ABSTRACT

Acute coronary syndrome describes a broad range of symptoms caused by myocardial ischemia and is a potentially life-threatening manifestation of coronary artery disease. The most recent update to the American College of Cardiology/American Heart Association guidelines for non–ST-elevation myocardial infarction and unstable angina was published in 2007. The update highlights early risk stratification; new indications for pursuing an early invasive strategy; the early use of aspirin, clopidogrel, and lipid-lowering therapy; the use of glycoprotein IIb/IIIa inhibitors; and the use of anticoagulants. Long-term outcomes will depend on medications used after patients leave the hospital, making it imperative for the community pharmacist to play an active role in encouraging adherence to their complex medication regimens.

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ACUTE CORONARY SYNDROME: THE COMMUNITY PHARMACISTS' ROLE IN THE CONTINUUM OF CARE

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Acute coronary syndrome (ACS) is an umbrella term describing a group of symptoms caused by acute myocardial ischemia that results from insufficient blood flow to the heart muscle. Upon presentation, patients with symptoms of ACS are typically classified by the absence or presence of ST-segment elevation on a 12-lead electrocardiogram (ECG), as well as abnormal elevations of certain cardiac enzymes. Based on these criteria, patients are classified into 1 of 3 categories (Figure):

• Unstable angina (UA)
• Non–ST-elevation myocardial infarction (NSTEMI; previously referred to as non–Q-wave myocardial infarction [MI])
• STEMI (previously referred to as Q-wave MI)

EPIDEMIOLOGY

Acute coronary syndromes represent a significant public health burden. According to the American Heart Association (AHA), preliminary estimates indicate that approximately 1.6 million patients were hospitalized for ACS in 2004, including 896 000 patients diagnosed with MI and 669 000 with UA. Approximately 21 000 of these patients were discharged with both diagnoses.1 UA/NSTEMI is the more common diagnosis, with only 30% to 45% of patients with MI diagnosed with acute STEMI.2

On a global scale, MI may be responsible for 40% to 50% of all mortality related to cardiovascular disease.3 Recent data show that 25% of men and 38% of women will die within 1 year of having an initial recognized MI,1 and reported 6-month mortality (including sudden death) among patients with UA ranged from 8% to 13%.4 At age 40 or older, approximately 18% of men and 23% of women will die within 1 year following a first MI. The risk of recurrent MI, stroke, development of heart failure, or sudden death is also substantial in these patients.1 More women than men present with STEMI, whereas more men than women will be diagnosed with NSTEMI. Women with STEMI tend to have a worse outcome than men with...
STEMI. Women appear to have better outcomes with UA, however, no gender differences in outcomes have been observed in NSTEMI.

Persistent ST-segment elevation accompanied by chest pain usually indicates total coronary occlusion, leading to irreversible myocardial damage that requires immediate reperfusion of the affected coronary artery. Approximately 33% of patients with STEMI die within 24 hours of the onset of ischemia, and many of the survivors suffer significant morbidity. Like STEMI, UA and NSTEMI are potentially life-threatening and are major causes of emergency medical care and hospitalization. Among patients with UA or NSTEMI, approximately 15% will die or have a reinfarction within 30 days of diagnosis, and approximately 30% of patients with UA will have an MI within 3 months. Early data from the Can Rapid Risk Stratification of UA Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology (ACC)/AHA Guidelines Registry observed an even higher in-hospital mortality rate (4.5%) compared with less than 2% reported in other ACS trials.

The prevalence of ACS also increases with age. Approximately 83% of patients who die from coronary artery disease were 65 or older. In the Global Use of Strategies to Open Occluded Coronary Arteries IIb study of coronary vascular occlusion, the median age for those with acute STEMI was 63 years, whereas that for patients with NSTEMI was 66 years. Predictions for the year 2020 and beyond suggest that ischemic heart disease will be the leading cause of death and disability worldwide. ACS is likely to remain a leading cause of hospitalization, both as a result of the aging population and also because of a growth in risk factors for coronary heart disease (CHD; eg, diabetes and obesity), and will continue to present a major healthcare challenge in the foreseeable future.

**FINANCIAL BURDEN OF ACS**

Acute coronary syndrome exacts a high toll in terms of direct, treatment-related, and management costs, as well as indirect, social, and economic costs. Direct US costs in 2007 for CHD—most of which consist of ACS, physician, and other professional costs—are estimated at $83.6 billion. These include hospital costs ($48.4 billion), nursing home costs ($11.6 billion), the cost of drugs and other medical durables ($9.2 billion), physicians/other professionals ($12.5 billion), and home healthcare at $1.9 billion bring the estimated total to $75.2 billion. Indirect US costs of CHD for 2006 (because of lost productivity) are estimated to be $68 billion.

**PATHOPHYSIOLOGY**

The myocardial ischemia associated with ACS is most often a result of rupture or erosion of atherosclerotic plaque within the coronary arteries. This disrup-
tion results in exposure of thrombogenic elements within the plaque on which platelets aggregate and a thrombus subsequently forms. This thrombus limits perfusion of blood beyond the disrupted plaque, thus reducing myocardial oxygen supply and causes myocardial ischemia. The extent and duration of coronary artery occlusion by the thrombus is an important determinant of whether a patient develops UA, NSTEMI, or STEMI. In general, more complete thrombotic occlusion results in greater myocardial injury. STEMI is often associated with complete occlusion of the infarct-related coronary artery, resulting in the characteristic ECG changes and release of biomarkers of myocardial injury (eg, troponin) into the blood. UA and NSTEMI are closely related and differ only in whether the myocardial ischemia is severe enough to produce sufficient myocardial damage to release these biomarkers. If no biomarker is detectable in the blood, then the patient with ACS is considered to have UA whereas NSTEMI is associated with elevated biomarkers.

**DIAGNOSIS**

Symptoms of ACS may, but do not always, include chest pain or pressure, referred pain, nausea, vomiting, dyspnea, diaphoresis, and lightheadedness. Some patients may present without chest pain; in 1 study, sudden dyspnea was the sole presenting feature in 4% to 14% of patients with acute MI. Pain may be referred to the arm, the jaw, the neck, the back, or even the abdomen. Pain radiating to the shoulder, left arm, or both arms somewhat increases the likelihood of ACS (Table). Although atypical symptoms do not necessarily rule out ACS, a combination of atypical symptoms improves identification of low-risk patients.

Typically, UA presents as chest pain or equivalent ischemic discomfort with at least 1 of 3 features:

- Pain occurs at rest (or with minimal exertion), usually lasting more than 10 minutes
- Pain is severe and of new onset (ie, within the prior 4–6 weeks)
- Pain occurs with a crescendo pattern (ie, distinctly more severe, prolonged, or frequent than previously)

Unstable angina and NSTEMI often present in a similar manner, and the distinction is often made hours or days later, when the results of cardiac biomarker analysis become available. A diagnosis of NSTEMI is not established until elevated cardiac biomarkers—evidence of myocardial necrosis—are detected in a patient with the clinical features of UA. The 3 important clinical biomarkers crucial for distinguishing NSTEMI from UA include creatine kinase (CK), the more specific isoenzyme CK-MB, and 2 cardiac troponins, troponin T and troponin I. The ACC/AHA guidelines recommend the use of cardiac troponins as the preferred biomarker for confirming a diagnosis of MI. Although the ECG may be completely normal in a patient with myocardial ischemia.

### Table. Potential Features of ACS Based on Clinical Features

<table>
<thead>
<tr>
<th>High Likelihood</th>
<th>Intermediate Likelihood</th>
<th>Low Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td>Chest or left arm pain or discomfort reproducing previously documented angina</td>
<td>Chest or left arm pain or discomfort</td>
</tr>
<tr>
<td><strong>History</strong></td>
<td>Known history of CAD or MI</td>
<td>Patient aged &gt;70 years, male, or diabetes mellitus</td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
<td>Transient mitral regurgitation, hypotension, diaphoresis, or rales</td>
<td>Manifestations of extracardiac vascular disease</td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td>New transient ST-segment deviation or T-wave inversions with symptoms</td>
<td>Q waves; abnormal ST-segment or T waves not documented to be new</td>
</tr>
<tr>
<td><strong>Cardiac biomarkers</strong></td>
<td>Elevated cardiac-specific troponin level or elevated CK-MB isoenzyme levels</td>
<td>Cardiac biomarker levels may or may not be elevated</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome; CAD = coronary artery disease; CK-MB = creatine kinase-MB; ECG = electrocardiogram; MI = myocardial infarction.

Data from Anderson et al.11

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ischemia and evolving infarction, ST-elevation noted on the ECG is consistent with STEMI.22

**Management of ACS**

Several classes of medications may be used in the acute management of ACS or as part of chronic therapy to reduce the amount of myocardial tissue damage and prevent recurrent events. These may include vasodilators, such as nitrates, β blockers to reduce myocardial oxygen demand and to prevent further myocardial damage, antiplatelet agents (aspirin and clopidogrel), antithrombotics, angiotensin-converting enzyme (ACE) inhibitors, and a statin. In cases in which STEMI is present, either percutaneous coronary intervention (PCI) or administration of a thrombolytic agent is indicated. Initial therapy to reduce myocardial damage, antiplatelet agents (aspirin and clopidogrel), angiotensin-converting enzyme (ACE) inhibitors, and a statin. In cases in which STEMI is present, either percutaneous coronary intervention (PCI) or administration of a thrombolytic agent is indicated. Initial therapy to reduce myocardial damage, antiplatelet agents (aspirin and clopidogrel), which work on separate pathways of platelet aggregation. During coronary interventional procedures, a parenteral platelet glycoprotein IIb/IIIa receptor blocking agent may be used. In some situations, loading doses of clopidogrel (300–600 mg) are used to produce a rapid onset of antiplatelet action. In some patients, a coronary artery stent (either bare-metal or drug-eluting) may be placed to keep a coronary artery open. Following stent implantation, a prolonged regimen of clopidogrel combined with aspirin is required to prevent thrombus formation within the stent. Recent observations suggest that clopidogrel (75 mg/day) in combination with aspirin may be necessary for more than 1 year after drug-eluting stent placement. Aspirin should be continued indefinitely after this period but the optimal duration of clopidogrel administration remains uncertain. Using clopidogrel plus aspirin to prevent ACS in patients at high risk has not been shown to be superior to aspirin alone.25

Because thrombosis plays a key role in the pathophysiology of ACS, hospitalized patients are likely to receive agents that block the effects of thrombin (heparin-related products or direct thrombin inhibitors) in addition to antiplatelet therapy. Before the introduction of low molecular weight heparin (LMWH) in the late 1980s, unfractionated heparin (UFH) was the mainstay of antithrombotic therapy, and it is still widely used in the management of ACS. LMWH does not bind as extensively to plasma and other proteins as UFH and thus, has greater bioavailability and a more predictable dose-response effect than UFH.

More recently, another class of antithrombotics—factor Xa inhibitors—have been studied in the setting of ACS. Data from 2 large, randomized trials suggest that the introduction of these novel agents in the acute management of ACS also have clinical advantages and potential cost savings. In patients with UA or NSTE-MI, the anti-Xa inhibitor fondaparinux (at the lower 2.5-mg dose) was similar to enoxaparin (1 mg/kg) in reducing the risk of ischemic events at 9 days, with an observed reduction in major bleeding and improved long-term mortality and morbidity.26 In patients with STEMI, fondaparinux was compared to standard therapy (UFH or placebo) and reduced the risk of death or recurrent heart attack at day 30, with significant reduction as early as day 9.27 In addition to antiplatelet and antithrombotic therapy, other agents, such as statins, β blockers, ACE inhibitors (or angiotensin receptor blockers), and aldosterone antagonists in selected patients, play an important role in reducing mortality and preventing recurrent events. In addition, nonpharmacologic interventions, such as exercise, behavioral changes, and smoking cessation, are additional keys to successful long-term outcomes. Use of an HMG-CoA (statin) may also be important to maintain to reduce the risk of recurrent events.28

**The Role of the Community Pharmacist**

The most recent update to the ACC/AHA guidelines for UA/NSTEMI ACS was published in August 2007, and to the ACC/AHA STEMI-ACS guidelines in 2004.8,11 In these updates, several areas were highlighted, including: (1) earlier risk stratification at multiple time points; (2) new indications for pursuing an early invasive strategy; (3) preference for primary PCI over fibrinolysis in patients with STEMI; (4) the early use of aspirin and clopidogrel; (5) the use of glycoprotein IIb/IIIa inhibitors, especially in patients undergoing PCI or those with high-risk features; (6) initiation of an anticoagulant therapy, such as UFH, enoxaparin, fondaparinux, or bivalirudin (invasive strategy only); and (7) the early use of lipid-lowering therapy.8,11 Therefore, it is likely that patients with ACS and/or resultant MI will return home on a variety of new medications, which may increase the likelihood of nonadherence. At present, lack of adherence to prescribed drug therapy is the most commonly reported cause of treatment failure. In several studies, only approximately 50% of patients receiving long-term treatment adequately adhered to their prescribed regimens regardless of disease state,29,31 which leads to exac-
erbage of disease, increased mortality, and increased health costs estimated at $100 billion per year in the United States.32,33

Poor adherence can result in recurrent ACS, morbidity, and mortality in addition to more diagnostic tests, dosage adjustments, changes in the treatment plan, emergency department visits, or hospitalization, which ultimately results in increased cost of medical care.8 In a 6-month study assessing whether community pharmacists can impact adherence to medication, Fischer et al9 collaborated with participants who were taking multiple medications for chronic medical conditions. Participants received initial drug therapy assessment, plan for drug therapy goals, education, interventions with other healthcare professionals if appropriate, and follow-up care. The participating patients reported receiving more information from pharmacists on all aspects of their medication, and the pharmacists were able to document improvement in compliance and patients’ increased awareness of potential adverse events from their medications. It is also important that community pharmacists ensure the correct continuation of prescribed medications when patients are transitioning from the inpatient or outpatient setting (ie, medication reconciliation). This can avoid additional confusion in the planned medication regimen. Therefore, it is important that the community pharmacist recognize the importance of the patients receiving and adhering to the prescribed drug therapy for the successful treatment of ACS and CHD in order to maximize patient outcomes and their quality of life.

CONCLUSIONS

Acute coronary syndrome is a potentially life-threatening manifestation of coronary artery disease. The most recent updates to the ACC/AHA guidelines for NSTEMI/UA were published in 2007. The new guidelines include treatment/propylaxis recommendations for newer anticoagulants, which may increase the likelihood of the patient’s nonadherence in the outpatient setting. Poor adherence can result in recurrent ACS, as well as increases in morbidity, mortality, and overall costs of medical care. Because community pharmacists play an important role during the patient’s transition from the outpatient to the inpatient setting, it is important that they be familiar with these newer agents and recognize the importance of medication adherence in the successful treatment of ACS and CHD.

REFERENCES


