Acute coronary syndrome (ACS) is a broad term encompassing a spectrum of acute myocardial ischemia and injury ranging from unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI) to ST-segment elevation myocardial infarction (STEMI). ACS accounts for approximately 1.2 million hospital admissions in the United States annually. The aging of the United States population, along with the national obesity epidemic and the associated increase in metabolic syndrome, means that the number of individuals at risk for ACS will continue to increase for the foreseeable future. This article reviews the current evidence and guidelines for the treatment of patients along the continuum of ACS.

DEFINITIONS

ACS is a syndrome defined by the presence of symptoms, electrocardiographic (ECG) changes, and/or biochemical markers consistent with myocardial ischemia or injury. Typical symptoms include chest pain or pressure, but ACS can also manifest with symptoms such as shortness of breath, nausea, or malaise. ECG changes run the gamut from ST-segment elevations to subtle ST-segment depressions or T-wave inversions. Dynamic ECG changes—those that change or evolve over time—raise particular concern for ACS. In the context of ischemic symptoms, biochemical evidence of myocardial necrosis defines acute myocardial infarction (MI), and the greater the elevation in cardiac biomarkers, the higher the risk of serious morbidity and mortality.

Primary ACS refers to a syndrome of acute myocardial ischemia initiated at the level of the coronary artery itself. The most common form of primary ACS is triggered by...
rupture of an atherosclerotic plaque, leading to intraluminal thrombus formation, and either complete or partial occlusion of a coronary artery. The process of coronary thrombus formation is complex. Activation of the coagulation cascade culminates in the production of fibrin, which catalyzes the polymerization of fibrinogen into a fibrin mesh. Platelets adhere and become activated via several receptor-mediated pathways (including the thrombin receptor). Activated platelets express fibrinogen receptors, allowing the aggregation of platelets into the thrombus via fibrin cross-links. Downstream myocardial ischemia and/or injury results directly from the thrombus occluding the coronary blood flow and/or from distal embolization of microthrombi. Less common forms of primary ACS include coronary artery spasm, coronary artery dissection, and coronary artery thromboembolism.

Secondary ACS refers to pathophysiology external to the coronary arteries that precipitates signs and symptoms of coronary ischemia or injury. Any condition that limits myocardial oxygen delivery—profound anemia, hypotension, or hypoxemia, for example—can produce a clinical picture indistinguishable from primary ACS, even in patients with normal coronary anatomy. Just as “supply-side” conditions can precipitate ACS, “demand-side” conditions such as uncontrolled hypertension or tachycardia can create myocardial energy imbalance and lead to ischemia or injury. It may actually be the case that secondary ACS is actually more common than primary ACS, particularly in patients who have underlying coronary artery disease. However, unlike primary ACS, for which management is focused on the coronary thrombus, the approach to secondary ACS is on balancing the supply-demand mismatch by treating the inciting condition, whether it be sepsis, hypovolemia, hypertensive crisis, or tachyarrhythmia.

ST-segment elevation MI (STEMI) is a diagnosis made solely via ECG (Box 1). Based on 2007 estimates, STEMI accounts for approximately one-third of all acute MIs. STEMI criteria identifies a subset of ACS patients that benefit from rapid coronary reperfusion therapy. As such, any patient presenting to the emergency department (ED) with symptoms concerning for STEMI should have an ECG done within 10 minutes of arrival. However, in considering the diagnosis of STEMI, it is also important to note that there are other conditions that may cause ST elevations on an ECG (Table 1).

It has been well established that early reperfusion of the infarct-related artery is associated with improved outcome in STEMI. Delay to reperfusion is associated with

<table>
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<th>Box 1 criteria</th>
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| **American College of Cardiology/American Heart Association ST-Segment Elevation Myocardial Infarction (STEMI) Diagnosis Guidelines**
| In a patient presenting with active chest pain, a 12-lead electrocardiogram showing: |
| 1. ST-segment elevation ≥1 mm (0.1 mV) in 2 or more adjacent limb leads (from aVL to III, including aVR) |
| 2. ST-segment elevation ≥1 mm (0.1 mV) in precordial leads V4 through V6 |
| 3. ST-segment elevation ≥2 mm (0.2 mV) in precordial leads V1 through V3 |
| 4. New left bundle-branch block |
| Therapy should not be delayed while awaiting results or cardiac biomarkers. Reciprocal depressions (ST depressions in the leads corresponding to the opposite side of the heart) make the diagnosis of STEMI more specific. |
a corresponding increase in STEMI-related mortality. The American Heart Association/
American College of Cardiology (AHA/ACC) recommendations establish the standard
of care in this regard: ED arrival to fibrinolysis ("door-to-needle" time) within 30 minutes;
and an ED arrival to percutaneous coronary intervention (PCI) ("door-to-balloon" time)
within 90 minutes.\(^1\)

Non–ST-segment elevation acute coronary syndrome (NSTE-ACS) is a term used to
denote ACS not meeting ECG criteria for STEMI. It includes non–ST elevation MI
(NSTEMI) and UA. If biomarkers for myonecrosis are positive, the diagnosis of NSTEMI
can be made. If not, the clinical syndrome is termed UA. From a clinical standpoint,
without a series of cardiac biomarkers for myocardial necrosis (which can take several
hours before becoming positive), a distinction between UA and NSTEMI cannot be
made (Fig. 1).

Other Causes of Myocardial Necrosis

ACS is one of many mechanisms for myocardial cell injury and necrosis, and not all
biomarker elevations represent cardiac ischemia. Myocardial cell death can be seen
in a wide range of conditions, including acute myocarditis, blunt trauma, chronic
cardiomyopathies, drug toxicity, and sepsis.

INITIAL TREATMENT

In some ways, the principles of therapy for all ACSs are fundamentally similar. The
common treatment objectives are to:

1. Balance myocardial supply and demand
2. Limit thrombus formation: antiplatelet and anticoagulant therapies
3. Restore lumen patency: angioplasty, stent placement, and coronary artery bypass
   grafting (CABG).

What distinguishes STEMI from most NSTE-ACS is the urgency and speed with
which myocardial blood flow must be restored to prevent irreversible transmural
damage, hence the emphasis on rapid reperfusion therapy.
Antiplatelet Therapy

All patients with suspected ACS should receive 162 to 325 mg of aspirin as close to the onset of symptoms as possible. Aspirin blocks platelet activation by limiting thromboxane production via the cyclooxygenase pathway. In the absence of reperfusion therapy, aspirin alone provides a near 25% reduction in mortality. Ideally aspirin should be chewed for rapid absorption and effect. If a patient is unable to take medications orally, aspirin can be administered via rectal suppository with an adjusted dose range of 300 to 600 mg. Peak serum levels are reached within 30 minutes with oral dosing and 90 minutes with rectal dosing. For patients with an aspirin allergy, a loading dose of clopidogrel should be given as an alternative. The recommended dose is 300 to 600 mg.

Oxygen

Providing supplemental oxygen is routine practice. However, in patients with normal oxygen saturations, the carrying capacity of their blood hemoglobin and soluble serum oxygen concentration is only minimally affected by increased concentrations of inhaled oxygen. Administering supplemental oxygen is the standard of care for any patient with demonstrated hypoxia, but is considered reasonable in any patient with ACS within the first 6 hours of presentation.
Nitroglycerin

Nitroglycerin (NTG) is considered a reasonable initial therapy for chest pain due to ACS. However, administration of nitrates confers no demonstrated survival benefit with NSTE-ACS,\textsuperscript{13} or with STEMI in the context of current reperfusion intervention.\textsuperscript{14} Patients can be given 0.4 mg sublingual NTG every 5 minutes, or a continuous intravenous infusion of NTG at a dose of 10 to 50 $\mu$g/min. Because of its preload reducing effects, NTG is contraindicated in patients with critical aortic stenosis, and should be used with caution in patients suspected of having right ventricular acute MI. Nitrates are also contraindicated in patients who have used sildenafil within 24 hours (or up to 72 hours with longer-acting phosphodiesterase type 5 inhibitors).

Morphine

Morphine is a reasonable second-line agent for relieving chest pain in patients with ACS in whom nitrates are either contraindicated or fail to eliminate pain.\textsuperscript{1} Retrospective data suggest higher morbidity among NSTE-ACS patients receiving morphine,\textsuperscript{15} but a causal link is far from established.

$\beta$-Blockers

The administration of $\beta$-blockers to STEMI patients has been shown to reduce rates of recurrent ischemia and reinfarction following reperfusion therapy.\textsuperscript{16} However, routine up-front administration of $\beta$-blockers to patients may lead to increased incidence of cardiogenic shock and may outweigh the benefits.\textsuperscript{17} Current guidelines recommend against routine intravenous administration of $\beta$-blocker for acute STEMI.\textsuperscript{18} For NSTE-ACS patients an oral $\beta$-blocker should be started within 24 hours of presentation. In all cases, $\beta$-blockers should be avoided when there are signs of congestive heart failure, evidence of a low cardiac output state, or other relative contraindications to $\beta$-blockade (PR interval $>$0.24 seconds, second- or third-degree heart block, active asthma, or reactive airway disease).

ST-ELEVATION MYOCARDIAL INFARCTION

The imperative to provide reperfusion therapy as early as possible cannot be overstated. It is generally accepted that all else being equal, primary PCI is preferable to fibrinolytic therapy, in terms of both success in establishing reperfusion and minimizing the risk of hemorrhagic complications. In practice, the choice between fibrinolytic therapy and PCI depends largely on the availability of PCI, such that if primary PCI is not available within 90 minutes of patient arrival, fibrinolytic therapy should be considered.\textsuperscript{19} The decision to proceed with fibrinolytic therapy should only occur after consideration of any contraindications (Table 2), and should also take into account the duration of symptoms. Fibrinolysis has been shown to have limited success when initiated beyond 3 hours from symptom onset.\textsuperscript{20,21} If a patient is not at a PCI-capable facility, transfer should be coordinated ideally within the 90 minute door-to-needle time frame (Fig 2).

Once the decision is made to perform PCI, the selection and timing of anticoagulation and antiplatelet adjuncts should be discussed with the receiving interventional cardiologist. For patients receiving fibrinolysis the choices for adjunctive therapy are outlined below.

Facilitated PCI

It has been hypothesized that the early administration of fibrinolytics will “facilitate” the success of eventual PCI. Studies examining the use of full-dose fibrinolytics have
shown greater complications and morbidity.\textsuperscript{22} Partial-dose fibrinolytics with a variety of combinations with high-dose heparin and glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors have shown no improvement in outcomes and in some cases have increased bleeding risk.\textsuperscript{19,23} Current guidelines do not support using full-dose fibrinolytics in STEMI patients. However, in moderate-risk and high-risk patients for whom PCI is the ideal strategy, and transport times are prolonged but PCI can be achieved within 2 hours, using partial-dose fibrinolytics may be considered in discussion with the receiving interventional cardiologist (see Fig. 2).\textsuperscript{19}

If fibrinolysis is planned as primary therapy, the patient must first be screened for risk of the life-threatening hemorrhage (Box 2). The most feared complication of fibrinolytic therapy is intracranial hemorrhage (ICH), which occurs with an incidence of 0.6\% to 1\%,\textsuperscript{24} and a mortality rate of about 50\%.\textsuperscript{25} Risk factors for fibrinolytic-associated ICH include advanced age and uncontrolled hypertension.

| Table 2 | Efficacy and risk of common fibrinolytic agents |
|---|---|---|---|
| | Alteplase (tPA or Activase) | Tenecteplase (TNKase) | Retepase (Retavase) |
| Reperfusion rate by 90 minutes | 79 | 80 | 80 |
| Lives saved per 100 persons treated | 3.5 | 3.5 | 3.0 |
| Risk of intracranial hemorrhage | 0.6\% | 0.5–0.7\% | 0.8\% |

Data from Refs.\textsuperscript{27–30}

![Fig. 2. Choosing between fibrinolytic therapy and percutaneous coronary intervention (PCI) for STEMI patients.](image-url)
Four fibrinolytic agents have been approved by the Food and Drug Administration for the treatment of STEMI. Selection of one agent over another generally occurs at an institutional level. Streptokinase, the first fibrinolytic, is no longer available in many institutions because of the risk of antibody formation and an immune reaction with exposure or reexposure to the drug. A comparison of the characteristics of various agents is shown in Table 2.

Follow-Up PCI

Routine PCI immediately following fibrinolytic administration has not been shown to improve outcomes. However, coronary perfusion following fibrinolytic therapy may be inadequate in up to one-third of cases, as evidenced by persistent ischemic
symptoms, failure to see ST-segment resolution, hemodynamic instability, or refractory electrical arrhythmias, and there is proven benefit to intervention with PCI in such cases. Current guidelines recommend an observation period of about 90 minutes, at which point rescue PCI should be considered. Emerging data suggest that routine transfer to a PCI center following fibrinolytic therapy may make sense, so as to facilitate rescue PCI if and when required.

**Thienopyridines**
This class of antiplatelet agents includes clopidogrel and prasugrel, along with the newly approved ticagrelor. These medications inhibit platelet activation by blocking the adenosine diphosphate receptor. Only ticagrelor binds reversibly, but experience with this drug in the ED is limited. Clopidogrel is the best studied drug in this class and the only one currently approved for administration with fibrinolytic, but it requires the longest time to reach maximal effect. To offset this, loading doses exceeding the usual 300 mg may be given, but caution should be exercised in elderly patients receiving fibrinolytic therapy. Alternatively, for patients undergoing PCI prasugrel may be administered with a loading dose of 60 mg, but patients with a prior history of cerebrovascular disease should not receive prasugrel because of a higher incidence of stroke.

**GPIIb/IIIa Inhibitors**
This class of intravenous antiplatelet agents, which includes abciximab, eptifibatide, and tirofiban, binds to the fibrinogen receptor to block platelet aggregation. Administration of a GPIIb/IIIa inhibitor at or around the time of primary PCI is standard practice; however, up-front use of GPIIb/IIIa inhibitors before transfer to the catheterization laboratory has not been shown to improve outcomes. For patients in whom a fibrinolytic strategy is selected, there is no demonstrated role for GPIIb/IIIa inhibitors in the ED.

**Anticoagulants**
For patients in whom a primary PCI strategy is chosen, reasonable choices for adjunct anticoagulation therapy include unfractionated heparin (UFH), enoxaparin, or bivalirudin. Unfractionated heparin is still the most widely used, and dosing should be weight based. Bivalirudin is an attractive option for PCI because as a more powerful anticoagulant it can obviate the need for GPIIb/IIIa inhibitors and thereby minimize the risk of bleeding. For patients receiving fibrinolytic therapy, UFH and enoxaparin are both reasonable choices. If enoxaparin is chosen, an intravenous loading dose of 60 mg should be administered along with the first subcutaneous dose to patients younger than 75 years. Fondaparinux is an attractive option for patients receiving fibrinolytic therapy who are at high risk of bleeding. Bivalirudin has not been studied as an adjunct to fibrinolytic therapy. For a summary of some of the advantages and disadvantages of various anticoagulants, see [Table 3](#).

**NON–ST-SEGMENT ELEVATION ACS**
For all NSTE-ACS patients, treatment focuses on the stabilization of a partially occlusive thrombus to minimize downstream ischemia and injury, as well as reduce the risk of progression to STEMI. Fibrinolytic therapy has no role, but PCI is increasingly used to prevent recurrent ischemia. In moderate-risk to high-risk cases, early PCI (ie, within 24–72 hours) is associated with improved 30-day outcomes. The precise timing of PCI in NSTE-ACS is dependent, among other things, on the presence of ongoing ischemia and the risk for recurrent ischemia or other cardiovascular morbidity. Risk scores such
<table>
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<th>Anticoagulant</th>
<th>Pros</th>
<th>Cons</th>
<th>Comparative Bleeding Risk</th>
<th>Expense</th>
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| Heparin (UFH)       | Immediate anticoagulation  
Easy to monitor  
Long clinical use history  
Easy to stop by discontinuing the infusion | Does not inhibit bound thrombin  
(only free thrombin)  
Variable anticoagulation effects  
requiring monitoring | PTT dependent | $ |
| Enoxaparin (LMWH)   | More effective thrombin inhibition than UFH  
Monitoring is not necessary  
Lower risk of HIT than UFH  
Long history of clinical use  
Does not cross the placenta | Does not inhibit bound thrombin  
(only free thrombin)  
Less reversible than UFH and bivalirudin  
Difficult to monitor  
Renally cleared  
Long half-life  
Risk of HIT | Highest | $$ |
| Fondaparinux        | Subcutaneous delivery  
Once-daily dosing  
Monitoring is not necessary  
No risk of HIT  
Does not cross the placenta | Most difficult to monitor  
Long half-life | Lower | $$$ |
| Bivalirudin         | Reduced risk of bleeding  
No risk of HIT  
Immediate anticoagulation  
Easy to stop by discontinuing the infusion | Limited clinical use history  
Not widely available | Lowest | $$$$ |

Abbreviations: HIT, heparin-induced thrombocytopenia; LMWH, low molecular weight heparin; PTT, partial thromboplastin time; UFH, unfractionated heparin. Data from Refs. 31–33
as TIMI (Thrombolysis in Myocardial Infarction) and GRACE (Global Registry of Acute Coronary Events) have been developed to predict short-term outcomes and define the population of patients most likely to benefit for earlier and more aggressive therapy. Correspondingly, the choice and timing of adjunctive antiplatelet and anticoagulant medications has a lot to do with whether and when PCI is being contemplated. Patients at highest risk include those with refractory anginal pain, evolving ECG changes, and rising biomarkers, as well as any patient with hemodynamic or electrical instability. In such cases urgent PCI is advisable, and the choice and timing of adjunctive antiplatelet and anticoagulant therapies are similar to the case of STEMI with primary PCI.

For patients who are stable but have a moderate to high risk score, PCI is generally planned within 24 to 48 hours of admission. Routine up-front administration of a GPIIb/IIIa inhibitor is not generally recommended, due to excess bleeding risk. Unless there is a high suspicion that the patient will require urgent CABG, administration of clopidogrel before PCI is reasonable, and either enoxaparin or heparin may be started in the ED. If the patient becomes unexpectedly more unstable, a GPIIb/IIIa inhibitor can be added as plans are made for urgent PCI.

For patients who are deemed to be at low risk and in whom a noninvasive strategy is planned, clopidogrel should still be administered, and enoxaparin is preferred as an anticoagulant. In patients with an increased risk of bleeding, fondaparinux is an acceptable alternative.

SUMMARY

ACS is a diagnosis that is made daily in the ED and includes a spectrum of disease ranging from STEMI to low-risk NSTE-ACS. The diagnosis of ACS depends variably on a combination of clinical symptoms, ECG findings, and cardiac biomarkers. Management of ACS is targeted at restoring and maintaining coronary blood flow and improving myocardial oxygen balance. The intensity of treatment, ranging from fibrinolytic therapy and primary PCI on the one hand to conservative and supportive therapy on the other, is commensurate with the severity of disease and the opportunity to improve short-term morbidity and mortality.

REFERENCES

7. Slater DK, Hlatky MA, Mark DB, et al. Outcomes in suspected acute myocardial infarction with normal or minimally abnormal admission electrocardiographic findings. Am J Cardiol 1987;60(10):766–70.


