Chapter 5: Acute Coronary Syndromes

INTRODUCTION

- *Acute coronary syndrome* (ACS) involves acute myocardial ischemia resulting from imbalance between myocardial oxygen demand and supply. Classification based on electrocardiographic (ECG) changes includes: (1) ST-segment-elevation myocardial infarction (STEMI) or (2) non–ST-segment-elevation ACS (NSTE-ACS), which includes non–ST-segment-elevation MI (NSTEMI) and unstable angina (UA).

PATHOPHYSIOLOGY

- Endothelial dysfunction, inflammation, and formation of fatty streaks contribute to development of atherosclerotic coronary artery plaques. Eventual plaque rupture and subsequent thrombus formation abruptly decreases myocardial blood flow and oxygen supply, leading to ischemia and potentially infarction.
- Atherosclerotic plaques that rupture typically have thin fibrous caps and tend to be nonobstructive, occluding <70% of the luminal diameter; thus, patients may not experience angina prior to plaque rupture due to adequate autoregulation that maintains blood flow and oxygen supply during increased myocardial oxygen demand. Increased catecholamine release during physical or emotional stress may enhance the likelihood of rupture of a thinning fibrous cap.
- Plaque rupture breaches the barrier between the necrotic plaque core and blood components; circulating platelets are attracted and adhere to the area of injury. Platelet adhesion occurs via platelet glycoprotein (GP) VI receptors binding to collagen within the damaged fibrotic cap, as well as platelet GP Ib-IX receptors and von Willebrand factor. Platelets are then activated by collagen, thrombin, thromboxane A_2, adenosine diphosphate (ADP), epinephrine, and serotonin. Binding of these activators to their specific receptors on the platelet surface (eg, $P2Y_{12}$ receptor for ADP, protease-activated receptor [PAR]-1 for thrombin) results in increased platelet surface area and release of further platelet activators from granules within platelets. Assembly of tenase and prothrombinase complexes within activated platelets produces most of the activated factor Xa and IIa (thrombin) in the coagulation cascade. A change in the conformation of the GP IIb/IIIa surface receptors of platelets cross-links platelets to each other through fibrinogen bridges, resulting in platelet aggregation and formation of a platelet plug in the area of plaque rupture.
- Activation of the clotting cascade forms a fibrin meshwork (thrombus) around the platelet plug that traps cellular components such as red blood cells and causes abrupt reduction in myocardial blood flow and oxygen supply. If ischemia is left untreated, myocyte necrosis and cell death may ensue.
- Subtypes of MI are based on etiology: (1) rupture, fissure, or erosion of an atherosclerotic plaque (90% of cases); (2) reduced myocardial oxygen supply or increased demand in the absence of a coronary artery process; (3) MI resulting in death without the possibility of measuring biomarkers; (4) MI associated with percutaneous coronary intervention (PCI; Type 4a) or stent thrombosis (Type 4b); and (5) MI associated with coronary artery bypass graft (CABG) surgery.
- After MI, acute and chronic adaptations occur to prevent hemodynamic collapse but may also lead to ventricular remodeling and post-MI complications. Stimulation of the sympathetic nervous system (SNS) and renin–angiotensin–aldosterone system (RAAS) compensates for decreased cardiac output. However, chronic hyperactivation of these systems can lead to ventricular hypertrophy and further impairment of contractility and cardiac output. Release of inflammatory mediators and collagen deposition contribute to myocardial fibrosis or scarring, which can lead to thinning of the left ventricular (LV) wall and eventual development of dilated cardiomyopathy.
- Complications of MI include ventricular arrhythmias, bradyarrhythmias, heart block, heart failure (HF), cardiogenic shock, LV free-wall or septal rupture, thromboembolism (including stroke secondary to LV thrombus embolization), aneurysm formation, and pericarditis. Many patients with

ACS develop depression during the convalescent period.

CLINICAL PRESENTATION

- The patient is typically in acute distress and may present with or develop hypertensive crisis, acute HF, cardiogenic shock, or cardiac arrest.
- The classic symptom of ACS is abrupt-onset substernal chest pain or discomfort often described as a squeezing, heaviness, or tightness that persists for 10 minutes or longer. Symptoms may radiate to the arms and shoulders (especially on the left side), back, abdomen, or jaw. Nausea, vomiting, diaphoresis, or shortness of breath may also be present.
- Many patients have atypical symptoms without chest pain, such as epigastric pain, indigestion, pleuritic chest pain, and increasing exertional dyspnea. Older adults, women, and patients with diabetes mellitus (DM), impaired renal function, and dementia are more likely to present with atypical features.
- No physical examination findings are specific for ACS. Nonspecific findings include S_4 or paradoxical splitting of S_2 heart sounds on auscultation. Signs of acute decompensated HF include jugular venous distention, pulmonary edema, and an S_3 on auscultation. Patients may also present with arrhythmias, heart block, hypertension (HTN), hypotension, or shock.

DIAGNOSIS

- Obtain 12-lead ECG within 10 minutes of presentation. Changes suggestive of acute ischemia include STE, ST-segment depression, and T-wave inversion. Presence of a new left bundle-branch block (LBBB) in patients with suspected ACS is strongly suggestive of acute MI. Some patients with ACS have no ECG changes, so appropriate evaluation and risk stratification must carefully assess medical history, presenting symptoms, and cardiac biomarkers.
- Cardiac troponin (either T or I) is measured at the time of presentation and repeated 3–6 hours later to detect myocardial injury; elevated blood levels (exceeding the 99th percentile of the upper reference limit) occur within 2–4 hours of myocyte injury or necrosis and may remain elevated as long as 2 weeks. Myocardial injury is considered acute if there is a dynamic rise and/or fall by 20% or more in serial troponin values. Elevated levels in a patient with ACS symptoms, ischemic changes on ECG, or other evidence of ischemia confirm the diagnosis of MI. Additional troponin levels should be obtained beyond 6 hours after symptom onset in patients with intermediate- to high-risk features of ACS but normal troponin levels during serial measurements.
- Elevated dynamic cardiac troponin levels with ST-segment elevation of at least 1 mm in two contiguous leads or new LBBB on the presenting ECG confirms the diagnosis of STEMI. In contrast, the diagnosis of NSTEMI is appropriate for patients with symptoms of ACS and elevated troponin levels without at least 1 mm ST-segment elevation on the ECG at presentation. Patients with symptoms consistent with ACS but in whom troponin is not elevated may have UA or an alternative diagnosis.

TREATMENT

- Goals of Treatment: Short-term goals includes: (1) early restoration of blood flow to the affected artery to prevent infarct expansion (in the case of MI) or prevent complete occlusion and MI (in UA), (2) prevention of death and other complications, (3) prevention of coronary artery reocclusion, and (4) relief of ischemic chest discomfort. Long-term goals include control of cardiovascular (CV) risk factors, prevention of additional CV events, and improvement in quality of life.

General Approach to Treatment of ACS

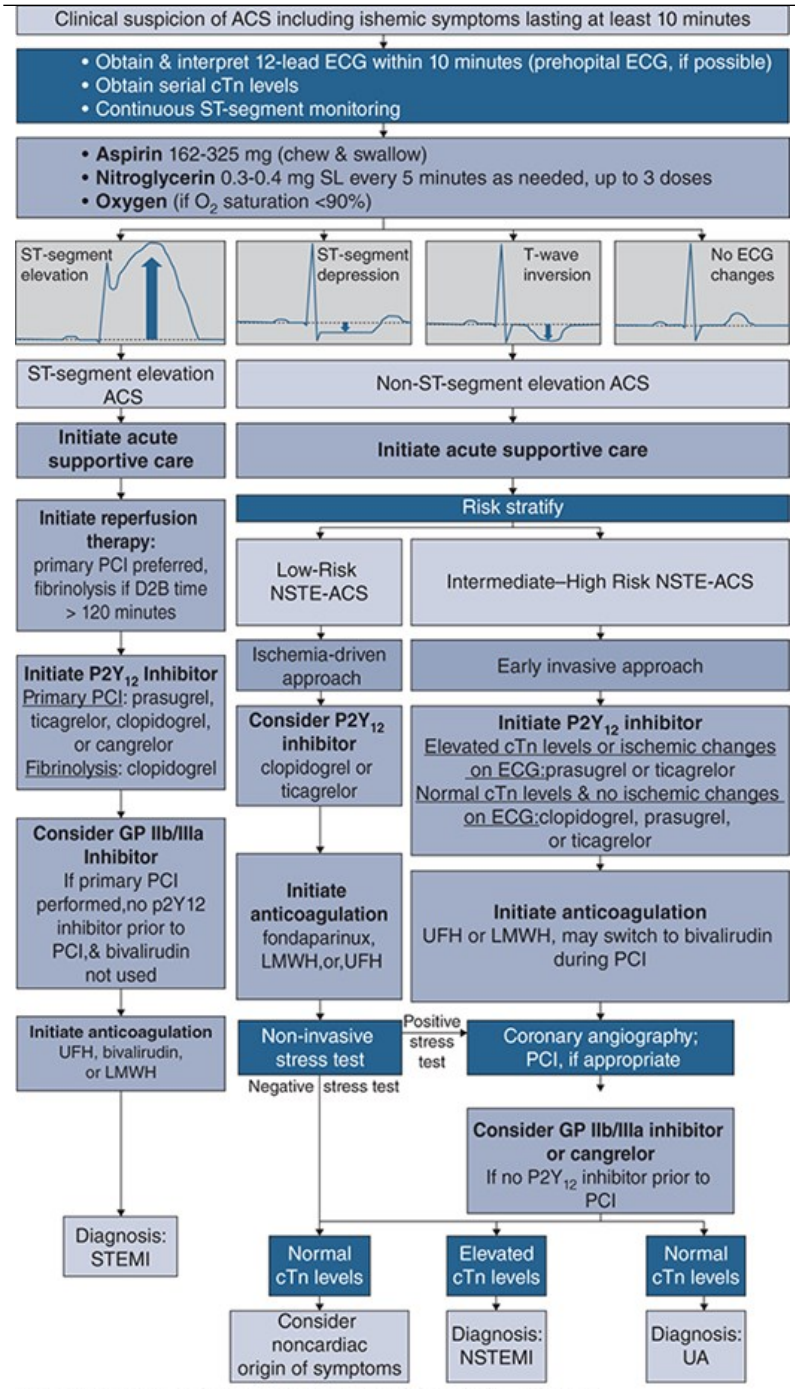
- The clinical presentation, past medical history, ECG, and biomarkers are used to stratify patients as low, medium, or high risk and determine which patients may benefit from reperfusion therapy, an early invasive approach, or medical management. Treatment decisions are based on the initial and ongoing risk stratification (**Fig. 5-1**).
- Because STEMI has the highest short-term risk of death, these patients should be emergently referred for primary PCI; confirmation of elevated

troponin should not delay treatment.

- General measures include hospital admission, oxygen administration if saturation is <90% (0.90) bed rest with continuous multilead ST-segment monitoring for arrhythmias and ischemia, frequent measurement of vital signs, ischemic pain relief, and prompt initiation of antithrombotic therapy.
- Assess kidney function (serum creatinine, creatinine clearance) to identify patients who may need dosing adjustments and those at high risk of morbidity and mortality.
- Measure serum potassium and magnesium levels, which may affect heart rhythm. Obtain complete blood cell count (CBC), fasting lipid panel, and coagulation tests (aPTT or anti-Xa levels, INR) because most patients will receive antithrombotic therapy.

FIGURE 5-1

Evaluation and initial management of patients with suspected ACS.



Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

Acute Supportive Care for ACS

- **Aspirin** is recommended for all ACS patients without contraindications, regardless of the type of ACS or management strategy. The initial dose is 162–325 mg (non-enteric coated) given as soon as possible and chewed and swallowed to speed dissolution and onset of platelet inhibition (<30 minutes). After the initial dose, aspirin 81 mg daily is continued indefinitely. Contraindications to aspirin include hypersensitivity and major GI intolerance. In these cases, clopidogrel with a loading dose followed by a maintenance dose should be used as an alternative.

- **Nitroglycerin** (NTG) is indicated for relief of anginal symptoms, uncontrolled HTN, and acute HF. The sublingual (SL) dose is 0.3–0.4 mg every 5

minutes for up to 3 doses as needed for angina. Consider intravenous (IV) NTG for persistent angina despite SL NTG at an initial dose of 10 mcg/min titrated to symptom relief and desired blood pressure (BP). Continue IV NTG until symptoms have resolved, BP is controlled, and HF symptoms have subsided. Gradually taper the infusion upon discontinuation. Nitrate administration is contraindicated in patients who have recently taken oral phosphodiesterase-5 (PDE-5) inhibitors (eg, sildenafil).

- **Oxygen** administration (2–4 L/min) should be reserved for select patients, particularly those with oxygen saturation <90% (0.90), because data suggest that routine use may adversely affect patients with ACS by increasing coronary vascular resistance and reducing coronary blood flow.
- **Morphine** is an analgesic, anxiolytic, and venodilator that reduces oxygen demand, but its role in ACS is uncertain because some studies have shown adverse outcomes. Current guidelines recommend IV morphine for pain relief in patients with STEMI. Recommended doses are 4–8 mg IV × 1 (lower dose in elderly), then 2–8 mg IV every 5–15 minutes as needed. In NSTE-ACS, IV morphine use is recommended only in patients refractory to treatment with other anti-ischemic medications; doses between 1 and 5 mg every 5–30 minutes are recommended.
- **β-Blockers** should be administered to all patients without contraindications because they reduce angina and the risk of MI and arrhythmias, even though their mortality benefit in the reperfusion era is uncertain. Current guidelines recommend initiation of an oral β-blocker within the first 24 hours of ACS presentation and continuation for at least 3 years in patients with normal LV ejection fraction (LVEF). For ACS patients with LV dysfunction (LVEF <40% [0.40]), β-blocker therapy is often lifelong. Recommended doses include:

  ✔ **Carvedilol:** 6.25 mg orally twice daily; target dose is 25 mg twice daily as tolerated.

  ✔ **Metoprolol:** 25–50 mg orally every 6–12 hours for 2–3 days, then once daily (metoprolol succinate) or twice daily (metoprolol tartrate); target dose is 200 mg daily. The IV dose is 5 mg every 5 minutes as tolerated up to 3 doses, titrated to BP and heart rate (HR); the IV route should be reserved for STEMI patients with acute uncontrolled HTN or refractory symptoms.

- **Calcium channel blockers** (CCBs) have anti-ischemic effects but may not have beneficial effects on mortality, MI, or recurrent MI. Guidelines recommend nondihydropyridine CCBs (diltiazem, verapamil) for angina symptoms in patients with ACS who have a contraindication, have intolerance, or are refractory to β-blockers in the absence of LV dysfunction, risk factors for cardiogenic shock, and atrioventricular conduction defects. Long-acting CCBs are recommended for patients with ACS with known or suspected vasospasm. Recommended doses include:

  ✔ **Diltiazem:** 120–360 mg/day orally

  ✔ **Verapamil:** 240–480 mg/day orally

  ✔ **Amlodipine:** 5–10 mg orally once daily

  ✔ **Nicardipine:** 60–120 mg/day orally

  ✔ **Nifedipine extended-release** (ER): 30–120 mg orally once daily

Treatment Strategies in STEMI

Primary PCI

- Mechanical reperfusion with PCI using intracoronary balloons, stents, or other devices within 90 minutes of first medical contact is the reperfusion treatment of choice. Patients presenting to hospitals unable to perform PCI should be transferred to a PCI-capable hospital to achieve reperfusion within 120 minutes of the first medical contact. Compared to reperfusion with fibrinolysis, primary PCI improves survival, establishes consistent revascularization to the infarct-related artery, reduces the risk of stroke and intracranial hemorrhage (ICH), and reduces reinfarction and recurrent ischemia.

Fibrinolysis

- Administer fibrinolysis to patients with STEMI when PCI cannot be performed within 120 minutes of first medical contact, provided no contraindications exist. Limit use of fibrinolytics between 12 and 24 hours after symptom onset to patients with clinical and/or ECG evidence of ongoing ischemia.

- Absolute contraindications to fibrinolytic therapy include any prior hemorrhagic stroke, ischemic stroke within 3 months, intracranial neoplasm or AV malformation, active internal bleeding, aortic dissection, considerable facial or closed head trauma in the past 3 months, intracranial or intraspinal surgery within 2 months, severe uncontrolled HTN, and for streptokinase, treatment within previous 6 months (if considering streptokinase again). Primary PCI is preferred in these situations.
- A fibrin-specific agent (alteplase, reteplase, or tenecteplase) is preferred over the non–fibrin-specific agent streptokinase because of greater reperfusion success and less systemic bleeding.
- Treat eligible patients within 30 minutes of hospital arrival with one of the following:

  ✔ **Alteplase:** 15-mg IV bolus over 1–2 minutes, then 0.75 mg/kg (maximum 50 mg) IV over 30 minutes, then 0.5 mg/kg (maximum 35 mg) IV over 60 minutes; maximum total dose 100 mg

  ✔ **Reteplase:** 10 units IV over 2 minutes, followed 30 minutes later with another 10 units IV over 2 minutes

  ✔ **Tenecteplase:** Single IV bolus given over 5 seconds based on patient weight: 30 mg if <60 kg; 35 mg if 60–69.9 kg; 40 mg if 70–79.9 kg; 45 mg if 80–89.9 kg; and 50 mg if ≥90 kg

- Fibrinolytic therapy is associated with a slight but statistically significant risk for stroke, largely attributed to ICH (0.9%–1.0% of patients). Predictors for ICH include advanced age, lower total body weight, female sex, preexisting cerebrovascular disease, and systolic and diastolic HTN at time of presentation.

Antithrombotic Therapy

- Administer antithrombotic therapy with antiplatelet agents and parenteral anticoagulation concomitantly with both primary PCI and fibrinolysis to improve vessel patency and prevent reocclusion (see Antithrombotic Therapy section below).

Treatment Strategies in NSTE-ACS

Early Invasive Approach

- Patients presenting with NSTE-ACS typically have a partially occluded coronary artery with some residual perfusion; therefore, the need for and urgency to perform PCI is not as critical. With an early invasive approach, diagnostic angiography is typically performed within the first 24 hours with the intent to perform revascularization if appropriate. Guidelines recommend this strategy in patients with intermediate to high risk for death, MI, refractory angina, acute HF, cardiogenic shock, or arrhythmias.

Ischemia-Guided Approach (Medical Management)

- If an early invasive strategy using PCI is not considered appropriate, select low-risk patients may receive more conservative ischemia-guided medical management, where antiplatelet and anticoagulants are administered and PCI is not initially planned. Patients are evaluated for signs and symptoms of recurrent ischemia or hemodynamic instability (eg, with noninvasive stress testing) and taken for coronary angiography and possible PCI only if symptoms recur.

Antithrombotic Therapy for ACS

- Both antiplatelet and anticoagulant therapy are necessary in the acute treatment phase of ACS because platelets dominate the pathophysiologic processes in arterial thrombosis, and thrombin is involved in both platelet activation and coagulation. After hospital discharge, most patients are continued on long-term antiplatelet therapy only, although long-term anticoagulant therapy may benefit some high-risk individuals.

Antiplatelet Therapy

- **Aspirin:** A dose of 81 mg daily is continued indefinitely (after the initial 162–325 mg dose) in patients with either STEMI or NSTE-ACS, regardless of the management strategy employed. Patients undergoing PCI for STEMI or NSTE-ACS already receiving chronic aspirin 81 mg daily should be given

an additional dose of 81–325 mg before the procedure.

- **$P2Y_{12}$ Inhibitors:** An oral agent (clopidogrel, prasugrel, ticagrelor) is typically given with aspirin as dual antiplatelet therapy (DAPT) to prevent stent thrombosis and thrombotic CV events. Cangrelor is an IV drug indicated as an adjunct to PCI to reduce periprocedural MI, repeat revascularization, and stent thrombosis in patients not receiving oral $P2Y_{12}$ inhibitors or planned GP IIb/IIIa inhibitors. Any of the four agents may be given with primary PCI, but only clopidogrel has been evaluated in large clinical trials in patients with STEMI receiving reperfusion with fibrinolysis. Recommended doses are as follows:

  ✔ **Clopidogrel:** 600-mg oral loading dose before primary PCI for STEMI or NSTE-ACS. Give a 300-mg oral loading dose to patients receiving a fibrinolytic or who do not receive reperfusion therapy. Avoid a loading dose in patients age ≥75 years. The maintenance dose is 75 mg daily.

  ✔ **Prasugrel:** 60-mg oral loading dose in patients undergoing PCI, followed by 10 mg orally once daily for patients weighing ≥60 kg; use 5 mg once daily for patients weighing <60 kg.

  ✔ **Ticagrelor:** 180-mg oral loading dose in patients undergoing PCI, followed by 90 mg orally twice daily.

  ✔ **Cangrelor:** 30 mcg/kg IV bolus prior to PCI followed by 4 mcg/kg/min infusion for duration of PCI or 2 hours, whichever is longer.

- Withhold clopidogrel and ticagrelor for at least 5 days and prasugrel for 7 days before elective surgery (eg, CABG surgery). Cangrelor can be continued until just a few hours before surgery because of its short duration of action.

Glycoprotein IIb/IIIa Inhibitors (GPIs)

- GPIs inhibit GP IIb/IIIa receptors on platelets, blocking the binding of fibrinogen to activated GP IIb/IIIa receptors, which is the final step in platelet aggregation.

- These agents must be given with unfractionated heparin (UFH) or a low-molecular-weight heparin (LMWH) that should be discontinued immediately after PCI to reduce the risk of major bleeding.

- Use of GPIs has been declining in recent years; patients likely to benefit most are those receiving PCI for NSTE-ACS with elevated troponin levels and patients with STEMI who have not been preloaded with a $P2Y_{12}$ inhibitor and are not being treated with bivalirudin. Recommended doses are as follows:

  ✔ **Abciximab:** 0.25 mg/kg IV bolus given 10–60 minutes before the start of PCI, followed by 0.125 mcg/kg/min (maximum 10 mcg/min) for 12 hours; alternatively, 0.25 mg/kg intracoronary bolus only.

  ✔ **Eptifibatide:** 180 mcg/kg IV bolus, repeated in 10 minutes, followed by IV infusion of 2 mcg/kg/min for 18–24 hours after PCI; reduce infusion dose by 50% if creatinine clearance (CrCl) is <50 mL/min (0.83 mL/sec).

  ✔ **Tirofiban:** 25 mcg/kg IV bolus, then 0.15 mcg/kg/min for up to 18–24 hours after PCI; reduce infusion dose by 50% if CrCl is ≤60 mL/min (1.0 mL/sec).

- GPIs are not beneficial and should not be used in patients with NSTE-ACS undergoing an ischemia-driven approach. GPIs should also be avoided in patients with STEMI receiving reperfusion with fibrinolytics because of significant increases in major bleeding and ICH.

- Besides bleeding, GPIs cause significant thrombocytopenia in about 1% of patients receiving abciximab and 0.5% with eptifibatide and tirofiban. Because GPIs are given with heparin, it is important to differentiate GPI-induced thrombocytopenia from heparin-induced thrombocytopenia (HIT).

Anticoagulants

- Although patients with ACS are typically on at least two antiplatelet agents for a year or more, a single anticoagulant is usually given for a short time (the initial few days of hospitalization).

- Current evidence in the acute management of ACS is with injectable anticoagulants. See **Table 5-1** for anticoagulant indications and drug doses in ACS.

- **Unfractionated heparin (UFH)** has been widely used in ACS management for several decades. Based on experience, UFH can be used across the spectrum of ACS and regardless of the management strategy. Because of significant interpatient variability in anticoagulant response, therapy must be monitored with the activated partial thromboplastin time (aPTT) every 6 hours until two consecutive readings are within the institution's therapeutic range (1.5–2 times the control value), then every 24 hours for the duration of UFH therapy. The activated clotting time (ACT) is monitored during PCI because it can be measured at the bedside with rapid results. Platelet counts should also be monitored daily or every other day to detect HIT. If HIT is suspected, discontinue UFH and provide anticoagulation with an IV direct thrombin inhibitor.

- **Low-molecular-weight heparins (LMWHs)** provide a predicable anticoagulant dose response with no need for routine therapeutic monitoring. Anti-Xa level monitoring may be helpful in obese patients (>190 kg) and patients with severe renal insufficiency (eg, CrCl <30 mL/min [0.5 mL/sec]). The target peak anti-Xa level is 0.3–0.7 IU/mL (kIU/L) drawn 4 hours after the third dose. The utility of anti-Xa monitoring is limited because patients with ACS typically receive anticoagulant therapy for only a few days. Although the incidence of HIT is lower with LMWHs (<2%) than with UFH (2%–5%), monitoring of platelet counts is still warranted. Due to 90% crossreactivity between HIT antibodies from LMWH and UFH, LMWH is not a safe alternative in patients who develop HIT from UFH and vice versa.

  ✔ **Enoxaparin** is the most widely studied agent in ACS and is the only LMWH recommended in current guidelines. Data support its efficacy in patients with STEMI and NSTE-ACS, regardless of the perfusion or management strategy used. However, enoxaparin dosing varies across these different situations (**Table 5-1**). In patients with STEMI receiving reperfusion with fibrinolytics, enoxaparin demonstrated a significant 17% reduction in death and MI compared to UFH. Based on clinical trial data, either UFH or enoxaparin is recommended in patients with NSTE-ACS.

- **Fondaparinux** provides a predicable anticoagulant dose response with no need for therapeutic monitoring (similar to LMWH). A clinical trial in NSTE-ACS patients receiving either an ischemia-driven or invasive management strategy demonstrated similar efficacy between fondaparinux and enoxaparin, with significantly less major bleeding in patients receiving fondaparinux. Although confounding factors may account for the bleeding difference, fondaparinux can be considered in patients undergoing an ischemia-driven approach who are at high risk of bleeding. Fondaparinux is not recommended in patients receiving primary PCI for STEMI because of clinical trial results demonstrating higher rates of catheter-related thrombosis compared to UFH. In patients with STEMI receiving fibrinolytics, fondaparinux had efficacy and safety similar to UFH. However, fondaparinux is rarely used in patients with STEMI based on the lack of superiority to UFH and the benefit shown with enoxaparin over UFH in this population.

- **Bivalirudin** is a direct thrombin inhibitor that is used only in patients with ACS who receive PCI and can be monitored with the ACT in the catheterization laboratory. Although current guidelines recommend bivalirudin use, UFH is often used instead because recent trials suggested that bivalirudin does not offer efficacy or safety benefits over UFH alone in the setting of primary PCI for STEMI. Bivalirudin has not been evaluated in patients with STEMI receiving reperfusion with fibrinolytics or in patients with NSTE-ACS undergoing an ischemia-driven approach.

TABLE 5-1

Anticoagulant Drug Use and Dosing for Treatment of Acute Coronary Syndrome

	STEMI		NSTE-ACS	
Drug	**Primary PCI**	**Fibrinolytic Perfusion**	**Early Invasive Strategy**	**Ischemia-Driven Strategy**
Bivalirudin	0.75 mg/kg IV bolus, followed by 1.75 mg/kg/hr IV infusion until completion of PCI; CrCl <30 mL/min (0.5 mL/sec): reduce infusion to 1 mg/kg/hr	No recommendation	0.10 mg/kg IV bolus, followed by 0.25 mg/kg/hr IV infusion until completion of PCI	No recommendation
Enoxaparin	0.5 mg/kg one-time IV bolus	30 mg IV bolus, followed within 15 min by 1 mg/kg SC every 12 hours for up to 8 days or hospital discharge; cap first two SC doses at 100 mg; CrCl <30 mL/min (0.5 mL/sec): 30 mg IV bolus, followed by 1 mg/kg SC every 24 hours; cap first dose at 100 mg; Age ≥75 years: omit IV bolus and initiate 0.75 mg/kg SC every 12 hours; cap first two doses at 75 mg; CrCl <30 mL/min (0.5 mL/sec) and age ≥75: omit IV bolus and initiate at 1 mg/kg every 24 hours	1 mg/kg SC every 12 hours until PCI; may give an initial 30 mg IV bolus; Give 0.3 mg/kg IV bolus if PCI occurs before two SC doses have been given, or if the last dose was given 8 hours or more prior to PCI; CrCl <30 mL/min (0.5 mL/s): 1 mg/kg SC every 24 hours	1 mg/kg SC every 12 hours for duration of hospitalization; may give an initial 30 mg IV bolus; CrCl <30 mL/min (0.5 mL/sec): 1 mg/kg SC every 24 hours
Fondaparinux	No recommendation	2.5 mg IV first dose, followed by 2.5 mg SC daily for up to 8 days or hospital discharge	2.5 mg SC daily until PCI; At time of PCI, if no GPI give 85 units/kg IV UFH[a]; if with GPI give 60 units/kg IV UFH[a]	2.5 mg SC daily for up to 8 days or duration of hospitalization.
Unfractionated heparin (UFH)	If no GPI, 70–100 units/kg IV bolus to achieve therapeutic ACT[a]; If taking GPI, 50–70 units/kg IV bolus to achieve therapeutic ACT[a]	60 units/kg (max. 4000 units) IV bolus, followed by 12 units/kg/hr (max. initial infusion rate 1000 units/hr)	60 units/kg (max. 4000 units) IV bolus, followed by 12 units/kg/hr (max. initial infusion rate 1000 units/hr)[a]	60 units/kg (max. 4000 units) IV bolus, followed by 12 units/kg/hr (max. initial infusion rate 1000 units/hr)

[a]Additional IV UFH boluses may be needed to maintain a therapeutic ACT.

ACT, activated clotting time; CrCl, creatinine clearance; GPI, glycoprotein IIb/IIIa inhibitor; IV, intravenous; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SC, subcutaneous; STEMI, ST-segment elevation myocardial infarction; UFH, unfractionated heparin.

Secondary Prevention of Ischemic Events

- After a diagnosis of ACS, patients are considered to have atherosclerotic cardiovascular disease (ASCVD) and should be treated aggressively because they are at the highest risk of recurrent major adverse cardiovascular events (MACE).
- Aggressive risk factor modification strategies should be initiated and continued indefinitely (eg, increased physical activity, dietary modification, weight loss, BP modification, and smoking cessation).
- Pharmacotherapy proven to decrease mortality, HF, reinfarction, stroke, and stent thrombosis should be initiated prior to hospital discharge in all patients without contraindications. This includes anti-ischemic, antiplatelet, lipid-lowering, and antihypertensive therapies.
- Medication reconciliation at discharge should include assessment for the medication classes listed below as appropriate unless a contraindication exists; drug regimen examples within medication classes listed here are not intended to be exhaustive.
- **Aspirin:** Treat with aspirin 81 mg once daily indefinitely.
- **$P2Y_{12}$ inhibitor:** Because the ischemic risk following ACS is high, DAPT with aspirin plus a $P2Y_{12}$ receptor inhibitor is indicated for most patients for at least 12 months regardless of the management strategy employed. Continuation of DAPT beyond 12 months may be reasonable for patients at higher ischemic risk if they also have a low bleeding risk. For patients with STEMI treated with fibrinolysis, the minimum recommended duration of DAPT is 14 days.

  ✔ Clopidogrel: 75 mg once daily

  ✔ Prasugrel: 10 mg once daily (5 mg daily if body weight <60 kg)

  ✔ Ticagrelor: 90 mg twice daily

- **β-Blocker:**

  ✔ Carvedilol: 6.25 mg twice daily; target dose (in patients with HF with reduced ejection fraction [HFrEF]) 25 mg twice daily as tolerated

  ✔ Metoprolol: 25–50 mg every 6–12 hours for 2–3 days, then once daily (metoprolol succinate) or twice daily (metoprolol tartrate); target dose (in patients with HFrEF) 200 mg daily

  Other β-blockers may be considered; in patients with HFrEF, use either metoprolol succinate, carvedilol, or bisoprolol, Continue therapy for at least 3 years and indefinitely in patients with concomitant HFrEF.

- **Statin:** Initiate high-intensity statin therapy during the index hospitalization once the patient has been stabilized and continue treatment indefinitely. All patients should receive the highest dose of maximally tolerated statin:

  ✔ Atorvastatin: 80 mg daily

  ✔ Rosuvastatin: 20–40 mg daily

  Moderate-intensity statins or lower doses of high-intensity statins may be considered for ACS patients with a history of statin intolerance or those at high risk for statin-related adverse effects. Patients over age 75 may be prescribed a moderate-intensity statin as initial therapy. Reassess a lipid panel 4–6 weeks after initiation of therapy with the goal of a 50% reduction in LDL-C from baseline.

- **Non-statin cholesterol-lowering medications:** For patients with very high risk ASCVD (eg, post-ACS) and LDL-C >70 mg/dL (1.81 mmol/L) on maximally tolerated statin therapy.

  ✔ Ezetimibe: 10 mg daily

  ✔ Simvastatin: 40 mg/ezetimibe 10 mg daily

✔ Alirocumab: 75 mg SC every 2 weeks

- **Angiotensin-converting enzyme (ACE) inhibitor:** Early administration (within 48 hours of presentation) is associated with lower mortality within the first month of therapy with additional benefit observed during over longer treatment durations.
  - ✔ Lisinopril: 2.5–5 mg daily; target dose 10–40 mg daily
  - ✔ Captopril: 6.25–12.5 mg three times daily; target dose 25–50 mg three times daily
  - ✔ Ramipril: 2.5 mg twice daily; target dose 5 mg twice daily
  - ✔ Trandolapril: 0.5–1 mg daily; target dose 4 mg daily
- **Angiotensin receptor blocker (ARB):** Patients intolerant to ACE inhibitors:
  - ✔ Valsartan: 20 mg twice daily; target dose 160 mg twice daily
- **Aldosterone antagonist:** To reduce mortality, consider administration within the first 14 days after MI in patients treated with both an ACE inhibitor (or ARB) and β-blocker with LV dysfunction (LVEF ≤40% [0.40]) and either HF symptoms or DM.
  - ✔ Eplerenone: 25 mg daily; target dose 50 mg daily
  - ✔ Spironolactone: 12.5–25 mg daily; target dose 25–50 mg daily
- **Nitroglycerin:** All patients not taking PDE-5 inhibitors should be prescribed and instructed on appropriate use of short-acting NTG, either SL tablets (0.3–0.4 mg SL every 5 minutes, up to 3 doses) or lingual spray to relieve acute anginal symptoms on an as-needed basis.

EVALUATION OF THERAPEUTIC OUTCOMES

- Evaluation of short-term efficacy focuses on restoration or preservation of coronary blood flow, symptom relief, and prevention of MACE.
- Determine restoration of blood flow and relief of ischemia by resolution of ischemic ECG changes on presentation, which should occur soon after revascularization.
- Although troponin levels may remain elevated for several days, levels in patients with MI should peak within 12–24 hours and then decline steadily once ischemia is relieved.
- Monitor for development of ACS complications (eg, HF, arrhythmias) frequently.
- Prior to hospital discharge, perform echocardiogram or equivalent modality to identify patients with LV dysfunction (LVEF <40% [0.40]) who are at high risk of death and candidates for guideline-directed medical therapy and device therapy.
- Assure that evidence-based therapies shown to reduce the risk of MACE following ACS have been initiated.
- Long-term outcome evaluation is directed at maintaining functional capacity, quality of life, and continued focus on risk reduction.
- Monitor patients at every healthcare encounter for development of adverse effects from ACS pharmacotherapy (**Table 5-2**).

TABLE 5-2

Adverse Drug Effect Monitoring for Acute Coronary Syndrome

Drug	Adverse Effects	Monitoring Parameters
Fibrinolytics	Bleeding (ICH)	Clinical signs of bleeding[a]; baseline aPTT, INR; Hgb, Hct, platelet count at baseline then daily; mental status every 2 hours for signs of ICH

Aspirin	Dyspepsia, GI bleeding	Clinical signs of bleeding[a]; GI upset; Hgb, Hct, and platelet count at baseline and every 6 months
$P2Y_{12}$ inhibitors	Bleeding, rash	Clinical signs of bleeding[a]; evidence of rash; Hgb, Hct, platelet count at baseline and every 6 months
	Ticagrelor: dyspnea, ventricular pauses, bradycardia	Ticagrelor: dyspnea, HR, telemetry during hospitalization
Glycoprotein IIb/IIIa inhibitors	Bleeding, thrombocytopenia (can be profound with abciximab)	Clinical signs of bleeding[a]; Hgb, Hct, and platelet count at baseline, 2 hours, then daily Eptifibatide and tirofiban: SCr at baseline then daily
Anticoagulants	Bleeding	Clinical signs of bleeding[a]; baseline aPTT, INR; Hgb, Hct, platelet count at baseline then daily
	UFH and LMWH: heparin-induced thrombocytopenia	UFH: aPTT every 6 hours until two consecutive aPTT values are at goal, then every 24 hours; monitor the ACT during PCI
		Enoxaparin, bivalirudin, and fondaparinux: SCr at baseline then daily
		Enoxaparin: may consider steady-state anti-Xa levels in select populations
β-Blockers	Hypotension, HF, bradycardia, cardiogenic shock, AV block, exacerbation of asthma or reactive airway disease	Continuous telemetry (while hospitalized); BP, HR, signs and symptoms of HF; monitor every 5 min before each IV bolus dose; monitor every shift while hospitalized then at each healthcare encounter after discharge
Nitroglycerin	Flushing, headache, hypotension, tachycardia	BP and HR; monitor every 5–15 min following dosage adjustment of IV NTG then every 1–2 hours; monitor every 5 min following administration of short-acting NTG
Morphine	Hypotension, respiratory depression, sedation, hypersensitivity	BP, HR, respiratory rate, sedation level 5 min after administration then every 1–2 hours for 4 hours after the last dose
Calcium channel blockers	Hypotension Verapamil and diltiazem: HF, cardiogenic shock, bradycardia, AV block	BP and HR every shift while hospitalized then at each healthcare encounter after discharge Verapamil and diltiazem: continuous telemetry (while hospitalized); signs and symptoms of HF every shift while hospitalized then at each healthcare encounter after discharge
Statins	GI discomfort, arthralgia, myalgia, musculoskeletal pain, hepatotoxicity	Liver function tests at baseline (prior to discharge) and if signs or symptoms of hepatotoxicity develop; creatine kinase if severe myalgia or musculoskeletal symptoms occur; LDL-C at baseline, 4–12 weeks after initiation or dose adjustment, then every 3–12 months
Nonstatin therapies for cholesterol management	Ezetimibe and combination: GI discomfort, arthralgia, myalgia, musculoskeletal pain Alirocumab: injection site pain, hypersensitivity	Simvastatin/ezetimibe: liver function tests at baseline (prior to discharge) and if signs or symptoms of hepatotoxicity develop; creatinine kinase if severe myalgia or musculoskeletal symptoms occur; LDL-C at baseline, 4–12 weeks after initiation or dose adjustment, then every 3–12 months Alirocumab: LDL-C at baseline and 4–8 weeks after initiation or dose adjustment; evaluation of injection site if injection site pain develops, signs and symptoms of hypersensitivity with each

		healthcare encounter
ACE inhibitors	Hypotension, hyperuricemia, hyperkalemia, worsening renal function, chronic cough, angioedema	BP every shift while hospitalized, 1–2 weeks after initiation or dose adjustment, then with each healthcare encounter; SCr and potassium at baseline, 1–2 weeks after initiation, then every 6–12 months; signs and symptoms of angioedema or cough with each healthcare encounter
ARBs	Hypotension, hyperuricemia, hyperkalemia, worsening renal function	BP every shift while hospitalized, 1–2 weeks after initiation or dose adjustment, then with each healthcare encounter; SCr and potassium at baseline, 1–2 weeks after initiation, then every 6–12 months
Aldosterone antagonist	Hyperkalemia, worsening renal function	BP every shift while hospitalized, 1–2 weeks after initiation or dose adjustment, then with each healthcare encounter; SCr and potassium at baseline, after initiation or dose adjustment: at 3 days, 1 week, monthly for 3 months, then every 3 months

[a] Clinical signs of bleeding include bloody stools, melena, hematuria, hematemesis, bruising, and oozing from arterial or venous puncture sites.

ACE, angiotensin-converting enzyme; ACT, activated clotting time; aPTT, activated partial thromboplastin time; ARB, angiotensin receptor blocker; AV, atrioventricular; BP, blood pressure; GI, gastrointestinal; Hct, hematocrit; HF, heart failure; Hgb, hemoglobin; HR, heart rate; ICH, intracranial hemorrhage; INR, international normalized ratio; LDL-C, low-density lipoprotein cholesterol; NTG, nitroglycerin; PCI, percutaneous coronary intervention; SCr, serum creatinine; UFH, unfractionated heparin.

See Chapter 33, Acute Coronary Syndrome, authored by Robert J. DiDomenico, Paul P. Dobesh, and Shannon W. Finks, for a more detailed discussion of this topic.