ABSTRACT

Acute coronary syndrome is a form of coronary artery disease, which has a broad range of clinical presentations. Generally, patients with acute coronary syndrome are categorized as having ST-segment elevation myocardial infarction, non–ST-segment elevation myocardial infarction, or unstable angina. The findings on the 12-lead electrocardiogram and other information from a thorough history and clinical examination allow patients to be stratified according to their risk for further myocardial damage. Risk stratification will determine an individual patient’s need for aggressive cardiac treatment, observation, or referral. The clinical characteristics that can be used to determine a patient’s risk of a subsequent cardiac event or death are reviewed along with the American College of Cardiology/American Heart Association guidelines for immediate management after risk stratification. (Adv Stud Med. 2006;6(6B):S483-S490)

INTRODUCTION

Acute coronary syndrome (ACS) is a potentially life-threatening manifestation of coronary artery disease (CAD), which is the leading cause of death in the United States. The term ACS describes a broad range of clinical presentations. Patients are generally categorized according to the results of an initial 12-lead electrocardiogram (ECG) as having ST-segment elevation myocardial infarction (STEMI) or non–ST-segment elevation myocardial infarction (NSTEMI). Patients with an initial ECG suggesting NSTEMI may be experiencing the closely related condition unstable angina (UA), which is a relatively high-risk intermediate state between stable angina and myocardial infarction (MI). Both conditions are common manifestations of CAD that present as ACS.

Persistent ST-segment elevation accompanied by chest pain usually indicates total coronary occlusion, resulting in irreversible myocardial damage. This presentation requires immediate reperfusion of the coronary vessel by medical or pharmacologic intervention to prevent further myocardial damage. Patients who present with chest pain but do not have persistent ST-segment elevation are likely suffering from NSTEMI or UA, both of which are usually caused by partial occlusion of a coronary artery. In these patients, ischemia and symptoms should be relieved by appropriate pharmacologic therapy, such as aspirin, low–molecular-weight heparin or heparin, glycoprotein IIb/IIIa inhibitors, clopidogrel, beta blockers, nitrates, and statins. All patients should be subsequently monitored by serial ECGs and measurements of serum markers for myocardial necrosis.

Despite treatment advances, the rates of mortality, subsequent cardiac events, and hospitalizations remain high for patients who present with ACS. The high rate of poor outcomes in these patients can be at least
partially attributed to the overlapping characteristics of STEMI and NSTEMI/UA that complicate the diagnosis upon initial presentation.2 This article reviews the various clinical characteristics, the American College of Cardiology/American Heart Association (ACC/AHA) risk stratification guidelines for patients experiencing ACS, and treatment implications for patients with NSTEMI/UA.

**CLINICAL EVALUATION**

Typical symptoms of ACS include chest pain, referred pain, nausea, vomiting, dyspnea, diaphoresis, and light-headedness. Although some patients may not complain of chest pain, the presence of symptoms such as referred pain that radiates to the shoulder, left arm, or both arms increases the likelihood of ACS. Patients presenting with the 3 classic symptoms of typical angina (substernal pain that occurs on exertion and is relieved by rest) have an increased risk of ACS.4 The presence of atypical symptoms does not rule out ACS. However, multiple atypical symptoms may be useful in identifying patients at low risk for ACS.5

In patients presenting with chest pain, ruling out noncardiac causes is the primary challenge, requiring a thorough initial evaluation. This includes assessing a patient’s history with risk factor analysis, physical examination, 12-lead ECG, and serum cardiac biomarker measurements, such cardiac-specific troponins T and I.2 Table 1 lists the clinical factors that characterize patients at high, medium, and low risk for ACS resulting from CAD. Patients with a history of ACS or persistent chest pain, unstable vital signs, and syncope should be considered at the highest risk. For these patients, immediate transfer to a cardiac monitoring unit or emergency department is warranted.2

For patients who are diagnosed with UA, the short-term risk of death or a cardiac event can be stratified into high-, moderate-, and low-risk categories (Table 2).2 The prognosis for patients with UA can be judged by the pace

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>High Risk</th>
<th>Medium Risk</th>
<th>Low Risk</th>
</tr>
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<tbody>
<tr>
<td>History</td>
<td>• Chest discomfort or left arm pain</td>
<td>• Chest or left arm pain</td>
<td>• Probable ischemic symptoms without intermediate risk findings</td>
</tr>
<tr>
<td></td>
<td>• Recurrent, documented angina</td>
<td>• Age &gt;70</td>
<td>• Recent cocaine use</td>
</tr>
<tr>
<td></td>
<td>• History of coronary artery disease or myocardial infarction</td>
<td>• Male sex</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• New transient mitral regurgitation</td>
<td>• Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td></td>
<td>• Extracardiac vascular disease</td>
<td>Chest discomfort on palpation</td>
</tr>
<tr>
<td></td>
<td>• Hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Diaphoresis</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>• Pulmonary edema or rales</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>• New transient ST deviation</td>
<td>• Fixed Q waves</td>
<td>• T-wave flattening</td>
</tr>
<tr>
<td></td>
<td>• T-wave inversion with symptoms</td>
<td>• Pre-existing abnormal ST or T waves</td>
<td>• T inversion in leads with dominant R waves</td>
</tr>
<tr>
<td>Serum cardiac markers</td>
<td>Elevated troponin T, troponin I, or CK-MB</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
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</tbody>
</table>

ECG = electrocardiogram; CK-MB = creatine kinase, myocardial bound.
of their clinical course, which can predict their short-term risk for a cardiac event and their chance of surviving an event. Estimating risk for patients with chest pain at rest can help the clinician determine the appropriate site of care and the appropriate therapy. Patients at the highest risk will likely benefit from treatment in coronary care units, whereas patients at lesser risk may be appropriately managed in monitored step-down units or as outpatients. Likewise, risk stratification will identify those patients who may benefit from more aggressive therapies, such as glycoprotein IIb/IIIa inhibitors.2

**Diagnostic ECG Morphology**

**ST-Elevation Myocardial Infarction**

Among the clinical presentations of ACS, STEMI is the most urgent because of the risk for progressive myocardial damage. Approximately 25% of patients with an ACS will present with new or presumed new ST elevation on their ECG.4 Normal or nondiagnostic ECGs do not preclude the presence or emergence of acute myocardial infarction (AMI). Therefore, ST deviation should be interpreted in the larger context of the clinical presentation and overall ECG characteris-

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**Table 2. Short-term Risk Stratification for Death or MI in Patients with Unstable Angina**

<table>
<thead>
<tr>
<th>Feature</th>
<th>High Risk</th>
<th>Moderate Risk</th>
<th>Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td>Presence of ≥1 symptoms in this column</td>
<td>Presence of ≥1 symptoms in this column, without high-risk features</td>
<td>Any symptom in this column without moderate- or high-risk features</td>
</tr>
<tr>
<td><strong>Character of pain</strong></td>
<td>Increasing ischemic symptoms in prior 48 hours</td>
<td>Prior MI, peripheral or cerebrovascular disease, CABG, prior aspirin use</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical findings</strong></td>
<td>Prolonged ongoing (&gt;20 minutes) rest pain</td>
<td>• Resolved but prolonged (&gt;20 minutes) rest angina with moderate or high likelihood of CAD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rest angina (&lt;20 minutes) or relieved with rest or sublingual nitroglycerin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>New-onset or progressive CCS Class III or IV angina in the past 2 weeks without prolonged (&gt;20 minutes) rest pain but with moderate or high likelihood of CAD</td>
<td></td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td>• Angina at rest with transient ST-segment changes &gt;0.05 mV</td>
<td>• T-wave inversions &gt;0.2 mV</td>
<td>Normal or unchanged ECG during an episode of chest discomfort</td>
</tr>
<tr>
<td></td>
<td>• Bundle-branch block, new or presumed new</td>
<td>• Pathological Q waves</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Sustained ventricular tachycardia</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac markers</strong></td>
<td>• Elevated troponin T or I (≥0.1 ng/mL)</td>
<td>Slightly elevated troponin T or I (&lt;0.1 ng/mL)</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**MI = myocardial infarction; CABG = coronary artery bypass graft; CAD = coronary artery disease; ECG = electrocardiogram.**
Many patients with normal or nondiagnostic ECGs will prove to have UA. Serial ECGs or ST-segment monitoring is useful in detecting ischemia with periodic occurrence as the result of spontaneous reperfusion and reocclusion. For patients with clearly diagnostic ST elevation, hyperacute T waves indicate early occlusion. Reperfusion therapy begun while T waves are prominent is associated with improved outcomes. Because patients with STEMI are at high risk for progressive myocardial damage, they require immediate reperfusion therapy (percutaneous coronary intervention or thrombolytic therapy) to open the occluded coronary artery.

NON–ST-ELEVATION MYOCARDIAL INFARCTION AND UNSTABLE ANGINA

Patients who present with primary ST depression should be suspected of experiencing NSTEMI/UA. The NSTEMI/UA characterized by ST depression is typically transient, may be induced by exercise, and usually results from a stable stenosis. ST depression is associated with increased mortality, especially when present in 2 or more ECG leads. Primary ST depression is not an indication for thrombolytic therapy. Patients with primary ST depression benefit from aggressive medical therapy including early percutaneous coronary intervention.6

In the presence of other ACS symptoms, abnormally inverted T waves indicate the presence of ischemia. Inverted T waves are typically transient and indicate UA in the absence of ST deviation. Sustained or evolving T waves usually indicate spontaneous coronary reperfusion. However, they may indicate prolonged occlusion if accompanied by QS waves. In the absence of ST elevation, T-wave inversions represent NSTEMI/UA and are not an indication for thrombolytic therapy.

Generally, pathologic Q waves are wider and deeper than normal Q waves, and their morphology correlates with the volume of affected myocardium. Large Q waves are commonly thought to indicate irreversible infarction. However, QR waves appear in a large percentage of patients, and these waves indicate ischemia of the conducting system that can be corrected by reperfusion therapy. Patients with QR waves benefit significantly from thrombolytic therapy. Early thrombolytic therapy in patients with Q waves is associated with the eventual normalization of Q-wave morphology. Reocclusion can be detected by subsequent ST elevation or pseudonormalization of inverted T waves in patients who have been reperfused spontaneously or by intervention.

### Diagnostic Serum Cardiac Markers

Table 3 summarizes the important clinical points for 3 serum cardiac markers that are crucial for distinguishing NSTEMI from UA. Creatine kinase (CK) is an enzyme found in many body organs and striated muscle. CK may be elevated in cardiac as well as noncardiac conditions; therefore, it is sensitive or specific for detecting myocardial injury. The more cardiac-specific CK isoenzyme CK-MB replaced CK testing, but because CK-MB is also found in skeletal muscle and the blood of healthy patients, it also lacks sensitivity for detecting cardiac necrosis. CK-MB is helpful in the early diagnosis of AMI because CK-MB is typically detectable in the blood earlier than other cardiac markers. Although CK-MB isoenzyme assays are not yet widely available, 1 large study suggested that CK-MB isoenzyme analysis has sensitivity and specificity of approximately 95% six hours after symptom onset.

The isoforms of cardiac troponins, troponin T and troponin I, are specific to cardiac muscle. Therefore,
they are the most reliable indicators of cardiac damage.\textsuperscript{14} Because of their high sensitivity and specificity for even small amounts of myocardial injury, the ACC and the European Society of Cardiology now recommend the use of cardiac troponins as the preferred biomarker for diagnosing MI.\textsuperscript{2} The level of serum troponins correlates with the risk of death and subsequent cardiac events. Patients with high troponin levels will require the most urgent intervention, whereas patients with low troponin levels may be monitored as outpatients.\textsuperscript{15,16} Troponins are also useful indicators of recent AMI because they remain elevated in the blood for 2 weeks after symptom onset.\textsuperscript{2} The low–molecular-weight protein, myoglobin, is useful for ruling out myocardial infarction. Myoglobin, which can be detected in the blood in 2 hours following symptoms, has low specificity but high sensitivity for cardiac damage.\textsuperscript{2} Sensitivity approaches 95\% if myoglobin levels are followed and remain elevated for 6 hours after symptom onset.\textsuperscript{17}

Elevated levels of other biochemical markers, such as highly sensitive C-reactive protein (hs-CRP) and fibrinogen, have been observed in patients with ischemic chest pain.\textsuperscript{18} Although data supporting the routine measurement of these markers are unavailable, they may provide supportive diagnostic information. Elevated fibrinogen, for example, indicates coagulation cascade activity and is associated with increased risk for poor outcomes in patients with ACS.\textsuperscript{2} Similarly, elevated hs-CRP is associated with increased risk of poor outcomes in patients with ACS.\textsuperscript{2} Further research is needed to determine whether these markers will have utility in risk stratification algorithms.

**RISK STRATIFICATION AND TREATMENT IMPLICATIONS**

Patient history, physical examination, and laboratory assessment are key for detecting the presence of cardiovascular disease risk factors. The degree of cardiovascular risk attributable to these risk factors is proportional to their severity and duration. Because the incidence of cardiac events increases with age, is higher in men than in women (and affects men at an earlier age), and is higher in people with a family history of heart disease, the AHA has identified age, male sex, and heredity as the major nonmodifiable cardiovascular risk factors. Similarly, the AHA has identified smoking, high cholesterol, hypertension, physical inactivity, excess body fat, and diabetes as the major modifiable risk factors for coronary disease.\textsuperscript{19} The presence of traditional risk factors should be taken into account when determining the prognosis of patients who present with ACS.

The estimation of risk level for patients with ACS depends on multiple variables and cannot be reduced to a simple algorithm. Nevertheless, an assessment of prognosis often determines the pace of initial evaluation and treatment strategies. There is a strong relationship between ischemia caused by CAD and poor prognosis. Therefore, determining the likelihood of CAD will aid in estimating prognosis, in addition to selecting the site of care and initial therapy.\textsuperscript{2} As a clinical presentation, NSTEMI/UA shares characteristics with lower and higher risk conditions, such as severe chronic stable angina and STEMI. Given these overlapping characteristics, the risk of death for patients with cardiac symptoms has been shown to be highest upon initial presentation and to decrease afterward.\textsuperscript{20} Studies have also shown an increase in the risk of non-fatal cardiac events in patients with NSTEMI/UA upon initial presentation.\textsuperscript{21}

The clinical features associated with increased risk of death in the ESSENCE trial were age >65, markers for myocardial necrosis on admission, lower body weight, severity of pre-existing angina, presence of rales, and presence of ST depression.\textsuperscript{22} The PURSUIT trial also showed that lower blood pressure, in addition to tachycardia or bradycardia, were associated with increased risk of death or MI.\textsuperscript{21} These results have

<table>
<thead>
<tr>
<th>Table 4. TIMI Risk Score for NSTEMI/UA</th>
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<tr>
<td><strong>Factor</strong></td>
</tr>
<tr>
<td>Age &gt;65</td>
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<tr>
<td>≥3 CAD risk factors</td>
</tr>
<tr>
<td>Prior coronary stenosis ≥50%</td>
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<tr>
<td>ST deviation at presentation</td>
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<tr>
<td>≥2 anginal events in past 24 hours</td>
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<tr>
<td>Aspirin use in prior 7 days</td>
</tr>
<tr>
<td>Elevated serum cardiac markers</td>
</tr>
<tr>
<td><strong>Total of 7</strong></td>
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</tbody>
</table>

TIMI = Thrombolysis in Myocardial Infarction; NSTEMI/UA = non-ST-segment elevation myocardial infarction/unstable angina; CAD = coronary artery disease.

Adapted with permission from Antman et al. *JAMA*. 2000;284(7):835-842.\textsuperscript{23}
promising clinical value because they will help clinicians stratify patients upon presentation according to their immediate risk of a poor outcome.2

The Thrombolysis in Myocardial Infarction (TIMI) risk score is a validated, arithmetic tool to predict a patient’s risk of death and cardiac ischemic events when they present with NSTEMI/UA.2 The TIMI risk score is calculated from the sum of variables that are easily attained during the initial evaluation (Table 4). For simplicity, each of 7 variables is assigned 1 point. Therefore, the minimum score is 0 and the maximum score is 7. Using the TIMI score system, Antman et al showed that as the TIMI score increased in the study population, the risk of death, MI, or recurrent ischemia requiring urgent revascularization increased significantly (Figure 1).23 Patients with the lowest number of factors upon presentation were at nearly 5% risk for reaching the composite endpoint, whereas patients with the highest number of factors upon presentation were at nearly 41% risk for the endpoint. The TIMI risk score can guide clinicians as they plan further evaluations and treatment by providing a reliable prognostic assessment for individual patients. Patients at progressively higher risk have been shown to benefit from newer therapies, such as low–molecular-weight heparin or glycoprotein IIb/IIIa inhibitors, in addition to an early invasive strategy, such as percutaneous coronary intervention or revascularization.24-26 Therefore, the TIMI risk score may be useful in identifying patients who would benefit from these newer therapies.7

The ACC/AHA recommendations for early risk stratification include the following assessments:

• In patients with chest pain, determine the risk of acute ischemia caused by CAD and rank likelihood as high, medium, or low (Table 1).
• In patients with chest discomfort, perform early risk stratification, focusing on anginal symptoms, physical findings, ECG findings, and biomarkers of cardiac injury (Table 2).
• In patients with ongoing chest discomfort, obtain a 12-lead ECG within 10 minutes of presentation (Table 2).
• In patients with a history of chest discomfort whose discomfort has resolved before evaluation, obtain a 12-lead ECG as rapidly as possible (Table 2).
• In patients with chest discomfort, measure biomarkers of cardiac injury. Cardiac-specific troponins or CK-MB by mass assay should be measured. If these tests are negative within 6 hours of symptom onset, the patient should be retested 6 to 12 hours after onset (Table 2).

IMMEDIATE MANAGEMENT FOLLOWING RISK STRATIFICATION

Patients who present without chest pain, have stable or normal ECGs, stable hemodynamics, and negative cardiac marker measurements represent a diagnostic challenge. However, determining their risk for ACS and performing a thorough clinical evaluation will be useful in confirming or denying the presence of ACS. These results will allow patients to be assigned to 1 of 4 treatment categories that will determine the immediate management strategy. These categories include noncardiac diagnosis, chronic stable angina, possible ACS, and definite ACS. The appropriate management strategy for each category (as outlined in the ACC/AHA guidelines) is detailed below and illustrated in Figure 2.

Noncardiac Diagnosis
• Patients who do not have CAD should be evaluated for other causes of chest pain, including musculoskeletal causes, peptic ulcers, esophageal spasm, gastritis, cholecystitis, pneumonia, pleurisy, pneumothorax, pericarditis, hyperventilation, or panic disorder.

Chronic Stable Angina
• Patients with suspected or known CAD whose follow-up ECG and cardiac marker measurements are normal should undergo stress testing. High-risk patients should have a stress test in the emergency department or cardiac monitoring unit. Low-risk patients may be tested as outpatients.

Possible Acute Coronary Syndrome
• Patients with possible ACS with normal initial cardiac markers and 12-lead ECG results should be observed in a cardiac monitoring facility. Cardiac marker testing and ECG should be repeated 6 to 12 hours after symptom onset.
• Patients with possible ACS who cannot exercise or have abnormal resting ECG should undergo a pharmacologic stress test.

Definite Acute Coronary Syndrome
• Patients with definite ACS who have normal ini-
tial cardiac markers and 12-lead ECG results should be observed in a cardiac monitoring facility. Cardiac marker testing and ECG should be repeated 6 to 12 hours after symptom onset.

• Patients with definite ACS and persistent chest pain accompanied by any of the following indications should be admitted to the hospital for further management: positive cardiac marker measurements, new ST deviations or deep T-wave inversions on ECG, positive stress test, or abnormal hemodynamics.

• Patients with definite ACS and ST elevation should receive immediate reperfusion therapy if not otherwise contraindicated.

CONCLUSIONS

In patients with chest pain, differentiating between cardiac and noncardiac causes represents a major challenge. Similarly, determining the immediate risk for patients with ACS requires a thorough clinical evaluation. Patients with persistent chest pain, unstable vital signs, and loss of consciousness should be considered at the greatest risk. Similarly, patients with ST elevation on their ECGs are at significant risk of progressive myocardial damage and require urgent revascularization. For patients who do not have ST elevation, other factors such as medical history, physical examination, and cardiac biomarkers are used to help identify those patients at higher risk who are likely to benefit from aggressive therapies. The cardiac troponins T and I are the gold standard for determining the presence and extent of resulting myocardial damage. A risk stratification method that uses easily obtained information, such as the TIMI risk score, can help identify those patients who are at the greatest risk for poor outcomes. Therefore, risk stratification is essential to determining...
an appropriate management strategy and may prove to be a factor in reducing the high rates of mortality associated with ACS.

REFERENCES


