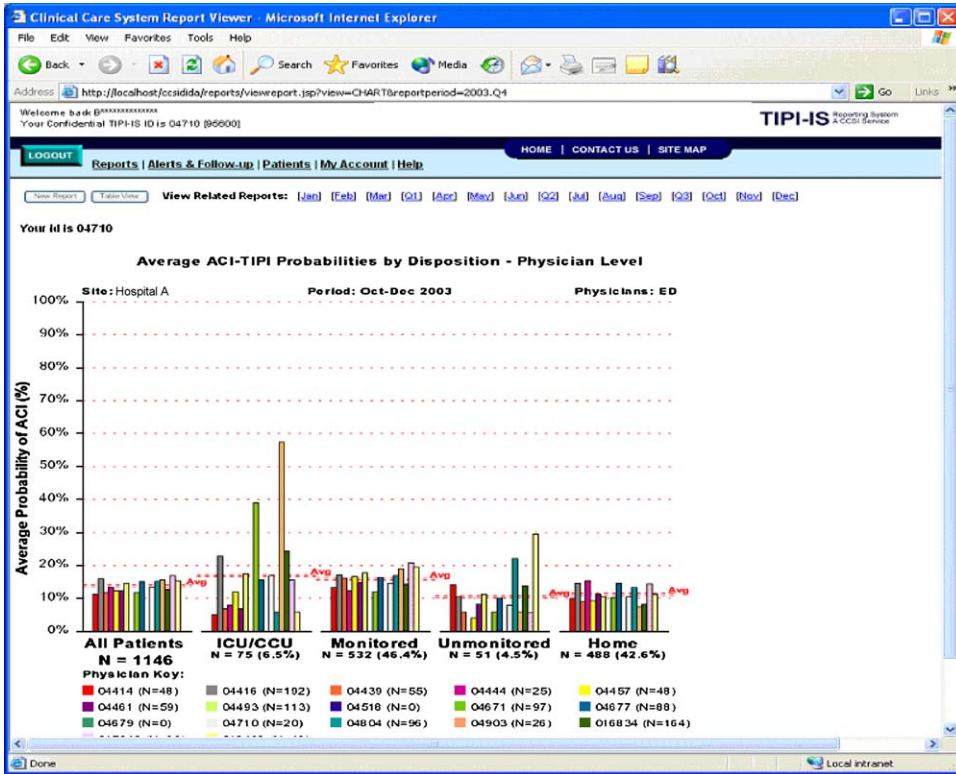


Fig. 5. TIPI-IS feedback report. (Courtesy of Clinical Care Systems, Inc., Bedford, MA.)

hospital's key computerized databases through electronic data interfaces to the TIPI-IS server; (4) testing of interface data; and (5) user training. Testing interfaces from feeder systems to the TIPI-IS at each site was conducted to ensure TIPI-IS captured data completely and mapped key data elements accurately for subsequent reporting. Electronic data collection eased the resources required to compile a large database, but also posed challenges in collecting accurate data because it depended on the diligence of staff entering the data for operational purposes rather than research purposes.

Access to data and reports through the web-based interface improved availability of data, and despite user testing and redesign of the original system, the web-based system continued to be available for use. Frequent users of the system were project staff and ED department Quality Improvement (QI) staff who had operational needs to access the data. When new reports or information were posted on the website, each physician received an e-mail with the link to the web page. A key advantage of the TIPI-IS approach,

which was successfully demonstrated, is the ability to compile large amounts of information for feedback reporting and error reduction through an automatic electronically compiled database. This process leveraged the clinical information systems already in place and minimized the resources required to collect and analyze data.

During the intervention period, ED QI nurses and physicians were given a general overview of the project and training in the use of the TIPI-IS, the content and significance of the concurrent alerts and feedback reports. These meetings were conducted with the ED physician leader who distributed physician-specific feedback reports with information from baseline data collection and a secure password to access their reports online.

Concurrent alerts were designed within the database system to signal patient cases that met criteria for immediate follow-up to prevent possible missed diagnosis of ACI. These thresholds included patients sent home from the ED with an ACI-TIPI value in the high-risk category or with a positive cardiac biomarker. The alert triggered an e-mail or pager message to the ED and ED

physician indicating a patient required follow-up/review (Fig. 6). The results of follow-up on these alerts were entered into the alert follow-up screen. Patients were contacted to return to the EDs if needed and hospitalized for further evaluation when appropriate.

Retrospective review of a sample of patients sent home from the ED with moderate- to high-risk ACI-TIPI probabilities was conducted to identify cases of missed diagnosis of ACI. This review, conducted at each site by the ED director, identified a series of issues ranging from incomplete documentation to variations in practice, sometimes within, though sometimes not within, standard expectations of that ED. Results were addressed with staff during monthly morbidity and mortality review, in individual feedback discussions, and in some cases, by changes in the ED's practices.

### Summary

Medical errors in the care of patients who present with ACS include errors in ED triage, such as the decision to send home a patient from the ED

who presents with ACS or to hospitalize a patient who does not prove to be experiencing ACS to the CCU, and errors in treatment, such as the failure to promptly use reperfusion therapy for patients with ST-elevation AMI. ECG-based ACI-TIPI and TPI predictive instruments, with a linked TIPI-IS, provide real-time, concurrent, and retrospective decision support tools and feedback for the prevention of medical errors in the care of patients who present with ACS. In real-time, ACI-TIPI probabilities printed on the ECG header for the ED physician, provide an additional piece of information for triage decision making, and the ACI-TIPI risk management form reduces liability risk by prompting consideration and documentation of key clinical factors in the diagnosis of ACI. Also in real-time, the TPI increases overall coronary reperfusion therapy use. Concurrent flagging by TIPI-IS uses electronically acquired ECG and hospital data to provide concurrent alerts about potential misdiagnosis or mis-triage of patients with ACS. Retrospectively TIPI-IS-based feedback reports allow performance improvement. These examples of information technology tools, integrated into ECG equipment already used in hospitals to deliver patient care, demonstrate the potential to adapt other existing equipment or other patient care activities to enhance patient safety and error reduction.

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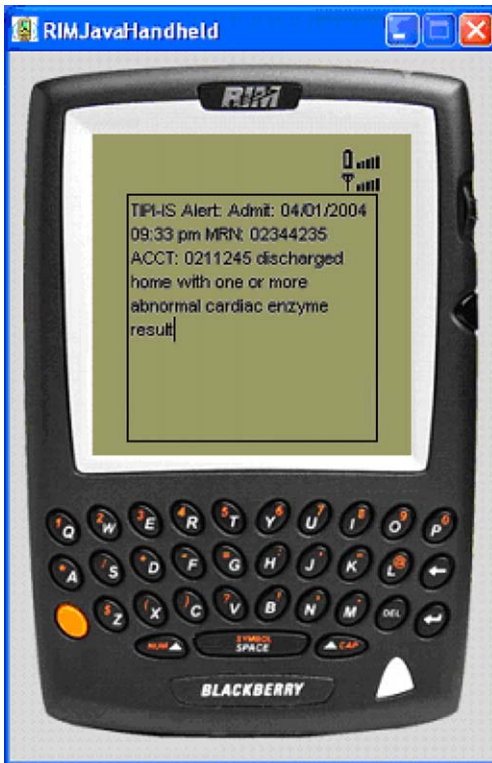


Fig. 6. TIPI-IS alert message. (Courtesy of Clinical Care Systems, Inc., Bedford, MA.)

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