EMERGENCY MEDICINE PRACTICE
EMPRACTICE.NET
AN EVIDENCE-BASED APPROACH TO EMERGENCY MEDICINE

Evidence-Based Risk Stratification Of Patients With Suspected UA/NSTEMI

April 2004
Volume 6, Number 4

Authors

Thomas Macfarlane, MD
Department of Emergency Medicine, Alameda County Medical Center, Oakland CA.

Eric R. Snoey, MD
Program Director, Department of Emergency Medicine, Alameda County Medical Center/Highland Hospital, Oakland CA.

Peer Reviewers

Keith A. Marill, MD
Emergency Medicine Attending, Massachusetts General Hospital; Faculty, Harvard Medical School, Boston, MA.

Jeffrey Tabas, MD
Assistant Professor of Medicine, University of California School of Medicine; Attending Physician, San Francisco General Hospital Emergency Services, San Francisco, CA.

CME Objectives

Upon completing this article, you should be able to:
1. discuss the terminology, epidemiology, and pathophysiology of unstable angina and non-ST-segment elevation myocardial infarction;
2. implement the initial risk stratification of patients with suspected UA/NSTEMI using the history, physical examination, ECG, and cardiac biomarkers;
3. tailor the intensity of diagnostic and therapeutic interventions based on the relative likelihood that a particular patient's symptoms are due to ACS; and
4. explain the advances in procedural and pharmaceutical interventions for UA/NSTEMI.

Date of original release: April 1, 2004.
Date of most recent review: March 12, 2004.
See "Physician CME Information" on back page.

During a typical busy afternoon, you're seeing two patients with possible acute coronary syndrome (ACS). One is a previously healthy, anxious 47-year-old male with several weeks of episodic left chest discomfort. The pain is non-exertional, non-radiating, and described as an ache. The other patient is a 74-year-old female with hypertension and diet-controlled diabetes who describes new-onset dyspnea and greatly reduced exercise tolerance. She has had no chest pain.

These two patients may carry the same diagnosis, but they differ dramatically in terms of their respective work-ups, management, and prognosis. The approach to ACS is never a one-size-fits-all prospect.

CORONARY artery disease (CAD) is pervasive, complex, and kills more Americans each year than any other disease process.[1] Many patients with symptomatic CAD use the ED as their initial point of entry into the medical system. Early recognition, risk stratification, and timely intervention are critical to securing a favorable outcome. Emergency physicians must therefore be expert both in the diagnosis of symptomatic CAD as well as the implementation of the complex, stepwise management protocols currently being recommended. This review highlights the advances in our understanding of ACS: its pathophysiology, clinical diagnosis, risk stratification, and therapeutics. There is a particular focus on the subgroup of unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI).

Definitions

ACS is a term referring to patients with clinical evidence of acute myocardial ischemia: UA, NSTEMI, and ST-segment elevation myocardial infarction (STEMI).[2] ACS represents a continuum of diseases with variations in pathophysiology, presentation, prognosis, and response to therapeutic intervention. The subgroup of UA / NSTEMI defines the phase of symptomatic CAD that occurs after stable angina. Angina is considered unstable when one of three situations exists: it is occurring for the first time, it occurs at rest, or it is accelerating in terms of frequency or severity. The presentation of NSTEMI is similar to that of UA, with the addition of an elevation in biochemical markers

for myocardial infarction (MI).[2] The presentation of STEMI is similar to that of NSTEMI, with the addition of diagnostic ST elevation on ECG testing. ACS is an area of abundant clinical research, with new studies, practice protocols, and therapeutics being introduced on almost a monthly basis. Sorting out what is *bona fide* and practical represents an ongoing challenge for the practicing emergency physician.

Critical Appraisal Of The Literature

The spectrum of ACS has produced intense scientific interest, leading to an enormous amount of high-quality literature. Even so, it is important to remember that pharmaceutical industry sponsorship of trials is frequent.

Much of the data referenced in this review are from large randomized, controlled clinical trials. A number of large meta-analyses are also cited.

In 2002, the American College of Cardiology (ACC) and the American Heart Association (AHA) issued practice guidelines on the diagnosis and management of UA and NSTEMI using a strict evidence-based approach.[2] These guidelines are evaluated in this issue of *Emergency Medicine Practice* as they apply to patients in the ED. (The June 2003 issue of *Emergency Medicine Practice* presents an evidence-based discussion of the management of patients with STEMI who are suitable for reperfusion by percutaneous coronary intervention or thrombolytics.) The Cochrane Library contains several pertinent reviews that are also discussed; the most applicable relate to the use of glycoprotein (GP) inhibitors and low-molecular weight heparin (LMWH).[3,4]

The American College of Emergency Physicians (ACEP) issued an updated clinical policy titled "Critical Issues in the Evaluation and Management of Adult Patients Presenting with Suspected Acute Myocardial Infarction or Unstable Angina," which is discussed in this text.[5]

Epidemiology And Pathophysiology

Of the 6 million ED visits for chest pain each year, approximately 800,000 patients are diagnosed with MI and an additional 1.5 million with UA or NSTEMI. Approximately 60% of those hospitalized are over 65, and half are women.[6]

ACS occurs when myocardial perfusion proves inadequate to meet demand. The result is angina—a characteristic sensation of pain or pressure within the chest that may radiate to the jaw or upper extremities, associated with diaphoresis, nausea, and dyspnea. In addition, angina may present without pain, manifesting only as shortness of breath, syncope, or nausea. A patient with exertional angina may experience these symptoms due to insufficient coronary flow through a fixed stenosis. A patient with rapidly accelerating angina, rest angina, or acute MI will experience symptoms when there is a sudden interruption in the blood supply to the myocardium. A common mechanism is when a previously stable atherosclerotic plaque ruptures, leading to platelet aggregation, thrombus formation, and myocardial ischemia.[7] The severity and duration of the ischemia, the likelihood of MI, and the eventual prognosis are determined by what happens next to this thrombus. In many cases, the thrombus quickly erodes, washes downstream, and symptoms abate. Alternatively, the thrombus may wax and wane but never fully occlude, causing a stuttering form of ischemia. Finally, the thrombus may consolidate and fully occlude, resulting in an MI. (See **Figure 1** on page 3.)

Less common causes of ACS include spasm of epicardial or intramural coronary arteries, progressive atherosclerotic narrowing in the absence of thrombus, and, rarely, inflammatory processes leading to coronary artery occlusion.[7]

Cost- And Time-Effective Strategies For Patients With UA/NSTEMI

1. Use aspirin in all patients who do not have an absolute contraindication. This treatment is so inexpensive yet so effective that no patient should be without. (*Caveat:* Active bleeding—especially non-compressible bleeding—may be increased with aspirin use.)

2. Low-molecular-weight heparin is both much easier and more effective than unfractionated heparin. The dosing is simple and patients do not require regular PTT checks, thereby reducing both the physician and nursing workload. (*Caveat:* Patients with diminished renal function may accumulate LMWH, causing a greatly increased risk of bleeding.)

3. Clinical risk stratification allows the emergency physician to tailor treatment to the patient's risk level. Those patients that are at highest risk gain the most from both antiplatelet and antithrombotic treatments. (*Caveat:* The emergency physician may have to choose to treat aggressively before all of the clinical data that help assign levels of risk have been obtained. The paucity of data that we sometimes have to deal with requires a reliance on judgment.)

4. If you do not have a chest pain center, consider outpatient provocative testing rather than admission. Low-risk patients with a normal ECG and a negative six-hour troponin level may be scheduled for outpatient stress testing. (*Caveat:* Patients must be low-risk, not have continuing pain, should have a normal or nearly normal ECG, and should have a negative troponin drawn at least six hours after the onset of pain. Follow-up must be ensured.)

5. Consider immediate stress testing in low-risk patients. Instead of prolonged observation, including serial testing of cardiac markers, some centers immediately stress low-risk patients to evaluate for cardiac disease. Trained emergency physicians can accurately interpret graded exercise stress tests performed on site. (*Caveat:* To safely employ this strategy, the patient must be pain-free and have a normal ECG [including no evidence of Wellens' syndrome]. While immediate stress testing has been studied even in patients with known CAD, most centers would perform serial markers in this population.)

6. Employ bedside cardiac markers. The use of point-of-care technology can speed decisions in patients with chest pain. Those with positive troponins can be consulted to cardiology minutes after arrival despite a normal ECG. The accuracy of these tests is comparable to standard laboratory assays. ▲

From a prognostic standpoint, UA / NSTEMI represents a continuum from low risk to high risk, depending on many thrombus-related elements as discussed above, the location of the occlusion, the presence of collaterals, and comorbid disease. It is interesting to note that in some cases UA / NSTEMI may carry a worse prognosis than STEMI, since the thrombus in UA is nonocclusive and the downstream vascular territory is exposed to ongoing risk, which predisposes the patient to renewed ischemia, STEMI, and the risk of lethal arrhythmia.

Differential Diagnosis

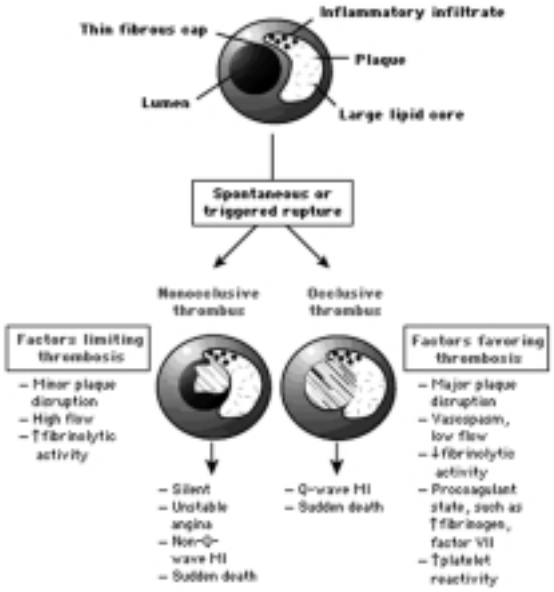
The differential diagnosis of chest pain is broad and includes several immediately life-threatening conditions. An abbreviated list appears in **Table 1**. (For further discussion, see the June 2003 issue of *Emergency Medicine Practice*.)

Prehospital Care

The prehospital care of patients with suspected ACS generally involves the administration of aspirin, sublingual nitrates, oxygen, and occasionally morphine. Patients should also be placed on three- or five-lead cardiac monitors and transported under lights and sirens. Data from studies of prehospital thrombolysis suggest that ECGs transmitted to the hospital by paramedics may lead to a reduction in the time to diagnosis of STEMI.[8] With an average of 3-5 additional minutes of scene time, paramedics can accurately identify thrombolytic candidates with a 12-lead ECG, reducing time to thrombolysis after ED arrival by 47 minutes.[9] Although not specifically evaluated, this same

Figure 1. The Vulnerable Plaque And Consequences Of Plaque Rupture.

A vulnerable plaque, which can potentially rupture, has a large lipid core with a thin fibrous cap; there is evidence of active inflammation within the plaque. Plaque rupture may result in a nonocclusive thrombus (producing unstable angina or a non-Q wave myocardial infarction) or an occlusive thrombus (producing a Q-wave myocardial infarction).



Reproduced with permission from: Kullo IJ, Edwards WD, Schwartz RS. Vulnerable plaque: pathobiology and clinical implications. *Ann Intern Med* 1998 Dec 15;129(12):1050-1060.

Table 1. Differential Diagnosis Of Patients With Presentations Suggestive Of ACS.

Diagnosis	History	Physical Examination	Diagnostic Tests
Aortic dissection	Tearing pain radiating to back, neurologic symptoms	New murmur, bruits, unequal pulses	Chest x-ray, CT angiogram, echocardiogram
Acute coronary syndrome	Pressure-like pain with radiation to arms/face, diaphoresis, dyspnea, risk factors	May have evidence of heart failure	ECG, biochemical markers
Pulmonary embolism	Sudden onset, pleuritic, dyspnea, risks for venous thrombosis	Tachypnea, tachycardia, venous thrombosis	Chest x-ray, V/Q scan, CT angiogram or pulmonary angiogram
Esophageal rupture (Boerhaave's syndrome)	Constant severe retrosternal/ epigastric pain, inciting event	Mediastinal rub/?crunch	Chest x-ray
Pneumothorax	Pleuritic pain and dyspnea	Diminished breath sounds over hemithorax	Chest x-ray
Pneumonia	Cough, fever, dyspnea, pleuritic pain	Abnormal breath sounds, fever, hypoxia, tachypnea	Chest x-ray
Pericarditis	Positional ache, dyspnea	Rub	ECG, chest x-ray, sonogram
Gastrointestinal causes	Associated abdominal pain, GERD symptoms	Abdominal tenderness, rebound or guarding	Amylase, lipase, KUB, ultrasound
Musculoskeletal causes	Pain increased with minimal muscular activity or movement	Chest wall tenderness to palpation	Normal

Adapted from: Green G, Hill P. Approach to chest pain and possible myocardial ischemia. In: Tintinalli J, Kelen G, Stapczynski J, eds. *Emergency Medicine: A Comprehensive Study Guide.* New York: McGraw-Hill; 2000:341-352.

reduction in time to diagnosis (and thereby treatment) may occur in patients with UA / NSTEMI.

Prehospital administration of aspirin and heparin has been shown in a single study to increase the patency of the infarct-related artery in patients with acute STEMI. Again, the benefit in those without ST-segment elevation is less well-characterized.[10]

Recent public awareness campaigns have focused on educating the public about the symptoms of cardiac ischemia so that appropriate activation of emergency medical services can occur expeditiously. The question remains whether this activation makes a difference in outcomes: There are no conclusive data to show that outcomes are improved in patients with ACS who are transported by ambulance vs. private car. However, some data suggest that patients may self-select for severity, with the sickest patients initiating ambulance transport.[11]

Emergency Department Evaluation

The adage "time is myocardium" is a graphic reminder that the diagnosis and treatment of ACS must be expeditious and largely empiric in the early stages. An ECG should be obtained within 10 minutes of arrival, since it serves as the key discriminator of patients who will require emergent revascularization either with thrombolytics or invasive strategies.[2] A focused history and physical examination can be performed simultaneously with other diagnostic and therapeutic measures. An emphasis should be placed on those key historical and physical features that establish the likelihood of significant CAD, as discussed in subsequent sections. This likelihood, together with ECG and cardiac biomarkers, is the essence of ACS risk stratification. The estimate of risk, in turn, defines short- and long-term prognosis, the need for subsequent testing, treatment categories, and, ultimately, disposition. **Table 2**, which is adapted from the ACC / AHA guidelines, is useful in determining the likelihood that a patient's signs and symptoms represent ACS secondary to CAD.[2]

Clinical History And Demographics

The clinical history should focus on establishing the likelihood that the symptoms are due to cardiac ischemia rather than the many non-cardiac causes. Typical angina is a deep, poorly localized chest or arm discomfort that is classically exertional and relieved with rest or nitrates.[12] Known coronary stenosis greater than 50% is a strong predictor of symptomatic CAD. In patients with known CAD and anginal symptoms, the emergency physician must establish the pattern of symptoms to determine whether they indicate stable or unstable angina. The most sensitive demographic indicators of CAD are age greater than 65 years and male gender.[13,14] The traditional risk factors of CAD—smoking, diabetes, family history, dyslipidemia, sedentary lifestyle, and hypertension—are less predictive of symptomatic CAD in the ED setting.[15,16] The thrombolysis in myocardial infarction (TIMI) risk score incorporates the most relevant historical findings. However, one must remember that patients with MI frequently present with atypical complaints. A large prospective, observational study of over 400,000 patients with confirmed MI showed that 33% did not have chest pain on presentation to the hospital. The patients without pain tended to be older, diabetic, women, and those with prior heart failure. These patients were less likely to receive reperfusion, beta-blockers, or heparin and had a threefold increase for in-hospital mortality.[17] In another smaller study, only 53% of patients with MI had an ED chief complaint of chest pain. Shortness of breath was the complaint in 17%, cardiac arrest in 7%, and dizziness / weakness / syncope in 4%.[18]

The usefulness of certain clinical features in determining the likelihood that a given patient with acute chest pain has ACS has been studied. These data are shown in **Table 3** on page 5. The rate of missed MI in the ED ranges from a low of about 2% in patients presenting to an ED to a high of

Table 2. Likelihood That Signs And Symptoms Are Due To Coronary Artery Disease.

Feature	High Likelihood *Any of the following*	Intermediate Likelihood *Absence of high-likelihood features and presence of any of the following*	Low Likelihood *Absence of high or intermediate features but may have*
History	Chest or left arm discomfort as chief complaint reproducing prior documented angina; known history of CAD, including MI	Chest or left arm pain or discomfort as chief symptom; age > 70 years; male sex; diabetes mellitus	Probable ischemic symptoms in absence of any of the intermediate likelihood characteristics; recent cocaine use
Examination	Transient MR, hypotension, pulmonary edema or rales	Peripheral vascular disease	Chest discomfort reproduced by palpation
ECG	New ST deviation (≥ 0.05 mV) or T-wave inversion (≥ 0.2 mV) with symptoms	Fixed Q waves; abnormal ST segments not documented to be new	T-wave flattening or inversion with dominant R waves; normal ECG
Biochemical markers	Elevated troponin or CK-MB	Normal	Normal

Adapted from: Braunwald E, Antman EM, Beasley JW, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—2002: summary article: 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). *Circulation* 2002 Oct 1;106(14):1893-1900.

36% if the presence of Q waves was found in the absence of a clinical history of MI. The factors most commonly associated with missed MI are age less than 55 years, female gender, non-white race, normal or nondiagnostic ECGs, and concurrent diabetes.[19-21]

Physical Examination

The value of the physical examination is limited, serving primarily to rule out ACS by confirming an alternative diagnosis. (See Table 1 on page 3.) One may further focus on identifying those patients with ACS-related complications; specifically, left ventricular failure and valvular abnormalities. Five percent of patients with NSTEMI will develop cardiogenic shock, which carries a mortality rate of 60%.[22] Therefore, physical examination findings that suggest shock—including heart rate greater than 100 beats per minute, systolic blood pressure 100 mmHg or less, and signs of heart failure—are the most important baseline physical findings.[22] Patients with significant peripheral or cerebrovascular disease often have simultaneous CAD and a high mortality rate, especially in diabetics.[23] Several of the therapies for UA / NSTEMI carry an increased risk of gastrointestinal bleeding. Testing for blood in the stool to exclude preexisting hemorrhage seems prudent in patients who will be treated with these modalities. No study directly investigates the risk of not performing a rectal examination, but a few methodologically flawed studies do purport to establish the safety of digital rectal examination in patients with AMI.[24]

Diagnostic Testing

Electrocardiogram

The ECG lies at the center of the evaluation of a patient with suspected ACS. Clear evidence exists to support the relationship between a delay in treatment and death in STEMI.[25] Therefore, a 12-lead ECG should be performed rapidly on all patients with a presentation consistent with ACS. This will expedite the use of reperfusion strategies if indicated. The following findings in the setting of ACS should prompt emergent consideration of reperfusion: ST-segment elevation of 0.1 mV (usually 1.0 mm with standard gain) in two or more contiguous leads, and new or presumably new left bundle branch block that obscures the ST segments. In the absence of these specific findings, other patterns have been evaluated for their predictive characteristics. Reversible ST-segment depression in patients with UA correlates with angiographic evidence of coronary thrombosis.[26] Symmetric T-wave inversions greater than 0.2 mV in the precordial leads suggest ischemia, particularly critical stenosis of the left anterior descending artery.[27] Other findings have been found to be less predictive, including ST-segment depression less than 0.05 mV or T-wave inversions of less than 0.2 mV.[28] Existing Q waves are not indicative of acute ischemia but do strongly suggest prior MI and the existence of underlying CAD.[2]

Unfortunately, the ECG is a fairly specific but relatively insensitive test for the presence of myocardial ischemia. Data show that emergency physicians are likely to misinterpret ECGs with ST elevation from left ventricular aneurysm, AMI with atypical ST elevation, benign early repolarization, pericarditis, left ventricular hypertrophy, or left bundle branch block with or without AMI.[29] Nearly 50% of patients with transmural MI have a nondiagnostic ECG. In 8% of patients with confirmed MI, the ECG is entirely normal. The sensitivity and specificity of the ECG in UA / NSTEMI are similar, with more than 50% of patients demonstrating normal or nonspecific ECG findings.[30] Data show that the diagnostic accuracy can be enhanced if a prior ECG tracing is available for comparison, thereby allowing for the appreciation of subtle, nondiagnostic changes related to ischemia.[31,32] This is particularly useful when ST-segment elevation is present and reperfusion is being considered. Similarly, serial ECGs increase the sensitivity for detecting STEMI.[33,34]

Additional leads can increase the sensitivity of the ECG for right-sided or posterior ischemia. Right-sided leads, specifically 1 mm or greater ST elevation in V_4R or V_5R, increase both the sensitivity (90%) and specificity (91%) of detecting right ventricular infarcts.[35] Posterior leads may help identify posterior wall infarcts. A V_9 Q wave of greater than 40 ms in duration is more sensitive and specific than a V_2 R-wave-to-S-wave ratio greater than 1.[36] However, Brady et al found that while routine 15-lead ECGs provided a more complete anatomic picture, they did not improve sensitivity or change the course of therapy.[37] Additional leads, either right-sided or posterior, may be most valuable when the standard 12-lead tracing is suggestive but not diagnostic of an injury to a particular area of the heart. (See also the June 2003 issue of *Emergency Medicine Practice*.)

Even when nondiagnostic, the ECG offers important risk-stratification information. For example, patients with confirmed MI but a normal ECG have only 50% of the in-hospital mortality rate of patients with diagnostic tracings.[2]

Continuous Multi-Lead ST-Segment Monitoring

Continuous multi-lead ST-segment monitoring is an evolving technology that may prove useful in identifying

Table 3. Analysis Of Clinical Predictors Of AMI Or ACS In Intermediate-Risk Patients.

Clinical feature	AMI Odds ratio (CI)	ACS Odds ratio (CI)
Chest pain radiation		
Left arm	1.5 (0.6-4.0)	1.7 (0.9-3.1)
Right arm	3.2 (0.4-27.4)	2.5 (0.5-11.9)
Both left and right arm	7.7 (2.7-21.9)	6.0 (2.8-12.8)
Nausea or vomiting	1.8 (0.9-3.6)	1.0 (0.6-1.7)
Diaphoresis	1.4 (0.7-2.9)	1.2 (0.8-1.9)
Exertional pain	3.1 (1.5-6.4)	2.5 (1.5-4.2)
Burning/indigestion pain	4.0 (0.8-20.1)	1.5 (0.5-4.5)
Crushing/squeezing pain	2.1 (0.4-10.9)	0.9 (0.4-2.9)
Relief with nitroglycerin	0.9 (0.1-6.5)	2.0 (0.6-4.9)
Pleuritic pain	0.5 (0.1-2.5)	0.5 (0.2-1.3)
Tender chest wall	0.2 (0.1-1.0)	0.6 (0.3-1.2)
Sharp /stabbing pain	0.5 (0.1-2.8)	0.8 (0.3-2.1)

Source: Goodacre S, Locker T, Morris F, et al. How useful are clinical features in the diagnosis of acute, undifferentiated chest pain? *Acad Emerg Med* 2002 Mar;9(3):203-208.

patients with episodes of silent ischemia. In a recent meta-analysis, data from three retrospective studies were analyzed. Over 24 hours, silent ischemic episodes were found in 27% of patients with UA. At 30 days, the composite endpoint of death and MI occurred in 5.7% of those without episodes and 19.7% of those with five or more episodes.[38] Fesmire et al have shown a clear increase in the sensitivity for ACS when an automated serial 12-lead ECG was performed in addition to the usual initial ECG.[39] Less convincing results were described among a cohort of ED observation unit patients being evaluated for suspected ACS.[40] The ACEP clinical policy on chest pain also supports the use of this technology. If continuous monitoring is not available, manual serial ECGs should be performed.

Chest X-Ray

The chest x-ray is typically normal in the setting of ACS and is most useful in eliminating alternative diagnoses. Evidence of pulmonary edema may support the physical findings of heart failure. An enlarged heart suggests an underlying cardiomyopathy or valvular disorder. A widened mediastinum may be the only clue to the presence of an aortic dissection, which may present atypically in a large percentage of cases. One trial showed that the management of patients with anterior chest pain was influenced by the chest x-ray about 15% of the time.[41]

Routine Laboratory Studies

Routine screening labs rarely impact ACS diagnosis and management. A complete blood count may have value in identifying patients with underlying anemia who would benefit from transfusion. A large retrospective study of patients 65 years or older with MI and anemia suggested that transfusing blood to maintain a hematocrit greater than 30% or even 33% could significantly reduce 30-day mortality.[42] The presence of renal insufficiency would influence the subsequent use of diagnostic modalities and signal caution in the use of LMWH. Serum electrolytes are frequently monitored and theoretically may allow detection of potentially arrhythmogenic abnormalities. Coagulation studies are often ordered in ACS, but their value has not been directly studied. With the advent of LMWH, which does not affect PTT, the routine ordering of coagulation studies will become less necessary.

Biochemical Markers

Biochemical markers provide a noninvasive means of determining whether infarction has occurred, and they also provide important prognostic information. When ischemia gives way to infarction, there is a loss of the integrity of the myocardial cell membrane. A series of macromolecules are in turn released into the systemic circulation. Of these, the optimal biological marker for infarction would be one highly specific to myocardium, rapidly released, and sufficiently persistent in the circulation to allow detection.[43]

The cardiac troponins are the markers that most closely meet these criteria. The troponin complex has three subunits: troponin T, troponin I, and troponin C. Troponin C isoforms exist in both smooth and cardiac muscle and therefore lack sufficient cardiac specificity for clinical use.[44] Both troponin I and troponin T currently have commercially available tests.

How do these markers perform in real-world conditions? A recent meta-analysis provides a look at the test performance of troponins in the ED. When considering only the diagnosis of AMI, a single isolated troponin measurement demonstrated sensitivities of 37%-49% and specificities of 87%-97%. For MI (not ACS), serial troponin tests had sensitivities of 79%-93% and specificities of 85%-96%. The variability in test sensitivity is due to timing. Sensitivity was improved, with longer symptom duration and longer intervals between tests. The authors of this study found a testing interval of four hours to be adequate for CK-MB and myoglobin but state that not enough data exist to determine the optimal interval for serial testing of troponins.[45] Current recommendations from ACEP are to measure a first troponin on arrival and a repeat level at least eight hours after continuous symptom onset.[5]

Troponin testing also provides valuable information in terms of risk-stratifying patients with ACS. There appears to be a clear link between the quantity of troponin measured and the subsequent risk of death.[46]

Concerns about the validity of troponin values (particularly TnT) in the setting of renal insufficiency were addressed in a recent study that showed that elevation of the troponin T level was independently predictive of risk across the entire spectrum of renal function.[47] McCullough et al found troponin I to be superior to myoglobin and CK-MB in the setting of chronic kidney disease.[48]

What about CK-MB? Long considered the gold standard, CK-MB performs less well than the cardiac troponins in terms of both sensitivity and specificity for MI. Case reports show that histologically proven MI is present in patients presenting with ACS who have normal levels of CK-MB but elevated troponins.[49,50] The clinical impact of cardiac troponins has been to increase the proportion of patients with a diagnosis of NSTEMI as opposed to UA. More importantly, patients with normal CK-MB and elevated troponins have been shown to be at higher risk of death in comparison to patients in whom both biomarkers are within normal limits.[46,50,51] CK-MB has similarly proven to be less specific than the troponin markers, particularly in the setting of renal insufficiency, where false-positive CK-MB elevations are common.[48] Myoglobin is a heme protein that is found in both skeletal and cardiac muscle, thereby limiting its specificity. The value of myoglobin is that it has very high early sensitivity and may be detectable as soon as two hours after the onset of MI.[52,53] This allows early diagnosis and risk stratification, with the caveat that a more specific test such as troponin should subsequently be used to confirm infarction.

The most definitive data on cardiac markers come from a large, randomized, double-blind trial that compared the performance of CK-MB, myoglobin, and the troponins.[54] This trial found great sensitivity and specificity of troponins in identifying those patients with infarction.

The timing of the rise of each of these biomarkers is variable. Myoglobin is elevated within 2-4 hours of infarction and rapidly returns to baseline. Troponins begin rising

at about six hours post-infarction and gradually return to baseline over approximately one week. CK-MB also begins rising in the six-hour range but dips below the AMI limit at about two days post-MI.[2]

Several novel biomarkers are also under investigation. C-reactive protein is a systemically measured marker of inflammation and is a new and important marker for unstable CAD. Elevation of this protein in the setting of UA / NSTEMI may indicate the presence of multiple unstable plaques. C-reactive protein elevations have been shown to be an independent risk factor for death from cardiac causes. This effect is independent of the prognostic value of troponin T.[22,55]

Brain natriuretic peptide is released primarily by the ventricles in response to increased wall tension. It is an emerging biomarker of ventricular dysfunction that has been shown to be a reliable predictor of death in patients with ACS.[56]

Risk Scores

Several clinical tools have been developed to assist clinicians in accurately predicting a particular patient's level of risk in the setting of ACS. Antman et al used multivariate logistic regression analysis of TIMI IIb and ESSENCE data to derive a useful prognostic tool.[14] They identified seven variables that predicted increasing risk for mortality, MI, or severe ischemia requiring revascularization at 14 days:

- Age greater than 65 years
- Presence of at least three risk factors for CAD
- Prior coronary stenosis of greater than 50%
- Use of aspirin within the previous seven days
- Presence of ST-segment deviation on admission ECG
- At least two anginal episodes in the prior 24 hours
- Elevated serum cardiac biomarkers

This prediction tool has since been validated in other cohorts.[57,58]

Currently, the TIMI score is being prospectively evaluated as a tool for determining which patients will benefit most from different treatment regimens. In this trial, patients with a risk score of four or greater were shown to derive a greater relative risk reduction from the use of tirofiban.[59]

A familiar and useful means of clinical risk stratification is proposed in the 2002 ACC / AHA guidelines and is presented in **Table 4**.[2]

Risk-Based Treatment

As our understanding of ACS has evolved, there has been a corresponding change in therapeutic priorities, with much greater emphasis being placed on the role of platelet aggregation and acute thrombosis. At present, there are three broad treatment categories: anti-ischemic, antiplatelet, and antithrombotic agents.

Anti-ischemic Therapy

Anti-ischemic treatments primarily address the demand side of the myocardial ischemia equation. Those in common usage today include oxygen, nitrates, morphine, beta-blockers, calcium-channel blockers, and angiotensin-converting enzyme (ACE) inhibitors. (See also **Table 5** on page 8.)

Oxygen

Standard practice entails the administration of oxygen to all patients with suspected myocardial ischemia. This practice, while common, is not supported by any randomized, controlled trials. The level of evidence to support this practice is therefore indeterminate. The ACC recommenda-

Table 4. Short-Term Risk Of Death Or Nonfatal MI In Patients With UA.

Feature	High Risk *At least one of the following*	Intermediate Risk *No high-risk features but at least one of the following*	Low Risk *No high- or intermediate-risk features but at least one of the following*
History	Accelerating tempo of ischemic symptoms in preceding 48 hours	Prior MI, peripheral or cerebrovascular disease, or CABG	
Character of pain	Prolonged, ongoing (>20 min) rest pain	Prolonged (>20 min) rest pain now resolved, with moderate or high likelihood of CAD	New-onset or progressive severe angina, but without prolonged rest pain but with moderate or high likelihood of CAD
Clinical findings	Pulmonary edema most likely due to ischemia, new or worsening MR, S3, hypotension, bradycardia, tachycardia; age >75 years	Age >70 years	
ECG	Rest angina with transient ST changes > 0.05mV; presumed new BBB; sustained VT	T-wave inversions >0.2 mV; pathological Q waves	Normal or unchanged ECG during an episode of chest discomfort
Cardiac markers	Elevated	Slightly elevated	Normal

Adapted from: Braunwald E, Antman EM, Beasley JW, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—2002: summary article: 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). *Circulation* 2002 Oct 1;106(14):1893-1900.

tions suggest administering oxygen only to those patients with a peripheral oxygen saturation of less than 90%, although this cut-off is apparently arbitrary.[2]

Nitrates

The theoretical benefits of nitrates are very encouraging, but the data are somewhat less impressive. Two small prospective trials and one larger randomized, controlled trial comparing intravenous nitrates to placebo were identified. All three showed a reduction in anginal symptoms.[60-62]

Nitroglycerin dilates coronary arteries and may redistribute flow to ischemic areas.[63] Nitroglycerin also decreases preload and, to a lesser extent, decreases afterload. This results in a reduction in ventricular wall stress and a diminished myocardial oxygen requirement. However, this effect may be offset by reflex tachycardia and increased inotropy if a beta-blocker is not used. Short-acting nitrates such as nitroglycerin seem the most appropriate for use in patients who have the potential for developing hypotension. The typical mode of administration is to give 0.4 mg per dose for three doses given five minutes apart. Consideration should then be made of instituting an intravenous nitroglycerin infusion with titration of the dose to anti-anginal effect. All routes of administration can cause hypotension. Nitrate use within 24 hours of the use of sildenafil (Viagra) is contraindicated, as it can precipitate profound and prolonged vasodilation leading to hypoperfusion and death.[64]

Morphine

This is another common treatment for ACS that lacks convincing data; thus, the level of evidence is indeterminate. While the effect of morphine on myocardial ischemia is not established, relieving pain is an important goal in emergency medical care. The potential benefits of morphine in this setting include a modest decrease in heart rate and systolic blood pressure that may decrease myocardial oxygen consumption. Adverse effects include the potential for nausea, respiratory depression, and, more importantly, hypotension. Give the recommended dose, 1-5 mg IV, if pain is not relieved with three doses of nitroglycerin.[2]

Beta-Blockers

Beta-blockers decrease myocardial oxygen consumption by diminishing the inotropic and chronotropic response to catecholamines. There are quality data supporting the use of beta-blockers for STEMI,[119] with somewhat less robust data in the setting of UA.[65-68] Beta-blocker use is very likely to be beneficial in all patients with ACS who do not have contraindications. Subgroup analysis in one large trial showed them to reduce the progression of UA to MI by 13%.[69] The best available evidence supports the administration of beta-blockers intravenously to all high-risk ACS patients without a contraindication. Oral agents can be used in those at lower risk. A variety of agents can be used, and no data suggest the superiority of any single agent. Dosing should be adjusted to achieve a heart rate of 50-60 beats per minute. Contraindications include a heart rate less than 50, systolic blood pressure less than 90 mmHg, PR interval greater than 240 mS, and acute congestive heart failure. Reactive airway disease is generally considered to be a relative contraindication. Patients at risk for worsening of their bronchoreactivity should be given low doses of short-acting beta-1-selective agents, such as metoprolol, if the potential benefits are estimated to be substantial.[2]

Calcium-Channel Blockers

These agents reduce influx of calcium, thereby inhibiting smooth muscle and myocardial contraction. They also inhibit the sinus node and depress AV conduction. Their use in UA / NSTEMI has been fairly well-studied. Short-acting dihydropyridines (e.g., nifedipine) have been clearly shown to cause harm in this clinical setting.[70,71] There is a trend toward benefit when the heart-rate-slowing non-dihydropyridines (e.g., verapamil and diltiazem) are used.[72] Therefore, nifedipine should not be used in this setting, and verapamil or diltiazem should be considered, mostly for control of blood pressure and heart rate and as an alternative when beta-blockers are contraindicated.

Table 5. Common Anti-Anginal Therapies For UA/NSTEMI.

Intervention	Benefit	Dose/Duration
Oxygen	Optimize oxygenation in those with or at risk for hypoxemia	As needed to keep SaO_2 > 90%
Bed rest with continuous ECG monitoring	Prevent and detect ischemia/arrhythmias	Bed rest until serum biomarkers negative
Nitrates	Coronary dilation, pre- and after-load reduction	0.4 mg SL q 5 min x3, consider infusion titrated to relieve symptoms
Beta-blockers	Decreased myocardial oxygen consumption	e.g., metoprolol 5 mg IV q 5 min x3, then 12.5-25.0 mg PO BID
Morphine	Analgesia, venodilation, decreased heart rate and blood pressure	1-5 mg IV
ACE inhibitors	Afterload reduction in those with CHF, possible myocardial remodeling benefit	Many possible agents; initiate within 24 hours of MI
Calcium-channel blockers	Decreased myocardial oxygen consumption	Diltiazem 240 mg PO or 10-15 mg IV followed by infusion

ACE Inhibitors

ACE inhibitors should be considered in select patients with ACS. Those with recent MI (especially anterior MI) and left ventricular systolic dysfunction benefit the most. This is postulated to be due to their effect on left ventricular remodeling after infarction.[73-76] A systematic overview of their use in this setting showed that they can reduce the relative risk of 30-day mortality by 7%.[73,75] They should be started within 24 hours of admission. Short-acting agents such as captopril are generally recommended initially because of the risk of hypotension associated with their use.

Antiplatelet Therapy

Plaque rupture with exposure of the underlying vascular endothelium is a potent stimulation for platelet aggregation and subsequent arterial thrombosis. At present, the principal antiplatelet medications indicated for the treatment of UA / NSTEMI are aspirin, the thienopyridines, and the GP IIb / IIIa inhibitors. (See also **Table 6**.)

Aspirin

Quality data overwhelmingly support the early administration of aspirin to all patients with UA / NSTEMI who do not have a contraindication.[77-83] Composite data show that in patients with ACS, aspirin reduces the endpoint of death from MI from 12.5% to 6.4%.[2] It should be emphasized that this is a much larger mortality benefit than that provided by the newer, much more expensive therapies. Aspirin reduces platelet aggregation by irreversibly inhibiting platelet cyclooxygenase-1, thereby reducing thromboxane A2. The data suggest that a dose of 160-325 mg be used in the acute treatment of ACS. The ACC recommends that the first dose of non-enteric-coated aspirin be chewed in order to achieve therapeutic levels more rapidly, although this has not been explicitly studied.[2] Contraindications include active bleeding, allergy, intolerance, severe untreated hypertension, or active peptic ulcer disease or gastritis.

Adenosine Diphosphate Receptor Antagonists (Ticlopidine And Clopidogrel)

The thienopyridines, ticlopidine and clopidogrel, are noncompetitive antagonists of the platelet adenosine diphosphate receptor.[84] In patients with UA, ticlopidine has been shown to significantly reduce the rate of nonfatal MI at six months as compared to placebo.[85] It is administered orally at a dose of 250 mg BID. The risk of adverse effects related to ticlopidine have limited its use. Clinical trials in stroke patients report that neutropenia occurs in 2.4% of patients. The incidence of ticlopidine-associated thrombocytopenia purpura is as high as one case in every 2000-4000 patients. The incidence of ticlopidine-associated aplastic anemia is one case per 4000-8000 patients. Because of this significant rate of adverse hematologic events, a complete blood count with differential is required at baseline and every two weeks for the first three months of therapy.[86] The use of ticlopidine should be limited to secondary prevention of cardiovascular events in those who are intolerant of aspirin or who have failed aspirin therapy.

Clopidogrel is the preferred thienopyridine because it has a much more rapid onset of action and fewer adverse effects than ticlopidine.[87-89] The CURE trial, a recent large randomized, controlled trial, reports a modest but statistically significant reduction in the composite endpoint of cardiovascular death, stroke, or MI in patients presenting with UA / NSTEMI. The trial randomized 12,562 patients within 24 hours of symptom onset to treatment with aspirin and placebo or aspirin and clopidogrel (300 mg PO loading dose, then 75 mg PO qd). Approximately 72% of patients in both groups were also receiving heparin or LMWH at the time of randomization. The addition of clopidogrel reduced the rate of cardiovascular death, stroke, or MI from 11.5% to 9.3% (RR, 0.80; $P < 0.001$). Subgroup analysis of the CURE data suggests that this beneficial effect begins within four hours of the onset of therapy, and 25% of the overall risk reduction is accounted for by the first 24 hours of treatment. The main contraindication is active bleeding. The principal adverse effect of clopidogrel in the CURE trial was major bleeding, which was found in 3.7% of the clopidogrel plus aspirin group and 2.7% of the placebo plus aspirin group ($P = 0.003$). This risk applied disproportionately to patients undergoing coronary artery bypass graft (CABG) after angiography.[90] In this group, the risk of perioperative major bleeding increased by 50%, from 6% to 9%. It is therefore recommended that clopidogrel be stopped 5-7 days before major surgery and that it be used with caution in patients who may require urgent CABG.

Table 6. Antiplatelet And Anticoagulant Therapies.

Medication Class	Medication	Dose
Aspirin	Aspirin	Initial dose 160-325 mg PO nonenteric, then 75-160 mg PO qd
Thienopyridines	Clopidogrel (Plavix) Ticlopidine (Ticlid)	75 mg PO qd; load with 300 mg PO if ACS 250 mg PO BID, for aspirin intolerant
Unfractionated heparin	Unfractionated heparin	Bolus 60-70 U/kg (max, 5000 U), then 12-15 U/kg/min IV infusion; goal aPTT 1.5-2.5x control
Fractionated heparin	Enoxaparin (Lovenox)	1 mg/kg SC q 12 hours
Glycoprotein IIb/IIIa inhibitors	Eptifibatide (Integrilin) Abciximab (ReoPro) Tirofiban (Aggrastat)	180 mcg/kg bolus, then 2.0 mcg/kg/min infusion for 72-96 hours 0.25 mg/kg bolus, then 0.125 mcg/kg/min (max, 10 mcg/min) for 12-24 hours 0.4 mcg/kg/min over 30 minutes, then 0.1 mcg/kg/min infusion for 48-96 hours

Glycoprotein IIb/IIIa Inhibitors

The final common and obligate pathway in platelet aggregation is the activation of the GP IIb / IIIa receptor.[91] Inhibition of this receptor could theoretically reduce thrombus formation over a disrupted atherosclerotic plaque. Many studies have investigated the efficacy and safety of these agents in UA / NSTEMI. Oral GP inhibitors have been shown to cause increased mortality, so only intravenous agents are used now.[92-94] As with many of the interventions in UA / NSTEMI, high-risk patients benefit more from these agents than low-risk patients. In particular, because of a differential benefit, patients in whom percutaneous coronary intervention (PCI) is planned should be considered separately from those in whom the intervention is not planned. The different agents and the data to support their use are discussed in the following sections.

Abciximab

This agent is a Fab fragment of a murine antibody. The CAPTURE trial randomized 1265 patients with UA and an angiographically proven culprit lesion to receive either placebo or abciximab for 20-24 hours before angioplasty. All patients received aspirin and heparin. Death, MI, or need for urgent revascularization—the composite endpoint that is used in all of the GP IIb / IIIa inhibitor trials—was seen within 30 days in 15.9% with placebo and 11.3% with abciximab (RR, 0.71; P = 0.012). At six months, a smaller nonsignificant benefit was found.[95] Subgroup analysis showed that only those with an elevated troponin benefited from abciximab.[96]

The GUSTO IV-ACS study enrolled 7800 patients with UA / NSTEMI in whom early revascularization was not planned. At 30 days, the primary endpoint of death or MI was found in 8% of the placebo group, 8.2% of those receiving 24 hours of abciximab, and 9.1% of those receiving 48 hours of abciximab (P = NS). Death at 48 hours occurred at a rate of 0.3% in placebo, 0.7% in the 24-hour treatment group, and 0.9% in the 48-hour treatment group.[97] These data suggest that the use of abciximab should be limited only to higher-risk patients with NSTEMI in whom PCI is planned.

Tirofiban

Tirofiban is a synthetic antagonist of the receptor and has a short half-life. The PRISM trial compared unfractionated heparin (UFH) and tirofiban in 3232 patients with UA / NSTEMI and found that tirofiban reduced the rates of MI, death, or urgent revascularization at 48 hours from 5.6% in the UFH group to 3.8% (RR, 0.67; P = 0.01). All patients received aspirin. At 30 days there was a difference in mortality favoring the tirofiban group (3.6% vs. 2.3%; P = 0.02).[98] Subgroup analysis showed that the treatment benefit occurred only in those patients with elevated troponins, a large percentage of whom underwent PCI. In the subgroup with elevated troponins, mortality was decreased from 6.2% to 1.6% in those receiving tirofiban (P = 0.004).[99] The PRISM-PLUS study randomized 1915 patients with UA / NSTEMI to receive tirofiban alone, UFH alone, or tirofiban and UFH for a period of 48-108 hours. Tirofiban plus UFH compared to UFH alone reduced the rate of death, MI, or refractory ischemia at seven days from 17.9% to 12.9% (RR, 0.68; P = 0.004). The benefit was sustained at six months. During the trial, an excess mortality rate was seen in the tirofiban-alone arm, prompting the investigators to drop this arm.[100] The RESTORE study randomized 2139 patients with ACS who were undergoing PCI within three days of presentation to receive placebo or tirofiban. All patients received aspirin and heparin. Patients in the tirofiban arm were given a 10 mcg / kg IV bolus followed by a continuous infusion of 0.15 mcg / kg / min for 36 hours. The primary composite endpoint occurred in 10.3% in the tirofiban group and 12.2% in the placebo group. The treatment benefit was again limited to those with elevated troponins.[101] As with the other medications in this class, the benefit appears to be limited to high-risk patients, especially those in whom PCI is planned.

Eptifibatide

Eptifibatide is also a synthetic antagonist of the platelet GP receptor. The study that is most applicable to the treatment of UA / NSTEMI with eptifibatide is the PURSUIT trial, which enrolled 10,948 patients who presented with UA and ECG changes indicative of ischemia or (in 46% of patients) elevations of CK-MB. All patients were treated with aspirin and UFH, and they were randomly assigned to receive a bolus and infusion of either placebo or eptifibatide (180 mcg / kg bolus plus 1.3 mcg / kg / min infusion or 180 mcg / kg bolus plus 2.0 mcg / kg / min infusion) for up to 72 hours. Treatment with eptifibatide reduced the 30-day event rate of death or MI to 14.2% compared to 15.7% (RR, 0.91; P = 0.042). The benefit persisted at six-month follow-up and was consistent across most subgroups except women (OR, 1.1).[102] Smaller studies such as the IMPACT-II trial and the ESPRIT trial confirm the benefit of eptifibatide in patients undergoing PCI.[103]

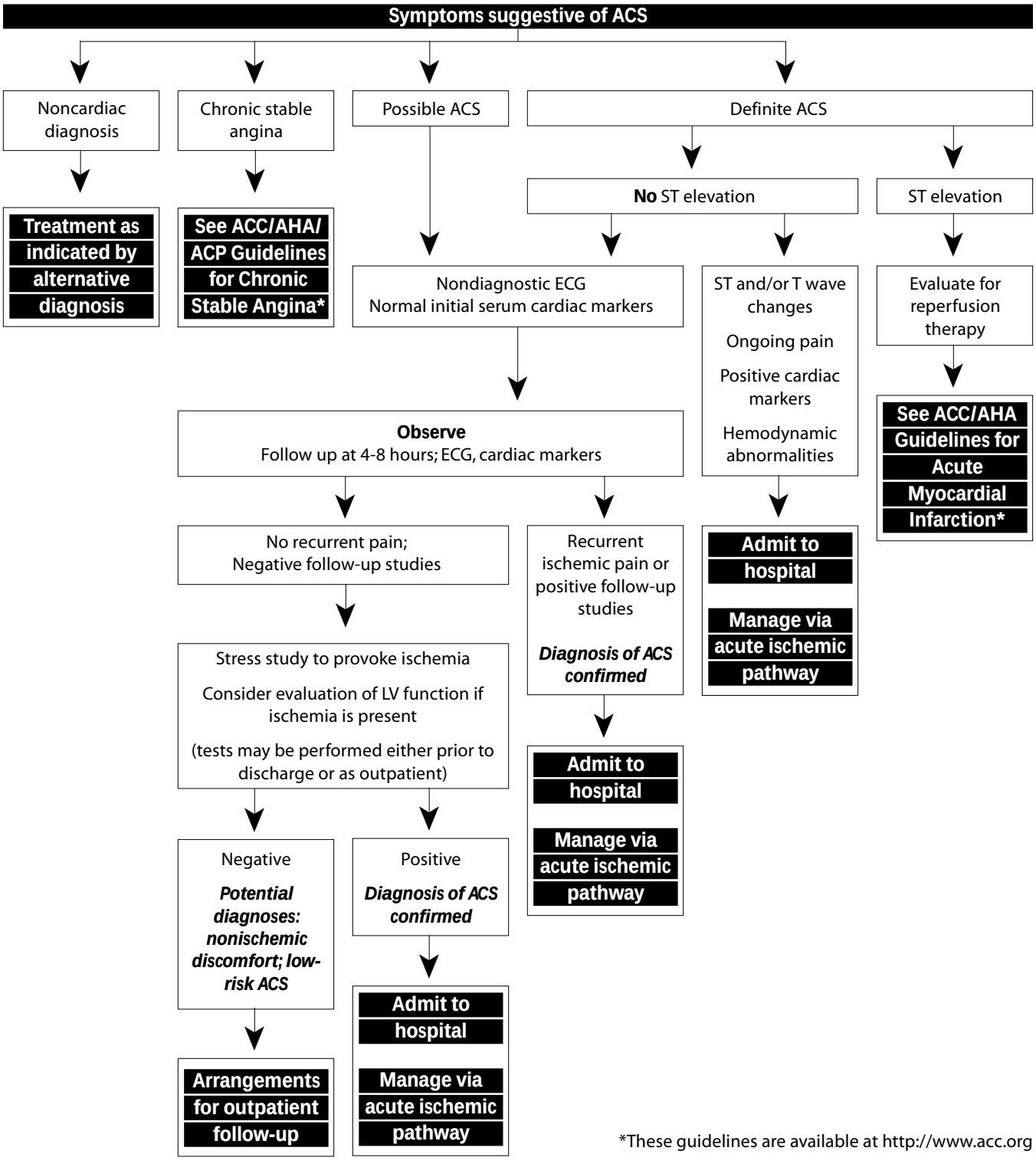
Only one trial has directly compared the efficacy of two GP IIb / IIIa inhibitors. The TARGET trial compared tirofiban with abciximab in 5308 patients going to PCI. The composite endpoint at 30 days occurred in 6.0% of those in the abciximab arm and 7.9% of those in the tirofiban arm (P = 0.038). The difference at six months was very small and nonsignificant.[104] This leaves the choice of GP IIb / IIIa inhibitor open to speculation. In patients who are not scheduled for PCI, abciximab should likely not be used, as stated above. Eptifibatide and tirofiban are significantly less expensive than abciximab.

The question of whether patients who are not scheduled for PCI should receive a GP IIb / IIIa inhibitor was addressed in a recent meta-analysis of all six major GP IIb / IIIa inhibitor trials, involving 31,402 patients. This composite analysis found a modest reduction in the odds of death or MI in the treatment arm (11.8% vs. 10.8%—OR, 0.91; 95% CI, 0.84-0.89; P = 0.015). The benefit was largest in high-risk subgroups, such as those with elevated troponins. No benefit was found in women without troponin elevations.[105]

The principal adverse event associated with the use of these agents is mucocutaneous and vascular access site bleeding. Rates of bleeding are similar to those experienced when UFH is used alone. Importantly, an increased rate of

Continued on page 12

Clinical Pathway: Evaluation And Management Of Patients Suspected Of Having An ACS



*These guidelines are available at http://www.acc.org

Used with permission from: Braunwald E, Antman EM, Beasley JW, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—2002: summary article: 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). *Circulation* 2002 Oct 1;106(14):1893-1900.

Continued from page 10

intracranial hemorrhage has not been seen with their use.

In conclusion, GP IIb/IIIa inhibitors are of "considerable" benefit in those patients in whom early PCI is planned, and they are of questionable or no benefit in patients in whom PCI is not planned.[2] This position is also supported by two recent systematic reviews.[106,107]

In the subgroup of patients in whom PCI is not planned, GP IIb/IIIa inhibitors should generally only be used in patients with high-risk features such as positive troponins, ongoing ischemia despite full medical management, or dynamic ECG changes strongly indicative of ischemia. They should be given in conjunction with aspirin and heparin, preferably enoxaparin. The use of "quadruple therapy"—aspirin, clopidogrel, LMWH, and a GP IIb/IIIa inhibitor—has been recommended but not directly studied.

Antithrombotics

This class of medications includes UFH, LMWH, hirudin, and oral warfarin. Heparin activates antithrombin, which ultimately prevents thrombus propagation but does not cause lysis of established thrombus.[108] Hirudin is approved only for patients with heparin-induced thrombocytopenia and will not be discussed here.

Unfractionated Heparin

Numerous randomized, controlled trials have established the benefit of administering UFH to patients with UA/NSTEMI.[109] The 2002 update to ACC/AHA guidelines for management of UA/NSTEMI stated that anticoagulation with subcutaneous LMWH or intravenous UFH should be added to antiplatelet therapy with aspirin, clopidogrel, or both (Class I, Level A evidence).[2]

There are several limitations when using UFH. The first is that it must be delivered via a continuous infusion. Second, marked variability in the response to UFH dictates monitoring with the activated partial thromboplastin time (aPTT) to gauge anticoagulant effect. A weight-based regimen using an initial bolus of 60-70 U/kg (maximum, 5000 U), followed by an infusion of 12-15 U/kg/hour (maximum, 1000 U/hour), is recommended. Subsequent dose adjustments should follow a hospital-specific nomogram, with a goal of achieving an aPTT of 45-75s.[110] Adverse effects include bleeding and thrombocytopenia.

Low-Molecular-Weight Heparin

The LMWHs are enzymatic degradation products of UFH. They bind less to cell membranes and plasma proteins than UFH and therefore have a much more predictable

Ten Pitfalls To Avoid

1. "But the ECG was normal."
The ECG should be interpreted and acted on early. However, it lacks sufficient sensitivity to exclude a cardiac etiology on its own, especially if other risk factors are present. Up to 8% of those who present with NSTEMI will have a normal (or nondiagnostic) ECG.[30]

2. "I know the troponin was elevated, but the patient has renal failure."
Recent data show that the troponin T level retains its prognostic value in all degrees of renal dysfunction.

3. "Thrombolytics work well in STEMI, so why can't I use them for UA?"
The pathophysiology is similar, but complete coronary occlusion is usually not present in UA/NSTEMI. Giving these people thrombolytics can worsen their outcomes.

4. "Aspirin is too inexpensive to be effective."
While it is true that aspirin is one of the least expensive interventions, it has a proven benefit that is equal to or greater than any other pharmacologic intervention. Give aspirin early and give it to everyone who does not have a contraindication (in which case use clopidogrel or ticlopidine).

5. "The admitting physician insisted that the patient did not have 'cardiac chest pain.'"
Be an expert. If you know the data about atypical presentations, the timing of the rise in cardiac biomarkers, and ECG test performance characteristics, you can educate consultants about the likelihood of a cardiac cause for a given patient.

6. "I know that he had persistent tearing back pain, but the chest x-ray was negative."
Giving a patient with an aortic dissection aspirin, LMWH, clopidogrel, and a GP IIb/IIIa inhibitor will not improve his or her outcome! Be aware that this is a difficult diagnosis to make and may be fatal when treated inappropriately.

7. "The heart rate was only 82 bpm, so I didn't think that she could tolerate beta-blockade."
Beta-blockers are very beneficial in patients with myocardial ischemia. The goal heart rate should be between 50 and 60 bpm. These are inexpensive and effective agents; always use them when indicated.

8. "Everyone with possible ACS should be treated with GP IIb/IIIa inhibitors."
The patients who will benefit most from this expensive intervention are those who are likely to undergo PCI. Patients at higher risk based on cardiac biomarkers and ECG changes may benefit as well.

9. "Only those patients with ST elevation will benefit from PCI."
Increasing data are being reported to support the expanded role of PCI in the acute treatment of UA/NSTEMI. High-risk patients should be considered for this potentially beneficial intervention.

10. "All patients with cocaine-associated chest pain need to be admitted to the hospital."
Recent data support discharging a certain subgroup of patients with cocaine-associated chest pain after a period of observation with serial ECGs and biomarkers.[132] This period of observation was 9-12 hours. Those patients without ischemic ECG changes or positive cardiac biomarkers were safely discharged home. ▲

bioavailability. The LMWHs are given subcutaneously, demonstrate fewer adverse interactions with platelets, and do not require laboratory monitoring. They produce slightly increased rates of minor bleeding, without an increase in major bleeding.[111-113] Extensive data support the use of LMWH in patients with UA / NSTEMI. The FRISC study demonstrated the superiority of subcutaneous dalteparin over placebo in patients with UA or non-Q-wave MI.[113] The FRIC trial demonstrated the equivalence of UFH and dalteparin.[114] The ESSENCE trial showed a reduction in the triple outcome of death, MI, or urgent revascularization in those treated with enoxaparin 1 mg / kg subcutaneously, twice daily compared with UFH.[111] The TIMI-IIB trial also showed a significant reduction in the same endpoint in those treated with enoxaparin vs. UFH.[115] A meta-analysis of the ESSENCE and TIMI-IIB trials with a total of over 7000 patients reported a 20% reduction in the death, MI, or urgent revascularization in those patients treated with enoxaparin vs. UFH.[116] The ACUTE II trial evaluated the safety and efficacy of tirofiban used in combination with either UFH or enoxaparin. Bleeding rates were similar, as was efficacy.[117] Enoxaparin has also been evaluated in an open-label trial for use with abciximab and found safe. LMWH is generally much easier to use, has equivalent or superior efficacy to UFH, and the overall cost is probably also favorable. Therefore, in patients with moderate- to high-risk UA / NSTEMI, the choice of antithrombotic should generally be a 1 mg / kg SC dose of enoxaparin. The dose should be adjusted for low body weight (< 45 kg) and for severe renal dysfunction (creatinine clearance < 30 mL / min).[86] The ACC / AHA guidelines state that enoxaparin is preferable to UFH as an anticoagulant in patients with UA / NSTEMI, unless CABG is planned within 24 hours (Class IIa, Level A evidence).[2]

Early Invasive vs. Early Conservative Treatment

The question of whether outcomes are improved with early invasive therapy vs. early conservative treatment is under intense scientific scrutiny. Several trials have examined whether select patients with UA / NSTEMI should undergo early coronary angiography and selective revascularization based on these angiographic findings. Significant heterogeneity exists with respect to study design and outcome.

An early trial, VANQWISH, randomized 920 patients with NSTEMI based on elevation of CK-MB to early invasive or conservative management. The primary endpoint of death or nonfatal MI occurred significantly more frequently in the invasive group—7.8% vs. 3.2% at the time of hospital discharge (P = 0.004). At one year, there were 58 deaths in the invasive group and only 36 in the conservative group (P = 0.025). At 23 months, the differences became nonsignificant. Several limitations of this study should be noted. The rates of use of GP IIb / IIIa inhibitors and coronary stents, while not reported specifically, are low because many of the patients were treated before the use of these technologies was widespread. Second, the 30-day mortality after CABG was high, at 7.7%. The 30-day mortality rates of percutaneous transluminal coronary angioplasty and conservative treatment were 1.3% and 1%, respectively.[118]

The MATE trial randomized 210 patients with MI and contraindications to thrombolysis to either early conservative or early invasive management. Death and MI occurred at similar rates in both groups, although in-hospital ischemic events were decreased in the invasive group. No difference was seen at a median follow-up of 21 months.[120] The TACTICS-TIMI trial randomized 2220 patients with UA or NSTEMI to either coronary angiography within 48 hours followed by revascularization or conservative treatment. All were treated with aspirin, heparin, and tirofiban. The composite endpoint of death, MI, or rehospitalization for ACS within six months was seen in 15.9% of those in the early invasive group and 19.4% of those in the conservative group (OR, 0.78; 95% CI, 0.62-0.97; p = 0.025).[121] As with the GP IIb / IIIa trials, the greatest benefits were seen in those at highest risk. Importantly, adverse event rates and costs were similar at six months.

A cost analysis comparing the two strategies in this same cohort found that the average six-month cost, excluding productivity costs, was $19,780 in the invasive group vs. $19,111 in the conservative group, a difference of $669. As noted above, all patients in this study received tirofiban in addition to aspirin and heparin.[122]

In the FRISC II study, patients received treatment with aspirin, beta-blockers, LMWH, and nitrates in the hospital for an average of six days followed by randomization to continued medical management or coronary angiography in the early invasive group. The one-year mortality rate was 2.2% in the invasive group and 3.9% in the conservative group (P = 0.016).[123] The benefit was confirmed in a one-year follow-up study.[124]

In the RITA 3 trial, 1810 patients with NSTEMI were similarly randomized to early conservative treatment or early intervention. At four months, there was a reduction in the primary endpoints of refractory angina, death, or MI, and this benefit was sustained at one year (9.6% vs. 14.5%; OR, 0.66: 95% CI, 0.51-0.85). However, this benefit was entirely due to the reduction in refractory angina. The rates of death or MI were nonsignificantly different in both groups at one year—7.6% of the interventional and 8.3% of the conservative group (RR, 0.91; 95% CI, 0.67-1.25; P = 0.58). The authors of this study performed a composite analysis of relevant large trials and found a relative risk of death or MI at one year to be 0.88 (95% CI, 0.78-0.99)—"on the borderline of significance."[125]

Patients with NSTEMI will likely benefit symptomatically from an early invasive approach. The one-year mortality, however, is only very slightly improved. The balance of these data may shift as more trials are reported in which GP IIb / IIIa inhibitors and coronary stents are more widely employed. Based on this trend, an early invasive strategy has been recommended in patients with UA / NSTEMI without serious co-morbidity who have any of the following high-risk features:[2]

- Recurrent angina / ischemia at rest or with low-level activities despite therapy
- Elevated troponin

- New ST-segment depression
- Recurrent angina with signs / symptoms of congestive heart failure, or new or worsening mitral regurgitation
- High-risk findings on noninvasive testing
- Left ventricular ejection fraction less than 0.40
- Hemodynamic instability
- Sustained ventricular tachycardia
- PCI within six months
- Prior CABG

Thrombolysis

Don't do it! Thrombolytics in UA / NSTEMI have been shown to increase the risk of MI while failing to improve survival and exposing patients to significant cost and bleeding risk.[126] This has been shown in a meta-analysis of data from the TIMI IIIB, ISIS-2, and GISSI-1 trials.[126,127] Thrombolytics should only be given to patients with STEMI who meet standard AHA inclusion criteria.

Special Circumstances

Cocaine-Related Chest Pain

Patients with a simultaneous presentation of chest pain and cocaine use are common in urban EDs. The problem is further complicated by the reluctance of some patients to disclose their drug use. Cocaine is a known catalyst for the development of CAD as well as an acute stressor for the cardiovascular system. Additionally, cocaine is a known precipitant of coronary spasm. It has been estimated that up to 6% of patients with cocaine-related chest pain develop an acute MI. The ACC guidelines suggest treatment with intravenous nitrates and a calcium-channel blocker.[128] The data to support the use of calcium-channel blockers in this setting are limited.[129] In the ED, patients are frequently treated with benzodiazepines, although the data supporting this practice are somewhat limited.[130,131] A recent trial of 334 patients confirms the safety of a nine- to 12-hour observation period with serial troponin I assays and continuous ST segment monitoring. Patients were eligible for inclusion if they demonstrated no acute ischemic ECG changes and negative troponin I assays. At 30 days there were no deaths from cardiovascular causes, but there were four nonfatal MIs in patients who continued to use cocaine.[132] Beta-blockers are contraindicated in this setting, as trials have shown an increase in cocaine-induced coronary vasospasm.[133,134] Labetalol is often cited as an alternative in this setting because of its action at both alpha- and beta-adrenergic receptors. However, the beta-blocking effect predominates at the typical doses, thereby still presenting a risk of "unopposed" alpha-adrenergic-mediated vasoconstriction.[135] Admission is recommended for patients with ST segment changes, positive stress tests, or an elevation in serum troponin levels.

Controversies/Cutting Edge

The benefits of GP IIb / IIIa inhibitors can be substantial in certain patient populations, particularly when PCI is planned. The cost of these agents is substantial, and the widespread use of these agents in low-risk patients with presumed UA could expose these patients to unnecessary cost and mildly increased risk of bleeding. The use of these agents should be carefully considered in each patient. As emphasized earlier, a careful risk assessment should underlie decisions about the aggressiveness of therapy. Those who will benefit from these agents are high-risk patients who are likely to undergo PCI. The benefit in other groups is much less clear.

A significant benefit may be seen with improved stent technology that is currently under study. A limitation of coronary stenting is the considerable rate of restenosis. Recent trials have shown impressive reduction in the rate of restenosis when stents are coated with an anti-mitotic agent eluting polymer such as sirolimus or paclitaxel.[136,137] This may further influence the balance of treatment toward early invasive therapy.

Provocative Testing

The most common noninvasive provocative tests for CAD include graded exercise testing, stress echocardiography, and nuclear imaging (sestamibi). Their purpose in the setting of ACS is to achieve a greater degree of precision, both in terms of the diagnosis of CAD as an explanation for symptoms as well as risk stratification. The results of noninvasive tests are not absolute, however, and must be viewed in the context of the overall clinical setting, the pre-test likelihood of CAD, and risk scores. The performance of noninvasive testing for the diagnosis of CAD remains unimpressive, with a sensitivity of 50%-85% and specificity of 70%-90%, depending on the study and method used. Patients with both low and high pretest probabilities for CAD experience significant false-positive and false-negative test results. The more useful aspect of provocative testing may lie in its ability to predict long-term prognosis. Low-risk patients with subsequent negative noninvasive testing have a less than 2% (0.0%-1.8%) rate of MI or death at one year. In contrast, patients with abnormal treadmill, stress echocardiography, or perfusion studies were found to have rates of MI / death upwards of 30%. Clearly, noninvasive testing has an important role to play in the overall assessment of CAD diagnosis and risk but should not trump other aspects of the evaluation: specifically, the TIMI score, ECG, and biologic markers.

There is no consensus on the optimal timing for noninvasive testing. In general, moderate-to-high risk patients should have near-term (24-72 hours) provocative testing in order to guide therapy, the need for angiography, and offer information on long-term prognosis. Low-risk patients must be given secure follow-up. The use of noninvasive testing in this group is a function of relative risk and local practice patterns. For more specific information on provocative testing, refer to the June 2003 edition of *Emergency Medicine Practice.*

Disposition

The disposition of patients with suspected ACS requires the emergency physician to gather and interpret key information. The ACC recommends combining data from the history, physical, ECG, and biomarkers to assign patients

into one of four categories: noncardiac causes, chronic stable angina, possible ACS, and definite ACS.[2] The ACC / AHA guidelines suggest that hemodynamically stable patients with UA / NSTEMI who have recurrent symptoms, and / or ECG ST segment deviations, or elevated cardiac markers should be admitted to a step-down unit. Hemodynamic instability or recurrent ischemic pain warrant admission to a coronary care unit for 24 hours.[2]

Those patients with noncardiac diagnoses should receive appropriate treatment and disposition for their condition. Patients with chronic stable angina generally do not need to be admitted and can be treated with a variety of anti-anginal agents.

The largest group of patients is made up of those with possible ACS. There is a spectrum of risk within this group of patients. Those with low-risk features, normal ECGs, and negative biomarkers can be discharged home. The lack of sensitivity of biomarkers within six hours suggests that a repeat assay at 6-8 hours is prudent. The timing of this may vary depending on the time of the assay relative to the patient's last episode of pain. These patients should receive ED stress testing or a prompt outpatient study. If a prompt outpatient study is not available, such patients may require admission. In moderate-risk patients, a repeat ECG and cardiac biomarkers should be obtained 6-12 hours after symptom onset.[2] This group of patients will likely benefit from hospitalization for treatment and monitoring. They should likely undergo noninvasive stress testing before discharge or shortly thereafter. The Clinical Pathway on page 11 incorporates these principles.

Summary

UA and NSTEMI are common manifestations of CAD, the leading cause of death in the United States. Rapid evaluation and treatment of these conditions can dramatically improve outcomes. Mortality due to these conditions is on the decline, and emergency physicians are at the forefront of this important reduction.

Emergency physicians have an ever-expanding array of diagnostic and therapeutic tools at their disposal. The targeted application of these resources to the patients who are most likely to benefit requires a clear understanding of the pathophysiology and clinical features of this malady. The intensity of treatment should be based on the likelihood that a particular patient's symptoms are due to an acute coronary thrombosis. The spectrum of treatment includes antiplatelet agents, anti-ischemics, antithrombotics, and PCI. Newer treatments, such as GP IIb / IIIa inhibitors and emergent PCI, have increased the need for a critical appraisal of the literature and a careful integration of the data into clinical practice. ▲

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in the paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.

1. Anderson RN. Deaths; Leading causes for 1999. *National Vital Statistics Reports;* vol 49. no. 11. Hyattsville, MD: National Center for Health Care Statistics; 2001. **(Observational; all death certificates in United States in 1999)**
2.* Braunwald E, Antman EM, Beasley JW, et al; American College of Cardiology / American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). ACC / AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—2002: summary article: 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). *Circulation* 2002 Oct 1;106(14):1893-1900. **(Practice guideline; consensus statement)**
3.* Bosch X, Marrugat J. Platelet glycoprotein IIb / IIIa blockers for percutaneous coronary revascularization, and unstable angina and non-ST-segment elevation myocardial infarction. *Cochrane Database Syst Rev* 2001;(4):CD002130. **(Systematic review; 17,788 patients)**
4.* Magee KD, Sevcik W, Moher D, et al. Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes. *Cochrane Database Syst Rev* 2003;(1):CD002132. **(Systematic review; 11,092 patients)**
5.* No authors listed. Clinical policy: critical issues in the evaluation and management of adult patients presenting with suspected acute myocardial infarction or unstable angina. American College of Emergency Physicians. *Ann Emerg Med* 2000 May;35(5):521-525. **(Practice guideline)**
6. National Center for Health Statistics. Detailed diagnoses and procedures: *National Hospital Discharge Survey*, 1996. Hyattsville, MD: National Center for Health Statistics; 1998:13. **(Data from vital and health statistics)**
7. Braunwald E, Zipes DP, Libby P, eds. Braunwald E. *Heart Disease: A Textbook of Cardiovascular Medicine.* 6th ed. Philadelphia: W.B. Saunders Co; 2001. **(Textbook)**
8. Canto JG, Rogers WJ, Bowlby LJ, et al. The prehospital electrocardiogram in acute myocardial infarction: is its full potential being realized? National Registry of Myocardial Infarction 2 Investigators. *J Am Coll Cardiol* 1997 Mar 1;29(3):498-505. **(Retrospective; 3768 patients)**
9. Aufderheide TP, Hendley GE, Thakur RK, et al. The diagnostic impact of prehospital 12-lead electrocardiography. *Ann Emerg Med* 1990 Nov;19(11):1280-1287. **(Feasibility study; 166 patients)**
10. Zijlstra F, Ernst N, de Boer MJ, et al. Influence of prehospital administration of aspirin and heparin on initial patency of the infarct-related artery in patients with acute ST elevation myocardial infarction. *J Am Coll Cardiol* 2002 Jun 5;39(11):1733-1737. **(Prospective; 1702 patients)**
11. Becker L, Larsen MP, Eisenberg MS. Incidence of cardiac arrest during self-transport for chest pain. *Ann Emerg Med* 1996 Dec;28(6):612-616. **(Retrospective; 13,187 patients)**
12. 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; 1994:1. AHCPR Publication 94-0602. **(Review)**
13. Boersma E, Pieper KS, Steyerberg EW, et al. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. *Circulation* 2000 Jun 6;101(22):2557-2567. **(Prospective; 9461 patients)**
14. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina / non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA* 2000 Aug 16;284(7):835-842. **(Prospective, randomized, controlled trial; 7081 patients)**
15. Selker HP, Griffith JL, D'Agostino RB. A tool for judging coronary care unit admission appropriateness, valid for both real-time and retrospective use. A time-insensitive predictive instrument (TIPI) for acute cardiac ischemia: a multicenter study. *Med Care* 1991 Jul;29(7):610-627. **(Prospective, multicenter; 5773 patients)**
16. Jayes RL Jr, Beshansky JR, D'Agostino RB, et al. Do patients' coronary risk factor reports predict acute cardiac ischemia in the emergency department? A multicenter study. *J Clin Epidemiol* 1992 Jun;45(6):621-626. **(Retrospective, multicenter; 5773 patients)**
17.* Canto JG, Shlipak MG, Rogers WJ, et al. Prevalence, clinical characteristics, and mortality among patients with myocardial infarction presenting without chest pain. *JAMA* 2000 Jun 28;283(24):3223-3229. **(Prospective, observational; 434,877 patients)**
18. Gupta M, Tabas JA, Kohn MA. Presenting complaint among patients with

myocardial infarction who present to an urban, public hospital emergency department. *Ann Emerg Med* 2002 Aug;40(2):180-186. **(Retrospective; 721 patients)**

19. Sheifer SE, Manolio TA, Gersh BJ. Unrecognized myocardial infarction. *Ann Intern Med* 2001 Nov 6;135(9):801-811. **(Review)**
20. McCarthy BD, Beshansky JR, D'Agostino RB, et al. Missed diagnoses of acute myocardial infarction in the emergency department: results from a multicenter study. *Ann Emerg Med* 1993 Mar;22(3):579-582. **(Retrospective; 5773 patients)**
21.* Pope JH, Aufderheide TP, Ruthazer R, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. *N Engl J Med* 2000 Apr 20;342(16):1163-1170. **(Retrospective, multicenter; 10,689 patients)**
22. Lindahl B, Toss H, Siegbahn A, et al. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. *N Engl J Med* 2000 Oct 19;343(16):1139-1147. (**Prospective; 917 patients)**
23. Barzilay JI, Kronmal RA, Bittner V, et al. Coronary artery disease in diabetic and nondiabetic patients with lower extremity arterial disease: A report from the Coronary Artery Surgery Study Registry. *Am Heart J* 1998 Jun;135(6 Pt 1):1055-1062. **(Prospective, randomized, controlled trial; 1400 patients)**
24. Akhtar AJ, Moran D, Ganesan K, et al. Safety and efficacy of digital rectal examination in patients with acute myocardial infarction. *Am J Gastroenterol* 2000 Jun;95(6):1463-1465. **(Prospective, randomized, controlled trial; 480 patients)**
25. Weaver WD, Cerqueira M, Hallstrom AP, et al. Prehospital-initiated vs hospital-initiated thrombolytic therapy. The Myocardial Infarction Triage and Intervention Trial. *JAMA* 1993 Sep 8;270(10):1211-1216. **(Prospective, randomized, controlled trial; 360 patients)**
26. Eisenberg PR, Kenzora JL, Sobel BE, et al. Relation between ST segment shifts during ischemia and thrombin activity in patients with unstable angina. *J Am Coll Cardiol* 1991 Oct;18(4):898-903. **(Prospective; 29 patients)**
27. de Zwaan C, Bar FW, Janssen JH, et al. Angiographic and clinical characteristics of patients with unstable angina showing an ECG pattern indicating critical narrowing of the proximal LAD coronary artery. *Am Heart J* 1989 Mar;117(3):657-665. **(Prospective; 1260 patients)**
28. Cannon CP, McCabe CH, Stone PH, et al. The electrocardiogram predicts one-year outcome of patients with unstable angina and non-Q wave myocardial infarction: results of the TIMI III Registry ECG Ancillary Study. Thrombolysis in Myocardial Ischemia. *J Am Coll Cardiol* 1997 Jul;30(1):133-140. **(Prospective; 1416 patients)**
29. Brady WJ, Perron AD, Chan T. Electrocardiographic ST-segment elevation: correct identification of acute myocardial infarction (AMI) and non-AMI syndromes by emergency physicians. *Acad Emerg Med* 2001 Apr;8(4):349-360. (**Questionnaire**)
30.* Welch RD, Zalenski RJ, Frederick PD, et al; National Registry of Myocardial Infarction 2 and 3 Investigators. Prognostic value of a normal or nonspecific initial electrocardiogram in acute myocardial infarction. *JAMA* 2001 Oct 24-31;286(16):1977-1984. **(Multicenter, observational; 391,208 patients)**
31. Lee TH, Cook EF, Weisberg MC, et al. Impact of the availability of a prior electrocardiogram on the triage of the patient with acute chest pain. *J Gen Intern Med* 1990 Sep-Oct;5(5):381-388. **(Prospective, multicenter; 5673 patients)**
32. Fesmire FM, Percy RF, Wears RL. Diagnostic and prognostic importance of comparing the initial to the previous electrocardiogram in patients admitted for suspected acute myocardial infarction. *South Med J* 1991 Jul;84(7):841-846. **(Prospective; 258 patients)**
33. Kudenchuk PJ, Maynard C, Cobb LA, et al. Utility of the prehospital electrocardiogram in diagnosing acute coronary syndromes: the Myocardial Infarction Triage and Intervention (MITI) Project. *J Am Coll Cardiol* 1998 Jul;32(1):17-27. **(Prospective, randomized, controlled trial; 3027 patients)**
34. Langer A, Freeman MR, Armstrong PW. ST segment shift in unstable angina: pathophysiology and association with coronary anatomy and hospital outcome. *J Am Coll Cardiol* 1989 Jun;13(7):1495-1502. **(Prospective; 135 patients)**
35. Croft CH, Nicod P, Corbett JR, et al. Detection of acute right ventricular infarction by right precordial electrocardiography. *Am J Cardiol* 1982 Sep;50(3):421-427. **(Prospective; 43 patients)**
36. Melendez LJ, Jones DT, Salcedo JR. Usefulness of three additional electrocardiographic chest leads (V_7, V_8, and V_9) in the diagnosis of acute myocardial infarction. *Can Med Assoc J* 1978 Oct 7;119(7):745-748. **(Prospective; 117 patients)**
37. Brady WJ, Hwang V, Sullivan R, et al. A comparison of 12- and 15-lead ECGs in ED chest pain patients: impact on diagnosis, therapy, and disposition. *Am J Emerg Med* 2000 May;18(3):239-243. **(Prospective, comparative; 595 patients)**
38. Akkerhuis KM, Klootwijk PA, Lindeboom W, et al. Recurrent ischaemia during continuous multilead ST-segment monitoring identifies patients with acute coronary syndromes at high risk of adverse cardiac events; meta-analysis of three studies involving 995 patients. *Eur Heart J* 2001 Nov;22(21):1997-2006. **(Meta-analysis; 995 patients)**
39. Fesmire FM, Percy RF, Bardoner JB, et al. Usefulness of automated serial 12-lead ECG monitoring during the initial emergency department evaluation of patients with chest pain. *Ann Emerg Med* 1998 Jan;31(1):3-11. **(Prospective, observational; 1000 patients)**
40. Decker WW, Prina LD, Smars PA, et al. Continuous 12-lead electrocardiographic monitoring in an emergency department chest pain unit: an assessment of potential clinical effect. *Ann Emerg Med* 2003 Mar;41(3):342-351. **(Prospective; 119 patients)**
41. Russell NJ, Pantin CF, Emerson PA, et al. The role of chest radiography in patients presenting with anterior chest pain to the Accident & Emergency Department. *J R Soc Med* 1988 Nov;81(11):626-628. **(Prospective; 120 patients)**
42. Wu WC, Rathore SS, Wang Y, et al. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 2001 Oct 25;345(17):1230-1236. **(Retrospective; 78,947 patients)**
43. Roberts R, Kleiman NS. Earlier diagnosis and treatment of acute myocardial infarction necessitates the need for a 'new diagnostic mind-set.' *Circulation* 1994 Feb;89(2):872-881. **(Review)**
44. Mair J, Morandell D, Genser N, et al. Equivalent early sensitivities of myoglobin, creatine kinase MB mass, creatine kinase isoform ratios, and cardiac troponins I and T for acute myocardial infarction. *Clin Chem* 1995 Sep;41(9):1266-1272. **(Prospective; 37 patients)**
45. Balk EM, Ioannidis JP, Salem D, et al. Accuracy of biomarkers to diagnose acute cardiac ischemia in the emergency department: a meta-analysis. *Ann Emerg Med* 2001 May;37(5):478-494. **(Meta-analysis; 2297 patients for troponin I and T)**
46. Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996 Oct 31;335(18):1342-1349. **(Prospective; 1404 patients)**
47. Aviles RJ, Askari AT, Lindahl B, et al. Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. *N Engl J Med* 2002 Jun 27;346(26):2047-2052. **(Retrospective; 7033 patients)**
48. McCullough PA, Nowak RM, Foreback C, et al. Performance of multiple cardiac biomarkers measured in the emergency department in patients with chronic kidney disease and chest pain. *Acad Emerg Med* 2002 Dec;9(12):1389-1396. **(Prospective; 817 patients)**
49. Apple FS, Falahati A, Paulsen PR, et al. Improved detection of minor ischemic myocardial injury with measurement of serum cardiac troponin I. *Clin Chem* 1997 Nov;43(11):2047-2051. **(Prospective; 48 patients)**
50. Pettijohn TL, Doyle T, Spiekerman AM, et al. Usefulness of positive troponin-T and negative creatine kinase levels in identifying high-risk patients with unstable angina pectoris. *Am J Cardiol* 1997 Aug 15;80(4):510-511. **(Prospective)**
51. Ohman EM, Armstrong PW, Christenson RH, et al. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. GUSTO IIA Investigators. *N Engl J Med* 1996 Oct 31;335(18):1333-1341. **(Prospective, randomized, controlled trial; 855 patients)**
52. Kontos MC, Anderson FP, Schmidt KA, et al. Early diagnosis of acute myocardial infarction in patients without ST-segment elevation. *Am J Cardiol* 1999 Jan 15;83(2):155-158. **(Prospective; 2093 patients)**
53. Zaninotto M, Altinier S, Lachin M, et al. Strategies for the early diagnosis of acute myocardial infarction using biochemical markers. *Am J Clin Pathol* 1999 Mar;111(3):399-405. **(Prospective; 96 patients)**
54. Zimmerman J, Fromm R, Meyer D, et al. Diagnostic marker cooperative study for the diagnosis of myocardial infarction. *Circulation* 1999 Apr 6;99(13):1671-1677. **(Prospective, multicenter; 955 patients)**
55. Morrow DA, Rifai N, Antman EM, et al. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. Thrombolysis in Myocardial Infarction. *J Am Coll Cardiol* 1998 Jun;31(7):1460-1465. **(Prospective, multicenter)**
56. de Lemos JA, Morrow DA, Bentley JH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med* 2001 Oct 4;345(14):1014-1021. **(Prospective; 2525 patients)**
57.* Morrow DA, Antman EM, Parsons L, et al. Application of the TIMI risk score for ST-elevation MI in the National Registry of Myocardial Infarction 3. *JAMA* 2001 Sep 19;286(11):1356-1359. **(Prospective; 84,029 patients)**
58. Scirica BM, Cannon CP, Antman EM, et al. Validation of the thrombolysis in myocardial infarction (TIMI) risk score for unstable angina pectoris and non-ST-elevation myocardial infarction in the TIMI III registry. *Am J Cardiol* 2002 Aug 1;90(3):303-305.
59. Morrow DA, Antman EM, Snapinn SM, et al. An integrated clinical approach to predicting the benefit of tirofiban in non-ST elevation acute coronary syndromes. Application of the TIMI Risk Score for UA / NSTEMI in PRISM-PLUS. *Eur Heart J* 2002 Feb;23(3):223-229. **(Prospective, randomized, controlled trial; 1915 patients)**
60. Karlberg KE, Saldeen T, Wallin R, et al. Intravenous nitroglycerin reduces ischaemia in unstable angina pectoris: a double-blind placebo-controlled study. *J Intern Med* 1998 Jan;243(1):25-31. **(Randomized, controlled, double-blinded; 162 patients)**
61. DePace NL, Herling IM, Kotler MN, et al. Intravenous nitroglycerin for rest angina. Potential pathophysiologic mechanisms of action. *Arch Intern Med* 1982 Oct;142(10):1806-1809. **(Prospective; 20 patients)**
62. Kaplan K, Davison R, Parker M, et al. Intravenous nitroglycerin for the

treatment of angina at rest unresponsive to standard nitrate therapy. *Am J Cardiol* 1983 Mar 1;51(5):694-698. **(Prospective; 35 patients)**

63. Armstrong PW. Stable ischemic syndromes. In: Topol EJ, ed. *Textbook of Cardiovascular Medicine.* Philadelphia: Lippincott-Raven; 1998:333-364. **(Textbook chapter)**
64. Cheitlin MD, Hutter AM Jr, Brindis RG, et al. ACC / AHA expert consensus document. Use of sildenafil (Viagra) in patients with cardiovascular disease. American College of Cardiology / American Heart Association. *J Am Coll Cardiol* 1999 Jan;33(1):273-282. **(Review, consensus development conference)**
65. No authors listed. Early treatment of unstable angina in the coronary care unit: a randomised, double blind, placebo controlled comparison of recurrent ischaemia in patients treated with nifedipine or metoprolol or both. Report of The Holland Interuniversity Nifedipine / Metoprolol Trial (HINT) Research Group. *Br Heart J* 1986 Nov;56(5):400-413. **(Multicenter, randomized, controlled trial; 338 patients)**
66. Brunner M, Faber TS, Greve B, et al. Usefulness of carvedilol in unstable angina pectoris. *Am J Cardiol* 2000 May 15;85(10):1173-1178. **(Randomized, controlled trial; 116 patients)**
67. Gottlieb SO, Weisfeldt ML, Ouyang P, et al. Effect of the addition of propranolol to therapy with nifedipine for unstable angina pectoris: a randomized, double-blind, placebo-controlled trial. *Circulation* 1986 Feb;73(2):331-337. **(Randomized, controlled trial; 81 patients)**
68. Hohnloser SH, Meinertz T, Klingenheben T, et al. Usefulness of esmolol in unstable angina pectoris. European Esmolol Study Group. *Am J Cardiol* 1991 Jun 15;67(16):1319-1323. **(Multicenter, randomized, controlled trial; 113 patients)**
69. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. II. Unstable angina, heart failure, primary prevention with aspirin, and risk factor modification. *JAMA* 1988 Oct 21;260(15):2259-2263. **(Review)**
70. Furberg CD, Psaty BM, Meyer JV. Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. *Circulation* 1995 Sep 1;92(5):1326-1331. **(Meta-analysis; 8350 patients)**
71. Lubsen J, Tijssen JG. Efficacy of nifedipine and metoprolol in the early treatment of unstable angina in the coronary care unit: findings from the Holland Interuniversity Nifedipine / metoprolol Trial (HINT). *Am J Cardiol* 1987 Jul 15;60(2):18A-25A. **(Multicenter, randomized, controlled trial; 515 patients)**
72. Pepine CJ, Faich G, Makuch R. Verapamil use in patients with cardiovascular disease: an overview of randomized trials. *Clin Cardiol* 1998 Sep;21(9):633-641. **(Meta-analysis; 4000 patients)**
73. Yusuf S, Pepine CJ, Garces C, et al. Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. *Lancet* 1992 Nov 14;340(8829):1173-1178. **(Multicenter, randomized, controlled trial; 6797 patients)**
74. Rutherford JD, Pfeffer MA, Moye LA, et al. Effects of captopril on ischemic events after myocardial infarction. Results of the Survival and Ventricular Enlargement trial. SAVE Investigators. *Circulation* 1994 Oct;90(4):1731-1738. **(Randomized, controlled trial; 2231 patients)**
75.* No authors listed. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. ACE Inhibitor Myocardial Infarction Collaborative Group. *Circulation* 1998 Jun 9;97(22):2202-2212. **(Systematic review; 100,000 patients)**
76.* Flather MD, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet* 2000 May 6;355(9215):1575-1581. **(Meta-analysis; 12,763 patients)**
77. No authors listed. Collaborative overview of randomised trials of antiplatelet therapy—I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. *BMJ* 1994 Jan 8;308(6921):81-106. **(Meta-analysis; 100,000 patients)**
78. Ridker PM, Cushman M, Stampfer MJ, et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997 Apr 3;336(14):973-979. **(Randomized, controlled trial; 543 patients)**
79. Lewis HD Jr, Davis JW, Archibald DG, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1983 Aug 18;309(7):396-403. **(Multicenter, randomized, controlled trial; 1266 patients)**
80. Cairns JA, Gent M, Singer J, et al. Aspirin, sulfinpyrazone, or both in unstable angina. Results of a Canadian multicenter trial. *N Engl J Med* 1985 Nov 28;313(22):1369-1375. **(Multicenter, randomized, controlled trial; 555 patients)**
81. Theroux P, Ouimet H, McCans J, et al. Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med* 1988 Oct 27;319(17):1105-1111. **(Randomized, controlled trial; 479 patients)**
82. No authors listed. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. The RISC Group. *Lancet* 1990 Oct 6;336(8719):827-830. **(Randomized, controlled trial; 796 patients)**
83. Cohen M, Adams PC, Parry G, et al. Combination antithrombotic therapy in unstable rest angina and non-Q-wave infarction in nonprior aspirin users. Primary end points analysis from the ATACS trial. Antithrombotic Therapy in Acute Coronary Syndromes Research Group. *Circulation* 1994 Jan;89(1):81-88. **(Randomized, controlled trial; 214 patients)**
84. Quinn MJ, Fitzgerald DJ. Ticlopidine and clopidogrel. *Circulation* 1999 Oct 12;100(15):1667-1672. **(Review)**
85. Balsano F, Rizzon P, Violi F, et al. Antiplatelet treatment with ticlopidine in unstable angina. A controlled multicenter clinical trial. The Studio della Ticlopidina nell'Angina Instabile Group. *Circulation* 1990 Jul;82(1):17-26. **(Multicenter, randomized, controlled trial; 652 patients)**
86. *Physicians' Desk Reference.* 56th ed. Montvale, NJ: Medical Economics Company Inc.; 2002. **(Reference text)**
87. Bertrand ME, Rupprecht HJ, Urban P, et al. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting : the clopidogrel aspirin stent international cooperative study (CLASSICS). *Circulation* 2000 Aug 8;102(6):624-629. **(Randomized, controlled trial; 1020 patients)**
88. Cadroy Y, Bossavy JP, Thalamas C, et al. Early potent antithrombotic effect with combined aspirin and a loading dose of clopidogrel on experimental arterial thrombogenesis in humans. *Circulation* 2000 Jun 20;101(24):2823-2828. **(Randomized, controlled trial; 18 patients)**
89. Helft G, Osende JI, Worthley SG, et al. Acute antithrombotic effect of a front-loaded regimen of clopidogrel in patients with atherosclerosis on aspirin. *Arterioscler Thromb Vasc Biol* 2000 Oct;20(10):2316-2321. **(Randomized, controlled trial; 20 patients)**
90. Yusuf S, Zhao F, Mehta SR, et al; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001 Aug 16;345(7):494-502. **(Multicenter, randomized, controlled trial; 12,562 patients)**
91. Lefkovits J, Plow EF, Topol EJ. Platelet glycoprotein IIb / IIIa receptors in cardiovascular medicine. *N Engl J Med* 1995 Jun 8;332(23):1553-1559. **(Review)**
92. No authors listed. Comparison of sibrafiban with aspirin for prevention of cardiovascular events after acute coronary syndromes: a randomised trial. The SYMPHONY Investigators. Sibrafiban versus Aspirin to Yield Maximum Protection from Ischemic Heart Events Post-acute Coronary Syndromes. *Lancet* 2000 Jan 29;355(9201):337-345. **(Multicenter, randomized, controlled trial; 9223 patients)**
93. Cannon CP, McCabe CH, Wilcox RG, et al. Oral glycoprotein IIb / IIIa inhibition with orbofiban in patients with unstable coronary syndromes (OPUS-TIMI 16) trial. *Circulation* 2000 Jul 11;102(2):149-156. **(Multicenter, randomized, controlled trial; 10,288 patients)**
94.* O'Neill WW, Serruys P, Knudtson M, et al. Long-term treatment with a platelet glycoprotein-receptor antagonist after percutaneous coronary revascularization. EXCITE Trial Investigators. Evaluation of Oral Xemilofiban in Controlling Thrombotic Events. *N Engl J Med* 2000 May 4;342(18):1316-1324. **(Multicenter, randomized, controlled trial; 7232 patients)**
95. No authors listed. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study. *Lancet* 1997 May 17;349(9063):1429-1435. **(Multicenter, randomized, controlled trial; 1265 patients)**
96. Hamm CW, Heeschen C, Goldmann B, et al. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) Study Investigators. *N Engl J Med* 1999 May 27;340(21):1623-1629. **(Multicenter, randomized, controlled trial; 1265 patients)**
97. Simoons ML; GUSTO IV-ACS Investigators. Effect of glycoprotein IIb / IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV-ACS randomised trial. *Lancet* 2001 Jun 16;357(9272):1915-1924. **(Multicenter, randomized, controlled trial; 7800 patients)**
98. No authors listed. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. *N Engl J Med* 1998 May 21;338(21):1498-1505. **(Multicenter, randomized, controlled trial; 3232 patients)**
99. Heeschen C, Hamm CW, Goldmann B, et al. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. PRISM Study Investigators. Platelet Receptor Inhibition in Ischemic Syndrome Management. *Lancet* 1999 Nov 20;354(9192):1757-1762. **(Randomized, controlled trial; 2222 patients)**
100. No authors listed. Inhibition of the platelet glycoprotein IIb / IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. *N Engl J Med* 1998 May 21;338(21):1488-1497. **(Multicenter, randomized, controlled trial; 1915 patients)**
101. No authors listed. Effects of platelet glycoprotein IIb / IIIa blockade with

tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. The RESTORE Investigators. Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis. *Circulation* 1997 Sep 2;96(5):1445-1453. **(Randomized, controlled trial; 2139 patients)**

102.* No authors listed. Inhibition of platelet glycoprotein IIb / IIIa with eptifibatide in patients with acute coronary syndromes. The PURSUIT Trial Investigators. Platelet Glycoprotein IIb / IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. *N Engl J Med* 1998 Aug 13;339(7):436-443. **(Multicenter, randomized, controlled trial; 10,948 patients)**

103. No authors listed. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II. *Lancet* 1997 May 17;349(9063):1422-1428. **(Multicenter, randomized, controlled trial; 2064 patients)**

104.* Roffi M, Moliterno DJ, Meier B, et al. Impact of different platelet glycoprotein IIb / IIIa receptor inhibitors among diabetic patients undergoing percutaneous coronary intervention: : Do Tirofiban and ReoPro Give Similar Efficacy Outcomes Trial (TARGET) 1-year follow-up. *Circulation* 2002 Jun 11;105(23):2730-2736. **(Randomized, controlled trial; 4809 patients)**

105.* Boersma E, Harrington RA, Moliterno DJ, et al. Platelet glycoprotein IIb / IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet* 2002 Jan 19;359(9302):189-198. **(Meta-analysis; 31,402 patients)**

106.* Schriger DL, Herbert ME. Platelet glycoprotein inhibitors in patients with medically managed acute coronary syndrome: does the enthusiasm exceed the science? *Ann Emerg Med* 2001 Sep;38(3):249-255. **(Systematic review; 12,674 patients)**

107. Lang ES, Afilalo M. Evidence-based emergency medicine. Use of platelet glycoprotein IIb / IIIa inhibitors in patients with unstable angina and non-ST-segment elevation myocardial infarction. *Ann Emerg Med* 2002 Nov;40(5):518-520. **(Systematic review; 30,006 patients)**

108. Hirsh J. Heparin. *N Engl J Med* 1991 May 30;324(22):1565-1574. **(Review)**

109.* Oler A, Whooley MA, Oler J, et al. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. *JAMA* 1996 Sep 11;276(10):811-815. **(Meta-analysis; 6 randomized trials)**

110. Theroux P, Waters D, Qiu S, et al. Aspirin versus heparin to prevent myocardial infarction during the acute phase of unstable angina. *Circulation* 1993 Nov;88(5 Pt 1):2045-2048. **(Randomized, controlled trial; 484 patients)**

111. Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. *N Engl J Med* 1997 Aug 14;337(7):447-452. **(Randomized, controlled trial; 3171 patients)**

112. Gurfinkel EP, Manos EJ, Mejail RI, et al. Low molecular weight heparin versus regular heparin or aspirin in the treatment of unstable angina and silent ischemia. *J Am Coll Cardiol* 1995 Aug;26(2):313-318. **(Randomized, controlled trial; 219 patients)**

113. No authors listed. Low-molecular-weight heparin during instability in coronary artery disease, Fragmin during Instability in Coronary Artery Disease (FRISC) study group. *Lancet* 1996 Mar 2;347(9001):561-568. **(Multicenter, randomized, controlled trial; 1506 patients)**

114. Klein W, Buchwald A, Hillis SE, et al. Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease. Fragmin in unstable coronary artery disease study (FRIC). *Circulation* 1997 Jul 1;96(1):61-68. **(Multicenter, randomized, controlled trial; 1482 patients)**

115. Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina / non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. *Circulation* 1999 Oct 12;100(15):1593-1601. **(Multicenter, randomized, controlled trial; 3910 patients)**

116.* Antman EM, Cohen M, Radley D, et al. Assessment of the treatment effect of enoxaparin for unstable angina / non-Q-wave myocardial infarction. TIMI 11B-ESSENCE meta-analysis. *Circulation* 1999 Oct 12;100(15):1602-1608. **(Meta-analysis; 7100 patients)**

117. Cohen M, Theroux P, Borzak S, et al; ACUTE II Investigators. Randomized double-blind safety study of enoxaparin versus unfractionated heparin in patients with non-ST-segment elevation acute coronary syndromes treated with tirofiban and aspirin: the ACUTE II study. The Antithrombotic Combination Using Tirofiban and Enoxaparin. *Am Heart J* 2002 Sep;144(3):470-477. **(Randomized, controlled trial; 515 patients)**

118. Boden WE, O'Rourke RA, Crawford MH, et al. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. *N Engl J Med* 1998 Jun 18;338(25):1785-1792. **(Multicenter, randomized, controlled trial; 920 patients)**

119. Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction. An overview of results from randomized controlled trials. *JAMA* 1993 Oct 6;270(13):1589-1595. **(Meta-analysis; 26,973 patients)**

120. McCullough PA, O'Neill WW, Graham M, et al. A prospective randomized trial of triage angiography in acute coronary syndromes ineligible for thrombolytic therapy. Results of the medicine versus angiography in thrombolytic exclusion (MATE) trial. *J Am Coll Cardiol* 1998 Sep;32(3):596-605. **(Randomized, controlled trial; 210 patients)**

121. Cannon CP, Weintraub WS, Demopoulos LA, et al; TACTICS (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy)—Thrombolysis in Myocardial Infarction 18 Investigators. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb / IIIa inhibitor tirofiban. *N Engl J Med* 2001 Jun 21;344(25):1879-1887. **(Multicenter, randomized, controlled trial; 2220 patients)**

122.* Mahoney EM, Jurkovitz CT, Chu H, et al; TACTICS-TIMI 18 Investigators. Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction. Cost and cost-effectiveness of an early invasive vs conservative strategy for the treatment of unstable angina and non-ST-segment elevation myocardial infarction. *JAMA* 2002 Oct 16;288(15):1851-1858. **(Randomized, controlled trial; 2220 patients)**

123.* No authors listed. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. *Lancet* 1999 Aug 28;354(9180):708-715. **(Multicenter, randomized, controlled trial; 2457 patients)**

124.* Wallentin L, Lagerqvist B, Husted S, et al. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC II invasive randomised trial. FRISC II Investigators. Fast Revascularisation during Instability in Coronary artery disease. *Lancet* 2000 Jul 1;356(9223):9-16. **(Randomized, controlled trial; 2457 patients)**

125. Fox KA, Poole-Wilson PA, Henderson RA, et al; Randomized Intervention Trial of unstable Angina Investigators. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. *Lancet* 2002 Sep 7;360(9335):743-751. **(Randomized, controlled trial; 1810 patients)**

126. No authors listed. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. *Circulation* 1994 Apr;89(4):1545-1556. **(Multicenter, randomized, controlled trial; 1473 patients)**

127.* Baigent C, Collins R, Appleby P, et al. ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. The ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *BMJ* 1998 May 2;316(7141):1337-1343. **(Randomized, controlled trial; 17,187 patients)**

128. Brogan WC 3rd, Lange RA, Kim AS, et al. Alleviation of cocaine-induced coronary vasoconstriction by nitroglycerin. *J Am Coll Cardiol* 1991 Aug;18(2):581-586. **(Controlled clinical trial; 23 patients)**

129. Schindler CW, Tella SR, Prada J, et al. Calcium channel blockers antagonize some of cocaine's cardiovascular effects, but fail to alter cocaine's behavioral effects. *J Pharmacol Exp Ther* 1995 Feb;272(2):791-798. **(Randomized, controlled trial; monkeys)**

130. Baumann BM, Perrone J, Hornig SE, et al. Randomized, double-blind, placebo-controlled trial of diazepam, nitroglycerin, or both for treatment of patients with potential cocaine-associated acute coronary syndromes. *Acad Emerg Med* 2000 Aug;7(8):878-885. **(Randomized, controlled trial; 40 patients)**

131. Honderick T, Williams D, Seaberg D, et al. A prospective, randomized, controlled trial of benzodiazepines and nitroglycerin or nitroglycerin alone in the treatment of cocaine-associated acute coronary syndromes. *Am J Emerg Med* 2003 Jan;21(1):39-42. **(Randomized, controlled trial; 37 patients)**

132. Weber JE, Shofer FS, Larkin GL, et al. Validation of a brief observation period for patients with cocaine-associated chest pain. *N Engl J Med* 2003 Feb 6;348(6):510-517. **(Randomized, controlled trial; 344 patients)**

133. Lange RA, Cigarroa RG, Flores ED, et al. Potentiation of cocaine-induced coronary vasoconstriction by beta-adrenergic blockade. *Ann Intern Med* 1990 Jun 15;112(12):897-903. **(Randomized, controlled trial; 30 patients)**

134. Vargas R, Gillis RA, Ramwell PW. Propranolol promotes cocaine-induced spasm of porcine coronary artery. *J Pharmacol Exp Ther* 1991 May;257(2):644-646. **(Animal study)**

135. Boehrer JD, Moliterno DJ, Willard JE, et al. Influence of labetalol on cocaine-induced coronary vasoconstriction in humans. *Am J Med* 1993 Jun;94(6):608-610. **(Prospective; 15 patients)**

136. Park SJ, Shim WH, Ho DS, et al. A paclitaxel-eluting stent for the prevention of coronary restenosis. *N Engl J Med* 2003 Apr 17;348(16):1537-1545. **(Multicenter, randomized, controlled trial; 177 patients)**

137. Morice MC, Serruys PW, Sousa JE, et al; RAVEL Study Group. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002 Jun 6;346(23):1773-1780. **(Multicenter, randomized, controlled trial; 238 patients)**

Physician CME Questions

49. Which of the following is *not* associated with unstable angina?
- a. An elevation in biochemical markers for myocardial infarction
- b. Symptoms are occurring for the first time
- c. Symptoms occur at rest
- d. Symptoms are accelerating in terms of frequency or severity

50. Which of the following non-cardiovascular conditions should be included in the differential diagnosis of a patient presenting with chest pain?
- a. Esophageal rupture
- b. Pneumonia
- c. Gastrointestinal causes
- d. Musculoskeletal causes
- e. All of the above

51. The historical factors most commonly associated with missed MI are age less than 55 years, female gender, non-white race, normal or nondiagnostic ECGs, and concurrent diabetes.
- a. True
- b. False

52. The principal elements in ACS risk stratification are a focused history and physical examination, ECG, and cardiac biomarkers.
- a. True
- b. False

53. Which of the following ECG findings suggests a *high* likelihood of CAD?
- a. T-wave flattening or inversion with dominant R waves; normal ECG
- b. Fixed Q waves; abnormal ST segments not documented to be new
- c. New ST deviation (≥ 0.05 mV) or T-wave inversion (≥ 0.2 mV) with symptoms
- d. None of the above

54. Which of the following historical findings, in the absence of other high-risk findings, suggests an *intermediate* likelihood of CAD?
- a. Chest or left arm discomfort as chief complaint reproducing prior documented angina; known history of CAD, including MI
- b. Chest or left arm pain or discomfort as chief symptom; age > 70 years; male sex; diabetes
- c. Recent cocaine use
- d. None of the above

55. The chest x-ray:
- a. may suggest an aortic dissection if a widened mediastinum is present.
- b. is typically abnormal in the setting of ACS.
- c. is ineffective in detecting cardiomyopathy or valvular disorders.
- d. is rarely useful in eliminating non-ACS diagnoses.

56. Which of the following physical examination findings, in the absence of other high- or intermediate-risk findings, suggests a *low* likelihood of CAD?
- a. Transient MR, hypotension, pulmonary edema or rales
- b. Peripheral vascular disease
- c. Chest discomfort reproduced by palpation
- d. None of the above

57. All of the following are correct regarding normal or nonspecific ECG findings *except*:
- a. They have been shown to occur in more than 50% of patients with UA / NSTEMI.
- b. They have been shown to occur in nearly 50% of patients with transmural MI.
- c. They have been shown to occur in up to 8% of patients with confirmed MI.
- d. Patients with confirmed MI but a normal ECG have three times the in-hospital mortality rate of patients with diagnostic tracings.

58. Which of the following is the *most* reliable cardiac marker in the setting of cardiac dysfunction?
- a. CK-MB
- b. Myoglobin
- c. Cardiac troponins
- d. Brain natriuretic peptide

59. The TIMI risk score:
- a. is a useful tool to predict mortality, MI, or severe ischemia within 14 days.
- b. is a useful tool to predict both short- and long-term mortality.
- c. has been studied in only one trial.
- d. all of the above.

60. Which of the following, in the absence of other high- or intermediate-risk factors, suggests the *lowest* risk of short-term mortality?
- a. New-onset or progressive severe angina, but without prolonged pain at rest
- b. Pain at rest of more than 20 minutes in duration that resolves, in the presence of moderate or high likelihood of CAD
- c. Elevated cardiac markers
- d. Accelerating tempo of ischemic symptoms in preceding 48 hours

61. At present, which of the following is *not* indicated for the treatment of UA/NSTEMI?
- a. Aspirin
- b. Thrombolytics
- c. Thienopyridines
- d. GP IIb / IIIa inhibitors

62. Patients with positive biomarkers, ongoing anginal pain, or positive stress tests can be managed on an outpatient basis if the ECG is normal and prompt follow-up is ensured.
- a. True
- b. False

63. The early administration of aspirin to patients with UA/NSTEMI:

a. is common, although it has not been proven to be beneficial in the literature.
b. is inferior to the newer, more expensive therapies.
c. reduces the risk of death from MI from 12.5% to 6.4%.
d. should only occur in patients in whom PCI is planned.

64. Tirofiban has been shown to be *least* beneficial among patients with elevated troponins.

a. True
b. False

Coming in Future Issues:

Hand Injuries • Pulmonary Embolism • The Suicidal Patient

Class Of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives an alpha-numerical score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case-control studies
- Less robust RCTs
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Significantly modified from: The Emergency Cardiovascular Care Committees of the American Heart Association and representatives from the resuscitation councils of ILCOR: How to Develop Evidence-Based Guidelines for Emergency Cardiac Care: Quality of Evidence and Classes of Recommendations; also: Anonymous. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part IX. Ensuring effectiveness of community-wide emergency cardiac care. *JAMA* 1992;268(16):2289-2295.

Physician CME Information

This CME enduring material is sponsored by Mount Sinai School of Medicine and has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education. Credit may be obtained by reading each issue and completing the printed post-tests administered in December and June or online single-issue post-tests administered at www.empractice.net.

Target Audience: This enduring material is designed for emergency medicine physicians.

Needs Assessment: The need for this educational activity was determined by a survey of medical staff, including the editorial board of this publication; review of morbidity and mortality data from the CDC, AHA, NCHS, and ACEP; and evaluation of prior activities for emergency physicians.

Date of Original Release: This issue of *Emergency Medicine Practice* was published April 1, 2004. **This activity is eligible for CME credit through April 1, 2007.** The latest review of this material was March 12, 2004.

Discussion of Investigational Information: As part of the newsletter, faculty may be presenting investigational information about pharmaceutical products that is outside Food and Drug Administration approved labeling. Information presented as part of this activity is intended solely as continuing medical education and is not intended to promote off-label use of any pharmaceutical product. *Disclosure of Off-Label Usage:* This issue of *Emergency Medicine Practice* discusses no off-label use of any pharmaceutical product.

Faculty Disclosure: In compliance with all ACCME Essentials, Standards, and Guidelines, all faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows: Dr. Macfarlane, Dr. Snoey, Dr. Marill, and Dr. Tabas report no significant financial interest or other relationship with the manufacturer(s) of any commercial product(s) discussed in this educational presentation.

Accreditation: Mount Sinai School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

Credit Designation: Mount Sinai School of Medicine designates this educational activity for up to 4 hours of Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit actually spent in the educational activity. *Emergency Medicine Practice* is approved by the American College of Emergency Physicians for 48 hours of ACEP Category 1 credit (per annual subscription). *Emergency Medicine Practice* has been reviewed and is acceptable for up to 48 Prescribed credit hours by the American Academy of Family Physicians. *Emergency Medicine Practice* has been approved for 48 Category 2-B credit hours by the American Osteopathic Association.

Earning Credit: Two Convenient Methods

- **Print Subscription Semester Program:** Paid subscribers with current and valid licenses in the United States who read all CME articles during each *Emergency Medicine Practice* six-month testing period, complete the post-test and the CME Evaluation Form distributed with the December and June issues, and return it according to the published instructions are eligible for up to 4 hours of Category 1 credit toward the AMA Physician's Recognition Award (PRA) for each issue. You must complete both the post-test and CME Evaluation Form to receive credit. Results will be kept confidential. CME certificates will be delivered to each participant scoring higher than 70%.
- **Online Single-Issue Program:** Paid subscribers with current and valid licenses in the United States who read this *Emergency Medicine Practice* CME article and complete the online post-test and CME Evaluation Form at www.empractice.net are eligible for up to 4 hours of Category 1 credit toward the AMA Physician's Recognition Award (PRA). You must complete both the post-test and CME Evaluation Form to receive credit. Results will be kept confidential. CME certificates may be printed directly from the Web site to each participant scoring higher than 70%.

***Emergency Medicine Practice* is not affiliated with any pharmaceutical firm or medical device manufacturer.**

President and CEO: Robert Williford. **Publisher**: Heidi Frost. **Research Editors**: Ben Abella, MD, University of Chicago; Richard Kwun, MD, Mount Sinai School of Medicine.

Direct all editorial or subscription-related questions to EB Practice, LLC: **1-800-249-5770** • Fax: 1-770-500-1316 • Non-U.S. subscribers, call: 1-678-366-7933
EB Practice, LLC • 305 Windlake Court • Alpharetta, GA 30022
E-mail: **emp@empractice.net** • Web Site: **EMPractice.net**

Emergency Medicine Practice (ISSN 1524-1971) is published monthly (12 times per year) by EB Practice, LLC, 305 Windlake Court, Alpharetta, GA 30022. Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. This publication is intended as a general guide and is intended to supplement, rather than substitute, professional judgment. It covers a highly technical and complex subject and should not be used for making specific medical decisions. The materials contained herein are not intended to establish policy, procedure, or standard of care. *Emergency Medicine Practice* is a trademark of EB Practice, LLC. Subscription price: $299, U.S. funds. (Call for international shipping prices.)