Acute Coronary Syndrome

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KEY POINTS

- Acute coronary syndrome (ACS) occurs as a spectrum of diseases that includes unstable angina pectoris, non–ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction.
- ACS is classically manifested as chest tightness or pressure with associated dyspnea, nausea, and diaphoresis.
- ACS is diagnosed through a careful history and analysis of the 12-lead electrocardiogram.
- Treatment of the spectrum of ACS involves oxygen, aspirin, beta-blockers, nitrates, and anticoagulants.
- Patients with evidence of myocardial infarction also benefit from clopidogrel and glycoprotein IIb/IIIa receptor inhibitors.
- Patients with ST-segment elevation myocardial infarction require early revascularization therapy with either fibrinolysis or primary percutaneous coronary intervention.
- Immediate complications of ACS include congestive heart failure, cardiogenic shock, and rhythm disturbances, both tachyarrhythmias and bradyarrhythmias.

Epidemiology

Ischemic heart disease occurs as a result of coronary artery disease and does not discriminate on the basis of gender, ethnicity, or race. Ischemic heart disease remains the leading cause of death in the United States and is responsible for more than half a million deaths annually—despite the marked advances over the past 5 decades in prevention as well as diagnosis and treatment of coronary artery disease. Advances include a reduction in smoking rates; improvements in the management of diabetes, hypertension, and hyperlipidemia; use of aspirin and other antiplatelet agents as both primary and secondary prevention; and improvements in the acute management of acute coronary syndrome (ACS). The last factor has evolved significantly, beginning with the advent of cardiac monitoring and the development of external cardiac defibrillators in the 1950s and progressing to widespread use of external cardiac massage and cohorting of patients with ACS within coronary care units in the 1960s. Pharmacologic developments in the management of ACS began with the use of beta-blockers and aspirin and advanced rapidly to include more sophisticated antiplatelet and anticoagulant agents.

The 1980s brought the widespread use of fibrinolytic therapy and ushered in the reperfusion era of therapy for ACS. Also in the 1980s, coronary angiography was first performed in the setting of acute myocardial infarction (MI) and demonstrated occlusion of the infarct-related artery (IRA), and mechanical interventions were subsequently developed to open the artery, beginning with balloon angioplasty and evolving to more sophisticated techniques such as stenting, thrombectomy, and atherectomy. All these advances have led to a significant decline in the overall age-adjusted mortality of patients with ischemic heart disease, primarily because of a diminution in both the incidence and case fatality rate of acute MI.

Nonetheless, the burden of ACS remains significant both from a health care perspective and from an economic perspective. More than 1 million acute MIs occur in the United States annually, and 20% of affected patients die before reaching the hospital, primarily from arrhythmias during the first hours of symptoms. Many survivors of acute MI are left with impaired cardiac function, which adversely affects their ability to perform activities of daily living and their quality of life. Approximately 6 million emergency department (ED) visits in the United States are made annually for the evaluation of chest pain, and as many as one in three of these patients are ultimately found to have ACS. The annual cost of providing care for patients with ACS, both immediately and then later for those who survive, is more than $100 billion. Finally, despite advances in diagnostic techniques, 2% to 5% of patients with acute MI are discharged from the ED because their disease is not identified. These “missed MI” patients represent the highest mean payments for emergency medicine–related medical malpractice claims.

Definitions

Angina pectoris or, simply, angina is defined as transient and episodic discomfort in the chest occurring as a result of myocardial ischemia. Chronic stable angina can be reproduced with a specific level of physical or emotional stress and reliably resolves with rest, relief of the stress, or nitroglycerin therapy. Unstable angina pectoris (UAP) is defined as angina of new onset that occurs at rest or in a crescendo pattern (with longer duration or intensity or with increasingly less exertion). If the angina is occurring at rest, it must be of at least 20 minutes’ duration to be characterized as unstable. Pathophysiologically, UAP is characterized by the presence of unstable coronary atherosclerotic plaque with thrombosis and partial obstruction of the involved coronary artery but without myocardial cell death. In contrast, chronic stable angina is generally related to fixed stable atherosclerotic lesions without rupture or thrombosis. Variant (or Prinzmetal) angina also occurs at rest...
but is due to coronary vasospasm rather than unstable coronary atherosclerotic plaque. It may be manifested as ST-segment elevation on an electrocardiogram (ECG) and mimic ST-segment elevation myocardial infarction (STEMI) but generally responds to nitroglycerin with resolution of the acute ECG abnormalities.

Myocardial infarction is defined as myocardial necrosis. Clinical criteria for the presence of an acute, evolving, or recent MI, which have been laid out jointly by the American College of Cardiology and the European Society of Cardiology, focus on any evidence of myocardial cell death. The exact definition of an acute or evolving MI is a rise above the upper limit of normal and subsequent fall in levels of cardiac biomarkers specific for myocardial necrosis (troponin or the MB fraction of creatine kinase MB [CK-MB]) along with at least one of the following:

• Symptoms consistent with ACS
• ECG evidence of myocardial ischemia, specifically, ST-segment elevation or depression or T-wave inversions
• Development of pathologic Q waves on the ECG
• Percutaneous coronary artery intervention

Myocardial infarction is further classified as STEMI and non–ST-elevation MI (NSTEMI). STEMI is present when the patient has (1) cardiac biomarkers for necrosis as previously defined and (2) new or presumed new ST-segment elevation in two or more contiguous ECG leads. The cutoff point for ST-segment elevation is 0.1 mV. Contiguous leads are defined in the chest leads as V1 through V6 and in the frontal plane as the sequence aVL, I, inverted aVR, II, aVF, and III. Patients who meet the clinical criteria for STEMI and left bundle branch block (LBBB) and are not old or who have ECG evidence of an isolated true posterior MI are also considered, for treatment algorithm purposes, to have STEMI. NSTEMI is present when the patient meets the criteria for MI as previously defined but exhibits no evidence of ST-segment elevation, new LBBB, or ECG evidence of an isolated posterior wall MI.

Acute coronary syndrome is the clinical manifestation of acute myocardial ischemia resulting from the presence of unstable coronary plaque. Accordingly, ACS is represented by the full spectrum of STEMI, NSTEMI, and UAP, which comprise a continuum of similar clinical and pathophysiological features. STEMI and NSTEMI are differentiated by the findings on a 12-lead ECG, whereas UAP is identical to NSTEMI except that the cardiac biomarkers remain normal in the former. Given that a laboratory result is the only distinguishing feature between patients with UAP and those with NSTEMI, patients are treated identically on arrival by the initial health care provider.

### PATHOPHYSIOLOGY

The pathophysiology of acute myocardial ischemia is related to an imbalance between myocardial oxygen supply and demand. Specifically, myocardial ischemia occurs when coronary perfusion is insufficient to meet myocardial oxygen consumption needs. Myocardial oxygen needs depend on the heart rate, afterload conditions, and contractility of the myocardium. Insufficient coronary perfusion is generally due to atherosclerosis involving the coronary arteries. In patients with chronic stable angina, fixed atherosclerotic lesions partially obstruct flow of blood to the myocardium; when demand for oxygen increases (e.g., because of exercise), flow may become insufficient to meet the demand, and myocardial ischemia and anginal symptoms occur.

The pathophysiology of ACS begins when an atherosclerotic plaque within a coronary artery becomes unstable as a result of plaque rupture or hemorrhage into the plaque. The atherosclerotic plaque need not be causing critical stenosis before becoming unstable. Plaque rupture or hemorrhage exposes the lipid-rich core of the plaque and the basement membrane proteins of the blood vessel wall. As part of the resultant inflammatory cascade, platelets adhere to the core of the ruptured plaque and start to release platelet agonists—adenosine diphosphate, thrombin, and epinephrine. These agonists induce platelet activation, which is characterized by the expression of 50,000 to 80,000 glycoprotein (GP) IIb/IIIa receptors on the surface of each platelet. Fibrinogen, freely circulating in the bloodstream, is a bivalent molecule with binding sites on each end that are specific for the GP IIb/IIIa receptor. Fibrinogen thus facilitates platelet aggregation because each strand cross-links two platelets. The resultant platelet-fibrinogen web is further stabilized by thrombin, which is released by activated platelets and by activation of the coagulation cascade. Thrombin cross-links and modifies fibrinogen to the more stable fibrin.

As the platelet-fibrin aggregation grows, it traps red and white blood cells moving through the coronary artery, and a thrombus forms. At the same time, the inflammatory process leads to the release of vasoactive mediators, which may induce vasospasm, further compromising coronary blood flow. If this process leads to complete occlusion of the epicardial coronary artery at the site of plaque rupture, STEMI will result. If the thrombus is partially obstructing coronary blood flow and generating microemboli to smaller coronary arterioles, which in turn may become obstructed or exhibit spasms, NSTEMI (if myocardial cell death has occurred as shown by a rise in cardiac biomarkers) or UAP (if biomarkers remain normal) results.

Much less commonly, ACS may be due to primary vasospasm rather than primary plaque rupture. Generally the result of sympathetic overstimulation by endogenous epinephrine or serotonin, coronary vasospasm may lead to platelet activation and thrombus formation, even in the absence of underlying coronary artery atherosclerosis. Coronary vasospasm is more likely to cause UAP than MI.

### PRESENTING SIGNS AND SYMPTOMS

#### HISTORY

Patients with ACS classically have chest discomfort in the substernal (precordial) area. Typically, this discomfort is described as pain, pressure, or tightness and may begin at rest or during exertion. It may also be located in the left or right anterior portion of the chest and may radiate to the shoulder, neck, jaw, arm, or back. Characteristically, the duration of discomfort ranges from several minutes to an hour. It is rare for the discomfort related to ACS to last only seconds or to persist continuously for hours. Associated symptoms that may be present are dyspnea, nausea, vomiting, diaphoresis, weakness, dizziness, and fatigue.
ATYPICAL PRESENTATIONS

The emergency physician (EP) should beware of atypical manifestations of ACS, which are common and portend a markedly worse clinical outcome. The quality of the chest discomfort cannot be relied on to exclude ACS. Patients with discomfort that is sharp or stabbing in quality or is pleuritic, palpable, or positional in nature make up a significant minority of patients with ACS. Furthermore, any of the associated symptoms listed previously can occur either alone or together without chest discomfort and still represent ACS. Findings of this type (without chest discomfort) are referred to as an anginal equivalent and require the same clinical management as cases manifested more classically. Other atypical manifestations include isolated back, neck, jaw, or arm discomfort; epigastric pain or burning; indigestion; isolated dyspnea; and generalized weakness. Elderly patients are particularly likely to have atypical symptoms, in particular, weakness and altered mentation. Other populations in whom ACS is likely to be manifested atypically are women, nonwhite patients, and diabetic patients. In all these groups ACS is much more likely to be misdiagnosed initially than in the overall population.

PHYSICAL FINDINGS

Physical examination is often unrevealing in patients with ACS because most of the findings are related to complications of ACS. The vital signs should be evaluated carefully and monitored for evidence of arrhythmia, respiratory compromise, and cardiogenic shock. Jugular venous distention, rales, and a third heart sound (S₃) are signs of congestive heart failure complicating ACS. When these signs are coupled with altered mental status and hypotension, cardiogenic shock is likely.

Physical findings can also help suggest an alternative diagnosis. For example, fever and signs of consolidation on lung examination are suggestive of pneumonia rather than ACS, whereas unilateral absence of breath sounds suggests pneumothorax as the most likely diagnosis. Although chest wall tenderness is suggestive of a musculoskeletal etiology, ACS should not be excluded as a diagnosis solely on the basis of chest discomfort that is reproducible on palpation.

DIFFERENTIAL DIAGNOSIS AND MEDICAL DECISION MAKING

The differential diagnosis in patients with ACS includes a host of other diseases that can be manifested as chest pain or dyspnea: stable angina, pericarditis, myocarditis, pulmonary embolism (PE), aortic dissection, pneumonia, pleurisy, pneumothorax, Boerhaave syndrome, esophageal reflux, esophageal spasm, gastritis, biliary colic, pancreatitis, peptic ulcer disease, musculoskeletal pain, and herpes zoster. One of the historical features that tends to favor a diagnosis of ACS is chest pressure or tightness rather than a sharp pain, which is more commonly associated with pericarditis, pleurisy, pneumothorax, PE, and aortic dissection. In addition, the chest discomfort in patients with ACS tends to gradually worsen, unlike the pain associated with PE or aortic dissection, which is generally worst at the onset and then persistently severe. Pain of a pleuritic nature tends to favor PE, pleurisy, or pneumothorax, whereas pain that is worse on palpation tends to suggest a chest wall musculoskeletal cause. Discomfort that is positional in nature tends to favor pericarditis or gastrointestinal causes rather than ACS. However, it is very important to remember that a significant percentage of patients with ACS have pleuritic, positional, or palpable chest pain and that these historical features cannot be used to exclude the diagnosis.

Although the differential diagnosis of chest discomfort is long and includes entities from several different organ systems, some bear special mention because of the risk that they pose to patients. In each patient with chest discomfort, the EP should consider and reasonably exclude aortic dissection, PE, pneumonia, pneumothorax, and Boerhaave syndrome. This does not mean that these diagnoses must be excluded by definitive diagnostic techniques. They may be reasonably excluded on the basis of the history and physical findings, but this thought process should be documented clearly in the medical record.

DIAGNOSTIC TESTING

ELECTROCARDIOGRAM

The 12-lead ECG is the most important diagnostic test for patients with suspected ACS. In addition to providing diagnostic information, the ECG can be used to assess progression of the syndrome and response to therapeutic interventions. In addition, ECG findings determine treatment pathways and assist with disposition decisions. The ECG in patients with suspected ACS should be carefully and systematically analyzed for evidence of ST-segment elevation, ST-segment depression, T-wave inversion, and pathologic Q waves as signs of myocardial ischemia or infarction. Also, the rate, rhythm, and intervals, along with QRS morphology, should be studied for evidence of complications of ACS. Finally, evidence of noncardiac causes of chest pain should be sought on the ECG, in particular, findings suggestive of PE and pericarditis.

It is important to remember that many patients with confirmed ACS have normal or nondiagnostic findings on the ECG. Even in patients with acute MI, the ECG findings can be normal in a small percentage of cases. In addition, the ECG represents only one static point in time, and ACS is a dynamic process. Hence, a single nondiagnostic ECG cannot be relied on to exclude the diagnosis of ACS, and the history elicited from the patient remains more important than findings on the ECG, particularly when they are negative or nondiagnostic. Nonetheless, specific ECG findings of myocardial ischemia or infarction are often present and are very helpful in determining treatment and disposition.

Electrocardiographic Findings in ST-Segment Elevation Myocardial Infarction

The initial ECG abnormality that occurs in patients with epicardial coronary artery occlusion is peaked hyperacute T waves in the distribution supplied by the IRA. T waves become tall and sharply peaked within minutes of occlusion of the IRA (Fig. 55.1, A). Peaked T waves may also be seen in patients with hyperkalemia, pericarditis, early repolarization, and LBBB. In the next several minutes, ST-segment elevation becomes evident on the ECG (see Fig. 55.1, B). To be diagnostic, the ST-segment elevation must be at least 1 mm above the baseline; this is generally considered the TP segment.
Fig. 55.1  A, An initial electrocardiogram (ECG) obtained shortly after the onset of symptoms shows hyperacute peaked T waves in leads V2 through V5, consistent with early anterior transmural injury current. B, A second ECG obtained several minutes later shows hyperacute T waves and ST-segment elevation in the precordial leads along with ST-segment elevation in leads 1 and aVL, consistent with acute anterolateral myocardial infarction secondary to proximal occlusion of the left anterior descending coronary artery.
Most typically, this ST elevation is convex or domed, though less commonly it may be straight or, rarely, concave. Concave ST-segment elevations are more characteristic of other conditions associated with ST-segment elevation (Box 55.1).

In addition to the clinical situation, a factor distinguishing STEMI from other conditions is the dynamic nature of the ST-segment changes with STEMI; serial ECGs commonly show waxing and waning ST-segment elevation. Hours to days later, the ST segments return toward baseline, the T waves invert, and pathologic Q waves develop in areas of the ECG that correspond to the IRA. The location of the ST elevations and other findings on the ECG generally correspond to the anatomic location of the myocardium and the associated IRA. Anterior infarctions exhibit ST elevation in leads V₁ through V₄ (Fig. 55.2). Findings in leads V₁ and V₂ indicate involvement of the septum. MIs with these findings are caused by occlusion of the left anterior descending (LAD) coronary artery. When additional ST elevations are seen in leads V₅, V₆, I, and aVL, the location of the LAD occlusion is probably proximal to the first diagonal branch, which causes an anterolateral infarction (see Fig. 55.1, B). Inferior infarctions are characterized by ST elevations in leads II, III, and aVF (Fig. 55.3, A) and are due most commonly to right coronary artery (RCA) occlusion. Reciprocal ST depressions may be present in leads I and aVL.

Inferior MIs are associated with concomitant right ventricular infarction, which can be evident on right-sided ECG leads, particularly in RV₄ and RV₅ (see Fig. 55.3, B). Inferior MIs are also frequently associated with posterior wall involvement, which is seen on the ECG as ST depressions in leads V₁ through V₃ and, on occasion, early R-wave progression with tall R waves in leads V₁ through V₃ (Fig. 55.4). Isolated posterior MIs, the rarest of transmural MIs, are the most easily misdiagnosed because the 12-lead ECG may show ST depressions in V₁ through V₃ and sometimes V₄ and V₅, often with tall R waves in V₁ through V₃ but without evidence of ST elevations (Fig. 55.5). This situation can be confused with anterior wall ischemia. Clues on the ECG to the diagnosis of isolated posterior wall MI include horizontal (rather than sloping) ST depressions with prominent R waves and tall upright T waves in leads V₁ through V₃. Occasionally, isolated posterior wall MIs are manifested as a nondiagnostic 12-lead ECG (Fig. 55.6, A), with small pathognomonic ST-segment elevations evident only when extended ECG leads are placed inferior to the tip of the left scapula (V₈) and in the left paraspinal line at the same level (V₉) (see Fig. 55.6, B). Posterior wall MIs are the result of occlusion of the posterior descending coronary artery or the posterior left ventricular branch.
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Fig. 55.3  A, A 12-lead electrocardiogram shows ST elevation in leads II, III, and aVF, consistent with acute inferior myocardial infarction (MI). Note the reciprocal ST depressions in leads I and aVL. B, The right-sided precordial leads in a patient with acute inferior ST-segment elevation MI show ST-segment elevation in leads RV₄ and RV₅, consistent with concomitant right ventricular infarction.
Fig. 55.4  A 12-lead electrocardiogram shows ST elevation in leads II, III, and aVF with ST depressions and prominent R waves in V₁ through V₃, consistent with acute inferoposterior myocardial infarction. Note the sinus arrhythmia and premature ventricular beat.

Fig. 55.5  A 12-lead electrocardiogram shows ST depressions in leads V₁ through V₄ with prominent R waves in V₁ and V₂, consistent with isolated acute posterior myocardial infarction. Note that a complete heart block is also present.
Fig. 55.6  A, A 12-lead electrocardiogram (ECG) in a patient with chest pain is notable only for prominent R waves in the precordial leads with early R-wave progression.  B, Extending the ECG to include right-sided and posterior leads demonstrates ST elevations in leads V₆ and V₉, consistent with isolated acute posterior myocardial infarction.
either of which can arise from the RCA (more commonly) or the left circumflex coronary artery.

Lateral wall MIs, characterized by ST-segment elevation in some or all of leads I, aVL, V₅, and V₆, may be associated with anterior MI as previously described or with inferior or posterior MI or may occur in isolation. This is because the lateral wall of the heart is variably supplied with blood by the LAD, the RCA, and the left circumflex artery. Isolated lateral wall MIs are most commonly associated with left circumflex artery occlusion; the ECG may show reciprocal ST depressions in leads II, III, and aVF (Fig. 55.7).

Electrocardiographic Findings in Non–ST-Segment Elevation Acute Coronary Syndrome

In the clinical setting of NSTEMI, the ECG may be normal or unchanged from baseline, although more commonly it will show ST-segment depressions, T-wave abnormalities, or both in the area of the ECG representing the area of ischemia or infarction in the heart (Fig. 55.8). As mentioned, ST-segment depressions in the precordial leads may also represent true posterior wall transmural infarction. In addition, ST depressions may also represent reciprocal changes, with STEMI occurring in another location; this is most commonly seen in the lateral leads in patients with an inferior STEMI or in the inferior leads in patients with a lateral STEMI (see Fig. 55.7). T-wave inversions are nonspecific findings, particularly when seen in isolation (without ST-segment depressions), but they do suggest ACS in the right clinical setting, especially when comparison with previous tracings shows that the findings are new. Note that T waves are normally inverted in leads aVR and V₁ and are variably inverted in leads III, aVF, aVL, and V₂.

One important subgroup of T-wave inversions occurs in the precordial leads. The changes may be symmetric deep T-wave inversions (Fig. 55.9, A) or more subtle biphasic T-wave changes. This pattern, referred to as Wellen syndrome, represents an unstable lesion in the LAD. Without prompt appropriate treatment, this lesion may lead to an anterior STEMI (see Fig. 55.9, B). The differential diagnosis of inverted T waves includes not only ACS but also left ventricular hypertrophy, LBBB, pericarditis, myocarditis, pulmonary embolism, Wolfe-Parkinson-White syndrome, ischemic or hemorrhagic stroke, hypokalemia, and a persistent juvenile pattern. These findings may also be normal variants. Occasionally, patients with chronically inverted T waves are found to have new upright T waves in the setting of chest pain or anginal equivalent. This finding, referred to as pseudonormalization of the T waves, is highly suggestive of ACS.

CARDIAC BIOMARKERS

Numerous cardiac biomarkers become elevated in the setting of myocardial cell death and are thus indicators of MI. The most sensitive and specific of these biomarkers at present are troponins, which are detectable in serum 4 to 10 hours after the onset of MI. Consequently, a single “negative” troponin value cannot be used to exclude MI. In addition to troponins, CK-MB and myoglobins are also useful and widely used. However, none of the cardiac biomarker measurements currently available represent an adequate test for unstable angina (without MI). For a complete discussion of cardiac biomarkers, see Chapter 54.

OTHER TESTS

Cardiac ultrasonography, nuclear imaging, and stress testing can be very important in confirming the diagnosis of ACS.

![Fig. 55.7](image_url) A 12-lead electrocardiogram shows ST-segment elevations in leads I and aVL, consistent with acute lateral wall ST-segment elevation myocardial infarction. Note the reciprocal ST depressions in leads III and aVF.
Fig. 55.8 A 12-lead electrocardiogram shows T-wave inversions in leads V_3 through V_6 and ST-segment depressions with T-wave inversions in leads II, III, and aVF, consistent with non-ST-segment elevation acute coronary syndrome.

Fig. 55.9 A, 12-lead electrocardiogram (ECG) in a woman with resolved chest pain. The deep symmetric precordial T-wave inversions represent Wellen syndrome. B, ECG from the same patient obtained 30 minutes later, now with recurrent chest pain. Note the anterior ST-segment elevation consistent with acute occlusion of the left anterior descending coronary artery.
or in suggesting an alternative cause of the symptoms. Most recently, contrast-enhanced multidetector computed tomography of the coronary arteries has been shown to have a role in the evaluation of patients with chest pain. These tests are discussed in detail in Chapter 56.

Findings on chest radiography are usually normal or unchanged from baseline in patients with ACS. However, the chest film can be useful to assess for other causes of chest pain, including pneumothorax, pneumonia, Boerhaave syndrome, and to a lesser degree, aortic dissection. In addition, chest radiography is valuable when ACS is complicated by congestive heart failure.

## TREATMENT

### PREHOSPITAL MANAGEMENT

Patients who activate the 911 system because of signs and symptoms associated with ACS should be assessed by paramedics, if available. Those exhibiting hemodynamic or respiratory compromise should be transported by an advanced life support unit. All patients should receive the following:

- Cardiac monitoring and, if possible, a prehospital 12-lead ECG
- Supplemental oxygen with pulse oximetry monitoring
- Intravenous access
- Aspirin, administered orally in the absence of known allergy
- Nitroglycerin administered sublingually in the absence of contraindications for ongoing chest pain

The prehospital staff should alert the receiving ED of the transport, and if evidence of STEMI is seen on the 12-lead ECG, this should be communicated to the ED staff specifically. In some communities, identification of STEMI in the prehospital setting will result in transport to a hospital capable of performing percutaneous coronary intervention (PCI), even if not the closest facility. Additionally, in some health care systems, prehospital identification of STEMI will allow immediate activation of cardiac catheterization laboratory personnel.

### HOSPITAL MANAGEMENT

Figures 55.10 and 55.11 present treatment algorithms for STEMI and non–ST-segment acute coronary syndromes.

Treatment of ACS is time sensitive and aimed at improving myocardial tissue oxygen supply; reducing myocardial oxygen demand, protecting ischemic myocardium, restoring coronary blood flow, and preventing reocclusion of the artery. Specific therapy depends on where along the spectrum of disease the individual case lies. Generally, unless contraindicated, all patients receive aspirin, oxygen, beta-blocker therapy, nitrates, and antithrombin therapy. Use of other antiplatelet agents depends in part on the clinical situation, whereas revascularization strategies are used only in patients with STEMI.

### Platelet Inhibitors

Aspirin remains the cornerstone of therapy across the spectrum of ACS. It is highly cost-effective and remains one of a few drugs with a mortality benefit in patients with ACS. In patients with STEMI, aspirin independently reduces mortality by approximately 23%. Aspirin is an antiplatelet agent that irreversibly inactivates platelet cyclooxygenase and also reduces the formation of prostacyclin by endothelial cells. It should be administered in the ED orally (chewed and swallowed) or rectally; the standard dose is 162 to 325 mg. The EP should take care to avoid using enteric-coated preparations in the acute treatment of ACS. The only true contraindication to aspirin in patients with ACS is a history of severe allergic reaction.

Clopidogrel is one of several currently available thienopyridines, a class of drugs that inhibits adenosine diphosphate–mediated platelet aggregation. These drugs are more potent platelet inhibitors than aspirin is. Ticlopidine, another drug in this class, is not generally used because of its slow onset of action and concerns about its adverse effects, which include neutropenia and, rarely, agranulocytosis. Prasugrel, a more potent thienopyridine recently approved for use in patients with ACS, may play an increasing important role in the future, but at present clopidogrel remains the most commonly used drug in this class. Clopidogrel has been shown to improve clinical outcomes in patients with non–ST-segment elevation ACS, particularly in those who undergo PCI. Clinical benefit is demonstrable within 24 hours of dosing, but it has been associated with a small increase in bleeding in those who undergo coronary artery bypass grafting (CABG) within 5 days of discontinuation of clopidogrel. The traditional loading dose of clopidogrel has been 300 mg orally, but 600 mg appears to be equally safe and may be more efficacious. Clopidogrel (300 to 600 mg orally) should be administered to all patients with ACS and documented aspirin allergy, as well as to those in whom a noninterventional approach is planned. Clopidogrel should also be administered to patients with non–ST-segment elevation ACS in whom emergency CABG is deemed unlikely; this may best be determined in consultation with a cardiologist. For patients with STEMI, clopidogrel, 300 mg, is indicated as an adjunct to fibrinolytic therapy. In patients with STEMI who will undergo PCI, it is reasonable to administer clopidogrel, 300 to 600 mg, in the ED, provided that transfer to the catheterization laboratory is not delayed as a result.

GP IIb/IIIa receptor blockers inhibit the final common pathway of platelet aggregation, namely, the cross-linking of two platelets by one strand of fibrinogen, a bivalent molecule with two binding sites specific for the GP IIb/IIIa receptor. As
Fig. 55.10 Assessment and treatment algorithm for ST-segment elevation myocardial infarction (STEMI). ACS, Acute coronary syndrome; ASA, acetylsalicylic acid; AV, atrioventricular; bpm, beats per minute; cath lab, catheterization laboratory; CCU, cardiac care unit; CHF, congestive heart failure; DTB, door-to-balloon time; ECG, electrocardiogram; EP, emergency physician; GP, glycoprotein; HR, heart rate; IV, intravenous/intravenous line; PCI, percutaneous coronary intervention; PO, orally; SBP, systolic blood pressure; UFH, unfractionated heparin.
Fig. 55.11 Assessment and treatment algorithm for non-ST-segment elevation myocardial infarction. ACS, Acute coronary syndrome; ASA, acetylsalicylic acid; CABG, coronary artery bypass grafting; CCU, cardiac care unit; CHF, congestive heart failure; ED, emergency department; ECG, electrocardiogram; GP, glycoprotein; IV, intravenous/intravenous line; LBBB, left bundle branch block; MI, myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UFH, unfractionated heparin; VT, ventricular tachycardia.
already mentioned, activated platelets have 50,000 to 80,000 receptors on their cell surfaces, so in the absence of GP IIb/IIIa inhibitors, a complete platelet-fibrinogen web can develop rapidly. With proper dosing, however, platelet inhibition of greater than 85% can be attained. For this reason, GP IIb/IIIa inhibitors are the most potent platelet inhibitors currently available. Nonetheless, GP IIb/IIIa inhibitors have been shown to provide benefit only to the subgroup of patients with ACS who undergo PCI.

Three GP IIb/IIIa inhibitors are currently available in the United States: abciximab, eptifibatide, and tirofiban. Abciximab, the first agent developed, is a unique chimeric monoclonal antibody to the GP IIb/IIIa receptor. It binds to the receptor by steric hindrance in a noncompetitive fashion and has a long half-life, with antiplatelet effects persisting for 24 hours after discontinuation of infusion. Eptifibatide and tirofiban, referred to as “small-molecule GP IIb/IIIa inhibitors,” are derived from the poisonous venom of two different vipers and bind competitively to the receptor. As a result, both can prevent fibrinogen from initially binding to the GP IIb/IIIa receptor and also displace bound fibrinogen from the receptor. These drugs are cleared renally and have shorter half-lives, with their antiplatelet effects persisting for several hours after discontinuation of infusion.

GP IIb/IIIa inhibitors have been shown to provide benefit to patients with ACS treated by PCI. Some data also show benefit in troponin-positive patients who test positive for troponins, but not in patients who test negative or who are managed medically. Consequently, current recommendations for the use of this class of drugs are as follows:\textsuperscript{13,14}: GP IIb/IIIa inhibitors should be administered, along with aspirin and a heparin preparation, to patients with ACS in whom PCI is planned, even when clopidogrel is also given. However, the best available evidence suggests that no benefit is seen when GP IIb/IIIa inhibitors are administered in the ED versus delayed provisional use in the cardiac catheterization laboratory.\textsuperscript{13,14} Furthermore, delaying this decision to the time of catheterization may reduce the likelihood of medication administration error, as well as the incidence of adverse effects and overall cost. With this in mind, the decision to use these drugs in the ED setting should be made with caution and limited to patients who have a compelling history of ACS, test positive for troponins, have no contraindication to cardiac catheterization, and are expected to have a delay in prompt interventional treatment.

**Beta-Blocking Agents**

Beta-blockers are an important first-line therapy for patients with ACS. These agents act by reducing the effects of catecholamines on the heart—they slow the heart rate, reduce myocardial contractility, and thereby lower myocardial demand for oxygen. They are also potent antiarrhythmic agents and lessen the likelihood of ventricular and atrial tachyarrhythmias. However, they have also been shown, when given intravenously to patients with STEMI, to increase risk for the development of cardiogenic shock, which counterbalances the salutary effects of beta-blockers and results in no overall mortality benefit.\textsuperscript{15} Thus beta-blockers should be administered intravenously with caution in the ED setting to patients with STEMI and specifically withheld, per the most recent American College of Cardiology and American Heart Association guidelines for STEMI, in the following settings:\textsuperscript{16}:

- Age greater than 70 years
- Signs of heart failure or heart block
- Heart rates lower than 60 or greater than 100 beats/min
- Systolic blood pressure less than 120 mm Hg

Oral administration of beta-blockers may be preferable in the ED across the spectrum of ACS, but this remains to be determined in clinical trials. When intravenous use is deemed appropriate, several different agents are available, including metoprolol, atenolol, propranolol, and the ultrashort-acting esmolol. Metoprolol is most commonly used; it is administered in 5-mg increments by slow intravenous “push” up to a total of 15 mg. This can be followed by 25 to 50 mg given orally. Atenolol is the longest acting and thus is not generally the best choice for ED use.

Propranolol is not selective for β\textsubscript{1}-adrenergic receptor blockade but has been used effectively for many years. It can be administered intravenously in 1-mg increments titrated to the desired effect. Esmolol is ultrashort acting and must be administered by intravenous bolus followed by continuous infusion. Its ED utility is generally limited to patients in whom it is strongly suspected that beta-blockers will not be tolerated, such as those with chronic obstructive pulmonary disease or asthma.

**Nitrate Preparations**

Nitrates may be administered in a number of forms to patients with ACS. Most commonly, sublingual tablets containing 0.3 or 0.4 mg of nitrate are given first, followed by intravenous, oral, or transdermal preparations as tolerated and as needed for ongoing symptoms. It is important to remember that although they do reduce symptoms of chest pain, nitrates have not been shown to reduce mortality. Because they may cause hypotension, it is important to administer nitrates judiciously in the ED. In addition, nitrates are contraindicated in the setting of acute right ventricular infarction, hypotension, critical aortic stenosis, and use of phosphodiesterase inhibitor drugs (e.g., sildenafil) within 24 to 48 hours.

**Oxygen**

Supplemental oxygen should be administered to all patients with ACS, even if the initial oxygen saturation value is normal. This step is particularly important in patients treated with nitrates, which cause pulmonary arterial dilation and thereby impair the ability of the lung to autoregulate pulmonary blood flow. Treatment with oxygen reduces the areas of the lungs that are poorly oxygenated, thus giving less opportunity for shunting and resultant hypoxia.

**Anticoagulants**

Anticoagulant (or antithrombin) therapy is indicated for patients with ACS who have no contraindications to its use. These agents are particularly useful in patients with recurrent anginal symptoms, “positive” cardiac biomarker values, or ischemic changes on the ECG. Available agents include unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), fondaparinux, and direct thrombin inhibitors (DTIs). The heparins (UFH and LMWH) work by activating antithrombin III, which in turn inhibits thrombin and factor Xa. LMWH can also directly inhibit factor Xa. Fondaparinux inhibits factor Xa as its principal mechanism of anticoagulation, and DTIs, as their name suggests, act directly on
thrombin. The net result of therapy with all the drugs in this class is to prevent the conversion of fibrinogen to fibrin, thereby avoiding clot propagation. These drugs are contraindicated in patients with active bleeding. In addition, heparin and LMWH are contraindicated in patients with a known history of heparin-induced thrombocytopenia.

UFH has a synergistic salutary effect on ischemic outcomes when combined with aspirin in patients with ACS, particularly those with MI. Several LMWH preparations have shown efficacy in patients with ACS, but only enoxaparin has demonstrated an improvement over UFH. Therefore, enoxaparin is the LMWH of choice for the treatment of ACS. Current guidelines recommend the administration of UFH or enoxaparin to patients with ACS in conjunction with antiplatelet therapy. For non–ST-segment elevation ACS, enoxaparin (1 mg/kg given subcutaneously twice daily) is the preferred agent unless urgent CABG is planned. UFH is dosed as an intravenous bolus of 60 U/kg (maximum, 4000 units), followed by an infusion at 12 U/kg/hr (maximum, 1000 U/hr). UFH use must be monitored by serial prothrombin time determinations; such monitoring is not necessary in patients treated with enoxaparin. Either drug should be discontinued immediately in patients with evidence of bleeding or if thrombocytopenia develops.

Fondaparinux is a relative newcomer to the class of anticoagulant drugs. It is a pentasaccharide molecule that represents the terminal five saccharide moieties of heparin. Principally a factor Xa inhibitor, this agent is administered as a subcutaneous injection, with dose reductions required in patients with renal insufficiency. Fondaparinux already has indications for the treatment of venous thromboembolic disease, and data suggest that it is similar to enoxaparin in terms of safety and efficacy for the treatment of non–ST-segment elevation ACS. Current published guidelines recommend fondaparinux as an acceptable alternative to UFH or enoxaparin in patients with non–ST-segment elevation ACS.

DTIs offer theoretic advantages over heparins in that they do not work through the intermediary antithrombin III to inhibit thrombin. Nevertheless, no convincing data have shown that DTIs provide clinical benefits over UFH or LMWH in ED patients with ACS. Because of this and their high cost, current ED use of the presently available DTIs—argatroban, hirudin, and bivalirudin—should be limited to patients with a history of heparin-induced thrombocytopenia.

Morphine
Morphine sulfate is an opioid analgesic that has fallen out of favor for the treatment of ACS. There is no compelling evidence in favor of its use, and reports suggest that its sedative effects are associated with an increased risk for respiratory compromise and aspiration. In addition, this agent may cause hypotension through arterial and venous dilation. Morphine has a small role in managing pain that is refractory to other antiischemic therapy and in reducing anxiety in patients in whom anxiety is a prominent feature. It may be delivered intravenously in 3- to 5-mg increments.

Angiotensin-Converting Enzyme Inhibitors
Angiotensin-converting enzyme (ACE) inhibitors have a limited role in the treatment of patients with ACS. This class of drugs, which causes afterload reduction, includes captopril, lisinopril, and enalapril. The principal acute adverse effect is hypotension. It is clear that ACE inhibitors are beneficial in the subset of patients with acute or preexisting left ventricular dysfunction. They are also useful as adjunctive therapy for patients with STEMI that is being treated with fibrinolytic therapy. However, no compelling data support the use of ACE inhibitors in the ED, and it is reasonable to defer their administration to the inpatient setting. If they are initiated in the ED, it is preferable to start with a low dose and increase it as tolerated by the blood pressure. Renal function should be monitored during the initial phases of therapy with ACE inhibitors.

Revascularization Therapy
Patients with STEMI who arrive at the ED within 12 to 24 hours of the onset of symptoms require urgent revascularization therapy. It can be accomplished mechanically with primary PCI or pharmacologically with fibrinolytic therapy. Although fibrinolytic therapy remains the most common strategy worldwide, use of primary PCI for STEMI has been growing rapidly in the United States and has been deemed a preferable approach in terms of safety and efficacy. If a primary PCI strategy is chosen, the IRA must be opened within 90 minutes of patient arrival at the health care system to achieve maximal efficacy. This interval includes time spent at the initial hospital if transfer to a PCI-capable facility is necessary. If the “door-to-balloon” target time of 90 minutes cannot be routinely achieved, a fibrinolytic strategy is preferable, particularly for patients who are seen early (within 3 hours of symptom onset).

For patients in cardiogenic shock or those with contraindications to fibrinolytic therapy, primary PCI should be performed as soon as possible. In addition, patients in whom fibrinolytic therapy fails, as evidenced by ongoing anginal symptoms and ST-segment elevations continuing an hour or more after therapy, should be referred for rescue PCI, which should be performed as soon as possible. Patients with STEMI who undergo primary PCI should also receive aspirin, clopidogrel, and UFH. It is reasonable to administer a GP IIb/IIIa inhibitor to these patients as well, and abciximab is the preferred agent in this setting. However, current evidence suggests that this decision can be safely deferred to the time of catheterization and PCI, which may allow the drug to be given more safely.

It is important to emphasize that none of these adjunctive therapies should delay transfer of the patient from the ED to the cardiac catheterization laboratory, which is the first priority. A number of validated strategies should be used to decrease door-to-balloon time. Those that specifically affect the ED are (1) empowering the EP to activate the entire cardiac catheterization laboratory team with a single phone call; (2) increasing, when possible, the capacity to obtain prehospital ECG tracings in patients with chest pain and activation of the catheterization laboratory team while the patient is still en route to the hospital; and (3) providing prompt feedback from a multidisciplinary quality improvement team to all clinical providers involved in care of the patient.

Fibrinolytic therapy remains an important treatment option for patients with STEMI, particularly those who go to community hospitals that do not have the capability of performing PCI. Rapid initiation of treatment is the standard of care, with a target goal “door-to-needle” time of less than 30 minutes. Fibrinolytic therapy is indicated for patients who have
Acute Coronary Syndrome

Several fibrinolytic agents are available. They include streptokinase, which is not fibrin specific and is administered as an intravenous infusion of 1.5 million units delivered over a 1-hour period, and tissue plasminogen activator (t-PA), which is fibrin specific and administered as a bolus followed by two separate weight-adjusted infusions. Considerable data suggest that the bolus-administered fibrinolytic agents reteplase (recombinant plasminogen activator [r-PA]) and tenecteplase are safer and easier to use than the infused fibrinolytic drugs and have equivalent clinical efficacy; cost are similar to that for t-PA. Both these newer agents are highly fibrin specific, and bolus administration lends itself to prehospital use if that is a consideration. r-PA is administered as a double bolus of 10 units intravenously at time 0 and again at 30 minutes; weight adjusting is not necessary. Tenecteplase is administered in a weight-tiered fashion as a single bolus of 30 to 50 mg based on known or estimated patient weight.

All patients with STEMI treated with fibrinolytic therapy should also receive aspirin and clopidogrel. Beta-blockers should be given with caution and perhaps should be limited in the ED setting to oral use in appropriate patients as discussed earlier. If a fibrin-specific agent is administered, UFH should be given in a bolus dose of 60 U/kg (maximum, 4000 units) and as an infusion of 12 U/kg/hr (maximum, 1000 U/hr). Enoxaparin can be safely and effectively substituted for UFH in patients with normal renal function who are younger than 75 years. If streptokinase is administered, either heparin preparation should be withheld.

Combination pharmacologic treatment of STEMI has attracted considerable interest. The most promising combination has been half-dose fibrinolytic therapy coupled with a GP IIb/IIIa inhibitor, which has been demonstrated to provide better angiographic outcomes in the IRA at 90 minutes. However, large-scale clinical trials have failed to show a mortality benefit of this combination, although they have suggested that it achieves reductions in the risk for recurrent MI and the need for rescue angioplasty. At present, combination therapy, because it is more expensive and cumbersome to administer, should be considered for use only in facilities whose remote locations make transfer of a patient for rescue PCI very difficult.
All patients with ACS should be admitted to a hospital bed equipped with cardiac monitoring. In some institutions, patients with negative initial troponin test values and nondiagnostic ECG findings who are deemed to be at low risk for ACS may be admitted to ED- or cardiology-based chest pain observation units, where the remainder of the diagnostic and therapeutic evaluation may take place. In most hospitals, however, patients with suspected ACS are admitted as inpatients and generally to a cardiac intensive care unit. Cardiac consultation is indicated. Patients with STEMI who are managed with primary PCI go directly from the ED to the cardiac catheterization laboratory and thereafter to a cardiac intensive care unit.

Complications of ACS that are manifested acutely include congestive heart failure or cardiogenic shock (because of a large infarction or acute valvular incompetence) and rhythm disturbances (ventricular fibrillation, atrial fibrillation, and atrioventricular nodal block, among others). In patients with STEMI, particularly those with delayed revascularization and those who are revascularized with fibrinolytic therapy, myocardial rupture of the infarcted portion of the left ventricle can occur, generally in the period 1 to 5 days after infarction, and result in an acute ventricular septal defect with flash pulmonary edema or free wall rupture with tamponade. The most important longer-term complication is chronic congestive heart failure, development of which is dependent on several things, including the extent of the index MI and the speed and success of revascularization, as well as the degree of underlying heart disease and preexisting left ventricular dysfunction, ischemic in origin or otherwise. Ventricular tachyarrhythmia may also be a long-term complication of patients with ACS.
REFERENCES


