Chapter 34: Acute Coronary Syndrome

Robert J. DiDomenico; Paul P. Dobesh; Shannon W. Finks

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 5, Acute Coronary Syndromes.

KEY CONCEPTS

KEY CONCEPTS

1. The cause of acute coronary syndrome (ACS) in more than 90% of patients is the acute rupture, fissure, or erosion of an unstable atherosclerotic plaque followed by subsequent thrombus formation that impairs distal blood flow resulting in acute myocardial ischemia.

2. Patients with symptoms of myocardial ischemia suspected of having ACS should undergo risk stratification that incorporates their past medical history, presenting signs and symptoms, 12-lead electrocardiogram (ECG), and cardiac troponin (cTn); dynamic elevation in serial cTn values confirms the diagnosis of myocardial infarction (MI).

3. Intravenous (IV) nitroglycerin should be considered to alleviate anginal pain and/or treat acute comorbidities such as uncontrolled hypertension (HTN) or heart failure (HF), oxygen should be administered to patients with hypoxia (oxygen saturation less than 90% [0.90]), and IV morphine may be considered in patients with refractory anginal pain.

4. In the absence of contraindications, an oral β-blocker should be initiated for all patients with ACS and continued for 3 years or more to reduce the risk of major adverse cardiac events (MACE); calcium channel blockers (CCBs) may be considered in patients with vasospasm and those refractory to or with contraindications or intolerance to β-blockers.

5. Reperfusion of the infarct-related artery in ST-segment elevation myocardial infarction (STEMI) with primary percutaneous coronary intervention (PCI) within 90 minutes of first medical contact is preferred to fibrinolytic therapy unless primary PCI cannot be performed within 120 minutes of presentation.

6. Antiplatelet therapy is a central component to the acute and chronic management of patients with ACS to reduce MACE, frequently includes aspirin plus a $P2Y_{12}$ inhibitor, and requires careful attention paid to the clinical scenario to select the regimen that optimizes efficacy and safety.

7. Use of parenteral anticoagulant agents (unfractionated heparin, low-molecular-weight heparin [LMWH], fondaparinux, bivalirudin) during hospitalization have the ability to reduce MACE in patients with ACS and requires knowledge of the diagnosis, selected management strategy, and other factors to select the drug and dosing regimen that optimize efficacy and safety.

8. Dual antiplatelet therapy (DAPT) with aspirin plus a $P2Y_{12}$ receptor inhibitor is indicated for all patients post-ACS for a minimum of 12 months regardless of whether the patient is managed with an ischemia-driven approach or if the patient undergoes revascularization.

9. All patients post-ACS should receive maximally tolerated high-intensity statin therapy to reduce the risk of MACE; patients with low-density lipoprotein cholesterol (LDL-C) of 70 mg/dL (1.81 mmol/L) or greater on maximally tolerated high-intensity statin therapy should be considered for the addition of nonstatin therapies (eg, ezetimibe, proprotein convertase subtilisin kexin 9 [PCSK9] inhibitor).

10. To reduce the risk of MACE, all post-MI patients should receive oral treatment with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) unless contraindicated and a mineralocorticoid receptor antagonist if the left ventricular ejection fraction (LVEF) is 40% (0.40) or less and HF symptoms or diabetes mellitus (DM) are also present.

BEYOND THE BOOK

BEYOND THE BOOK

To better understand the pathophysiology of acute coronary syndrome (ACS), clinical presentation, and the rationale for pharmacotherapy to treat ACS, please watch the videos below. These videos should enhance learner understanding regarding the COLLECT, ASSESS, and PLAN steps in the Patient Care Process.

1. Thrombotic cascade in ACS—Acute coronary syndrome (ACS) pathology—Thrombosis Advisor https://www.youtube.com/watch?v=VIYAAdkOOrk (Duration 1:48 minutes)
2. Acute Coronary Syndrome DETAILED Overview (MI, STEMI, NSTEMI)—Armando Hasudungan https://www.youtube.com/watch?v=TBG9Jw3yd9I (Duration: 24:10)

Learners are encouraged to review Chapter 16: Acute coronary syndrome "ST-elevation myocardial infarction: I can't handle the pressure level III" in the *Pharmacotherapy Casebook: A Patient-Focused Approach* to practice applying their knowledge to develop a patient-centered care plan for a patient with ACS.

INTRODUCTION

Acute coronary syndrome (ACS) is an acute manifestation of coronary artery disease (CAD) and, for many patients, is the first indication they have CAD. Patients with ACS typically experience an acute reduction in coronary blood flow most often due to a ruptured atherosclerotic plaque and subsequent formation of an intracoronary thrombus. The reduction in coronary blood flow produces myocardial ischemia and, if left untreated, may lead to myocardial infarction (MI).

Patients with ACS typically experience acute chest discomfort similar to those with stable ischemic heart disease (SIHD) but the symptoms are often more severe, prolonged, or refractory despite medical interventions. Like patients with SIHD, those experiencing ACS are at risk for complications such as MI, heart failure (HF), ventricular arrhythmias, and death. The spectrum of ACS includes ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA). The American College of Cardiology (ACC) and the American Heart Association (AHA) have published guidelines for the diagnosis and management of patients with STEMI and non-ST-segment elevation acute coronary syndrome (NSTE-ACS), which includes NSTEMI and UA.[1,2]

EPIDEMIOLOGY

The AHA estimates that every 40 seconds an American will experience an MI.[3] There is a direct relationship between age and the prevalence of both CAD and CAD-related events such as MI. More than 1 million persons are discharged from the hospital annually with a primary or secondary diagnosis of an ACS.[3] MI accounts for more than 70% of these hospitalizations, the majority of cases are the first occurrence of a coronary event.[3] The presentation of MI has changed over the last two decades. Since 2000, the proportion of all patients with MI experiencing STEMI has declined while the proportion experiencing an NSTEMI has increased, the latter representing 74% of patients with MI between 2010 and 2014 in one study.[4] While many patients who experience an MI have symptoms prompting emergent care, an estimated 170,000 Americans will suffer an MI with minimal or no symptoms (eg, "silent MI") that may go undetected, placing them at high risk for major adverse cardiovascular events (MACE).[3]

Patients who experience ACS are at high risk for developing complications. The 1-year and 5-year mortality rates for patients experiencing MI are estimated at 18% to 23% and 36% to 47% for males and females, respectively.[3] Patients experiencing STEMI have a greater short-term (eg, 30 days) risk of complications, including death, compared to patients experiencing NSTEMI, whereas NSTEMI is associated with a greater long-term (eg, 2 years) risk.[3] In addition to death, patients experiencing ACS are also at risk for developing HF, cardiogenic shock, and ventricular arrhythmias, each of which contributes to the mortality associated with this disease state. Fortunately, declines in STEMI prevalence and overall severity of MI coupled with therapeutic advances have contributed to a reduction in complications associated with ACS globally. For instance, the rate of HF hospitalizations following MI declined more than 60% between 2000 and 2015 and the risk of death has similarly declined.[5] Lower rates of in-hospital death and MACE have been associated with increased utilization of percutaneous coronary intervention (PCI) and optimal medical therapy in patients treated for MI.[6]

Therefore, the use of evidence-based therapies to treat ACS, the focus of this chapter, improves outcomes in these patients and should be prioritized in care plans.

The treatment of ACS is associated with significant healthcare resource utilization and related costs. For patients hospitalized for ACS, the mean and median length of stay were 5.5 and 4 days, respectively, in a recent analysis.[7,8] Frequent hospitalizations and utilization of revascularization therapies (eg, PCI, coronary artery bypass grafting [CABG]) lead to high costs associated with treating patients with ACS. In the United States, the mean cost of treating patients hospitalized for UA was $7,916 (median cost $7,841) while the average cost of hospitalization for MI was $24,695 (median cost $26,749).[9] In fact, MI ranks among the top 10 most expensive conditions treated in the United States.[3] While the adjusted hospitalization cost of treating MI remained relatively unchanged between 2001 and 2011 in one analysis, hospital costs increased by 10% if MI was treated with PCI and approximately 20% if CABG surgery was performed.[8]

ETIOLOGY

1 Endothelial dysfunction, inflammation, and the formation of fatty streaks contribute to the formation of atherosclerotic coronary artery plaques, the underlying cause of CAD.[9] The predominant cause of ACS in more than 90% of patients is the acute rupture, fissure, or erosion of an unstable atherosclerotic plaque followed by subsequent thrombus formation that impairs distal blood flow resulting in acute myocardial ischemia. If myocardial ischemia persists sufficiently long, MI can occur. This presentation of MI is classified as a type 1 MI.[10] Less commonly, ACS may occur due to an acute mismatch between oxygen supply and demand (eg, coronary vasospasm, coronary embolism, coronary artery dissection, a concomitant condition that acutely increases oxygen demand). When the latter results in myocardial injury, it is classified as a type 2 MI.[10] Other classifications of MI include patients who suffer cardiac death with symptoms suggestive of myocardial ischemia for whom biomarker detection is not possible (type 3), MI associated with PCI-related myocardial injury (type 4), and MI associated with CABG surgery (type 5).[10]

PATHOPHYSIOLOGY

The “Vulnerable Plaque”

1 The basic pathophysiologic process leading to an ACS event typically involves the rupture of an atherosclerotic plaque and subsequent thrombus formation. This thrombus formation produces an abrupt decrease in myocardial blood flow and oxygen supply leading to ischemia and potentially the death of myocytes and infarction.[11] The development of atherosclerotic plaques is complex and discussed in detail in Chapter 32, “Dyslipidemia.” The atherosclerotic plaques that produce demand-driven angina in patients with SIHD are different from those that produce an ACS. The atherosclerotic plaques in patients with SIHD typically have thicker fibrous caps, and rarely rupture. The atherosclerotic plaques that rupture in patients with ACS typically have thin fibrous caps and are “vulnerable” to rupture.[12] The plaques in patients with ACS also have a larger cholesterol necrotic core while those in patients with SIHD are more likely to be solidified with calcium deposits. Atherosclerotic plaques that rupture in patients with ACS tend to be “nonobstructive,” occluding less than 70% of the luminal diameter. Thus, patients with nonobstructive plaques may not experience angina symptoms prior to plaque rupture due to adequate autoregulation to maintain blood flow and oxygen supply in times of increased myocardial oxygen demand (coronary autoregulation is discussed in Chapter 33, “Stable Ischemic Heart Disease”). Therefore, patients are often unaware they have atherosclerotic plaques until the ACS event occurs.

The fibrous cap of an atherosclerotic plaque is what separates its lipid core from circulating platelets and coagulation factors in the blood. The cap initially is normal arterial intima or thickened intima tissue. As the atherosclerotic plaque grows this is replaced and expanded by fibrous tissue with high amounts of type 1 collagen.[13] In “vulnerable plaques,” increased breakdown of collagen in the fibrous matrix and a reduction in collagen production cause the fibrous cap to become thinned and prone to rupture. Inflammatory processes are involved with both mechanisms.

The reduction in collagen production originates from a reduction in the number of secretory smooth muscle cells within the plaque, and a reduction in the synthesis within these cells.[13,14] Alteration of collagen synthesis and breakdown by macrophages and T cells demonstrates the significant role inflammation plays in thinning and weakening of the fibrous cap and increasing the potential for plaque rupture triggering an ACS event.[13-15] Altering the role of these inflammatory processes continues to be an active area of investigation to prevent and treat patients with atherosclerosis and ACS.

A thinning fibrous cap by itself does not usually produce plaque rupture. There is typically a connection to physiological or psychological stress which enhances the likelihood of an acute event.[16,17] Approximately two-thirds of ACS events occur in the morning. This is likely related to circadian rhythm activation of the sympathetic nervous system (SNS) and catecholamine release that produces an increase in heart rate, blood pressure, and vasoconstriction. An increase in catecholamines may occur due to physical and emotional stress. These changes in conjunction with a thin fibrous cap place patients at risk for ruptured atherosclerotic plaque and subsequent ACS.

Plaque Rupture and Clot Formation

1 The process of thrombus formation at the site of the ruptured atherosclerotic plaque is complex. Thrombus formation involves platelets and the coagulation cascade. While these two components of thrombus formation are often described separately, they are intertwined and each depends on the other.[18] These components do not contribute equally to thrombus formation in all vascular types. In venous thrombosis, the coagulation cascade dominates thrombus formation and platelets play a more minor role. In arterial thrombosis, such as ACS, platelets dominate, with the coagulation process having less contribution. This is evident by the use of pharmacotherapy to manage thrombosis in each vascular type. While the prevention and treatment of venous thrombosis are managed with anticoagulant agents almost exclusively, patients with arterial thrombosis are treated with two, and sometimes three, antiplatelet agents and typically receive a single anticoagulant agent for a short duration.

Upon plaque rupture, the barrier between the necrotic core of the plaque and blood components is breached.[18] Circulating platelets are initially attracted and adhere to the area of injury. The adhesion of these initial platelets 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 may then be activated by numerous substances including collagen, thrombin, thromboxane A_2, adenosine diphosphate (ADP), epinephrine, and serotonin. These substances have different potency in their ability to activate platelets, with thrombin (from the clotting cascade) and collagen being the strongest activators. Each of these activators has individual receptors found on the platelet surface (eg, $P2Y_{12}$ receptor for ADP, protease-activated receptor [PAR]-1 for thrombin).

Once an activator binds to its specific receptor a chain reaction is initiated within the platelet with an influx of calcium leading to multiple changes in the platelet.[18] During platelet activation, the platelet changes shape from a disc-like structure to a polymorphic structure with protruding arms that significantly increases the surface area of the platelet. Granules with high concentrations of platelet activators (eg, thromboxane A_2, ADP, serotonin) make their way to the surface of the platelet and release their contents into the circulation. This leads to additional localized activation of platelets that have not adhered to the area of vascular injury. The activated platelet is also the location of the assembly of the tenase and prothrombinase complex that produces most of the activated factors Xa and IIa (thrombin) in the coagulation cascade. Therefore, this represents the interface between platelets and the clotting cascade in thrombosis. Finally, platelet activation leads to the expression of active GP IIb/IIIa receptors.[18] Upon platelet activation, there are approximately 90,000 to 100,000 GP IIb/IIIa receptors, making it the most abundant receptor found on any cell in the body.[18] Through activation, the GP IIb/IIIa receptors undergo a conformational change that exposes the binding site. The main ligand that binds to this receptor is fibrinogen, a linear molecule with a binding site for GP IIb/IIIa on each side. Therefore, each fibrinogen molecule can bind to a GP IIb/IIIa receptor on different platelets, linking those platelets together. The linking of platelets together via the GP IIb/IIIa receptors and fibrinogen is the process of platelet aggregation. Hence, the process of platelet adhesion, activation, and aggregation produces a platelet plug in the area of atherosclerotic plaque rupture.

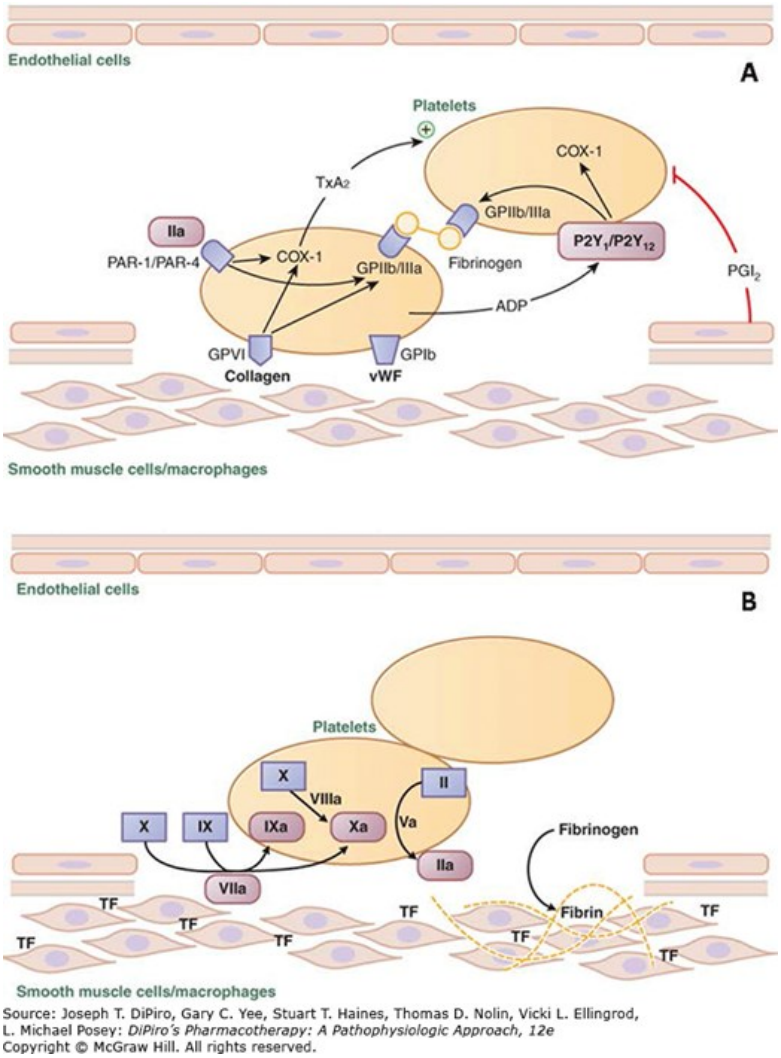
The platelet plug by itself is rarely enough to significantly occlude myocardial blood flow and oxygen supply.[16] A fibrin meshwork then forms within and on top of the platelet plug that more completely traps cellular components such as red blood cells and produces the abrupt reduction in myocardial blood flow. The formation of this fibrin meshwork involves activation of the clotting cascade.

The initiation of the clotting cascade begins with the interaction and activation of factor VII and tissue factor.[18] Tissue factor is found in endothelial cells, as well as on macrophages at the site of the ruptured fibrous cap. This tissue factor–factor VIIa complex is able to activate small amounts of factor X, which then can activate small amounts of thrombin (factor IIa). The amount of thrombin produced during this initiation phase of coagulation is not enough to promote thrombosis. However, this initial amount of thrombin activates factor VIII. Activated factor VIII (factor VIIIa), with factor IXa (produced from the tissue factor–factor VIIa complex as well as factor XIa), creates the tenase complex on the platelet surface which activates large amounts of factor X. The initial thrombin produced also activates factor V. Activated factor V (factor Va) and activated factor X (factor Xa produced from the tenase complex) create the prothrombinase complex on the surface of the activated platelet where the majority of the thrombin involved in thrombosis is produced. Thrombin is now able to convert fibrinogen into fibrin, which creates the meshwork in the thrombosis and solidifies the clot.

Thrombin also activates factor XIII, which provides additional clot stability, continues the positive feedback with the creation of factors VIIIa and Va, as well as provides significant platelet activation via PAR-1 receptors. The contributions of platelets and the coagulation cascade in thrombus formation in ACS are depicted in Fig. 34-1.

FIGURE 34-1

Role of platelets and coagulation cascade in thrombus formation in ACS. Panel A depicts receptors and mediators of platelet adhesion, activation, and aggregation during acute coronary syndrome (ACS). Panel B depicts components of the coagulation cascade during thrombus formation in ACS. Boxes enclose the coagulation factor zymogens (indicated by Roman numerals); the rounded boxes represent the active proteases. Activated coagulation factors are followed by the letter a: II, prothrombin; IIa, thrombin. (TxA2, thromboxane; PAR, protease-activated receptor; GP, glycoprotein; ADP, adenosine diphosphate; COX, cyclooxygenase; PG, prostaglandin; vWF, von Willebrand factor; TF, tissue factor.) (*From Reference 19.*)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Thrombus formation in the area of atherosclerotic plaque rupture produces an abrupt reduction in myocardial blood flow and oxygen supply. This abrupt blockage produces ischemia and, if untreated, potentially infarction which results in myocyte necrosis and cell death.[12,16,17] Therefore, early recognition and prompt initiation of treatment can limit ACS-related sequelae. The progression to infarction and the extent of infarction depends on a number of factors. These may include both the location and size of the thrombus, activity of the endogenous fibrinolytic system, as well as the extent of collateral circulation.[16,17]

Ventricular Remodeling After MI

In the setting of MI, acute and chronic adaptations occur to prevent hemodynamic collapse that may also lead to ventricular remodeling and the development of post-MI complications. Similar to what occurs locally within the infarct-related artery, inflammation at the site of myocardial injury plays a key role in ventricular remodeling. In addition, stimulation of the neurohormonal system occurs and contributes to this process.

In patients who experience a decrease in cardiac output following MI, stimulation of both the SNS and renin–angiotensin–aldosterone system (RAAS) occurs to compensate for the decrease in cardiac output similar to what is observed in patients with acute and chronic HF (see Chapter 36, "Chronic Heart Failure" and Chapter 37, "Acutely Decompensated Heart Failure"). Activation of the SNS is immediate, resulting in increased contractility, heart rate, and peripheral resistance.[20] However, because the synthesis of components of the RAAS is dependent on an increase in mRNA and protein levels, the response is slower.[20] Stimulation of the RAAS results in sodium and water retention as well as peripheral vasoconstriction in an attempt to maintain adequate hemodynamics and perfusion. Vasopressin and endothelin are also released following MI but play a lesser role.[20]

Following MI, some patients experience chronic hyperactivity of either or both the SNS and RAAS, both of which contribute to adverse cardiac remodeling.[20] Chronic hyperactivation of the SNS leads to desensitization and downregulation of β_1-adrenergic receptors, modification of the excitation-contraction coupling mechanism, ventricular hypertrophy, and further impairment of contractility and cardiac output. Likewise, increased production of both angiotensin II and aldosterone via chronic hyperactivation of the RAAS leads to ventricular hypertrophy. Angiotensin II also increases oxidative stress, the release of inflammatory mediators, and collagen deposition, each of which contributes to myocardial fibrosis, or scarring. While myocardial fibrosis is essential for tissue repair following MI, its development impairs ventricular contraction and elasticity. This can lead to the thinning of the left ventricular wall and eventually to the development of dilated cardiomyopathy.

Complications

Depending on the extent and area of ischemia, various complications are possible in patients with ACS, particularly those with MI, which can manifest hours to weeks after the index event.[21] Electrophysiologic disturbances including ventricular arrhythmias, bradyarrhythmias, and heart block are possible and may occur either in the acute phase of the ischemic event due to electrical instability generated during myocyte destruction or in the recovery phase due to ventricular remodeling. HF is possible depending on the extent of myocardial necrosis and subsequent impairment of ventricular contractility. In fact, approximately 5% to 6% of patients with STEMI develop cardiogenic shock, an acute, severe form of HF associated with hypotension, systemic hypoperfusion, and poor outcomes.[21] Myocardial rupture of the papillary muscle, ventricular septum, or free wall of the ventricle is possible within the first 10 days of infarction due to extensive myocyte necrosis in those areas.[21] Thromboembolism, including stroke, is also possible due to the embolization of left ventricular thrombi that can form due to infarct-related ventricular aneurysm or left ventricular dysfunction. Pericarditis, an autoimmune-mediated inflammation of the pericardium, can occur weeks after an MI, particularly after a large infarct.[21] Mental health can also be impacted as many patients with ACS develop depression during the convalescent period.

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Acute Coronary Syndrome

General

- The patient is typically in acute distress and may develop or present with hypertensive crisis, acute HF, cardiogenic shock, or cardiac arrest.

Symptoms

- 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, shoulders, back, abdomen, or jaw. Nausea, vomiting, diaphoresis, or shortness of breath may also be present.
- Patients likely to present with atypical symptoms include those aged 75 years or greater, women, and patients with diabetes mellitus (DM), impaired renal function, and dementia.

Signs

- No physical findings are specific for ACS. Nonspecific findings include S_4 or paradoxical splitting of S_2 on auscultation.
- Patients with ACS may present with signs of acute decompensated HF including jugular venous distention, pulmonary edema, and an S_3 on auscultation.
- Patients with ischemia-related papillary muscle dysfunction may present with a new murmur of mitral regurgitation.
- Patients may also present with arrhythmias, including tachycardia or bradycardia, as well as heart block.
- Hemodynamic abnormalities may include hypertension (HTN) and hypotension or shock.

Laboratory Tests

- Cardiac troponin (cTn, either cTnI or cTnT) is measured at the time of presentation and repeated 3 to 6 hours later (1 to 3 hours later if high-sensitivity cTn assays used) to detect myocardial injury; elevated levels in a patient with ACS symptoms, ischemic changes on ECG, or other diagnostic evidence of ischemia confirm the diagnosis of MI. Additional cTn levels should be obtained beyond 6 hours after symptom onset in patients with intermediate to high-risk features of ACS but normal cTn levels during serial measurements.
- For patients with ACS symptoms who do not have ST-segment elevation on ECG but an elevated cTn, NSTEMI is the appropriate diagnosis. Patients with ACS symptoms but normal cTn may have unstable angina (UA) or an alternative diagnosis.
- Blood chemistry tests are performed with particular attention given to potassium and magnesium, which may affect heart rhythm.
- Serum creatinine (SCr) is measured and creatinine clearance (CrCl) is used to identify patients who are at high risk of morbidity and mortality—dosage adjustments for renally cleared medications may be necessary.
- Baseline complete blood count and coagulation tests (activated partial thromboplastin time [aPTT] or anti-Xa levels, international normalized ratio [INR]) should be obtained; most patients will receive antithrombotic therapy and these tests are useful in monitoring for complications related to antithrombotic therapy, including bleeding.
- Fasting lipid panel.

Other Diagnostic Tests

- The 12-lead ECG is the first step in evaluating a patient with ACS. Patients are risk-stratified into two groups: those with STEMI and those without (NSTE-ACS). Patients with NSTE-ACS may have other ischemic ECG changes including ST-segment depression or T-wave inversion.
- Patients with STEMI and intermediate- to high-risk NSTE-ACS are likely to undergo coronary angiography via a left heart catheterization to diagnose CAD and may be treated with PCI during the procedure.
- An assessment of left ventricular (LV) function via echocardiography or equivalent modality should be performed to identify patients with LV dysfunction (LV ejection fraction [LVEF] less than 40% [0.40]) who are at high risk of death and candidates for guideline-directed medical therapy and device therapy.
- Selected intermediate-risk patients may undergo coronary computed tomography angiography or stress testing in lieu of invasive coronary angiography.
- Selected low-risk patients may undergo early stress testing or coronary artery calcium scanning.

Risk Stratification

- A risk assessment that incorporates the clinical presentation, past medical history, ECG, and cTn should be performed to identify high-risk patients and guide therapeutic interventions. One or more of the validated risk estimators (see Table 34-1) should be used for this purpose and incorporated into clinical decision pathways.

TABLE 34-1

Tools to Assess Risk of Major Adverse Cardiac Events in Patients with Acute Coronary Syndrome

TIMI Risk Score (STEMI)[22]	TIMI Risk Score (NSTE-ACS)[23]	GRACE Risk Score[24]	HEART Score[25]
Component (points)	**Each component worth 1 point**	**Points for each component vary based on value**	**Component (points)**
Age <65 years (0)	Age ≥65 years	Age	History highly suspicious (2)
Age 65-74 years (2)	≥3 CAD risk factors[a]	Killip class	Moderately suspicious (1)
Age ≥75 years (3)	Known CAD[b]	Systolic BP	Slightly suspicious (0)
HTN, DM, or angina[c] (1)	Aspirin use within 7 days	Heart rate	ECG: significant ST
Systolic BP <100 mm Hg (3)	≥2 angina episodes within 24 hours	Serum creatinine	Depression (2), nonspecific
Heart rate >100 bpm (2)	Transient STE or ST depression	Cardiac arrest on admission	Repolarization disturbance (1)
Killip class II–IV (2)	Elevated biomarkers (eg, cTn)	Elevated biomarkers (eg, cTn)	Normal (0)
Weight <67 kg (1)		ST deviation[d]	Age: ≤65 years (2), 45-65 years (1),
Anterior STE or LBBB (1)			<45 years (0)
Time to treatment >4 hours (1)			Risk factors for CAD: ≥3 (2),
			1-2 (1), no risk factors (0)
			cTn: ≥2× ULN (2),
			1-2× ULN (1), ≤ULN (0)
Calculate point total and determine risk for major adverse cardiac events			
Low risk: 0-3 points	Low risk: 0-2 points	Low risk: <109 points	Low risk: 0-3 points
Intermediate risk: 4-5 points	Intermediate risk: 3-4 points	Intermediate risk: 109-140 points	Intermediate risk: 4-6 points
High risk: ≥6 points	High risk: ≥5 points	High risk: >140 points	High risk: ≥7 points

BP, blood pressure; DM, history of diabetes; cTn, cardiac troponin; ECG, electrocardiogram; GRACE, Global Registry of Acute Coronary Events; HEART, History, Electrocardiogram (ECG), Age, Risk factors, Troponin; LBBB, left bundle branch block; ST, ST-segment; STE, ST-segment elevation; STEMI, ST-segment elevation

myocardial infarction; TIMI, thrombolysis in myocardial infarction; ULN, upper limit of normal.

Online calculator available for TIMI Risk Score (STEMI) at: https://www.mdcalc.com/timi-risk-score-stemi

Online calculator available for TIMI Risk Score (NSTE-ACS) at: https://timi.org/calculators/timi-risk-score-calculator-for-ua-nstemi/

Online calculator available for GRACE score at: https://www.outcomes-umassmed.org/grace/acs_risk2/index.html

[a]Risk factors include a family history of coronary artery disease, hypertension, hypercholesterolemia, diabetes, and current smoker.

[b]Prior coronary stenosis ≥50%.

[c]History of angina.

[d]Includes transient ST-segment elevation ≥1 mm, ST-segment depression ≥1 mm, new T wave inversions ≥1 mm, pseudo-normalization of previously inverted T waves, new Q waves, new R wave >S wave in lead V_1, new left bundle branch block.

Signs and Symptoms

The symptoms and clinical presentation of ACS are similar to those of stable angina (see Chapter 33, "Stable Ischemic Heart Disease"). The "classic" presentation of ACS is an abrupt onset of substernal chest pain often described as a sensation of squeezing, heaviness, or tightness in the chest that radiates to either or both arms or shoulders (radiation to the left side is more common), the neck, or the jaw. Patients with ACS may also experience diaphoresis, nausea, vomiting, and dyspnea. Many patients—as many as one-third—with ACS may present with atypical symptoms that do not include substernal chest pain.[1] Atypical symptoms include epigastric pain, indigestion, stabbing, or pleuritic chest pain, and increasing exertional dyspnea, the latter representing the most common "angina equivalent."[2] Older adults (75 years of age or older), women, and patients with diabetes mellitus (DM), impaired renal function, and dementia are more likely to present with atypical features.[2]

Features that differentiate ACS from stable angina include symptom severity and duration. Unlike SIHD, patients with ACS often experience symptom durations lasting 10 minutes or longer.[2] New or worsening symptoms or a change in symptom pattern (eg, acute increase in frequency or severity, occurring at rest or minimal exertion, longer duration) may be indicative of ACS.[1,2]

On physical examination, there are no specific findings indicative of ACS. In fact, the physical examination may be normal in many patients. Acute myocardial ischemia can cause an S_4 or paradoxical splitting of S_2 on auscultation, but these are nonspecific findings. Rather, clinicians should evaluate for the presence of complications of MI (eg, HF, new murmur of mitral regurgitation due to papillary muscle dysfunction) which, if present, should expedite the evaluation and therapeutic interventions.[2]

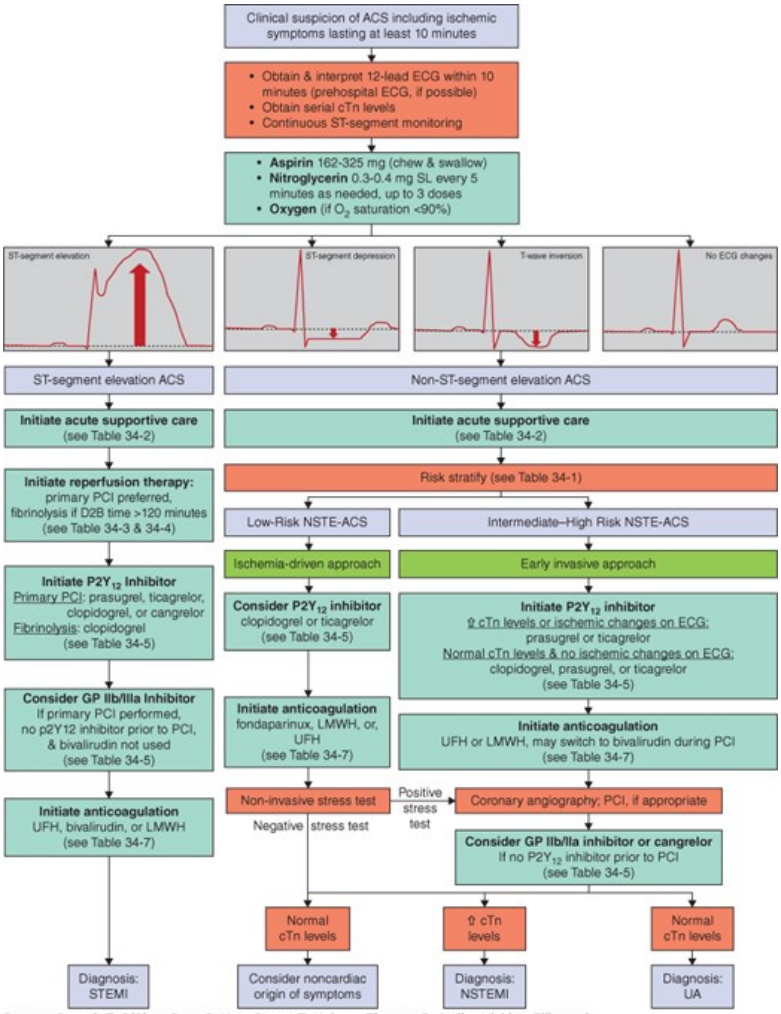
12-Lead Electrocardiogram

The presenting electrocardiogram (ECG) is critical for expeditious risk stratification and triage of patients presenting with ACS. Patients with possible ACS should have a 12-lead ECG performed and interpreted within 10 minutes of presentation to an emergency department (ED).[2] Ideally, a 12-lead ECG should be performed by emergency medical services (EMS) providers and communicated to the ED staff prior to hospital arrival in order to expedite reperfusion, if necessary.[1] Electrocardiographic changes suggestive of acute ischemia include ST-segment elevation or ST-segment depression of 0.05 mm or greater and T-wave inversion of at least 1 mm in at least two contiguous leads (Fig. 34-2).[2,10] Except for leads V_2-V_3 where greater ST-segment elevation is required, when ST-segment elevation of at least 1 mm is present in patients suspected of having ACS, the presumptive diagnosis of STEMI is made and the patient should be considered for emergent reperfusion therapy (Fig. 34-2).[1,10] In addition, the presence of a new left bundle–branch block (LBBB) in patients suspected of having ACS is strongly suggestive of acute MI and has been considered a STEMI equivalent.[1] However, because new LBBB occurs infrequently, a prior 12-lead ECG should be reviewed, if available, to determine if the LBBB is new or old. Patients with a high suspicion of ACS but with a normal ECG on presentation should have serial ECGs performed (eg, every 15-30 minutes for the first hour) to detect ischemic changes.[2] In approximately 1% to 6% of patients with ACS, often those with occlusions of the left circumflex or right coronary arteries,

the 12-lead ECG may be normal or "electrically silent." Therefore, appropriate evaluation and risk stratification for patients with ACS must incorporate the evaluation of the patient's medical history, presenting symptoms, ECG findings, and biomarkers.

FIGURE 34-2

Evaluation and initial management of patients with suspected acute coronary syndrome (ACS). (O2, oxygen saturation; D2B, door-to-balloon; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin.)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Cardiac Troponin

The cardiac troponins (cTn) are part of the contractile apparatus of myocardial cells and are the most sensitive and specific biomarkers for detecting myocardial injury.[2,10] Within 2 to 4 hours of myocyte injury or necrosis, these proteins are released into the bloodstream resulting in elevated blood levels (exceeding the 99th percentile of the upper reference limit).[2,10] The emerging high-sensitivity cTn assays are capable of measuring relatively low concentrations much earlier in the clinical course of myocardial injury that could not be detected with traditional cTn assays. The use of high-sensitivity cTn assays likely increases the frequency of NSTEMI diagnosis. Elevations in cTn may persist for several days, and as long as 2 weeks.[2]

2 There are several nonischemic causes of myocardial injury (eg, HF, myocarditis, Takotsubo syndrome, chronic kidney disease) that result in elevated cTn, particularly if high-sensitivity cTn assays are used.[2,10] Therefore, clinical context is required to establish the diagnosis of ACS. Myocardial injury is considered acute if there is a dynamic rise and/or fall by 20% or more in serial cTn values.[10] In contrast, when using a high-sensitivity cTn

assay, the absolute change (in ng/L), rather than a relative change, increases diagnostic accuracy and may be useful in distinguishing an MI from other causes of cTn elevation.[10] Attention must be paid to the units of measure between traditional and high-sensitivity cTn; they are not interchangeable. When an acute myocardial injury is detected (eg, the dynamic elevation of cTn) in a patient presenting with ACS symptoms, ischemic changes on ECG, or other diagnostic evidence of ischemia (eg, imaging that demonstrates loss of myocardium or new regional wall motion abnormality, coronary thrombus detected during angiography or autopsy), the diagnosis of MI is appropriate.[10] Classification of MI is made based on the presenting ECG findings. For patients with dynamic cTn elevations whose presenting ECG demonstrated ST-segment elevation of at least 1 mm in two contiguous leads or new LBBB, the diagnosis of STEMI is confirmed.[10] In contrast, for patients with symptoms of ACS without at least 1 mm ST-segment elevation on the ECG at presentation but with a dynamic elevation of cTn, the diagnosis of NSTEMI is appropriate.[2,10] Patients with symptoms consistent with ACS but in whom the cTn is not elevated may have UA or an alternative diagnosis.[10]

Given that dynamic changes in cTn are needed to establish the diagnosis of MI, serial cTn levels should be obtained when the patient presents to the ED and again 3 to 6 hours after symptom onset (1-3 hours later if using high-sensitivity cTn).[2,26] If the time of symptom onset is unclear from the patient's history, the time of presentation to the ED should be considered the time of symptom onset.[2] For patients with intermediate- to high-risk features of ACS (eg, ECG changes, clinical presentation) but normal cTn values during serial measurements, an additional measurement of cTn after the 6 hours (3 hours if using high-sensitivity cTn) may be warranted.[2,26]

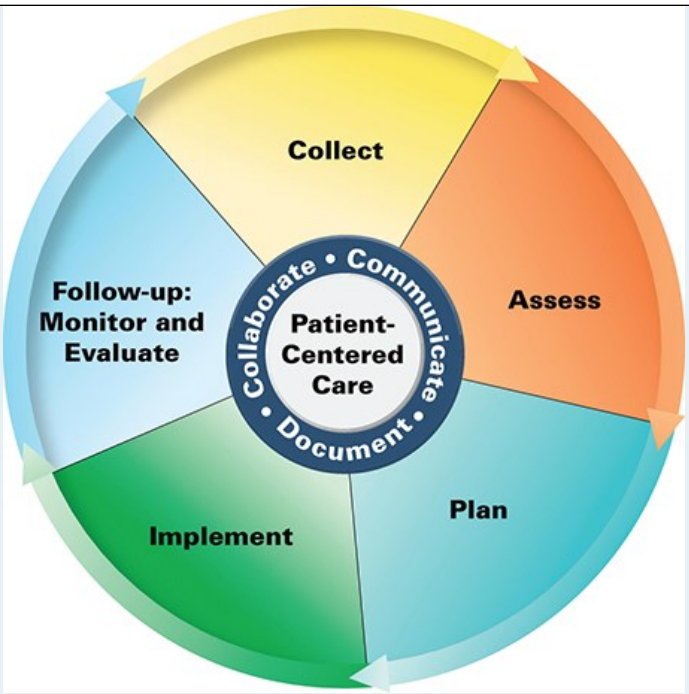
Risk Stratification

2 For patients with ACS, acute risk stratification is essential to determine which patients may benefit from reperfusion therapy, an early invasive approach, or medical management (Fig. 34-2).[1,2] Initial evaluation of risk should include the clinical presentation, past medical history, and both ECG and cTn upon presentation. For example, because STEMI has the highest short-term risk of death, patients with ACS who present with significant ST-segment elevation on ECG should be considered for emergent reperfusion therapy; confirmation of elevated cTn should not delay treatment.

Several risk scoring tools have been developed that predict both short-term and long-term event rates, such as mortality, in patients with ACS (Table 34-1).[22-25] These tools have been well-studied and can be easily applied in the clinical setting. Each of the risk assessment tools incorporates the patient's symptoms, past medical history, ECG, and cTn, while the Global Registry of Acute Coronary Events (GRACE) score also includes additional clinical indicators. For each risk estimator, there is a linear relationship between increasing score and the risk of MACE. For example, in patients with NSTE-ACS, the incidence of MACE through 14 days was 4.7% to 8.3%, 13.2% to 19.9%, and 26.2% to 40.9% in the low (Thrombolysis in Myocardial Infarction [TIMI] risk score 0-2), intermediate (TIMI risk score 3-4), and high (TIMI risk score 5-7) risk groups, respectively.[23] Compared to both the TIMI and GRACE risk estimators, the History, ECG, Age, Risk factors, and Troponin (HEART) score is better at identifying patients who present to the hospital with suspected ACS at low risk of MACE.[27] While this prognostic information is useful, the ability of the risk scoring tools to identify patients with ACS who may benefit from specific therapeutic interventions described below makes them particularly useful in the development of the treatment plan.

PATIENT CARE PROCESS

Patient Care Process for Acute Coronary Syndrome



Collect

- Patient characteristics (eg, age, sex, pregnant)
- Description of chest discomfort and/or related symptoms (eg, quality, location, severity, radiation, precipitating factors, palliative measures, time of onset, duration of symptoms)
- Patient medical (personal and family) and social histories (eg, tobacco/ethanol, drugs of abuse [eg, cocaine])
- Current medications with particular attention to phosphodiesterase-5 inhibitors, over-the-counter medications (eg, aspirin-containing medications, nonsteroidal anti-inflammatory drugs), and herbals/dietary supplement use
- History of allergy or intolerance to medications
- Objective data
  - Blood pressure, heart rate, respiratory rate, height, weight, O_2-saturation, physical exam
  - Labs: cTn, Scr, potassium, hemoglobin, platelets, lipid profile
  - Diagnostic tests: 12-lead ECG; coronary angiogram and stress testing as necessary

Assess

- Description of chest discomfort to determine differential diagnosis and classification of ACS
- Presence of provoking factors (eg, exertion, mental/emotional stress, tachyarrhythmia, high adrenergic state including the use of stimulant medications, exposure to cold)
- Presence/control of risk factors for CAD (eg, HTN, dyslipidemia, DM, smoking, obesity, family history of premature CAD)
- Presence of ACS-related complications (eg, HF, cardiogenic shock, arrhythmias, heart block, stroke)
- Previous/recent revascularization procedures (eg, PCI with/without stenting, CABG surgery)

- Presence of ST-segment elevation or equivalent on 12-lead ECG
- Risk for major adverse cardiac events (MACE) (eg, perform risk stratification [see Table 34-1])
- Contraindications or intolerance to medications used to treat/prevent angina symptoms and MACE
- Barriers that may impair adherence to the care plan

Plan*

- Initiate antithrombotic therapy to treat and prevent intracoronary thrombosis as well as drug therapy to alleviate angina symptoms and prevent MACE including specific drug(s), dose, route, frequency, and duration (see Figs. 34-2 and 34-3; Tables 34-2–34-5, 34-7, and 34-8).
- Monitoring parameters: efficacy (eg, resolution of signs and symptoms of angina and ACS-related complications) and adverse effects; frequency and timing of follow-up (see Table 34-10)
- Patient education: purpose of treatment, lifestyle modifications, planned procedures, drug-specific information (eg, indication, dose, route, frequency, adverse effects)
- Self-monitoring for recurrent angina symptoms, signs and symptoms of ACS-related complications, adverse effects, when to seek emergency medical attention
- Address barriers to adherence to medications and lifestyle modification
- Referrals to other providers (eg, primary care provider, endocrinologist, dietician, smoking cessation)

Implement*

- Provide patient education regarding all elements of the treatment plan as described above.
- Use motivational interviewing and coaching strategies to maximize adherence.
- Schedule follow-up (eg, usually within 1-2 weeks but no later than 6 weeks after discharge).

Follow-up: Monitor and Evaluate

- Presence of angina symptoms, exercise tolerance, presence/control of CAD risk factors, presence/control of ACS-related complications
- Appropriate use and doses of evidence-based pharmacotherapy for ACS
- Presence of adverse effects and drug-drug interactions
- Patient adherence to treatment plan using multiple sources of information

****Collaborate with patients, caregivers, and other healthcare professionals.***

TREATMENT

Treatment decisions for patients with ACS are made based on the initial and ongoing risk stratification (Fig. 34-2). Rapid identification and delineation of ACS subtype (STEMI, NSTE-ACS) are imperative as treatment goals and timeframes for intervention differ slightly based on the clinical presentation and subsequent risk of death or complications from the index event (eg, patient with STEMI). When ACS is suspected, the patient should be immediately referred to an ED, chest pain unit, or equivalent facility for evaluation which should include 12-lead ECG and cTn such that expeditious treatment can be initiated.[1,2] Patients with possible ischemic symptoms, particularly if high-risk features (persistent chest pain, severe dyspnea, syncope or presyncope, or palpitations) are present, should be educated to activate the EMS system (eg, call 9-1-1) and seek transport via ambulance.

EMS personnel are equipped to treat cardiac arrest should it occur; this approach is associated with earlier initiation of reperfusion therapy.

Desired Outcomes

In patients with ACS, treatment is aimed at achieving both short-term and long-term outcomes. Desired short-term outcomes in a patient with ACS are as follows: (a) early restoration of blood flow to the infarct-related artery to prevent infarct expansion (in the case of MI) or prevent complete occlusion and MI (in UA); (b) prevention of death and other MI complications; (c) prevention of coronary artery reocclusion; and (d) relief of ischemic chest discomfort. Long-term goals are control of atherosclerosis risk factors, prevention of additional MACE, including reinfarction, stroke, and HF, and improvement in quality of life.

General Approach to Treatment

The general treatment approach to ACS includes rapid diagnostic triage to determine an appropriate management strategy (Fig. 34-2). Patients with STEMI are of the highest priority and should be emergently referred to the cardiac catheterization lab for primary PCI with the goal of mechanically restoring blood flow to the infarct-related artery as quickly as possible. Patients with NSTE-ACS will undergo additional risk stratification to determine the best approach, which is usually an early invasive approach (eg, PCI) for intermediate- and high-risk patients or a more conservative, ischemia-guided management plan without planned PCI for those with either the lowest risk for coronary event or contraindications to the invasive procedure itself (Fig. 34-2). Regardless of treatment strategy planned (early invasive approach or ischemia-guided approach), general treatment measures for intermediate- and high-risk patients include admission to the hospital, oxygen administration (if oxygen saturation is <90% [0.90]), bed rest with continuous multi-lead ECG monitoring for arrhythmias and ischemia, frequent measurement of vital signs, ischemic pain relief, and prompt initiation of antithrombotic therapy.

Acute Supportive Care

Historically, clinicians and educators have used the mnemonic MONA (Morphine, Oxygen, Nitroglycerin, Aspirin) as a reminder for acute supportive care interventions to be considered in patients with ACS. However, in recent years, recommendations for the routine use of some of these therapies (eg, morphine, oxygen) have been tempered. Further, MONA ignores other potentially useful interventions to consider in the early phase of ACS treatment. Thus, the mnemonic THROMBINS$_2$ (Thienopyridine, Heparin, Renin-angiotensin-aldosterone system, Oxygen, Morphine, β-blocker, Intervention [eg, PCI], Nitroglycerin, Statin/Salicylate [eg, aspirin]) has been developed as a more contemporary reminder for early interventions to consider in patients with ACS.[28] Acute supportive therapies used to treat patients with ACS are summarized in Table 34-2.

TABLE 34-2

Acute Supportive Care Medications Initiated During the Initial 24 Hours of ACS Treatment

Drug	Indication (Class of Recommendation)[a]	Contraindication/Caution	Dose/Administration	Adverse Effects
Morphine	Refractory pain (IIb)	Known hypersensitivity Hypotension Bradycardia Lethargic or moribund patient	STEMI: 4-8 mg IV × 1 (lower dose in older patients), then 2-8 mg IV every 5-15 minutes PRN NSTE-ACS: 1-5 mg IV every 5-30 minutes PRN	Constipation, nausea, vomiting, hypotension, respiratory depression
Oxygen	Oxygen saturation <90% [0.90] (I)	Chronic obstructive pulmonary disease Carbon dioxide retention	2-4 L/min, increasing rate and/or changing to face mask PRN	Increased coronary vascular resistance, decreased coronary blood flow, increased mortality
Nitroglycerin	Angina (I)	SBP less than 90 mm Hg	SL: 0.3-0.4 mg every 5 minutes, up to	Flushing, headache,

	Uncontrolled hypertension (I) Acute heart failure (I)	or greater than 30 mm Hg below baseline Avoid if recent PDE_5 inhibitor use: ○ Avanafil: within 12 hours ○ Sildenafil: within 24 hours ○ Vardenafil: within 24 hours ○ Tadalafil: within 48 hours Use with caution if RV infarct suspected Avoid abrupt cessation of IV nitroglycerin; wean gradually	3 doses PRN IV: 10 mcg/min titrated to symptom relief and desired blood pressure	hypotension, tachycardia
β-Blockers	All patients without contraindications (I) *Associated with mortality reduction, especially in patients with HFrEF*	Signs of heart failure Low cardiac output state Risk factors for cardiogenic shock: ○ Age 70 years or greater ○ SBP less than 120 mm Hg ○ Sinus tachycardia (HR greater than 110 bpm) ○ Sinus bradycardia (HR less than 60 bpm) ○ Killip class III ○ Prolonged time from symptom onset High-grade AV block Active asthma or reactive airway disease	Carvedilol 6.25 mg twice daily; target dose is 25 mg twice daily as tolerated Metoprolol ○ Oral: 25-50 mg every 6-12 hours for 2-3 days, then once (metoprolol succinate) or twice daily (metoprolol tartrate); target dose is 200 mg daily ○ IV: 5 mg every 5 min as tolerated up to 3 doses, titrated to BP and HR; should only be considered if BP is uncontrolled or refractory symptoms Continue indefinitely in patients with concomitant HFrEF Other β-blockers may be considered; in patients with HFrEF, use either metoprolol succinate, carvedilol, or bisoprolol	Hypotension, heart failure, bradycardia, cardiogenic shock, AV block, exacerbation of asthma or reactive airway disease
Calcium channel blockers	Angina, normal LVEF, and contraindication or intolerance to	Signs of heart failure Low cardiac output state Risk factors for	Diltiazem 120-360 mg/day orally[b] Verapamil 240-480 mg/day orally[b] Amlodipine 5-10 mg orally once daily	Hypotension, diltiazem and verapamil: heart failure, cardiogenic shock, bradycardia, AV block

	β-blocker (I) Angina refractory to β-blocker and normal LVEF (I) Coronary vasospasm (I)	cardiogenic shock: ○ Age 70 years or greater ○ SBP less than 120 mm Hg, sinus tachycardia (HR greater than 110 bpm) ○ Sinus bradycardia (HR less than 60 bpm) ○ Killip class III ○ Prolonged time from symptom onset High-grade AV block	Nicardipine 60-120 mg/day orally[b] Nifedipine ER 30-120 mg orally once daily	

[a]Dose and frequency may differ based on formulation.

[b]AHA/ACC class of recommendations: I, benefit far outweighs the risk, treatment should be administered; IIb, the benefit is equal to or exceeds the risk, additional studies with broad objectives are needed, treatment may be considered.

AV, atrioventricular; BP, blood pressure; ER, extended-release; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; IV, intravenous; PDE5, phosphodiesterase-5; PRN, as needed; RV, right ventricular; SBP, systolic blood pressure.

Data from References 1,2, and 29.

Nitroglycerin

Nitrates, including nitroglycerin, are effective anti-ischemic medications and are routinely recommended as part of the initial management of patients with ACS.[1,2] Nitrates promote the release of nitric oxide from the endothelium, which results in venous and arterial vasodilation. Venodilation, the predominant effect, decreases preload, reducing ventricular wall tension, and myocardial oxygen demand. The effects on arterial vasodilation are less prominent but may lower systemic vascular resistance and blood pressure at higher doses, thus reducing myocardial oxygen demand. Nitrates also dilate coronary arteries and increase collateral blood flow.

However, the rationale for treating ACS patients with nitrates is extrapolated from an understanding of the pathophysiology of ACS, pharmacology of nitrates, numerous uncontrolled studies, and clinical experience—not their ability to reduce MACE.[2] In the reperfusion era, there is a paucity of data demonstrating that nitrate administration to patients with ACS is effective in providing symptom relief or reducing the incidence of MACE. In two large studies of patients with suspected MI, neither IV nitroglycerin (for 24 hours) followed by daily transdermal nitroglycerin nor daily isosorbide mononitrate reduced the incidence of MACE.[30,31] Postinfarction angina and cardiogenic shock were lower with the IV followed by transdermal nitroglycerin approach but not with the isosorbide mononitrate strategy. The use of IV sodium nitrite in 229 patients with STEMI treated with primary PCI had no effect on infarct size.[32]

3 Because nitroglycerin is effective in relieving angina symptoms, it is often utilized in patients with ACS with ongoing angina who are not hypotensive.[1,2] The recommended use for nitroglycerin in patients with ACS is provided in Table 34-2. Initially, SL nitroglycerin should be administered every 5 minutes for up to three doses as needed for angina. For patients with persistent angina despite SL nitroglycerin, IV nitroglycerin should be considered, particularly in patients with uncontrolled HTN or evidence of HF on presentation. Because nitroglycerin dilates coronary arteries, it is useful in treating ACS related to vasospasm, particularly if cocaine intoxication is thought to be contributory. In fact, in patients with cocaine-induced

chest pain, IV nitroglycerin is often the initial anti-ischemic medication recommended, especially if uncontrolled HTN is present.[33] Intravenous nitroglycerin should be continued until symptoms have resolved, blood pressure is controlled, and HF symptoms (if present) have subsided. Hemodynamic tolerance to IV nitroglycerin can occur within 8 to 12 hours, requiring higher doses with prolonged therapy. The most significant adverse effects of nitrates are flushing, headache, hypotension, and tachycardia. Because a synergistic reduction in blood pressure can occur leading to hypotension, nitrate administration is contraindicated in patients who have recently taken oral phosphodiesterase-5 inhibitors (Table 34-2).[1,2,34]

Morphine

Intravenous morphine is a potent analgesic and anxiolytic agent that also causes venodilation and increases vagal tone which reduces heart rate.[1,2] The analgesic and anxiolytic effects may improve patient comfort while the hemodynamic effects may reduce oxygen demand, thereby making IV morphine an attractive treatment option in patients with ACS. However, randomized clinical trials have not been conducted to determine the optimal dose nor evaluate the safety and efficacy of IV morphine in patients with ACS.

The safety of routinely using IV morphine to treat ACS has been recently questioned. Patients treated for ACS with IV morphine had higher rates of in-hospital death, MACE, and bleeding.[35] Studies evaluating IV morphine to treat ACS have high risk of bias, contributing to low confidence in the observed outcomes.

A proposed mechanism for the adverse outcomes associated with IV morphine in patients with ACS is the presence of a drug-drug interaction with $P2Y_{12}$ inhibitors. Morphine stimulates opioid receptors in the GI tract leading to inhibition of gastric emptying, which may slow the absorption of the antiplatelet agent.[36] Additionally, common side effects of morphine include nausea and vomiting. The coadministration of IV morphine and $P2Y_{12}$ inhibitors prolongs the time to peak concentrations, decreases total drug exposure, and produces less platelet inhibition.[36]

3 There is uncertainty regarding the role of IV morphine in patients with ACS. In patients with STEMI, current guidelines state that IV morphine is the drug of choice for pain relief but do not provide a class recommendation.[1] In NSTE-ACS, the use of IV morphine is recommended only in patients refractory to treatment with other anti-ischemic medications (Class IIb recommendation).[2] If IV morphine is used to treat patients with ACS, doses between 1 and 5 mg every 5 to 30 minutes are recommended (Table 34-2).[1,2] While nausea and vomiting are common, the most serious adverse effects to monitor are hypotension and respiratory depression.

Oxygen

3 Although routine oxygen is often administered to patients with ACS, it should be reserved for a minority of patients, particularly those with oxygen saturation less than 90% [0.90].[1,2] The routine use of oxygen may adversely affect patients with ACS by increasing coronary vascular resistance and reducing coronary blood flow.[1,2] The routine use of supplemental oxygen to patients treated for MI was of no benefit with signals suggesting infarct size may be increased.[37]

β-Blockers

Because β-blockers not only possess beneficial anti-ischemic effects but also lower the risk of MACE, their use is recommended for all patients with ACS without contraindications.[1,2] β-Blockers antagonize the β_1-adrenergic receptors causing a decrease in heart rate, contractility, blood pressure, and, subsequently, myocardial oxygen demand. Additionally, the reduction in heart rate increases diastole, prolonging myocardial perfusion and filling time. β-Blockers increase coronary blood flow to the ischemic myocardium by increasing coronary collateral resistance, preventing the shunting of blood away from ischemic areas.[19] The reduction in myocardial oxygen demand coupled with improved coronary blood flow to ischemic areas make β-blockers effective anti-ischemic medications in patients with ACS.

The anti-ischemic effects described above also contribute to the reduction in risk of MACE observed in patients with ACS treated with β-blockers. The risk of reinfarction and post-infarction angina is reduced in patients with MI treated with β-blockers.[38,39] Additionally, β-blockers improve survival in patients with MI, although this benefit has been questioned in recent years. Many β-blocker trials in MI that demonstrated a mortality benefit were conducted in the pre-reperfusion era. In a contemporary trial conducted in patients with MI during the reperfusion era, the use of early IV followed by

oral metoprolol was associated with reductions in reinfarction, ventricular fibrillation, and arrhythmic death.[40] However, the primary composite endpoint (death, reinfarction, ventricular fibrillation, or cardiac arrest) was not significantly different from placebo and the risk of developing shock, including cardiogenic shock, was significantly increased. Consistent with this theme, the evaluation of β-blockers in MI had a modest mortality benefit for studies conducted during the pre-reperfusion era but no benefit was observed in studies completed during the reperfusion era.[38] Some of the uncertainty regarding mortality stems from variations in the duration of therapy and follow-up duration in many of the trials. β-Blockers had no influence on the odds of death in short-term trials (up to 6 weeks of treatment) but were associated with a 23% lower risk in long-term trials (treatment durations of 6-48 months).[39] In a recent observational study of patients with MI, 5-year mortality was approximately 30% lower for patients treated with β-blockers at hospital discharge; however, the benefits were no longer significant for those continuing therapy beyond 1 year.[41,42] Consequently, at least one international guideline recommends initiating a discussion with patients who are post-MI with normal left ventricular ejection fraction (LVEF greater than 40% [0.40]) regarding the risks and benefits of continuation beyond 12 months based on recent evidence.

4 Although the mortality benefit of β-blockers in the reperfusion era is uncertain, because they reduce the risk of MI, angina, and arrhythmias, in the absence of contraindications, current ACC/AHA guidelines recommend the initiation of oral β-blockers within the first 24 hours of presentation and continuation of therapy for at least 3 years (Table 34-2).[1,2,29] For patients with ACS and concomitant left ventricular dysfunction (LVEF less than 40% [0.40]), β-blocker therapy is often lifelong.[1,29] Although several β-blockers have been studied in the setting of ACS, the most commonly used agents are metoprolol and carvedilol largely due to the mortality benefit associated with their use in the treatment of HF, a common complication of ACS.

The most serious adverse effects observed in patients with ACS treated with β-blockers include HF, hypotension, bradycardia, and cardiogenic shock.[40] Therefore, in patients with evidence of or risk of developing these complications, β-blocker therapy should be withheld and initiation reassessed later during hospitalization.[1,2] Advanced age (70 years or older), presenting systolic blood pressure less than 120 mm Hg, sinus tachycardia (heart rate greater than 110 bpm) or bradycardia (heart rate less than 60 bpm) upon presentation, Killip class III (eg, pulmonary edema), and a prolonged time from symptom onset are patient characteristics associated with an increased risk of cardiogenic shock for whom β-blocker initiation should be postponed.[1,2,40] While β-blocker initiation should be avoided in patients with ACS and decompensated HF due to left ventricular dysfunction, the initiation of β-blocker therapy once HF symptoms have been stabilized and prior to discharge is safe, has been associated with lower mortality, and should be considered for all patients with ACS and compensated HF with reduced ejection fraction (HFrEF).[2,43] For patients with ACS and acute intoxication with cocaine or methamphetamine, β-blockers should be avoided unless a concomitant coronary vasodilator is also used to minimize the risk of causing or potentiating coronary vasospasm via unopposed α_1-adrenergic stimulation.[2,33,44] Because early initiation of IV β-blockers has been associated with an increased risk of HF and cardiogenic shock, parenteral therapy should be reserved for patients with STEMI who have acute, uncontrolled HTN or refractory symptoms and no contraindications.[1,29]

Calcium Channel Blockers

Calcium channel blockers (CCBs) possess beneficial anti-ischemic effects and are recommended for some patients with ACS, particularly those who are unable to take β-blockers.[1,2] CCBs cause arterial vasodilation, including coronary vasodilation, decreasing peripheral resistance, afterload, blood pressure, and myocardial oxygen demand.[19] All CCBs are also negative inotropes. However, because dihydropyridine (DHP) CCBs are potent peripheral vasodilators, they cause a baroreceptor-mediated increase in sympathetic activity that negates their negative inotropic effect.[19] Non-DHP CCBs decrease sinoatrial node activity and slow atrioventricular node conduction resulting in a decreased heart rate.[19]

4 Although CCBs are effective as anti-ischemic agents, reports of harm, lack of consistent benefit in clinical trials, and the data supporting β-blockers have narrowed the indications for CCBs in patients with ACS. In a systematic review, CCBs had no effect on mortality, MI, or recurrent MI in patients treated for ACS.[42] Consequently, current guidelines recommend non-DHP CCBs (eg, diltiazem, verapamil) to treat angina symptoms in patients with ACS who have a contraindication, have an intolerance, or are refractory to β-blockers in the absence of left ventricular dysfunction, risk factors for cardiogenic shock, and atrioventricular conduction defects (Table 34-2).[1,2] Because of their ability to dilate coronary arteries, long-acting CCBs are recommended in patients with ACS with known or suspected vasospasm.[2] However, if vasospasm is secondary to cocaine intoxication, the use of CCBs should be considered only after treatment with IV nitroglycerin and benzodiazepines.[33,44] Although long-acting formulations may be reasonable, immediate-release nifedipine should be avoided as it has been associated with increased mortality risk in patients with CAD, including those with

ACS.[2,45] The most common adverse effects associated with the use of non-DHP CCBs in patients with ACS include heart block, bradycardia, hypotension, and GI disturbances.

Treatment Strategies in STEMI

The widespread use of reperfusion during ACS is responsible for the dramatic decrease in MI-related mortality over the past three decades in the United States.[46] Reperfusion strategies include fibrinolysis and mechanical intervention via PCI with or without stenting, both with the aim of restoring blood flow to the infarct-related artery. Appropriate choice and timing of reperfusion in ACS to facilitate revascularization are critical in STEMI to improve outcomes. Strategies to reduce delays in reperfusion include prehospital assessment of the initial ECG by EMS, early anti-ischemic medication administration, and transport to a hospital with PCI-capable facilities.

Primary PCI

5 In STEMI, the degree of myonecrosis is curvilinear, with the maximum amount of damage occurring in the first few hours of infarction.[47] Therefore, prompt efforts to restore blood flow to the infarct-related artery are paramount. During PCI, mechanical reperfusion is performed using intracoronary balloons, stents, and other devices. The reader is referred to Chapter 33, "Stable Ischemic Heart Disease," for a more detailed description of both coronary angiography and PCI. Compared to reperfusion with fibrinolysis, primary PCI improves survival, establishes consistent revascularization to the infarct-related artery, significantly reduces the risk of stroke and intracranial hemorrhage, and reduces reinfarction and recurrent ischemia. However, the mortality benefit of primary PCI over fibrinolysis is lost when door-to-balloon time exceeds 120 minutes.[48] More rapid performance of primary PCI can result in superior clinical outcomes for patients with STEMI.[1,49,50] In patients with STEMI treated with primary PCI, the risk of in-hospital death was increased by more than 40% when the door-to-balloon time was more than 90 minutes compared to 90 minutes or less.[51] In the United States, quality improvement programs have reduced mean door-to-balloon times from 120 minutes to 87 minutes, decreasing the in-hospital mortality rate from 8.3% to 6.6%.[52] Therefore, early reperfusion with primary PCI is of utmost importance and is preferred by guidelines for patients presenting with STEMI, with the goal of reperfusion within 90 minutes from the time of first medical contact.[1] However, in the United States, only 39% of all hospitals can perform PCI.[53] Given the benefits of primary PCI, patients presenting with STEMI to a hospital unable to perform PCI should be transferred to a PCI-capable hospital to achieve reperfusion within 120 minutes of the first medical contact.[1] Every minute delay results in additional myocardial cell damage that may be irreversible. Patients with STEMI undergoing primary PCI also require adjunctive antiplatelet and anticoagulant therapy which is discussed in greater detail later in this chapter.[1]

Fibrinolysis

5 When primary PCI for patients with STEMI is not possible within a timely fashion, pharmacological reperfusion, or fibrinolysis, is an alternative to primary PCI. The available fibrinolytic agents are plasminogen activators that increase the conversion of plasminogen to plasmin. Plasmin binds to the fibrin strands within the thrombus, breaking them down and allowing blood flow to be restored.

Fibrinolysis is an important means of reperfusion and prevents 30 early deaths per 1,000 patients treated within 6 hours of symptom onset.[54] The mortality advantage of primary PCI over fibrinolysis in patients with STEMI is lost when primary PCI is delayed more than 120 minutes.[48] Therefore, guidelines recommend fibrinolysis when primary PCI cannot be performed within 120 minutes.[1] This may apply when patients have immediate contraindications to receiving contrast dye, the facility to which patients present is unable to perform PCI and transfer time would exceed 120 minutes, or when patients present at off-peak hours when the catheterization laboratory cannot be adequately staffed within 120 minutes. Non-PCI-capable hospitals should aspire to transfer patients with STEMI to a PCI-capable hospital within 30 minutes of arrival (door-in-door-out goal).[1] Yet, when the anticipated time to PCI is expected to exceed 120 minutes, fibrinolytic therapy should be given within 30 minutes of hospital arrival provided no contraindications are present.[1] In fact, for patients with STEMI, the time from hospital presentation until the start of fibrinolytic therapy (door-to-needle time) is a quality performance measure of timely and effective care.[55] In a recent analysis evaluating the timeliness of reperfusion for patients with STEMI, the median door-to-needle time for patients treated with fibrinolytics was approximately 24 minutes with approximately 60% meeting the goal of less than 30 minutes.[56] A coordinated approach among EMS, ED, cardiology, and pharmacy personnel is needed in order to improve this further.

Indications and contraindications to fibrinolytic therapy are outlined in Table 34-3. Fibrinolytic therapy is associated with a slight but significant risk for stroke, largely attributed to intracranial hemorrhage (ICH), which occurs in 0.9% to 1.0% of patients.[57] Significant predictors for ICH include advanced age, lower total body weight, female sex, preexisting cerebrovascular disease, and systolic and diastolic HTN at time of presentation.[57]

TABLE 34-3

Indications and Contraindications to Fibrinolytic Therapy for STEMI

Indications	Absolute Contraindications	Relative Contraindications
• Symptoms of acute coronary syndrome with an onset within 12 hours of first medical contact • ST-segment elevation of 1 mm or greater in two contiguous leads or new left bundle branch block on a 12-lead ECG • Anticipated that primary PCI cannot be performed within 120 minutes of first medical contact	• Any prior hemorrhagic stroke • Ischemic stroke within 3 months (except in past 4.5 hours) • Intracranial neoplasm or arteriovenous malformation • Active internal bleeding • Aortic dissection • Considerable facial trauma or closed-head trauma in the past 3 months • Intracranial or intraspinal surgery within 2 months • Severe, uncontrolled hypertension (unresponsive to emergency therapy) • For streptokinase,[a] treatment within the previous 6 months (if considering streptokinase again)	• BP >180/110 mm Hg on presentation or history of chronic poorly controlled hypertension • History of ischemic stroke greater than 3 months before • Recent major surgery (less than 3 weeks before) • Traumatic or prolonged CPR (greater than 10 minutes) • Recent internal bleeding (within 2-4 weeks) • Active peptic ulcer • Noncompressible vascular punctures • Pregnancy • Known intracranial pathology (dementia) • Oral anticoagulant therapy

[a]Streptokinase is no longer marketed in the United States but is available in other countries.

BP, blood pressure; CPR, cardiopulmonary resuscitation.

Data from Reference 1.

Relative contraindications to fibrinolytic therapy should be mitigated where possible (eg, giving antihypertensive medications to reduce blood pressure to less than 185/110 mm Hg) to reduce the risk for ICH, prior to administration. Patients at high risk for major bleeding (including a history of ICH) presenting with an absolute contraindication should not receive fibrinolytic therapy and should be transferred to a hospital capable of performing PCI. It is important to weigh the potentially life-saving effect against the life-threatening potential for an adverse event in those with contraindications to fibrinolytic therapy, taking into consideration alternative options such as delayed PCI. The mortality benefit of fibrinolysis is highest when administered early after symptom onset but is negligible if administered to patients with symptom durations exceeding 12 hours. The use of fibrinolytics between 12 and 24 hours after symptom onset should be limited to patients with clinical and/or electrocardiographic evidence of ongoing ischemia.[1] Noncerebral bleeding from fibrinolysis has been reported to be as high as 13%.[57]

When fibrinolytic therapy is indicated, a fibrin-specific agent (alteplase, reteplase, or tenecteplase) is recommended over a non-fibrin-specific agent (eg, streptokinase) because of greater reperfusion success and less systemic bleeding with fibrin-specific agents.[1] Any fibrin-specific agent is acceptable as no drug has demonstrated superiority over the others with regard to the mortality benefit.[58] However, in a systematic review, there was a trend toward a lower risk of major bleeding with tenecteplase compared to other fibrin-specific agents.[58] Therefore, safety considerations along with ease of administration or formulary restrictions may dictate the institutional preference of one agent over another. All hospitals should have protocols addressing fibrinolysis eligibility, dosing, and monitoring. Dosing considerations for the use of fibrinolytics in STEMI are provided in Table 34-4.

TABLE 34-4

Fibrinolytic Therapy Dosing in Patients with STEMI

Drug	Dosing Considerations
Alteplase (tPA)	15 mg IVP 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; total dose not to exceed 100 mg
Reteplase (rPA)	10 units IVP over 2 minutes × 2 doses given 30 minutes apart
Tenecteplase (TNK-tPA)	<60 kg: 30 mg IVP[a];
	60-69 kg: 35 mg IVP[a];
	70-79 kg: 40 mg IVP[a];
	80-89 kg: 45 mg IVP[a];
	>90 kg: 50 mg IVP[a]

[a]In patients 75 years or older, the dose may be reduced by 50% to decrease the risk of intracranial hemorrhage.[59]

IVP, intravenous push. Please refer to Tables 34-5 and 34-7 for appropriate adjunctive antiplatelet and anticoagulant therapy for patients with STEMI treated with fibrinolytics.

Data from Reference 1.

TABLE 34-5

Antiplatelet Drug Use and Dosing Across the Spectrum of ACS and Management Strategy

Drug	STEMI		NSTE-ACS	
	Primary PCI	Fibrinolytic Reperfusion	Early Invasive Strategy	Ischemia-Driven Strategy
Aspirin				
Loading dose	162-325 mg	162-325 mg	162-325 mg	162-325 mg
Maintenance dose	81 mg daily	81 mg daily	81 mg daily	81 mg daily
$P2Y_{12}$ inhibitors				
Clopidogrel				
Loading dose	600 mg	300 mg	600 mg	300 mg
		Age greater than 75 years: No		

		loading dose given		
Maintenance dose	75 mg daily	75 mg daily	75 mg daily	75 mg daily
Prasugrel		No recommendation		No recommendation[a]
Loading dose	60 mg		60 mg	
Maintenance dose	10 mg daily		10 mg daily	
	Weight less than 60 kg: 5 mg daily		Weight less than 60 kg: 5 mg daily	
Ticagrelor		No recommendation		
Loading dose	180 mg		180 mg	180 mg
Maintenance dose	90 mg twice daily		90 mg twice daily	90 mg twice daily
Cangrelor	30 mcg/kg IV bolus, followed by 4 mcg/kg/min IV infusion for at least 2 hours or duration of PCI	No recommendation	30 mcg/kg IV bolus, followed by 4 mcg/kg/min IV infusion for at least 2 hours or duration of PCI	No recommendation
GP IIb/IIIa inhibitor				
Eptifibatide	180 mcg/kg IV bolus × 2 given 10 minutes apart, followed by 2 mcg/kg/min IV infusion started after first bolus and continued for 18-24 hours after PCI	No recommendation	180 mcg/kg IV bolus × 2 given 10 minutes apart, followed by 2 mcg/kg/min IV infusion started after first bolus and continued for 18-24 hours after PCI	No recommendation
	CrCl less than 50 mL/min (0.83 mL/s):		CrCl less than 50 mL/min (0.83 mL/s):	
	Reduce infusion by 50%		Reduce infusion by 50%	
	Hemodialysis: Avoid use		Hemodialysis: Avoid use	
Tirofiban	25 mcg/kg IV bolus, followed by 0.15 mcg/kg/min	No recommendation	25 mcg/kg IV bolus, followed by 0.15 mcg/kg/min	No recommendation
	CrCl less than 60 mL/min (1.0 mL/s):		CrCl less than 60 mL/min (1.0 mL/s):	
	Reduce infusion by 50%		Reduce infusion by 50%	

CrCl, creatinine clearance; IC, intracoronary; IV, intravenous.

[a]Not mentioned in the ACC/AHA guidelines, but evidence of noninferiority compared to clopidogrel exists. Prasugrel dosing was a 30 mg loading dose followed by 10 mg daily. Patients weighing less than 60 kg or age 75 years or more received a maintenance dose of 5 mg daily.

Data from References 1 and 2.

As with primary PCI, antiplatelet therapy and parenteral anticoagulation should be given concomitantly in patients treated with fibrinolytic therapy to improve vessel patency and to prevent reocclusion.[1] Adjunctive antiplatelet and anticoagulant therapies are discussed later in this chapter.

Despite data suggesting a benefit and the feasibility of pre-hospital fibrinolysis, the administration of fibrinolytic therapy by EMS personnel to patients during transport to the hospital is not routine practice in the United States. Early angiography after fibrinolytic therapy, a practice referred to as a pharmacoinvasive approach, may reduce cardiovascular events compared to patients transferred for immediate PCI, yet increased rates of ICH have been implicated with this approach.[46,59] Transfer to a PCI-capable facility for possible "rescue PCI" after fibrinolysis is appropriate for those who fail fibrinolytic therapy and those patients with acute, severe HF or cardiogenic shock.[1]

Treatment Strategies in NSTE-ACS

Early Invasive Approach

While patients presenting with STEMI benefit from immediate reperfusion of the infarct-related artery due to complete arterial occlusion, patients presenting with NSTE-ACS typically have a partially occluded coronary artery with some residual perfusion and, therefore, the need for and urgency to perform PCI is not as critical. With an early invasive approach, the patient has a diagnostic angiography performed early in the hospital course, typically within the first 24 hours, with the intent to perform revascularization if appropriate, depending on the coronary anatomy.[2] An early invasive strategy improves cardiovascular outcomes in patients presenting with NSTE-ACS with the greatest benefits achieved in those patients with the highest risk for MACE. Risk stratification is, therefore, essential in NSTE-ACS to determine which patients will derive the most benefit from an early invasive approach. The benefit of routine invasive therapy is superior to an ischemia-guided approach (a more conservative watch and wait approach) usually in patients with advanced age (older than age 70), previous MI or revascularization, ST-segment changes, HF (especially with left ventricular dysfunction), elevated cTn, DM, and in those with positive results from noninvasive stress tests. Practice guidelines recommend an early invasive strategy in those with an elevated risk for death or MI (eg, high-risk and select intermediate-risk patients [see Table 34-1]), those with refractory angina, acute HF, other symptoms of cardiogenic shock, or arrhythmias.[2,26,60]

Ischemia-Guided Approach ("Medical Management")

In contrast to an early invasive approach, a more conservative management strategy for those with the lowest risk is referred to as an ischemia-guided approach, or "medical management," where anti-ischemic, antiplatelet, and anticoagulant medications are administered and PCI is not initially planned. The patient is evaluated for signs and symptoms of recurrent ischemia or hemodynamic instability and taken for invasive coronary angiography and possible PCI only if recurrent symptoms develop or noninvasive diagnostic testing (eg, coronary computed tomography angiography, stress testing) suggest obstructive CAD. This strategy is appropriate for select low- and intermediate-risk patients, for those with serious comorbidities or contraindications to angiography/PCI (eg, renal failure), or when the risks of the procedure outweigh the benefits of revascularization.[2] The ischemia-driven approach is also preferred by guidelines for those with a low likelihood of ACS, in women without troponin elevation, and in those who do not consent for revascularization.[2]

Antithrombotic Therapy

Due to the role of thrombus formation in the setting of ACS, timely and appropriate antithrombotic therapy is an important component of optimal pharmacotherapy. Antithrombotic therapy consists of antiplatelet and anticoagulant therapy. While platelets dominate the pathophysiologic process in arterial thrombosis, the central role of thrombin in both platelet activation and coagulation makes both types of therapy necessary in the acute phase of treatment in a patient with ACS. After hospital discharge, most patients are typically continued on long-term antiplatelet therapy only, although evidence for use of long-term anticoagulant therapy after ACS is emerging for some high-risk groups.

One of the most challenging aspects of the use of antithrombotic therapy in patients with ACS is that not all agents have been studied across the spectrum of ACS and its different management strategies. While some agents may have data in the setting of NSTE-ACS, they may not have data in

STEMI. For patients with NSTE-ACS, data are different for patients being managed with an ischemia-driven approach compared to those receiving PCI.[2] Some agents may have data in the setting of primary PCI in STEMI, but not with the use of fibrinolytics in STEMI.[1] Lastly, agents may have data in these different settings, but the doses may differ depending on the diagnosis or management strategy. Therefore, clinicians must know the evidence on appropriate antithrombotic drug use, dose, and duration based on the patient's diagnosis and management strategy to optimize patient outcomes and prevent adverse events.

Antiplatelet Therapy

The use and dosing of antiplatelet therapies for the treatment of ACS are summarized in Table 34-5.

Aspirin

Aspirin, or acetylsalicylic acid, has been a standard part of the treatment for ACS for several decades. Aspirin provides its antiplatelet effect by acetylating a hydroxyl group of serine 530 on the cyclooxygenase (COX)-1 enzyme on platelets and thereby preventing the conversion of arachidonic acid into a number of prostaglandins, and eventually thromboxane A_2.[61] Thromboxane A_2 produces platelet activation as well as vasoconstriction. While unbound aspirin has a half-life of only about 15 to 20 minutes, the irreversible binding of aspirin to the platelet COX-1 enzyme inhibits thromboxane A_2–induced platelet activation for the life of the platelet (7-10 days).

6 Aspirin is recommended for all patients with ACS without contraindications, regardless of the type of ACS or the management strategy. The initial dose of aspirin should be 162 to 325 mg (non-enteric coated) given as soon as possible.[1,2] Typically, this is given as 2 to 4 "baby" aspirin (81 mg in the United States) to be chewed and swallowed. The process of chewing allows for faster dissolution time and platelet inhibition in less than 30 minutes compared to about 60 minutes when tablets are consumed whole.[61] Patients undergoing PCI for NSTE-ACS or STEMI already receiving chronic aspirin doses of 81 mg daily should be given an additional dose of 81 to 325 mg before the procedure.[1,2]

After the initial dose of aspirin, daily doses of aspirin should be 81 mg daily and continued indefinitely.[1,2] Higher daily maintenance doses of aspirin (300-325 mg) do not reduce CV death, MI, or stroke compared to lower daily maintenance doses (75-100 mg), but significantly increase the incidence of gastrointestinal (GI) bleeding.[62]

Contraindications to aspirin include hypersensitivity to aspirin and major GI intolerance. In these rare cases, clopidogrel with a loading dose followed by a maintenance dose should be used as an alternative.[1,2] While ticagrelor may also be considered, there are no direct comparative data to aspirin available. The main adverse effects of aspirin include dyspepsia and GI bleeding, which is an extension of its inhibition of prostaglandins responsible for GI protection.[61] The use of low-dose and/or enteric-coated aspirin can provide a reduction in these adverse effects. Aspirin with an antacid, known as "buffered aspirin," does not provide GI protection. Although most surgical procedures can be conducted with patients on aspirin, it should be discontinued approximately 5 days before the procedure if desired.

$P2Y_{12}$ Inhibitors

6 Aspirin is rarely used as the sole antiplatelet agent in patients with ACS and is typically combined with an oral $P2Y_{12}$ inhibitor as part of dual antiplatelet therapy (DAPT). There are three orally administered $P2Y_{12}$ inhibitors (clopidogrel, prasugrel, and ticagrelor) and one IV agent (cangrelor) available in the United States, and their pharmacology is summarized in Table 34-6. Clopidogrel and prasugrel both belong to the chemical class of thienopyridines that are prodrugs requiring hepatic activation. Both agents have a thiol ring that must be opened to expose the sulfur atom. This sulfur then interacts with the sulfur within the $P2Y_{12}$ receptor creating an irreversible disulfide bond. The binding of the thienopyridine agent to the receptor prevents the receptor's ability to be activated by adenosine diphosphate and subsequent platelet activation and aggregation.

TABLE 34-6

$P2Y_{12}$ Inhibitor Pharmacology Comparisons

Property	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Drug class	Thienopyridine	Thienopyridine	Cyclopentyltriazolopyrimidine	ATP analogue
Absorption	≥50%	80%	36%	100%
Tmax	2 hours	30 minutes	60 minutes	2 minutes
Onset of action	75 mg: 3-5 days			2 minutes
	300 mg: 6-8 hours	10 mg: 3 days	90 mg: 2-3 days	
	600 mg: 2-4 hours	60 mg: 30-60 minutes	180 mg: 60 minutes	
Metabolism	Hepatic	Hepatic	Hepatic	ATPases in vascular endothelium
(CYP isoenzymes)	(2C19, 3A4, 1A2, 2B6)	(2B6, 3A4, 2C9, 2C19)	(3A4, 2C9)	
Prodrug	Yes	Yes	No	No
$P2Y_{12}$ Binding	Irreversible	Irreversible	Reversible	Reversible
Half-life	6 hours	7 hours	12 hours	3-5 minutes
Platelet recovery after cessation of therapy	~5 days	~7 days	~3 days	1-2 hours

ATP, adenosine triphosphate; CYP, cytochrome p450.

Data from References 61 and 63.

Ticagrelor and cangrelor are not thienopyridines, and therefore do not require hepatic activation to provide their antiplatelet effect. Cangrelor is an adenosine triphosphate analog and ticagrelor belongs to the chemical class of a cyclopentyltriazolopyrimidine that has structural components similar to adenosine triphosphate. While adenosine diphosphate is a known activator of platelets through the $P2Y_{12}$ receptor, adenosine triphosphate is a known inhibitor of this receptor. Ticagrelor and cangrelor do not form an irreversible bond with the $P2Y_{12}$ receptor as thienopyridines but instead, bind reversibly in a different location. With ticagrelor and cangrelor, adenosine diphosphate is allowed to bind to the $P2Y_{12}$ receptor, but the signal is blocked and does not lead to platelet activation and aggregation. Hence, ticagrelor and cangrelor are $P2Y_{12}$ receptor inhibitors, just by a different mechanism than thienopyridines. Because they reversibly bind to the $P2Y_{12}$ receptor, more frequent dosing of ticagrelor (twice-daily dosing) and cangrelor (continuous infusion) is required.

6 Bleeding risk in patients treated with $P2Y_{12}$ inhibitors undergoing major surgery is of concern. In patients with ACS treated with a clopidogrel-based DAPT regimen, the risk of CABG-related major bleeding was approximately 50% higher in clopidogrel-treated patients when surgery was performed within 5 days of clopidogrel cessation compared to patients treated with aspirin alone.[64] The risk of CABG-related major bleeding in ACS

patients treated with DAPT is more than four times higher with prasugrel than clopidogrel.[65] Consequently, clopidogrel and ticagrelor should be held for at least 5 days and prasugrel should be held for 7 days prior to elective surgery (eg, CABG surgery).[1,2] Because of its short duration of action, cangrelor can be continued until just a few hours before surgery, which is a favorable property of this agent.[63] Given the known bleeding risk associated with $P2Y_{12}$ inhibitor use and CABG, preloading patients with NSTE-ACS with a $P2Y_{12}$ inhibitor prior to PCI is controversial given that some may require CABG surgery. Administration of an oral $P2Y_{12}$ inhibitor prior to PCI does not offer a reduction in thrombotic outcomes compared to administration immediately following PCI.[66,67] It would still be prudent to preload the oral $P2Y_{12}$ inhibitor in patients with STEMI undergoing primary PCI, especially since CABG surgery is uncommon in these patients.

Clopidogrel

Conversion of clopidogrel to its active compound takes two cytochrome P450 (CYP) enzyme steps.[61] While multiple CYP enzymes take part in this conversion, CYP2C19 is responsible for at least 50% of this conversion. Patients with loss of function alleles (*2 or *3) have demonstrated a reduced ability to convert clopidogrel to its active form and have less platelet inhibition compared to patients with wild-type CYP2C19 (*1). It has also been demonstrated that up to 40% of patients receiving clopidogrel fail to achieve an optimal antiplatelet effect.[68] While there is a fair amount of variability in how the antiplatelet effect is determined, patients who fail to respond adequately to clopidogrel have a greater risk for MACE compared to patients with an adequate antiplatelet response. Clopidogrel is less effective than prasugrel or ticagrelor in patients with loss-of-function alleles, but has comparable efficacy to other oral $P2Y_{12}$ inhibitors in patients wild-type CYP2C19.[1,2,69,70] Although genetic polymorphisms of CYP2C19 contribute to the inadequate response to clopidogrel, CYP2C19 status only explains 12% to 15% of the variability demonstrated with clopidogrel.[68] Consequentially, lack of response to clopidogrel is multifaceted and can occur in patients with wild-type CYP2C19. Patients treated for ACS in whom de-escalation of DAPT is being considered (discussed below), platelet function testing to screen for high platelet reactivity may be considered 1 week after switching to clopidogrel in special circumstances (bleeding event, high bleeding risk, financial barriers).[70] Since proton pump inhibitors are known inhibitors of CYP2C19, concern has been raised about an increased risk for MACE in patients receiving these agents with clopidogrel. While the clopidogrel labeling information lists omeprazole and esomeprazole as being contraindicated, clinical evidence supporting this interaction is inconsistent.[68]

Clopidogrel has been extensively evaluated in patients with ACS. The CURE trial (Clopidogrel in Unstable Angina to Prevent Recurrent Events) compared aspirin alone to clopidogrel given as a 300 mg loading dose, followed by 75 mg daily for up to 12 months.[64] Patients receiving DAPT demonstrated a significant reduction in CV death, MI, and stroke compared to aspirin alone. This trial not only demonstrated the efficacy of clopidogrel but also established DAPT as the standard of care for patients presenting with ACS. Since 80% of the patients in this trial were medically managed, this dosing regimen is used in patients undergoing an ischemia-driven approach for NSTE-ACS.

A 600-mg loading dose provides a more potent and faster onset of antiplatelet activity and has demonstrated better efficacy in patients undergoing PCI compared to initially receiving a 300-mg loading dose of clopidogrel.[62] Patients who received an ischemia-driven approach did best with a 300-mg loading dose as in the CURE trial in regards to efficacy and safety outcomes. These data support the 600-mg clopidogrel loading dose in patients undergoing PCI for NSTE-ACS and STEMI.

Finally, clopidogrel is the only $P2Y_{12}$ inhibitor to be evaluated in large clinical trials in patients with STEMI receiving reperfusion with fibrinolytic therapy. Two trials have demonstrated the efficacy and safety of clopidogrel as part of DAPT in these patients.[71,72] Due to the increased concern of ICH in patients receiving fibrinolytics, only a 300 mg loading dose is used except for patients aged 75 or older who should not receive any loading dose.

Prasugrel

Prasugrel must also be converted to an active compound through hepatic conversion, but the conversion of prasugrel is more efficient, requiring a single CYP enzyme step, and multiple enzymes are capable of making the conversion.[19] Consequentially, the ability of prasugrel to be converted to its active compound is not limited and leads to faster and more potent platelet inhibition compared to clopidogrel. In patients undergoing PCI for NSTE-ACS or STEMI, prasugrel (as part of DAPT with aspirin) provided a significant reduction in CV death, MI, or stroke compared to clopidogrel.[65] The benefit of prasugrel was similar in the first few days of therapy, and after the first few days out to 1 year. Therefore, the reduction in MACE was due to not only more potent early antiplatelet therapy but also sustained potent antiplatelet therapy.

Greater efficacy, however, came at a cost of more non-CABG major bleeding and fatal bleeding. Upon further evaluation of the net clinical benefit (CV death, MI, stroke, and major bleeding), patients entering the trial with a history of stroke or transient ischemic attack were at greater risk for harm from prasugrel.[65] Therefore, these patients have an absolute contraindication to receiving prasugrel. Patients over the age of 75 years and those weighing less than 60 kg also had more bleeding with prasugrel compared to clopidogrel, but the overall net clinical benefit was neutral. Prasugrel should generally be avoided in patients over the age of 75 years. Exceptions may be made for patients who present with prior MI or DM, as the benefit in these patients outweighed the harm. Finally, in patients weighing less than 60 kg, the 60 mg loading dose of prasugrel is still given, but a 5 mg maintenance dose is recommended instead of the typical 10 mg dose.

Prasugrel has been compared to clopidogrel in patients undergoing an ischemia-driven approach.[73] Although there was no increased risk of bleeding with prasugrel in this trial, there was also no difference in efficacy. The use of prasugrel in these patients is not mentioned in the current guidelines.[2] Prasugrel has also not been evaluated in patients with STEMI receiving reperfusion therapy with fibrinolytics.

Ticagrelor

As with prasugrel, ticagrelor provides faster and more potent inhibition of platelets compared to clopidogrel.[74] Although ticagrelor does not require hepatic activation, it is metabolized by CYP3A4. Therefore, ticagrelor is contraindicated in patients receiving strong CYP3A4 inhibitors such as azole antifungals and protease inhibitors, as well as strong inducers of this enzyme such as carbamazepine, phenytoin, rifamycins, and St. John's Wort. Patients on ticagrelor should not receive doses of simvastatin or lovastatin higher than 40 mg daily. Due to competition for P-glycoprotein, ticagrelor can increase digoxin concentrations by 30% to 50%.

Ticagrelor has been compared to clopidogrel as part of DAPT with aspirin in patients undergoing PCI (NSTE-ACS or STEMI) or undergoing an ischemia-driven approach for NSTE-ACS in a large clinical trial.[75] Patients receiving ticagrelor had a significant reduction in CV death, MI, or stroke compared to clopidogrel. While this reduction was evident within the first 30 days of therapy, two-thirds of the benefit was after the first 30 days out to 1 year. As with prasugrel, the benefit of ticagrelor was not simply due to more potent antiplatelet therapy early but also sustained potent antiplatelet therapy. The magnitude of benefit was similar in patients receiving an ischemia-driven approach to those receiving PCI. There was also a significant 21% reduction in CV mortality with the use of ticagrelor over clopidogrel, which has not been seen in other trials of $P2Y_{12}$ inhibitors. In the trial, higher doses of aspirin attenuated the benefit of ticagrelor compared to clopidogrel; only patients receiving low-dose aspirin (daily dose of 100 mg or less) received a benefit.[76] Based on these data, ticagrelor is contraindicated in patients receiving chronic aspirin daily doses of more than 100 mg. The mechanism of this interaction remains unknown. Although non-CABG major bleeding was significantly increased, there was no increase in fatal bleeding. Due to the increased risk of bleeding in older patients, clopidogrel may be a safer option based on data from trials evaluating patients aged 70 or 80 years or older.[77,78]

Ticagrelor has been compared to prasugrel as part of DAPT with aspirin in patients with ACS (NSTE-ACS or STEMI) for whom an early invasive treatment strategy was planned.[79] Prasugrel-treated patients had significantly lower rates of death, MI, or stroke compared to ticagrelor with similar rates of major bleeding. While ticagrelor is noninferior to clopidogrel for major bleeding risk in patients with STEMI receiving reperfusion with fibrinolytics, clopidogrel is the only $P2Y_{12}$ inhibitor with specific recommendations as an adjunct to fibrinolytic therapy in patients with STEMI.[80]

While all antiplatelet agents have the adverse effect of bleeding, the unique structure of ticagrelor produces additional adverse effects. Ticagrelor can interfere with adenosine degradation and increase adenosine concentrations via inhibition of adenosine uptake by erythrocytes.[1,74] This interaction most likely occurs through inhibition of the sodium-independent equilibrative nucleoside transporter (ENT)-1. Erythrocyte ENT-1 is responsible for the uptake of adenosine into the cell where it is metabolized by multiple mechanisms. The ability of ticagrelor to inhibit adenosine's uptake via ENT-1 is likely due to the adenosine core of the ticagrelor chemical structure.[74,77] This interaction produces an increase in adenosine exposure that likely explains these unique adverse effects. Significantly more patients receiving ticagrelor complained of dyspnea (13.8%) compared to those receiving clopidogrel (7.8%).[75] Symptoms of dyspnea are typically mild to moderate, require no specific therapy or workup, and usually dissipate within 2 to 4 weeks. Coaching of the patient through these episodes is often successful as ticagrelor was discontinued due to dyspnea in less than 1% of patients in the clinical trial. The use of ticagrelor has also been associated with an increase in asymptomatic ventricular pauses, increases in uric acid, and small increases in serum creatinine.[1,74]

Cangrelor

Cangrelor is the only available intravenously administered $P2Y_{12}$ inhibitor. Similar to ticagrelor, cangrelor is a reversible inhibitor of the $P2Y_{12}$ receptor and binds to the receptor at a different location than adenosine diphosphate. Despite the recommended loading doses, oral $P2Y_{12}$ inhibitors take a minimum of 1 to 2 hours to obtain maximum platelet inhibition and 3 to 7 days for platelet recovery after discontinuation.[63] Cangrelor achieves maximum platelet inhibition within approximately 2 minutes of an IV bolus dose, with the restoration of normal platelet reactivity within 1 to 2 hours of cessation of the infusion.[63] Cangrelor has an elimination half-life of less than 9 minutes and is metabolized by ATPases in the blood. Therefore, hepatic or renal dysfunction are not likely to impact the pharmacokinetics of cangrelor.[63] The fast return to normal platelet function may provide safety advantages for cangrelor over other $P2Y_{12}$ inhibitors in the context of bleeding or transition to CABG surgery.

The use of cangrelor in patients with ACS is not well defined. In a clinical trial evaluating the efficacy and safety of cangrelor for patients undergoing PCI (44% of whom had ACS), cangrelor provided a significant reduction in MACE with an increase in minor bleeding, but not major bleeding.[81] When used in this setting, cangrelor (bolus dose followed by an infusion) should be initiated before PCI. After PCI, an oral P2Y12 inhibitor (loading dose followed by maintenance dose) should be initiated; the overall duration of cangrelor infusion should be at least 2 hours. Since the chemical structure is similar to ticagrelor, dyspnea may occur with the use of cangrelor, but the shorter drug exposure time likely contributes to a lower incidence (1.2%) and discontinuation rate (0.1%) compared to ticagrelor (13.8% and 0.9%, respectively).[81,82]

Cangrelor may interfere with the binding of the active metabolites of clopidogrel and prasugrel. When clopidogrel is given with cangrelor, the ability of the thienopyridines to irreversibly inhibit platelet function was reduced.[82,83] Cangrelor directly prevents binding of the short-lived but irreversible active metabolite of clopidogrel. Once the infusion is discontinued, no impact on the pharmacodynamic effect of clopidogrel was seen. This same interaction would be expected with prasugrel. Therefore, if cangrelor is used, the loading dose of the thienopyridine should not be given until the cangrelor infusion has been discontinued. This interaction does not exist with ticagrelor.

Switching Antiplatelet Agents

Situations may occur after initial DAPT is chosen whereby therapy needs to change based upon some unique clinical scenario. Switching of therapy can be described as an escalation of therapy whereby clopidogrel is switched to a more potent $P2Y_{12}$ inhibitor such as ticagrelor or prasugrel. Reasons for escalation include cases of heightened risk for a coronary event or stent thrombosis, development of drug interaction, intolerance or nonadherence, identification of a genetic polymorphism to clopidogrel, or confirmation of inadequate platelet inhibition. In contrast, de-escalation typically refers to switching from a more potent $P2Y_{12}$ inhibitor to clopidogrel. Need for a de-escalation of $P2Y_{12}$ inhibitor therapy may be needed in response to bleeding, when there is a new indication to concurrently use an oral anticoagulant, or in cases when the cost is limiting medication access or leading to suboptimal adherence. Data on switching antiplatelet therapies is limited and is primarily based on pharmacodynamic studies. The efficacy and safety of switching agents during the first 12 months following ACS, therefore, is not fully known. But clinical decisions based on the reason for switching (ie, escalation versus de-escalation) and the timing from index event (ie, acute/early phase within the first 30 days versus later) must be weighed. One international consensus panel recommends that no loading dose be given when de-escalating therapy due to bleeding.[84] Loading doses are generally not needed when de-escalating therapy except when being when switching from ticagrelor to another $P2Y_{12}$ inhibitor.[84] Any escalation in therapy should be accompanied by a loading dose of the new agent regardless of the time of last $P2Y_{12}$ inhibitor dose, followed by maintenance therapy 24 hours after the last $P2Y_{12}$ inhibitor dose.[84] Finally, when switching between $P2Y_{12}$ inhibitors within 30 days of the index event, loading doses are recommended in most cases, except when the reason for switching is because of bleeding.[84] In general, the switch should occur 24 hours after the last dose of previous $P2Y_{12}$ inhibitor.[84]

Glycoprotein IIb/IIIa Inhibitors

The binding of fibrinogen to activated GP IIb/IIIa receptors represents the final step in platelet aggregation, making inhibition of this receptor an ideal target in patients with ACS. Each of the agents is only available as an IV infusion.

Eptifibatide and tirofiban are peptide and nonpeptide inhibitors of the GP IIb/IIIa receptor, respectively. These agents have a reversible binding of the

GP IIb/IIIa receptor. Therefore, platelet function recovery occurs in 2 to 4 hours after discontinuation of the infusion. The reversible binding of these agents requires that they overwhelm the ability of fibrinogen to bind to the GP IIb/IIIa receptor with high concentrations. Consequently, platelet transfusion would not be able to absorb the excess drug and would not be helpful in the management of bleeding with eptifibatide or tirofiban.

Besides bleeding, GP IIb/IIIa inhibitors can also cause significant thrombocytopenia in about 0.5% of patients.[19] Given that GP IIb/IIIa inhibitors should be administered with a heparin, it is important to differentiate GP IIb/IIIa inhibitor-induced thrombocytopenia from heparin-induced thrombocytopenia (HIT).[85] Thrombocytopenia from a GP IIb/IIIa inhibitor occurs more rapidly (within hours) and the platelet count nadir is typically lower (about 20,000/μL [20×10^9/L]) compared to HIT. While the efficacy of platelet transfusion for thrombocytopenia from eptifibatide or tirofiban is limited, it would unlikely be harmful as in HIT.[85]

Although GP IIb/IIIa inhibitors significantly reduce MACE, the majority of trials were conducted before DAPT became standard-of-care and before the more potent $P2Y_{12}$ inhibitors prasugrel and ticagrelor were available. In a study comparing the combination of a GP IIb/IIIa inhibitor and unfractionated heparin to unfractionated heparin alone in patients with NSTE-ACS receiving PCI and a 600 mg loading dose of clopidogrel, patients treated with the GP IIb/IIIa inhibitor had a significant reduction in MACE but the benefit was only in patients who had an elevated cTn.[86] Therefore, GP IIb/IIIa inhibitors provide added benefit in the setting of early DAPT but should be reserved for high-risk patients with elevated cTn. The ability of GP IIb/IIIa inhibitors to reduce MACE in patients receiving prasugrel or ticagrelor remains unknown. In trials comparing a strategy of GP IIb/IIIa inhibitors plus unfractionated heparin to bivalirudin alone in patients with ACS undergoing PCI, no differences in MACE were observed, but there was significantly less major bleeding with bivalirudin alone.[87,88] While these trials have many limitations, clinicians have consistently used less GP IIb/IIIa inhibitors over the last decade.

Patients with NSTE-ACS undergoing an ischemia-driven approach do not derive benefit from GP IIb/IIIa inhibitors and should not be used in these patients.[2] Patients with STEMI receiving reperfusion with fibrinolytics have significant increases in major bleeding and ICH when GP IIb/IIIa inhibitors are used concomitantly and they should be avoided in these patients as well.[1]

6 While the use of GP IIb/IIIa inhibitors has been diminishing over the years, the patient for whom GP IIb/IIIa inhibitors may provide the most benefit is one receiving PCI for NSTE-ACS with elevated cTn, (eg, suffering MI) or STEMI who has not been preloaded with a $P2Y_{12}$ inhibitor and is not being treated with bivalirudin. Guidelines also state that it is reasonable to use a GP IIb/IIIa inhibitor in patients who are preloaded with clopidogrel.[1,2,60,86] In this setting, consensus guidelines recommend the use of an 18- to 24-hour infusion (eptifibatide and tirofiban) but the contemporary use of these drugs continues to evolve. These agents should always be given concurrently with unfractionated heparin or a low-molecular-weight heparin (LMWH) but the anticoagulant should be discontinued immediately following the PCI procedure to reduce the risk of major bleeding.

Anticoagulants

Although patients with ACS are typically treated with two antiplatelet agents for at least a year, usually a single anticoagulant is used in these patients and the duration is abbreviated (typically the initial few days of hospitalization).[1,2] Currently available anticoagulants inhibit the production of thrombin by inhibiting factor Xa, inhibiting thrombin itself, or a combination of these. While the use of oral anticoagulants may be common for other thromboembolic disease states, all of the current evidence in the acute management of ACS is with injectable agents. The use and dosing of anticoagulant therapies for the treatment of ACS are summarized in Table 34-7.

TABLE 34-7

Anticoagulant Drug Use and Dosing Across the Spectrum of ACS and Management Strategy

Drug	STEMI		NSTE-ACS	
	Primary PCI	Fibrinolytic reperfusion	Early invasive strategy	Ischemia-driven strategy
Bivalirudin	0.75 mg/kg IV bolus, followed by 1.75 mg/kg/hr	No recommendation	0.10 mg/kg IV bolus, followed by 0.25 mg/kg/hr IV infusion continued until completion of	No recommendation

	IV infusion until completion of PCI CrCl less than 30 mL/min (0.5 mL/s): Reduce infusion to 1 mg/kg/hr		PCI	
Enoxaparin	0.5 mg/kg one time IV bolus[a]	30 mg IV bolus, followed by 1 mg/kg SC every 12 hours for up to 8 days or hospital discharge SC doses should be initiated within 15 minutes of the IV bolus. The first two SC doses should be capped at 100 mg CrCl less than 30 mL/min (0.5 mL/s): 30 mg IV bolus, followed by 1 mg/kg SC every 24 hours The first SC dose should be capped at 100 mg Age 75 years or more: No IV bolus. Initiate at 0.75 mg/kg SC every 12 hours The first two SC doses should be capped at 75 mg CrCl less than 30 mL/min (0.5 mL/s) AND age 75 years or more: No IV bolus. Initiate at 1 mg/kg every 24 hours The first dose should be capped at 100 mg	1 mg/kg SC every 12 hours until PCI A 0.3 mg/kg IV bolus should be given 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 less than 30 mL/min (0.5 mL/s): 1 mg/kg SC every 24 hours An initial 30 mg IV bolus can be given	1 mg/kg SC every 12 hours for the duration of hospitalization An initial 30 mg IV bolus can be given CrCl less than 30 mL/min (0.5 mL/s): 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 the time of PCI: No GP IIb/IIIa: IV UFH 85 units/kg[b] With GP IIb/IIIa: IV UFH 60 units/kg[b]	2.5 mg SC daily for up to 8 days or duration of hospitalization
Unfractionated heparin	No GP IIb/IIIa: 70-100 units/kg IV bolus to achieve	60 units/kg (maximum initial bolus: 4,000 units) IV bolus, followed by 12	60 units/kg (maximum initial bolus: 4,000 units) IV bolus, followed by 12 units/kg/hr	60 units/kg (maximum initial bolus: 4,000 units) IV bolus, followed by 12

	a therapeutic ACT[b] GP IIb/IIIa: 50-70 units/kg IV bolus to achieve a therapeutic ACT[b]	units/kg/hr (maximum initial infusion rate: 1,000 units/hr)	(maximum initial infusion rate: 1,000 units/hr)[b]	units/kg/hr (maximum initial infusion rate: 1,000 units/hr)

[a]Not mentioned in the ACC/AHA guidelines, but evidence exists.

[b]Additional IV boluses of unfractionated heparin may be needed to maintain a therapeutic ACT.

ACT, activated clotting time; CrCl, creatinine clearance; IV, intravenous; SC, subcutaneous; UFH, unfractionated heparin.

Data from References 1 and 2.

Unfractionated Heparin

Unfractionated heparin has been widely used in the management of patients with ACS for several decades. The unfractionated heparin molecule is a highly sulfated polysaccharide. Unfractionated heparin provides its anticoagulant activity by binding to the endogenous anticoagulant antithrombin (AT) via a unique pentasaccharide sequence, substantially increasing its affinity for clotting factor inhibition.[89] These unfractionated heparin–AT complexes can then inhibit clotting factors IXa, Xa, XIa, XIIa, and thrombin, with most of the impact provided through inhibition of factor Xa and thrombin. Inhibition of thrombin requires a tertiary binding between the unfractionated heparin–AT and thrombin molecules. This requires that the chain length of the inhibitory molecule be at least 18 saccharides long.[89] This additional binding is not necessary for inhibition of factor Xa. Since most unfractionated heparin molecules are approximately 45 to 50 saccharides long, unfractionated heparin can inhibit factor Xa and thrombin in an equal 1:1 ratio.[89]

The anticoagulant effect of unfractionated heparin has significant interpatient variability.[89] This is due to the additional binding of unfractionated heparin with endothelial cells, plasma protein, and ingestion by macrophages. As a result of the unpredictable anticoagulant response of unfractionated heparin, therapy needs to be monitored with an activated partial thromboplastin time (aPTT). The aPTT should be measured every 6 hours until two consecutive readings are within the therapeutic range, as determined by the individual institutional protocols, then every 24 hours for the duration of unfractionated heparin therapy. Although goal ranges for aPTT vary by institution based on the assays used, an aPTT goal of 1.5 to 2 times the institution's control value is recommended.[1] If a dose adjustment is made, the same monitoring schedule should be restarted. While some institutions have adopted the use of anti-Xa levels instead of aPTT to monitor heparin therapy, guideline recommendations are specific to aPTT. Due to the short duration of anticoagulant therapy in patients with ACS, it is not uncommon for unfractionated heparin to be discontinued before the patient ever achieves two consecutive therapeutic aPTT measurements. Platelet counts should also be monitored daily or every other day to monitor for HIT. While HIT typically presents 5 days or more after unfractionated heparin exposure, it can occur within hours if the patient has been exposed to heparin in the last 3 months.[85] If HIT is suspected, unfractionated heparin should be discontinued and anticoagulation with an IV direct thrombin inhibitor should be provided.

7 Based on experience, unfractionated heparin can be used across the spectrum of ACS, and regardless of the management strategy.[1,2] The recommended dosing of unfractionated heparin has changed several times over the past decades in an attempt to maximize efficacy and minimize bleeding. The recommended dose of unfractionated heparin is an IV bolus of 60 units/kg (initial maximum total dose of 4,000 units) and an initial infusion rate of 12 units/kg/hr (initial maximum 1,000 units/hr). This is the recommended dose regardless of the ACS diagnosis or management strategy.[1,2] After initiation of heparin, dosage adjustments can exceed the recommended maximums as necessary to achieve the aPTT goal. Bolus doses of 2,000 to 5,000 units can also be given in the cardiac catheterization laboratory at the time of PCI to maintain an adequate activated clotting time (ACT). In a meta-analysis comparing the use of heparin plus aspirin to aspirin alone in patients with NSTE-ACS, the risk of death or MI was reduced by 33% in heparin-treated patients.[90] Because of the long-standing experience and use of unfractionated heparin in patients with ACS, it is the

standard-of-care comparison in clinical trials.

Low-Molecular-Weight Heparins

Similar to unfractionated heparin, LMWHs must first bind to AT to provide their anticoagulant activity. LMWHs are created through chemical or enzymatic depolymerization of unfractionated heparin molecules.[89] This creates a mixture of lower molecular weight fragments compared to the larger intact unfractionated heparin molecule. Most of these fragments are less than 18 saccharides long. Consequently, LMWH's anticoagulants primarily inhibit factor Xa due to the fewer number of larger fragments able to inhibit thrombin. The ratio of factor Xa to thrombin inhibition for a LMWH is typically 3:1 or 4:1, depending on the process of depolymerization.[89]

Compared to unfractionated heparin, LMWHs provide a predicable anticoagulant dose-response with no need for routine therapeutic monitoring. While most patients receiving a LMWH do not require therapeutic monitoring, an anti-Xa level may be desired in certain patient populations.[89] Patient groups where anti-Xa monitoring may be helpful would be pediatrics, pregnancy, obesity (greater than 190 kg), and patients with severe renal insufficiency (eg, creatinine clearance [CrCl] less than 30 mL/min [0.5 mL/s]). While pediatric and pregnant patients rarely have ACS, obesity and severe renal insufficiency are more common in patients with ACS. The target peak anti-Xa level is 0.3 to 0.7 IU/mL (kIU/L) drawn 4 hours after the third dose. Since patients with ACS typically receive anticoagulant therapy for only a few days, the utility of anti-Xa monitoring in these patients is limited. There is also a lower incidence of HIT with the use of LMWHs (less than 2%) compared to unfractionated heparin (2%-5%).[85] Even though the risk of HIT is lower with LMWH, the monitoring of platelet counts is still warranted. Due to the 90% cross-reactivity between HIT antibodies from LMWH and unfractionated heparin, LMWH is not considered a safe alternative in patients who develop HIT from unfractionated heparin and vice versa.[85]

While other LMWHs are available, enoxaparin is the most widely studied agent in patients with ACS and is the only LMWH recommended in the ACC/AHA guidelines.[1,2] Data supporting the use of enoxaparin exist in patients with NSTE-ACS and STEMI regardless of the management or reperfusion strategy used. Unfortunately, the dosing of enoxaparin varies across these different settings, requiring careful attention to assure the right dose is used in the right patient to maximize efficacy and safety (Table 34-7).

7 In patients with NSTE-ACS undergoing an ischemia-driven approach, the use of subcutaneous (SC) enoxaparin 1 mg/kg every 12 hours for up to 3 days significantly reduces the risk of MACE without increasing major bleeding compared to IV unfractionated heparin.[91] In patients with NSTE-ACS treated with an early invasive strategy, SC enoxaparin (1 mg/kg every 12 hours) has similar efficacy but more major bleeding compared to unfractionated heparin.[92] This trial was complicated by a large number of patients receiving both anticoagulants during the trial. Interestingly, in patients who were treated with either enoxaparin or IV unfractionated heparin alone, those randomized to enoxaparin had a 17% reduction in the risk of death or MI at 30 days and at 6 months without a significant increase in major bleeding compared to IV unfractionated heparin. Based on these data, either unfractionated heparin or enoxaparin is recommended in patients with NSTE-ACS. Patients who have received less than two SC doses prior to PCI should receive a supplemental IV enoxaparin bolus dose of 0.3 mg/kg to provide sufficient anticoagulation during the procedure.[2] Patients who have received at least two SC doses and arrive at PCI within 8 hours of their last dose do not require any additional anticoagulation for PCI.[2,92] Patients having PCI performed within 8 to 12 hours of their last dose should also receive the supplemental IV enoxaparin bolus dose.[2,92] Patients with a CrCl less than 30 mL/min (0.5 mL/s) should receive enoxaparin 1 mg/kg every 24 hours instead of every 12 hours.

7 In patients with STEMI receiving reperfusion with fibrinolytics, enoxaparin significantly reduced death and MI when compared to unfractionated heparin.[93] Major bleeding was increased, but there was no increase in ICH which occurred in less than 1% of patients. Dosing of enoxaparin in this trial used a 30 mg IV bolus followed immediately by 1 mg/kg SC every 12 hours. The bolus dose is necessary in the setting of STEMI due to the rapid need for reperfusion therapy. Patients aged 75 years or greater and those with a CrCl less than 30 mL/min (0.5 mL/s) need to receive altered dosing to reduce the risk of bleeding in these higher-risk patients (Table 34-7). Trials in patients receiving primary PCI for STEMI have used a single IV dose of 0.5 mg/kg of enoxaparin. In a meta-analysis of trials evaluating this dose of enoxaparin in primary PCI, there is a reduction in mortality and significantly less major bleeding compared to unfractionated heparin.[94] Despite these data, a definitive clinical trial has not been conducted with enoxaparin in this setting.

Fondaparinux

Fondaparinux is a synthetic molecule existing of only the five saccharides needed to bind to and potentiate the activity of AT.[89] While others have been investigated, fondaparinux is the only available pentasaccharide worldwide. Due to the small size of the molecule, once it binds to AT it can only inhibit

factor Xa and has no activity against thrombin. Similar to LMWH, fondaparinux also provides a predictable anticoagulant dose-response and no need for therapeutic monitoring.[89] While case reports of fondaparinux-induced thrombocytopenia have been reported, the incidence is thought to be extremely rare.[85] Based on the lack of antibody cross-reactivity, it is reasonable to consider the use of fondaparinux in patients with a history of HIT.[85] Based on the long half-life of fondaparinux, the SC dose (2.5 mg) is only given once daily. Fondaparinux is contraindicated in patients with a CrCl of less than 30 mL/min (0.5 mL/s) due to the significant degree of renal elimination. There can also be accumulation in patients with a CrCl between 30 and 60 mL/min (0.5 and 1.0 mL/s), but this is typically not a factor with the short duration of therapy in patients with ACS.[95]

The use of fondaparinux in patients with ACS has been evaluated in two large trials.[96,97] The trial in NSTE-ACS evaluated patients receiving either an ischemia-driven or invasive management strategy and found similar efficacy between fondaparinux and enoxaparin, with significantly less major bleeding in patients receiving fondaparinux.[97] Although a number of issues in the trial may have explained the observed difference in bleeding, fondaparinux can be considered in patients undergoing an ischemia-driven approach who are at a high risk of bleeding.[2] Patients undergoing PCI experienced an increase in catheter-related thrombosis if they received fondaparinux compared to enoxaparin.[97] Due to this concern, supplemental doses of IV unfractionated heparin must be given if a patient receiving fondaparinux requires PCI.[2] Consequently, fondaparinux is rarely used and not recommended in the United States for patients with NSTE-ACS receiving an invasive management approach.[60]

The trial utilizing fondaparinux in STEMI evaluated patients receiving reperfusion with either fibrinolytics or primary PCI.[96] In this trial, fondaparinux was compared to unfractionated heparin. Similar to the NSTE-ACS trial, patients receiving primary PCI had significantly higher rates of catheter-related thrombosis if they received fondaparinux compared to unfractionated heparin.[1,96] As in NSTE-ACS, fondaparinux use has been constrained by this limitation and is not recommended in patients receiving primary PCI.[60] In patients receiving fibrinolytics, the use of fondaparinux has similar efficacy and safety compared to unfractionated heparin.[96] Based on the lack of benefit over unfractionated heparin, and the benefit with enoxaparin over unfractionated heparin in this population, fondaparinux is rarely used in patients with STEMI.

Bivalirudin

Bivalirudin is an intravenously administered direct thrombin inhibitor. Being a “direct” inhibitor means bivalirudin does not have to first bind to AT to provide its anticoagulant effect.[89] Because of the lack of AT binding, bivalirudin can inhibit not only free or soluble thrombin, similar to unfractionated heparin and LMWH but also fibrin-bound thrombin. Fibrin-bound thrombin is still enzymatically active, but the large AT–anticoagulant complexes are unable to gain access and, therefore, exert anticoagulant activity.[89] The clinical benefit of bivalirudin’s inhibition of this larger pool of thrombin is difficult to quantify.

Bivalirudin has not been evaluated in patients with NSTE-ACS undergoing an ischemia-driven approach or in patients with STEMI receiving reperfusion with fibrinolytics. Therefore, bivalirudin is only used in patients with ACS who receive PCI and can be monitored with an ACT in the catheterization laboratory.[1,2,89] In one NSTE-ACS trial evaluating anticoagulation as part of an early invasive approach, patients received a heparin derivative (unfractionated heparin or enoxaparin) with a GP IIb/IIIa inhibitor, bivalirudin with a GP IIb/IIIa inhibitor, or bivalirudin alone.[87] There was no difference in efficacy or safety in patients receiving heparin or LMWH with a GP IIb/IIIa inhibitor compared to bivalirudin with a GPII/IIIa inhibitor. Consequently, because of the lack of benefit and increased cost associated with the combination of bivalirudin and a GP IIb/IIIa inhibitor, this regimen is not recommended in patients with NSTE-ACS undergoing PCI. Patients receiving bivalirudin alone had similar efficacy but significantly less major bleeding compared to heparin or LMWH with a GP IIb/IIIa inhibitor. The patients who were not preloaded with clopidogrel in the trial had significantly more MACE if they received bivalirudin alone.[2,87] Therefore, bivalirudin may not be as protective in patients who do not receive a $P2Y_{12}$ inhibitor prior to PCI. Similar to the study in NSTE-ACS, bivalirudin alone had similar efficacy with significantly less major bleeding compared to unfractionated heparin with a GP IIb/IIIa in patients undergoing primary PCI for STEMI.[88] These data led to a significant reduction in the use of GP IIb/IIIa inhibitors. Bivalirudin does not offer efficacy or safety benefit over unfractionated heparin alone in the setting of primary PCI for STEMI, particularly as vascular access to perform PCI has moved from a predominantly femoral arterial approach associated with higher rates of bleeding to a radial artery approach associated with less bleeding.[98-100] While the role of bivalirudin in these patients is recommended in the guidelines, many cardiologists have come full circle and often use unfractionated heparin for primary PCI for patients with STEMI instead of bivalirudin.

Secondary Prevention of Ischemic Events

For most patients, the initial 24 hours of ACS care are focused on reperfusion (if appropriate), antithrombotic therapy, and acute supportive measures. 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 MACE. Secondary prevention strategies proved to accomplish these goals typically include anti-ischemic, antiplatelet, lipid-lowering, and antihypertensive therapies (Table 34-8).[1,2,29] Specific pharmacotherapy proved to decrease mortality, HF, reinfarction or stroke, and stent thrombosis should be initiated prior to hospital discharge in all patients without contraindications. Medication reconciliation at discharge should include assessment for DAPT, β-blocker, angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), and statin therapy unless a contraindication exists (Fig. 34-3). In addition, short-acting nitroglycerin should be prescribed as needed for any subsequent episode of acute angina for patients not taking phosphodiesterase-5 inhibitors. Select patients may also meet the criteria for aldosterone antagonist use.

FIGURE 34-3

Secondary prevention of ischemic events over time. (AA, aldosterone antagonist; CI, contraindications; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol [70 mg/dL is expressed in SI units as 1.81 mmol/L]; NSAID, nonsteroidal anti-inflammatory drug; SL NTG, sublingual nitroglycerin.)

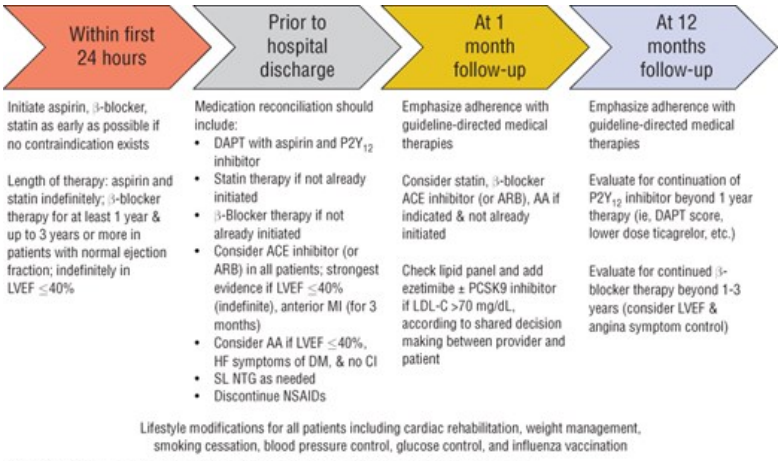


TABLE 34-8

Chronic Medications to Reduce Risk of MACE and Control Symptoms Following ACS

Drug	Indication in ACS Patients (Class of Recommendation)[a]	Contraindication/Caution	Dose (All doses are oral unless indicated)	Adverse Effects
Aspirin	All patients without contraindications	• Hypersensitivity to aspirin or NSAID • History of asthma, rhinitis, and nasal polyps • History of upper GI bleeding • Bleeding disorder/active bleeding	• 81 mg once daily	• Dyspepsia, GI bleeding

$P2Y_{12}$ inhibitors	All patients without contraindications	• Thienopyridine hypersensitivity • Bleeding disorder/active bleeding • Previous intracranial hemorrhage • Prasugrel: prior TIA or stroke • Ticagrelor: aspirin doses greater than 100 mg daily; strong CYP3A4 inhibitors or inducers	• Clopidogrel 75 mg once daily • Prasugrel 10 mg once daily; weight less than 60 kg: 5 mg daily • Ticagrelor 90 mg twice daily	Bleeding, rash; Ticagrelor: dyspnea, ventricular pauses, bradycardia
β-Blockers	All patients without contraindications	• Signs of heart failure • Low cardiac output state • High-grade AV block • Active asthma or reactive airway disease	• Carvedilol 6.25 mg twice daily; target dose (in patients with HFrEF): 25 mg twice daily as tolerated • Metoprolol 25-50 mg every 6-12 hours for 2-3 days, then once (metoprolol succinate) or twice daily (metoprolol tartrate); target dose (in patients with HFrEF): 200 mg daily • Continue therapy for at least 3 years, indefinitely in patients with concomitant HFrEF • Other β-blockers may be considered; in patients with HFrEF, use either metoprolol succinate, carvedilol, or bisoprolol	Hypotension, heart failure, bradycardia, cardiogenic shock, AV block, exacerbation of asthma or reactive airway disease
Statins	All patients without contraindications	• Active liver disease • Pregnancy • Breastfeeding • Concomitant use of fibrate	• Atorvastatin 80 mg daily • Rosuvastatin 20-40 mg daily	GI discomfort, arthralgia, myalgia, musculoskeletal pain, hepatotoxicit
Nonstatin therapies	Patients with very high-risk ASCVD (eg, post-ACS) with LDL-C greater than 70 mg/dL (1.81 mmol/L) on maximally tolerated statin therapy	• Hypersensitivity • Simvastatin/ezetimibe: strong CYP3A4 inhibitors	• Ezetimibe 10 mg daily • Simvastatin 40 mg/ezetimibe 10 mg • Alirocumab 75 mg SC every 2 weeks or 300 mg SC every 4 weeks • Evolocumab 140 mg SC every 2 weeks or 420 mg SC monthly	Ezetimibe and combination: GI discomfort, arthralgia, myalgia, musculoskeletal pain Alirocumab: injection site pain, hypersensitiv

ACE inhibitors	All patients without contraindications	• Hypotension • Renal failure • Hyperkalemia	• Lisinopril 2.5-5 mg daily; target dose: 10-40 mg daily • Enalapril 2.5-5 mg twice daily; target dose: 10-20 mg twice 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	Hypotension, hyperuricemia, hyperkalemia, worsening renal function, chronic cough, angioedema
ARBs	Patients intolerant to ACE inhibitors	• Hypotension • Renal failure • Hyperkalemia	• Valsartan 20 mg twice daily; target dose: 160 mg twice daily	Hypotension, hyperuricemia, hyperkalemia, worsening renal function
Aldosterone antagonist	Patients with LVEF 40% (0.40) or less and either DM or symptoms of HF	• Elevated serum creatinine • Men: 2.5 mg/dL (221 µmol/L) or greater • Women: 2.0 mg/dL (177 µmol/L) or greater • CrCl 30 mL/min (0.5 mL/s) or less • Serum potassium 5.0 mEq/L (mmol/L) or greater	• Eplerenone 25 mg daily; target dose: 50 mg daily • Spironolactone 12.5-25 mg daily; target dose: 25-50 mg daily	Hyperkalemia, worsening renal function

Nitroglycerin	All patients without contraindications	• Hypotension
		• Avoid if recent PDE_5 inhibitor use
		  ○ Avanafil: within 12 hours
		  ○ Sildenafil: within 24 hours
		  ○ Vardenafil: within 24 hours
		  ○ Tadalafil: within 48 hours
			• SL: 0.3-0.4 mg every 5 minutes, up to 3 doses PRN	Flushing, headache, hypotension, tachycardia

[a]AHA/ACC class of recommendations: I, benefit far outweighs the risk, treatment should be administered; IIb, the benefit is equal to or exceeds the risk, additional studies with broad objectives are needed, treatment may be considered.

AV, atrioventricular; CrCl, creatinine clearance; CYP3A4, cytochrome p450 isoenzyme 3A4; GI, gastrointestinal; HF, heart failure; NSAID, nonsteroidal anti-inflammatory drug; PDE5, phosphodiesterase-5; PRN, as needed; SC, subcutaneously; TIA, transient ischemic attack.

Data from References 1,2,and 101-103.

In addition to evaluating patients for the use of medications proved to reduce the risk of MACE or recurrent symptoms of angina, additional interventions may be appropriate to optimize outcomes and improve safety. Aggressive risk factor modification strategies such as increased physical activity, dietary modification, weight loss, blood pressure modification, and smoking cessation should be communicated to all patients, initiated, and continued indefinitely.[104] Proton pump inhibitors provide a protective benefit in patients at the highest risk for GI bleeding from DAPT and may be considered for select patients (eg, history of GI bleeding, triple therapy with DAPT, and an oral anticoagulant with or without a history of GI bleeding).[2] All patients should refrain from chronic use of nonsteroidal anti-inflammatory drugs with a high degree of cyclo-oxygenase-2 selectivity as they are associated with increased cerebrovascular and cardiovascular events.[1,2] Finally, for patients with cardiovascular disease, including those hospitalized for ACS, an annual influenza vaccination lowers the risk of MACE and is recommended as part of the care plan.[1,2,105,106]

Duration of Dual Antiplatelet Therapy (DAPT)

8 The ACC/AHA has published guidelines specifically related to dosing, initiation, and duration of DAPT after ACS, including situations when therapy should be discontinued.[1,2,107] In general, shorter durations of DAPT are appropriate for those patients with a lower ischemic risk who are at high-risk for bleeding. Conversely, longer durations of DAPT may be reasonable in patients at higher ischemic risk if bleeding risk is low. No randomized trials have compared different durations of DAPT specifically in the ACS setting. Yet, because the ischemic risk following ACS is considered high, DAPT with aspirin plus a $P2Y_{12}$ receptor inhibitor is indicated for most patients treated for ACS for a minimum of 12 months regardless of whether the patient was medically managed or if the patient undergoes some type of revascularization.[1,2,107] For patients with STEMI treated with fibrinolysis, the minimum recommended duration of DAPT is 14 days.[1,107] Every patient receiving DAPT should understand the benefit as well as risks associated with the therapy and the importance of maintaining adherence with therapy for the appropriate duration of therapy. For patients at high risk of bleeding, a shorter duration of DAPT may be warranted. In these patients, a brief (1 to 3 months) duration of DAPT followed by $P2Y_{12}$ monotherapy or 6-month duration of DAPT followed by aspirin monotherapy may lower the risk of bleeding.

Continuation of DAPT beyond 12 months may be reasonable for patients at higher ischemic risk provided they also have a lower bleeding risk. This should be an individualized decision, considering both ischemic and bleeding risks. The DAPT risk score has been derived from the DAPT study and is supported by guidelines to aid in making decisions regarding prolonging DAPT beyond 12 months (Table 34-9).[107,108] A risk score of 2 or more suggests that prolonging therapy is favorable and would reduce ischemic events with perhaps only a modest increase in bleeding risk. Conversely, for those with a DAPT risk score less than 2, the risk for bleeding is anticipated to be greater than an ischemic benefit and the $P2Y_{12}$ inhibitor should be discontinued. The DAPT score was developed from a study comparing standard DAPT (12 months) to an extended duration of 30 months of therapy in patients who had PCI with intracoronary stenting for either SIHD or ACS and is not appropriate for determining DAPT duration shorter than 12 months. Further, 65% of patients enrolled in this study were administered clopidogrel and 35% were treated with prasugrel; ticagrelor was not used. Other risk prediction models are being developed and evaluated.

TABLE 34-9

Factors Used to Calculate DAPT Score and Predict Ischemic and Bleeding Events

Points	+2	+1	−1	−2
Clinical variables	CHF or LVEF less than 30% (0.30) Saphenous vein graft PCI	Current tobacco user DM NSTEMI or STEMI at presentation Prior MI or PCI Stent diameter less than 3 mm Paclitaxel-eluting stent	Age 65-74	Age ≥75 years

Risk factors ordered from left to right include those with highest ischemic risk and highest point accrual to those with the highest bleeding risk and negative point accrual. A score of ≥2 favors prolonged DAPT; a score of <2 is of unfavorable risk/benefit. Total score ranges from −2 to 10.

Data from References 107 and 108.

Continued use of DAPT with ticagrelor beyond 12 months after ACS can be considered. One trial compared standard-dose ticagrelor to a reduced dose of 60 mg twice daily in combination with low-dose aspirin to aspirin alone in patients who had suffered an MI 1 to 3 years prior.[109] Continuation of DAPT with either dose of ticagrelor decreased the composite of CV death, MI, or stroke compared to aspirin alone. While major bleeding was increased in patients treated with ticagrelor compared to aspirin alone, there were fewer bleeds in the low-dose ticagrelor group compared to the standard dose. The lower dose of ticagrelor (60 mg twice daily) has not been studied in the first 12 months after ACS; therefore, only the 90 mg twice daily is appropriate for the first year after the index event.

Cholesterol Management

Statins

9 Following ACS, statins reduce total mortality, CV mortality, MI, and stroke. Results from landmark clinical trials have unequivocally demonstrated the value of statins in secondary prevention following MI and provide an approximate 1% reduction in risk of ASCVD event per 1% reduction in low-density lipoprotein cholesterol (LDL-C) over time.[101] Further, clinical trial results confirm the benefit of high-intensity statins initiated 1 to 10 days after ACS presentation. In a meta-analysis of randomized controlled clinical trials of patients with recent ACS (less than 14 days), statin therapy reduces mortality by 19%, with benefits observed after approximately 4 months of treatment.[110] Therefore, high-intensity statin therapy should be initiated during the index hospitalization once the patient has been stabilized and continued indefinitely. Risk reductions from high-intensity statin therapy occur regardless of cholesterol concentrations at presentation. Therefore, all patients with ACS should receive the highest dose of maximally tolerated statin, even those with “normal” LDL-C at baseline.[1,2,101]

In those patients who are already taking low- or moderate-intensity statin therapy at the time of ACS presentation, consideration should be given to switching to a high-intensity statin. For ACS patients with a history of statin intolerance or those at high risk for statin-related adverse effects (older patients, drug interaction, etc.), the use of moderate-intensity statins or lower doses of high-intensity statins may be considered.[101] Patients aged greater than 75 years may be prescribed a moderate-intensity statin as initial therapy because they are at higher risk of adverse drug effects and the data using high-dose statins in this patient subgroup are less robust.[101]

A lipid panel should be reassessed 4 to 6 weeks after initiation of therapy with the goal of a 50% reduction in LDL-C from baseline. Baseline lipid concentrations should be drawn as early as possible, ideally within the first 24 hours of ACS presentation, as phasic changes may occur that falsely lower total cholesterol, LDL-C, and high-density lipoprotein cholesterol. Triglycerides may be falsely elevated during this immediate period of ACS. See Chapter 32, “Dyslipidemia,” for a more detailed discussion on the management of patients with dyslipidemia.

Other Cholesterol-Lowering Therapies

Nonstatin therapies lower the risk of MACE in patients with ACS already receiving statin therapy and may be considered as add-on therapy in select patients. The combination of moderate-dose simvastatin and ezetimibe, a nonstatin, in patients with recent (within 10 days) ACS and an LDL-C level between 50 and 100 mg/dL (1.29 and 2.59 mmol/L) resulted in a modest reduction (6.4% relative risk reduction) in the rate of MACE compared to moderate-dose simvastatin alone.[111] Event rates were lower in patients who achieved lower LDL-C, suggesting a direct relationship between LDL-C and benefit. A new class of potent, injectable cholesterol-lowering drugs, the proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, lower the risk of MACE when added to high-intensity statin therapy in patients with recent ACS (within 1 to 12 months). Alirocumab reduced LDL-C by approximately 60% and the risk of MACE at 4 years by 15% compared to high-intensity statin therapy alone.[102] Another PCSK9 inhibitor, evolocumab, yielded similar reductions in LDL-C and MACE in patients with ASCVD, most of whom had a distant history of MI.[103] However, at the current cost of approximately $6,000 to $7,000 annually, the cost-effectiveness of PCSK9 inhibitors in this setting remains uncertain and may be dependent on baseline LDL-C.[101,112] Nevertheless, for patients with clinical ASCVD treated with maximally tolerated statin therapy at very high risk (eg, recent ACS event) and persistently elevated LDL-C (70 mg/dL [1.81 mmol/L]or greater), current guidelines suggest adding ezetimibe.[101] If LDL-C remains elevated despite maximally tolerated statin therapy and ezetimibe, the addition of a PCSK9 inhibitor is reasonable.[101]

ACE Inhibitors or Angiotensin Receptor Blockers

10 Following MI, ACE inhibitors lower mortality, reinfarction rates, and HF, most likely through the prevention of adverse cardiac remodeling.[1,2,113,114] While the use of IV enalaprilat within 24 hours of MI should be avoided due to increased risk of adverse events, early administration (within 48 hours of presentation) of ACE inhibitors is associated with lower mortality within the first month of therapy with additional benefit observed during longer treatment durations.[113,114] Data supporting the use of ACE inhibitors is strongest for those with left ventricular dysfunction (LVEF 40% [0.40] or less) or in those who developed HF symptoms in the early phase of ACS.[113] Therefore, treatment with ACE inhibitor is recommended in all patients with MI and concomitant HFrEF, HTN, DM, or stable chronic kidney disease.[1,2,29] For patients without those comorbidities who suffer an MI, treatment with an ACE inhibitor is also reasonable.[1,29] Because they have a comparable benefit to ACE inhibitors in patients with MI, an ARB may be prescribed for those who cannot tolerate an ACE inhibitor.[1,2,29,115]

Although ACE inhibitors and ARBs are generally well-tolerated, it is important to monitor closely for the development of noteworthy adverse effects. The most common adverse effects associated with ACE inhibitors and ARBs are worsening renal function and hypotension. Hyperkalemia is also possible and is more likely in patients who develop acute kidney injury. Therefore, close monitoring of renal function, potassium levels, and blood pressure are warranted 1 to 2 weeks following initiation and dose adjustments. Although angioedema and chronic cough are possible with each of these therapies, both adverse effects are more common with ACE inhibitors and occur infrequently with ARBs.

Aldosterone Antagonists

10 To reduce mortality, administration of an aldosterone antagonist, either eplerenone or spironolactone, should be considered within the first 14 days following MI in all patients with left ventricular dysfunction (LVEF of 40% [0.40] or less) and either HF symptoms or DM treated with both an ACE inhibitor (or ARB) and β-blocker.[1,2,29] Aldosterone antagonists attenuate the adverse hemodynamic and metabolic effects from chronic excessive aldosterone production as well as the cardiac remodeling that occurs in patients with MI.[116] In patients who suffered MI, aldosterone antagonists improved LVEF, lower ed the risk for new or worsening HF by 26%, and reduced the risk of both all-cause mortality and CV mortality by 18%.[116] Although mortality was lower in patients with and without HF treated with aldosterone antagonists, the difference was only significant in patients with HF.

Both eplerenone and spironolactone block the mineralocorticoid receptor to which aldosterone binds contributing to some of the observed adverse effects. Spironolactone is a nonspecific steroid hormone receptor antagonist that also binds progesterone and androgen receptors and can cause gynecomastia in men and menstrual irregularities in women.[19] In contrast, eplerenone is selective for the mineralocorticoid receptor, thereby minimizing the risk of gynecomastia, sexual dysfunction, and menstrual irregularities.[19] In post-MI clinical trials, aldosterone antagonists have been associated with a more than twofold increase in the risk of hyperkalemia with an overall incidence of 11.6%.[116] Therefore, patients who are post-MI

with serum potassium concentrations greater than 5 mmol/L (mEq/L) should not receive an aldosterone antagonist.[2] Additional contraindications for aldosterone antagonists include a serum creatinine greater than 2.5 mg/dL (221 µmol/L) for men or 2 mg/dL (177 µmol/L) for women, or CrCl less than 30 mL/min (0.5 mL/s).[2] Because of the increased risk of hyperkalemia, especially in patients with chronic kidney disease, both serum potassium and renal function should be monitored diligently: 3 days and 1 week after initiation or dose titration, then monthly for the first 3 months, and every 3 months thereafter. There are no data to support the use of the more selective but more expensive eplerenone over the generically available spironolactone unless a patient experiences gynecomastia, breast pain, or impotence while receiving spironolactone.

Nitroglycerin

All patients should be prescribed and instructed on the appropriate use of short-acting nitroglycerin, typically either sublingual tablets or lingual spray, to relieve acute anginal symptoms on an as-needed basis.[1,2] Appropriate patient education for patients prescribed short-acting nitroglycerin is provided in Chapter 33, "Stable Ischemic Heart Disease." Chronic long-acting nitrate therapy does not reduce MACE following ACS and its role is typically limited to the prevention of recurrent symptoms of angina for patients treated for ACS with significant coronary stenoses not amenable to revascularization who experience symptomatic SIHD. For patients with ACS for whom vasospasm is believed to be contributory, long-acting nitrates are recommended to treat and reduce the frequency of anginal episodes.[2]

EVALUATION OF THERAPEUTIC OUTCOMES

Evaluation of short-term efficacy focuses on the restoration or preservation of coronary blood flow, symptom relief, and prevention of MACE. Restoration of blood flow and relief of ischemia can be detected by resolution of the ischemic changes on ECG at the time of presentation, which should occur soon after revascularization. Although cTn levels may remain elevated for several days, for patients with MI, cTn levels should peak within 12 to 24 hours and should decline steadily thereafter once ischemia is relieved. More importantly, if blood flow is restored or preserved and the angina is managed effectively, the patients should have a resolution of symptoms rather quickly. In terms of MACE, monitoring for the development of complications from ACS (eg, HF, arrhythmias) should occur frequently. Lastly, assuring that evidence-based therapies that reduce the risk of MACE following ACS have been initiated in appropriate patients is critical.

Long-term evaluation of outcomes is directed largely at functional capacity and continued focus on risk reduction. Returning to and maintaining a high quality of life is an important goal following an ACS hospitalization. Patients should eventually be able to return to their activities of daily living, perhaps following a cardiac rehabilitation program to assist them with this goal. Additionally, patients should be monitored at every healthcare encounter for the development of adverse effects from ACS pharmacotherapy (Table 34-10). If patients show signs of adverse effects or intolerance, particularly serious adverse events such as bleeding or hypotension, the offending agent(s) may need to be discontinued until the symptoms have resolved. Clinical signs of bleeding include bloody stools, melena, hematuria, hematemesis, bruising, and oozing from arterial or venous puncture sites. Oral antiplatelet agents are a leading cause of hospitalizations and ED visits for adverse drug reactions among senior citizens.[117] Patients should be counseled on the risks and sites of potential bleeding and should be told to seek medical care immediately if significant bleeding is noticed. If bleeding occurs while on chronic therapy, the patient should be referred to the prescribing physician as the severity of the bleed and the timing since index event (and presence of stent placement) may influence supportive measures and cessation of therapy.

TABLE 34-10

Therapeutic Drug Monitoring of Pharmacotherapy for ACS

Drug	Adverse Effects	Monitoring
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 & 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, heart rate, 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: serum creatinine at baseline then daily
Anticoagulants	Bleeding	Clinical signs of bleeding[a]; baseline aPTT, INR; Hgb, Hct, platelet count at baseline then daily
	Unfractionated heparin and LMWH: heparin-induced thrombocytopenia	Unfractionated heparin: aPTT every 6 hours until two consecutive aPTT values are at goal, then every 24 hours; ACT during PCI
		Enoxaparin, bivalirudin, and fondaparinux: serum creatinine at baseline then daily
		Enoxaparin: may consider steady-state anti-Xa levels in special populations
β-Blockers	Hypotension, heart failure, bradycardia, cardiogenic shock, AV block, exacerbation of asthma or reactive airway disease	Continuous telemetry (while hospitalized); blood pressure, heart rate, signs and symptoms of heart failure; monitor every 5 minutes before each IV bolus dose; monitor every shift while hospitalized then at each healthcare encounter after discharge
Nitroglycerin	Flushing, headache, hypotension, tachycardia	Blood pressure and heart rate; monitor every 5-15 minutes following dosage adjustment of intravenous nitroglycerin then every 1-2 hours; monitor every 5 minutes following administration of short-acting nitroglycerin
Morphine	Hypotension, respiratory depression, sedation, hypersensitivity	Blood pressure, heart rate, respiratory rate, sedation level 5 minutes after administration then every 1-2 hours for 4 hours after the last dose
Calcium channel blockers	Hypotension	Blood pressure, heart rate, every shift while hospitalized then at each healthcare encounter after discharge
	Verapamil and diltiazem: heart failure, cardiogenic shock, bradycardia, AV block	Verapamil and diltiazem: continuous telemetry (while hospitalized); signs and symptoms of heart failure 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; 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
Nonstatin therapies	Ezetimibe and combination: GI discomfort, arthralgia, myalgia, musculoskeletal pain	Simvastatin/ezetimibe: liver function tests at baseline (prior to discharge) and if signs or symptoms of hepatoxicity 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
	PCSK9 inhibitors: injection site pain,	PCSK9 inhibitors: LDL-C at baseline and 4-8 weeks after initiation or dose adjustment;

	hypersensitivity, nasopharyngitis	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	Blood pressure every shift while hospitalized, 1-2 weeks after initiation or dose adjustment, then with each healthcare encounter; serum creatinine 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	Blood pressure every shift while hospitalized, 1-2 weeks after initiation or dose adjustment, then with each healthcare encounter; serum creatinine and potassium at baseline, 1-2 weeks after initiation, then every 6-12 months
Aldosterone antagonist	Hyperkalemia, worsening renal function	Blood pressure every shift while hospitalized, 1-2 weeks after initiation or dose adjustment, then with each healthcare encounter; serum creatinine and potassium at baseline, after initiation or dose adjustment: at 3 days, 1 week, monthly for 3 months, then every 3 months

GI, gastrointestinal; Hct, hematocrit; Hgb, hemoglobin; ICH, intracranial hemorrhage; INR, international normalized ratio; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin-kexin type 9.

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

For long-term risk reduction, the focus centers on control of CAD risk factors and the appropriate use of and adherence to an evidence-based medication regimen known to reduce the risk of MACE. Lifestyle modifications should be reinforced during each healthcare encounter. Similarly, control of CAD risk factors should be assessed and interventions made to improve risk factor control, if necessary. Finally, it is important to reassess the evidence-based regimen to determine the need to either escalate (eg, add additional evidence-based ACS therapies or increase their doses) or de-escalate therapy (eg, consider discontinuation of $P2Y_{12}$ inhibitor after 12 months or β-blocker after 3 years in a post-MI patient with a normal LVEF).

Medication adherence must also be assessed during each healthcare encounter. Despite evidence to support mortality reduction with secondary prevention strategies, typically less than 50% of patients remain adherent at 1 year.[118] Because nonadherence with secondary prevention medications following ACS leads to poor CV outcomes, patients must receive thorough medication counseling (including counseling prior to hospital discharge) and be monitored for medication persistence.[1,2,104] Counseling should include assessments of health literacy level, barriers to adherence, access to medications, and understanding of instructions.[104] Additionally, patients and their caregivers should be provided written and verbal instructions about the purpose of each medication, changes to previous medication regimen, the optimal time to take each medication, new allergies or medication intolerances, need for a timely prescription fill after discharge, anticipated duration of therapy, consequences of nonadherence, common and/or serious adverse reactions that may develop, and drug-drug and drug-food interactions.[104] Early follow-up (within 6 weeks) after discharge has been associated with improved medication adherence and, for this reason, post-discharge follow-up is often scheduled within 1 to 2 weeks.[119]

CONCLUSION

For the majority of patients, the pathophysiology of ACS involves an acute disruption of an atherosclerotic plaque followed by platelet activation and aggregation leading to intracoronary thrombus formation. Myocardial ischemia ensues due to an acute imbalance between myocardial oxygen supply and demand and may lead to infarction depending on the severity and duration of thrombotic occlusion. Therefore, the acute pharmacotherapeutic management of ACS is focused on antiplatelet, anticoagulation, and anti-ischemic therapies. Appropriate selection of these agents depends upon patient presentation (eg, STEMI or NSTE-ACS), the decision for reperfusion (eg, PCI, fibrinolysis, or no reperfusion), and individual considerations for efficacy and safety associated with individual agents (eg, pharmacokinetic alterations, drug-drug interactions, contraindications). High-intensity statins should be initiated early and continued indefinitely for all patients with ACS without contraindications to lower LDL-C and stabilize atherosclerotic plaques. Long-term use of DAPT lowers the risk of MACE after ACS and maintains stent patency in patients who had intracoronary stent implantation during PCI. Neurohormonal blocking drugs such as β-blockers and inhibitors of the RAAS system are also associated with a lower risk of MACE and should be initiated prior to hospital discharge in appropriate patients. Each member of the healthcare team plays an important role in the

patient care process for ACS, collecting and analyzing clinical information, collaborating in the development and implementation of the care plan, and evaluating therapeutic outcomes.

ABBREVIATIONS

ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
ACT	activated clotting time
ADP	adenosine diphosphate
AHA	American Heart Association
aPTT	activated partial thromboplastin time
ARB	angiotensin receptor blocker
ASCVD	atherosclerotic cardiovascular disease
AT	antithrombin
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CCB	calcium channel blocker
COX	cyclooxygenase
CrCl	creatinine clearance
cTn	cardiac troponin
CV	cardiovascular
CYP	cytochrome P450
DAPT	dual antiplatelet therapy
DHP	dihydropyridine
DM	diabetes mellitus
ECG	electrocardiogram
ED	emergency department

EMS	emergency medical services
ENT	equilibrative nucleoside transporter
GI	gastrointestinal
GP	glycoprotein
GRACE	Global Registry of Acute Coronary Events
HEART	History, ECG, age, risk factors, and troponin
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HIT	heparin-induced thrombocytopenia
HTN	hypertension
ICH	intracranial hemorrhage
IV	intravenous
LBBB	left bundle branch block
LDL-C	low-density lipoprotein cholesterol
LMWH	low-molecular-weight heparin
LVEF	left ventricular ejection fraction
MACE	major adverse cardiovascular events
MI	myocardial infarction
MONA	morphine, oxygen, nitroglycerin, aspirin
NSTE-ACS	non-ST-segment elevation acute coronary syndromes
NSTEMI	non-ST-segment elevation myocardial infarction
PAR	protease-activated receptor
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin-kexin type 9
RAAS	renin–angiotensin–aldosterone system
SCr	serum creatinine

SIHD	stable ischemic heart disease
SNS	sympathetic nervous system
STEMI	ST-segment-elevation myocardial infarction
SC	subcutaneous
TIMI	thrombolysis in myocardial infarction
UA	unstable angina

REFERENCES

1. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013;61:e78–e140. [PubMed: 23256914]

2. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;64:e139–e228. [PubMed: 25260718]

3. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics—2021 update. *Circulation*. 2021;143:e254–e743. doi: 10.1161/cir.0000000000000950.

4. Chi GC, Kanter MH, Li BH, et al. Trends in acute myocardial infarction by race and ethnicity. *J Am Heart Assoc.* 2020;9:e013542. doi: 10.1161/jaha.119.013542.

5. Wellings J, Kostis JB, Sargsyan D, et al. Risk factors and trends in incidence of heart failure following acute myocardial infarction. *Am J Cardiol.* 2018;122:1–5. doi: 10.1016/j.amjcard.2018.03.005.

6. Jernberg T, Johanson P, Held C, et al. Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction. *JAMA.* 2011;305:1677–1684. doi: 10.1001/jama.2011.522.

7. Tickoo S, Bhardwaj A, Fonarow GC, Liang L, Bhatt DL, Cannon CP. Relation between hospital length of stay and quality of care in patients with acute coronary syndromes (from the American Heart Association's Get with the Guidelines—coronary artery disease data set). *Am J Cardiol.* 2016;117:201–205. [PubMed: 26651452]

8. Sugiyama T, Hasegawa K, Kobayashi Y, Takahashi O, Fukui T, Tsugawa Y. Differential time trends of outcomes and costs of care for acute myocardial infarction hospitalizations by ST elevation and type of intervention in the United States, 2001–2011. *J Am Heart Assoc.* 2015;4:e001445. [PubMed: 25801759]

9. Nicholson G, Gandra SR, Halbert RJ, Richhariya A, Nordyke RJ. Patient-level costs of major cardiovascular conditions: A review of the international literature. *Clinicoecon Outcomes Res.* 2016;8:495–506. [PubMed: 27703385]

10. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol.* 2018. doi: 10.1016/j.jacc.2018.08.1038.

11. Ford TJ, Berry C, De Bruyne B, et al. Physiological predictors of acute coronary syndromes: Emerging insights from the plaque to the vulnerable

patient. *JACC Cardiovasc Interv.* 2017;10:2539–2547. [PubMed: 29268883]

12. Crea F, Liuzzo G. Pathogenesis of acute coronary syndromes. *J Am Coll Cardiol.* 2013;61:1–11. [PubMed: 23158526]

13. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. *N Engl J Med.* 2013;368:2004–2013. [PubMed: 23697515]

14. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. *Circ Res.* 2014;114:1852–1866. [PubMed: 24902970]

15. Libby P, Tabas I, Fredman G, Fisher EA. Inflammation and its resolution as determinants of acute coronary syndromes. *Circ Res.* 2014;114:1867–1879. [PubMed: 24902971]

16. Crea F, Libby P. Acute coronary syndromes: The way forward from mechanisms to precision treatment. *Circulation*. 2017;136:1155–1166. [PubMed: 28923905]

17. Fuster V, Kovacic JC. Acute coronary syndromes: Pathology, diagnosis, genetics, prevention, and treatment. *Circ Res.* 2014;114:1847–1851. [PubMed: 24824094]

18. Furie B, Furie BC. Mechanisms of thrombus formation. *N Engl J Med.* 2008;359:938–949. [PubMed: 18753650]

19. Brunton LL, Hilal-Dandan R, Knollmann BC. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics.* 13th ed. New York, NY: McGraw Hill; 2018.

20. Gabriel-Costa D. The pathophysiology of myocardial infarction-induced heart failure. *Pathophysiology.* 2018;25:277–284. [PubMed: 29685587]

21. Reed GW, Rossi JE, Cannon CP. Acute myocardial infarction. *Lancet*. 2017;389:197–210. [PubMed: 27502078]

22. Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation*. 2000;102:2031–2037. [PubMed: 11044416]

23. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA.* 2000;284:835–842. [PubMed: 10938172]

24. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med.* 2003;163:2345–2353. [PubMed: 14581255]

25. Six AJ, Backus BE, Kelder JC. Chest pain in the emergency room: Value of the HEART score. *Neth Heart J.* 2008;16:191–196. [PubMed: 18665203]

26. Gulati Martha, Levy Phillip D, Mukherjee Debabrata, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the evaluation and diagnosis of chest pain: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;144:e368–e454. 10.1161/cir.0000000000001029.

27. Poldervaart JM, Langedijk M, Backus BE, et al. Comparison of the GRACE, HEART and TIMI score to predict major adverse cardiac events in chest pain patients at the emergency department. *Int J Cardiol.* 2017;227:656–661. [PubMed: 27810290]

28. Kline KP, Conti CR, Winchester DE. Historical perspective and contemporary management of acute coronary syndromes: From MONA to THROMBINS2. *Postgrad Med.* 2015;127:855–862. [PubMed: 26457728]

29. Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: A guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. *J Am Coll Cardiol.* 2011;58:2432–2446. [PubMed:

22055990]

30. GISSI-3: Effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. *Lancet*. 1994;343:1115–1122. [PubMed: 7910229]

31. ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. *Lancet*. 1995;345:669–685. [PubMed: 7661937]

32. Siddiqi N, Neil C, Bruce M, et al. Intravenous sodium nitrite in acute ST-elevation myocardial infarction: A randomized controlled trial (NIAMI). *Eur Heart J.* 2014;35:1255–1262. [PubMed: 24639423]

33. McCord J, Jneid H, Hollander JE, et al. Management of cocaine-associated chest pain and myocardial infarction: A scientific statement from the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. *Circulation*. 2008;117:1897–1907. [PubMed: 18347214]

34. Ventimiglia E, Capogrosso P, Montorsi F, Salonia A. The safety of phosphodiesterase type 5 inhibitors for erectile dysfunction. *Expert Opin Drug Saf.* 2016;15:141–152. [PubMed: 26752541]

35. Duarte GS, Nunes-Ferreira A, Rodrigues FB, et al. Morphine in acute coronary syndrome: Systematic review and meta-analysis. *BMJ Open* 2019;9(3):e025232. 10.1136/bmjopen-2018-025232.

36. Kubica J, Kubica A, Jilma B, et al. Impact of morphine on antiplatelet effects of oral P2Y12 receptor inhibitors. *Int J Cardiol.* 2016;215:201–208. [PubMed: 27128531]

37. Cabello JB, Burls A, Emparanza JI, Bayliss SE, Quinn T. Oxygen therapy for acute myocardial infarction. *Cochrane Database Syst Rev.* 2016;12:CD007160. [PubMed: 27991651]

38. Bangalore S, Makani H, Radford M, et al. Clinical outcomes with beta-blockers for myocardial infarction: A meta-analysis of randomized trials. *Am J Med.* 2014;127:939–953. [PubMed: 24927909]

39. Freemantle N, Cleland J, Young P, Mason J, Harrison J. Beta blockade after myocardial infarction: Systematic review and meta regression analysis. *BMJ.* 1999;318:1730–1737. [PubMed: 10381708]

40. Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: Randomised placebo-controlled trial. *Lancet*. 2005;366:1622–1632. [PubMed: 16271643]

41. Park JJ, Kim SH, Kang SH, et al. Effect of beta-blockers beyond 3 years after acute myocardial infarction. *J Am Heart Assoc.* 2018;(7):e007567.

42. Held PH, Yusuf S, Furberg CD. Calcium channel blockers in acute myocardial infarction and unstable angina: An overview. *BMJ.* 1989;299:1187–1192. [PubMed: 2513047]

43. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: The CAPRICORN randomised trial. *Lancet*. 2001;357:1385–1390. [PubMed: 11356434]

44. Agrawal PR, Scarabelli TM, Saravolatz L, et al. Current strategies in the evaluation and management of cocaine-induced chest pain. *Cardiol Rev.* 2015;23:303–311. [PubMed: 25580707]

45. Furberg CD, Psaty BM, Meyer JV. Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. *Circulation*. 1995;92:1326–1331. [PubMed: 7648682]

46. Bagai A, Dangas GD, Stone GW, Granger CB. Reperfusion strategies in acute coronary syndromes. *Circ Res.* 2014;114:1918–1928. [PubMed: 24902975]

47. Gersh BJ, Stone GW, White HD, Holmes DR Jr. Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction: Is the slope of the curve the shape of the future? *JAMA.* 2005;293:979–986. [PubMed: 15728169]

48. Pinto DS, Frederick PD, Chakrabarti AK, et al. Benefit of transferring ST-segment-elevation myocardial infarction patients for percutaneous coronary intervention compared with administration of onsite fibrinolytic declines as delays increase. *Circulation*. 2011;124:2512–2521. [PubMed: 22064592]

49. Bagai A, Jollis JG, Dauerman HL, et al. Emergency department bypass for ST-segment-elevation myocardial infarction patients identified with a prehospital electrocardiogram: A report from the American Heart Association Mission: Lifeline program. *Circulation*. 2013;128:352–359. [PubMed: 23788525]

50. Ting HH, Krumholz HM, Bradley EH, et al. Implementation and integration of prehospital ECGs into systems of care for acute coronary syndrome: A scientific statement from the American Heart Association Interdisciplinary Council on Quality of Care and Outcomes Research, Emergency Cardiovascular Care Committee, Council on Cardiovascular Nursing, and Council on Clinical Cardiology. *Circulation*. 2008;118:1066–1079. [PubMed: 18703464]

51. McNamara RL, Wang Y, Herrin J, et al. Effect of door-to-balloon time on mortality in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol.* 2006;47:2180–2186. [PubMed: 16750682]

52. Gibson CM, Pride YB, Frederick PD, et al. Trends in reperfusion strategies, door-to-needle and door-to-balloon times, and in-hospital mortality among patients with ST-segment elevation myocardial infarction enrolled in the National Registry of Myocardial Infarction from 1990 to 2006. *Am Heart J.* 2008;156:1035–1044. [PubMed: 19032997]

53. Langabeer JR, Henry TD, Kereiakes DJ, et al Growth in percutaneous coronary intervention capacity relative to population and disease prevalence. *J Am Heart Assoc.* 2013;2:e000370. [PubMed: 24166491]

54. Bonnefoy E, Lapostolle F, Leizorovicz A, et al. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: A randomised study. *Lancet*. 2002;360:825–829. [PubMed: 12243916]

55. Jneid H, Addison D, Bhatt DL, et al. 2017 AHA/ACC clinical performance and quality measures for adults with ST-elevation and non-ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *Circ Cardiovasc Qual Outcomes*. 2017;70(16):2048–2090.

56. Dasari TW, Roe MT, Chen AY, et al. Impact of time of presentation on process performance and outcomes in ST-segment-elevation myocardial infarction: A report from the American Heart Association: Mission Lifeline program. *Circ Cardiovasc Qual Outcomes*. 2014;7:656–663. [PubMed: 25074371]

57. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2018;39:119–177. [PubMed: 28886621]

58. Jinatongthai P, Kongwatcharapong J, Foo CY, et al. Comparative efficacy and safety of reperfusion therapy with fibrinolytic agents in patients with ST-segment elevation myocardial infarction: A systematic review and network meta-analysis. *Lancet*. 2017;390:747–759. [PubMed: 28831992]

59. Armstrong PW, Gershlick AH, Goldstein P, et al. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med.* 2013;368:1379–1387. [PubMed: 23473396]

60. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. A report of the American

College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol.* 2011;58:e44–e122. [PubMed: 22070834]

61. Dobesh PP, Varnado S, Doyle M. Antiplatelet agents in cardiology: A report on aspirin, clopidogrel, prasugrel, and ticagrelor. *Curr Pharm Des.* 2016;22:1918–1932. [PubMed: 26642781]

62. Current-Oasis Investigators. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med.* 2010;363:930–942. [PubMed: 20818903]

63. Akers WS, Oh JJ, Oestreich JH, Ferraris S, Wethington M, Steinhubl SR. Pharmacokinetics and pharmacodynamics of a bolus and infusion of cangrelor: A direct, parenteral P2Y12 receptor antagonist. *J Clin Pharmacol.* 2010;50:27–35. [PubMed: 19779037]

64. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med.* 2001;345:494–502. [PubMed: 11519503]

65. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2007;357:2001–2015. [PubMed: 17982182]

66. Montalescot G, Bolognese L, Dudek D, et al. Pretreatment with prasugrel in non–ST-segment elevation acute coronary syndromes. *N Engl J Med.* 2013;369:999–1010. doi: 10.1056/nejmoa1308075.

67. Tarantini G, Mojoli M, Varbella F, et al. Timing of oral P2Y12 inhibitor administration in patients with non-ST-segment elevation acute coronary syndrome. *J Am Coll Cardiol.* 2020;76:2450–2459. doi: 10.1016/j.jacc.2020.08.053.

68. Tantry US, Bonello L, Aradi D, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. *J Am Coll Cardiol.* 2013;62:2261–2273. [PubMed: 24076493]

69. Pereira NL, Rihal C, Lennon R, et al. Effect of CYP2C19 genotype on ischemic outcomes during oral P2Y12 inhibitor therapy. *J Am Coll Cardiol Intv.* 2021;14:739–750. doi: 10.1016/j.jcin.2021.01.024.

70. Sibbing D, Aradi D, Alexopoulos D, et al. Updated expert consensus statement on platelet function and genetic testing for guiding $P2Y_{12}$ receptor inhibitor treatment percutaneous coronary intervention. *JACC Cardiovasc Interv.* 2019;12:1521–1537. [PubMed: 31202949]

71. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: Randomised placebo-controlled trial. *Lancet*. 2005;366:1607–1621. [PubMed: 16271642]

72. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med.* 2005;352:1179–1189. [PubMed: 15758000]

73. Roe MT, Armstrong PW, Fox KA, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *N Engl J Med.* 2012;367:1297–1309. [PubMed: 22920930]

74. Dobesh PP, Oestreich JH. Ticagrelor: Pharmacokinetics, pharmacodynamics, clinical efficacy, and safety. *Pharmacotherapy.* 2014;34:1077–1090. [PubMed: 25164528]

75. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009;361:1045–1057. [PubMed: 19717846]

76. Mahaffey KW, Wojdyla DM, Carroll K, et al. Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation*. 2011;124:544–554. [PubMed: 21709065]

77. Gimbel M, Qaderdan K, Willemsen L, et al. Clopidogrel versus ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome (POPular AGE): The randomised, open-label, non-inferiority trial. *Lancet*. 2020;395:1374–1381. doi: 10.1016/s0140-6736(20)30325-1.

78. Szummer K, Montez-Rath ME, Alfredsson J, et al. Comparison between ticagrelor and clopidogrel in elderly patients with an acute coronary syndrome. *Circulation*. 2020;142:1700–1708. doi: 10.1161/circulationaha.120.050645.

79. Schüpke S, Neumann FJ, Menichelli M, et al. Ticagrelor or prasugrel in patients with acute coronary syndromes. *N Engl J Med.* 2019;381:1524–1534. [PubMed: 31475799]

80. Berwanger O, Nicolau JC, Carvalho AC, et al. Ticagrelor vs clopidogrel after fibrinolytic therapy in patients with ST-elevation myocardial infarction: A randomized clinical trial. *JAMA Cardiol.* 2018;3:391–399. [PubMed: 29525822]

81. Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med.* 2013;368:1303–1313. [PubMed: 23473369]

82. Steinhubl SR, Oh JJ, Oestreich JH, Ferraris S, Charnigo R, Akers WS. Transitioning patients from cangrelor to clopidogrel: Pharmacodynamic evidence of a competitive effect. *Thromb Res.* 2008;121:527–534. [PubMed: 17631948]

83. Dovlatova NL, Jakubowski JA, Sugidachi A, Heptinstall S. The reversible P2Y antagonist cangrelor influences the ability of the active metabolites of clopidogrel and prasugrel to produce irreversible inhibition of platelet function. *J Thromb Haemost.* 2008;6:1153–1159. [PubMed: 18485086]

84. Angiolillo DJ, Rollini F, Storey RF, et al. International expert consensus on switching platelet P2Y12 receptor-inhibiting therapies. *Circulation*. 2017;136:1955–1975. [PubMed: 29084738]

85. Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141:e495S–e530S. [PubMed: 22315270]

86. Kastrati A, Mehilli J, Neumann FJ, et al. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: The ISAR-REACT 2 randomized trial. *JAMA.* 2006;295:1531–1538. [PubMed: 16533938]

87. Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med.* 2006;355:2203–2216. [PubMed: 17124018]

88. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med.* 2008;358:2218–2230. [PubMed: 18499566]

89. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141:e24S–e43S. [PubMed: 22315264]

90. Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. *JAMA.* 1996;276:811–815. [PubMed: 8769591]

91. Antman EM, Cohen M, Radley D, et al. Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction. TIMI 11B-ESSENCE meta-analysis. *Circulation*. 1999;100:1602–1608. [PubMed: 10517730]

92. Ferguson JJ, Califf RM, Antman EM, et al. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: Primary results of the SYNERGY randomized trial. *JAMA.* 2004;292:45–54. [PubMed: 15238590]

93. Antman EM, Morrow DA, McCabe CH, et al. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med.* 2006;354:1477–1488. [PubMed: 16537665]

94. Navarese EP, De Luca G, Castriota F, et al. Low-molecular-weight heparins vs. unfractionated heparin in the setting of percutaneous coronary intervention for ST-elevation myocardial infarction: A meta-analysis. *J Thromb Haemost.* 2011;9:1902–1915. [PubMed: 21777368]

95. Turpie AG, Lensing AW, Fuji T, Boyle DA. Pharmacokinetic and clinical data supporting the use of fondaparinux 1.5 mg once daily in the prevention of venous thromboembolism in renally impaired patients. *Blood Coagul Fibrinolysis.* 2009;20:114–121. [PubMed: 19339838]

96. Yusuf S, Mehta SR, Chrolavicius S, et al. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: The OASIS-6 randomized trial. *JAMA.* 2006;295:1519–1530. [PubMed: 16537725]

97. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes I, Yusuf S, Mehta SR, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med.* 2006;354:1464–1476. [PubMed: 16537663]

98. Kastrati A, Neumann FJ, Mehilli J, et al. Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. *N Engl J Med.* 2008;359:688–696. [PubMed: 18703471]

99. Schulz S, Richardt G, Laugwitz KL, et al. Prasugrel plus bivalirudin vs. clopidogrel plus heparin in patients with ST-segment elevation myocardial infarction. *Eur Heart J.* 2014;35:2285–2294. [PubMed: 24816809]

100. Shahzad A, Kemp I, Mars C, et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): An open-label, single centre, randomised controlled trial. *Lancet*. 2014;384:1849–1858. [PubMed: 25002178]

101. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2018. https://doi.org/10.1016/j.jacc.2018.11.003.

102. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med.* 2018;379:2097–2107. [PubMed: 30403574]

103. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med.* 2017;376:1713–1722. doi: 10.1056/nejmoa1615664.

104. Wiggins BS, Rodgers JE, DiDomenico RJ, Cook AM, Page RL II. Discharge counseling for patients with heart failure or myocardial infarction: A best practices model developed by members of the American College of Clinical Pharmacy's Cardiology Practice and Research Network based on the Hospital to Home (H2H) Initiative. *Pharmacotherapy.* 2013;33:558–580. [PubMed: 23529897]

105. Frøbert O, Götberg M, Erlinge D, et al. Influenza vaccination after myocardial infarction: A randomized, double-blind, placebo-controlled, multicenter trial. *Circulation*. 2021;144(18):1476–1484. doi: 10.1161/circulationaha.121.057042.

106. Udell JA, Zawi R, Bhatt DL, et al. Association between influenza vaccination and cardiovascular outcomes in high-risk patients. *JAMA.* 2013;310:1711–1720. doi: 10.1001/jama.2013.279206.

107. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2016;68:1082–1115. [PubMed: 27036918]

108. Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA.* 2016;315:1735–1749. [PubMed: 27022822]

109. Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med.* 2015;372:1791–1800. [PubMed: 25773268]

110. Hulten E, Jackson JL, Douglas K, George S, Villines TC. The effect of early, intensive statin therapy on acute coronary syndrome: A meta-analysis of randomized controlled trials. *Arch Intern Med.* 2006;166:1814–1821. [PubMed: 17000936]

111. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med.* 2015;372:2387–2397. [PubMed: 26039521]

112. Bhatt DL, Briggs AH, Reed SD, et al. Cost-effectiveness of alirocumab in patients with acute coronary syndromes. *J Am Coll Cardiol.* 2020;75:2297–2308. doi: 10.1016/j.jacc.2020.03.029.

113. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA.* 1995;273:1450–1456. [PubMed: 7654275]

114. Rodrigues EJ, Eisenberg MJ, Pilote L. Effects of early and late administration of angiotensin-converting enzyme inhibitors on mortality after myocardial infarction. *Am J Med.* 2003;115:473–479. [PubMed: 14563504]

115. Lee VC, Rhew DC, Dylan M, Badamgarav E, Braunstein GD, Weingarten SR. Meta-analysis: Angiotensin-receptor blockers in chronic heart failure and high-risk acute myocardial infarction. *Ann Intern Med.* 2004;141:693–704. [PubMed: 15520426]

116. Bossard M, Binbraik Y, Beygui F, et al. Mineralocorticoid receptor antagonists in patients with acute myocardial infarction: A systematic review and meta-analysis of randomized trials. *Am Heart J.* 2018;195:60–69. [PubMed: 29224647]

117. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med.* 2011;365:2002–2012. [PubMed: 22111719]

118. Kumbhani DJ, Steg PG, Cannon CP, et al. Adherence to secondary prevention medications and four-year outcomes in outpatients with atherosclerosis. *Am J Med.* 2013;126:693–700e1. [PubMed: 23800583]

119. Faridi KF, Peterson ED, McCoy LA, Thomas L, Enriquez J, Wang TY. Timing of first postdischarge follow-up and medication adherence after acute myocardial infarction. *JAMA Cardiol.* 2016;1:147–155. [PubMed: 27437885]

SELF-ASSESSMENT QUESTIONS

1. A 47-year-old patient (weight 78 kg) with a history of stable ischemic heart disease (SIHD) presents with substernal chest pressure. His electrocardiogram (ECG) shows ST-segment depression. His initial troponin (cTn) is elevated. The patient undergoes percutaneous coronary intervention (PCI) with two drug-eluting stents. According to practice guidelines, in addition to aspirin 81 mg daily, which $P2Y_{12}$ inhibitor regimen is most appropriate for this patient at discharge?

   A. Clopidogrel 75 mg daily for 6 months

   B. Prasugrel 10 mg daily for 1 year

   C. Ticagrelor 60 mg twice daily for 1 year

   D. Ticagrelor 90 mg twice daily for 6 months

2. A patient presents to the emergency department (ED) with lower back pain, diaphoresis, and nausea and is treated for unstable angina with aspirin 325 mg and intravenous (IV) unfractionated heparin. Which option depicts the most appropriate monitoring of parameters during IV unfractionated heparin administration?

A. Activated partial thromboplastin time (aPTT) every 3 hours until therapeutic

B. aPTT every 6 hours until therapeutic

C. Activated clotting time (ACT) every 12 hours until therapeutic

D. ACT daily until therapeutic

3. A 72-year-old African American patient presents with chest pain after a recent drug-eluting stent placement 3 months ago and is treated for ST-segment elevation myocardial infarction (STEMI) due to in-stent thrombosis with successful PCI. The patient reports compliance with his dual antiplatelet therapy, which consisted of clopidogrel 75 mg daily and aspirin 81 mg daily. He also takes ranitidine for indigestion-related symptoms. Which of the following best describes a rationale for clopidogrel's reduced activity in this patient?

A. Presence of CYP3A4 polymorphism

B. Presence of CYP2C19 polymorphism

C. Drug interaction with ranitidine

D. Improper clopidogrel dose

4. A 55-year-old African American patient with hypertension (HTN) but no history of coronary artery disease presents to the ED for one episode of back pain accompanied by nausea and vomiting which resolved after one dose of sublingual nitroglycerin. Social history is unremarkable. Home medications include chlorthalidone 25 mg daily and amlodipine 5 mg daily. ECG shows some ST-segment depression. Laboratory values are within normal limits and her estimated creatinine clearance (CrCl) is 67 mL/min (1.12 mL/s). cTn is undetectable. Weight = 80 Kg. Based on the patient's Thrombolysis in Myocardial Infarction (TIMI) risk score, which is the most appropriate strategy for this patient?

A. Early invasive approach

B. Fibrinolytic therapy

C. Ischemia-guided approach

D. Primary PCI

5. A patient with a past medical history significant for diabetes mellitus (DM) is hospitalized for STEMI, has PCI performed, and is now being prepared for discharge. Estimated CrCl is 50 mL/min (0.83 mL/s), and LDL-C is 79 mg/dL (2.05 mmol/L). Pertinent laboratory data include sodium 134 mEq/L (mmol/L), potassium 3.4 mEq/L (mmol/L), and creatinine 1.5 mg/dL (133 µmol/L). Blood pressure is 115/80 mm Hg and heart rate is 78 beats per minute. Current medications include aspirin 81 mg daily, atorvastatin 80 mg daily, metoprolol succinate 50 mg daily, lisinopril 10 mg daily, and ticagrelor 90 mg twice daily. Echocardiogram reveals a left ventricular ejection fraction (LVEF) of 25% (0.25). Which guideline-directed medical therapy would be best to add to this patient's regimen?

A. Alirocumab 75 mg SC every 2 weeks

B. Diltiazem extended-release 180 mg daily

C. Losartan 25 mg daily

D. Spironolactone 25 mg daily

6. A 57-year-old patient (weight 92 kg) with a history of SIHD presents with a 4-hour history of substernal chest pressure. The ECG shows 3 mm ST-segment elevation in leads V2–V4. The initial cTn is 5.2 ng/mL (mcg/L), SCr 1.1 mg/dL (97 µmol/L), and potassium 3.7 mEq/L (mmol/L). The nearest hospital with catheterization laboratory facilities is 2.5 hours away by ambulance. Blood pressure is 210/85 mm Hg at present. Which of the following is the most appropriate reperfusion strategy for this patient?

A. Blood pressure must be lowered before fibrinolytic therapy is considered.

B. Primary PCI is preferred over fibrinolytic therapy in this patient.

C. Tenecteplase 50 mg IVP once.

D. Reteplase 10 units IVP once.

Please use the following case to answer questions 7 to 9.

RJ is a 68-year-old patient (weight 100 kg) who presents to the hospital with consistent substernal chest pain rated 8 out 10 for the last 4 hours that radiates to his left arm and up into his jaw. Past medical history includes DM, HTN, ischemic stroke, depression, and dyslipidemia. ECG reveals ST-segment depression and the initial cTn is elevated. All other laboratory values are within normal limits including renal and liver function. Blood pressure is 124/74 mm Hg and heart rate is 78 beats per minute. RJ has received 3 doses of sublingual nitroglycerin with minimal relief. The plan is for RJ to go to the catheterization laboratory for PCI and stent placement in the next 12 hours.

7. Which of the following represents the most likely pathophysiologic mechanism of RJ's ACS event?

   A. Vasospasm

   B. Ruptured atherosclerotic plaque

   C. Increase in myocardial oxygen demand in the setting of a fixed decrease in supply

   D. Smooth muscle cell proliferation

8. Which of the following represents the most appropriate antiplatelet regimen, in addition to aspirin, for RJ while he is still in the ED before going to PCI?

   A. Clopidogrel 300 mg, followed by 75 mg daily

   B. Ticagrelor 180 mg, followed by 90 mg twice daily

   C. Prasugrel 60 mg, followed by 10 mg daily

   D. Eptifibatide 180 mcg/kg IV bolus × 2 given 10 minutes apart, followed by 2 mcg/kg/min IV infusion started after first bolus

9. Which of the following represents the most appropriate anticoagulant regimen to initiate in the ED?

   A. Unfractionated heparin 8,000 units IV bolus, then 1,800 units/hr IV infusion

   B. Fondaparinux 5 mg subcutaneously (SC) every 24 hours

   C. Bivalirudin 0.10 mg/kg IV bolus, followed by 0.25 mg/kg/hr IV infusion

   D. Enoxaparin 100 mg SC every 12 hours

10. Which of the following substances is central in the clotting cascade as well as involved in platelet activation and aggregation?

    A. Von Willebrand factor

    B. Collagen

    C. Thrombin

    D. Tissue factor

11. A 72-year-old patient presents to the ED with chest tightness that started 8 hours ago. This is the third episode, is associated with diaphoresis and dyspnea, and is refractory to sublingual nitroglycerin. Blood pressure is 114/78 mm Hg, heart rate is 112 bpm, respiratory rate is 26 breaths/min, and oxygen saturation is 89% (0.89) on room air. ECG shows 2-mm ST-segment depression. Bilateral crackles are noted at the bases bilaterally on physical examination. Which of the following acute supportive measures should be avoided in this patient?

    A. IV metoprolol

    B. IV morphine

    C. IV nitroglycerin

    D. Oxygen

12. A 54-year-old patient presents to the ED complaining of acute-onset chest pain radiating down his left arm, which started 2 hours ago. He admits to cocaine ingestion just prior to the onset of symptoms. Blood pressure is 220/108 mm Hg, heart rate is 108 bpm, and oxygen saturation is 98% (0.98) on room air. ECG shows 1 mm ST-segment depression. Laboratory values are pending. Which of the following acute supporting measures is most appropriate at this time?

    A. IV metoprolol

    B. IV morphine

    C. IV nitroglycerin

    D. Oxygen

13. A patient treated for STEMI complicated by symptomatic heart failure (LVEF 35% [0.35]) is being started on eplerenone. Baseline serum creatinine and potassium were within normal limits. When should serum creatinine and potassium levels be reassessed?

    A. 3 days

    B. 1 week

    C. 2 weeks

    D. 1 month

14. A patient is treated for NSTEMI. An echocardiogram reveals an LVEF of 20% (0.20). The patient is hemodynamically stable and being discharged on the following medications: aspirin 81 mg daily, prasugrel 10 mg daily, rosuvastatin 40 mg daily, carvedilol 3.125 mg twice daily, ramipril 10 mg daily, and spironolactone 25 mg daily. What is the most appropriate duration of carvedilol therapy for this patient?

    A. 6 months

    B. 1 year

    C. 3 years

    D. Indefinitely

15. EP, a 66-year-old patient, complains of sudden onset tightness in his chest and jaw, shortness of breath, diaphoresis and headache that began 3 hours ago when shoveling snow on the patio. The patient has no known medical problems, takes no medications, and has no known drug allergies. Blood pressure is 194/98 mmHg, heart rate 98 bpm. Electrocardiogram reveals T wave inversion in 2 contiguous leads. Creatinine is 1.1 mg/dL (97 µmol/L; creatinine clearance 77 mL/min [1.28 mL/s]) and cardiac troponin is 4.6 ng/mL (mcg/L; normal <0.02 ng/mL [mcg/L]). Which of the following antithrombotic therapies should be avoided in this patient?

    A. Alteplase

B. Aspirin

C. Enoxaparin

D. Ticagrelor

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** The 2014 NSTE-ACS guideline gives a class I recommendation for clopidogrel, prasugrel, or ticagrelor in the ACS setting with PCI and stent placement (Table 34-5). After any ACS event (regardless of PCI with stent placement), the preferred duration for dual antiplatelet therapy is at least 12 months (A and D are incorrect). B is correct because prasugrel is an appropriate antiplatelet in this setting, is dosed correctly at a maintenance of 10 mg, and is continued for the correct time frame of 12 months post ACS. C is incorrect because the appropriate ticagrelor dose during the initial 12 months following an ACS event is 90 mg (not 60 mg) twice daily.

2. **B.** Unfractionated heparin may be monitored by aPTT, anti-Xa, or ACT for therapeutic accuracy (Table 34-10). In patients going to the cath lab, an activated clotting time (ACT) is normal, as it can be tested at the bedside with relatively instant results during the procedure. Conversely, an ACT is not measured in a patient such as this who is managed with an ischemia-guided approach (ie, not going to the cath lab) (C and D are incorrect). In patients receiving an unfractionated heparin infusion, an aPTT should be monitored every 6 hours until therapeutic and daily thereafter (A is incorrect). B represents the correct time frame for aPTT monitoring. In addition, hemoglobin, hematocrit, and platelets (at least every other day if not more often) should be monitored in patients receiving unfractionated heparin infusions.

3. **B.** Reduced efficacy can occur with clopidogrel for a number of reasons, non-adherence to therapy being the most important (see "Clopidogrel" section). When patients report being adherent with this daily therapy, reduced activity can occur because of the presence of a genetic polymorphism of the CYP2C19 gene (B is correct), responsible for converting clopidogrel into its active form, not CYP3A4 (A is incorrect). Drug interactions have been theorized to reduce activity as well, especially with potent inhibitors of CYP2C19 such as esomeprazole and omeprazole. But, ranitidine is not known to interact with clopidogrel (C is incorrect). Finally, although higher doses of clopidogrel have been studied to overcome resistance, those dosing strategies are not recommended (D is incorrect).

4. **C.** This patient has a TIMI risk score of 1 (ST-segment depression on ECG) indicating low-risk (Table 34-1). Women who present with NSTE-ACS without cTn elevation and low-risk features, like the patient in this case, should not undergo early invasive treatment because of the lack of benefit and potential for harm (Class III) (A is incorrect). In the absence of ST-segment elevation or new-onset left bundle branch block, immediate reperfusion with either a fibrinolytic (B) or primary PCI (D) is incorrect. Women with low-risk features should be treated with an ischemia-guided approach (Fig. 34-2), where she should be treated medically while monitoring her symptoms (C is correct).

5. **D.** To reduce mortality, administration of a mineralocorticoid receptor antagonist, such as spironolactone (D is correct) should be considered within the first 14 days of post-myocardial infarction in patients who are already receiving an ACE inhibitor (or ARB) and a β-blocker in patients who have a LVEF of 40% (0.40) or less and either HF symptoms or DM as long as no contraindications exist (Fig. 34-3 and Table 34-8). C is incorrect because this patient is already receiving an ACE inhibitor and the addition of an ARB to an ACE will increase risk for adverse events but not reduce mortality further. Diltiazem is not indicated because the patient is already receiving metoprolol succinate and does not have refractory symptoms (B is incorrect). A is not correct because additional lowering of LDL-C is not necessary and the patient is already treated with high-intensity statin therapy.

6. **A.** Fibrinolytic therapy is indicated and should be administered for patients with STEMI when PCI cannot be performed within 120 minutes (Table 34-3). Because the nearest cath lab is 2.5 hours away, this patient would benefit from fibrinolytic therapy. (B is incorrect.) However, his current blood pressure of 210/85 mm Hg represents a relative contraindication to fibrinolytic administration (C and D are incorrect; Table 34-3). Blood pressure must be lowered prior to administration in order to reduce risk for bleeding complications from therapy, including intracranial hemorrhage (A is correct). If systolic blood pressure is successfully lowered to <185 mm Hg, C and D become correct options. However, only the dosing in answer C would be correct (Table 34-4). Reteplase is given as a double bolus, not a one-time dose (D is incorrect; Table 34-4).

7. **B.** The most common pathophysiologic mechanism creating an acute coronary syndrome is rupture atherosclerotic plaque, making B correct (see "Pathophysiology" section). While vasospasm can produce an ACS event, it is much less likely and when it occurs without atherosclerosis, it typically occurs in younger patients. C is incorrect as this is the main pathophysiologic mechanism in patients with stable ischemic heart disease

and not for an ACS event. D is also not correct as this is the main mechanism of restenosis of previously revascularized vessels and does not typically present as an ACS event due to the process taking 3 to 6 months to occur.

8. **B.** While the guidelines do say that clopidogrel is an acceptable option, the use of ticagrelor and prasugrel are preferred in patients undergoing PCI due to better efficacy in the head-to-head trials. When clopidogrel is used in patient undergoing PCI, the 600 mg loading dose should be used instead of the 300 mg loading dose (Table 34-5). Therefore, A is incorrect and B is correct. The dose of prasugrel is correct, but prasugrel is contraindicated in patients with a history of stroke or transient ischemic attack due to excessive bleeding and no additional efficacy. Therefore, C is incorrect. If the patient is preloaded with a more potent $P2Y_{12}$ inhibitor such as ticagrelor or prasugrel, the use of a GP IIb/IIIa inhibitor adds unknown value. GP IIb/IIIa inhibitors are also best used at the time of PCI instead of upstream use in the emergency department, making D incorrect.[12]

9. **D.** While all of these anticoagulants can be used in patients with NSTE-ASC, they are not all appropriate or appropriately dosed in this patient. Initial unfractionated heparin bolus doses are capped at 4,000 units and initial infusion rates are capped at 1,000 units per hour for patients with ACS (Table 34-7). The dosing in A is incorrect as this represents the dosing of unfractionated heparin in patients with venous thromboembolism. Fondaparinux is generally not used in patients undergoing PCI due to the increase in catheter thrombosis. The dose is also too high for the setting of ACS. Dosing should be 2.5 mg and not 5 mg (Table 34-7), making B incorrect. Bivalirudin is started at the time of PCI and not in the emergency department, making C incorrect. Enoxaparin dosed at 1 mg/kg every 12 hours is an acceptable option in the guidelines (Table 34-7), and therefore, D is correct.

10. **C.** (See "Pathophysiology" section.) The von Willebrand factor in endothelial cells is mainly involved in the initial adhesion of platelet to the area of atherosclerotic plaque rupture, but has no role in the clotting cascade. Therefore, A is incorrect. Collagen is responsible for the stability of the fibrous cap on the atherosclerotic plaque, as well as platelet adhesion at the site of plaque rupture, and a very potent platelet activator. It does not have a role in the clotting cascade, making B incorrect. Thrombin is the central component of the clotting cascade and responsible for multiple positive feedback loops to potentiate the clotting cascade. All currently used anticoagulants either target thrombin directly or its production. Thrombin is also a very potent platelet activator. Being an important link between the two pathways, C is correct. Tissue factor released from damaged endothelial cells is responsible for initiation of the extrinsic clotting cascade, but does not impact platelets, making D incorrect.

11. **A.** This patient has evidence of acute heart failure (bilateral basilar crackles) and several risk factors for the development of cardiogenic shock (age >70 years, systolic BP <120 mm Hg, heart rate >110 bpm; Table 34-2). Therefore, IV beta-blockers should be avoided (A is correct). Because this patient's symptoms are refractory to sublingual nitroglycerin, both IV morphine (B) and IV nitroglycerin (C) are reasonable supportive care measures in this patient (Table 34-2); avoiding them is incorrect. This patient is hypoxic; therefore, avoidance of oxygen (D) would be incorrect.

12. **C.** Because this patient is presenting with ACS following acute cocaine ingestion and is also experiencing acute, uncontrolled HTN, the most appropriate acute supportive measure is IV nitroglycerin (C is correct, see "Nitroglycerin" section). Because of the cocaine ingestion, the use of IV beta-blockers is not recommended (A is incorrect). IV morphine is not appropriate at this time because his symptoms are not refractory; he has not yet been given anything to treat his symptoms (B is incorrect). Oxygen saturation is acceptable at 98% (0.98); therefore, supplemental oxygen is unnecessary (D is incorrect).

13. **A.** Because of the risk of hyperkalemia, patients initiated on aldosterone antagonists should have their serum creatinine and potassium levels monitored closely: at 3 days, 1 week, and at least monthly for the first 3 months (Table 34-10). Therefore, A is correct. While a patient initiated on an aldosterone antagonist should have creatinine and potassium measured at 1 week (B) and 1 month (D), the initial reassessment should occur at 3 days; therefore, these answers are incorrect. Two weeks would not be soon enough to monitor for the development of hyperkalemia (C is incorrect).

14. **D.** Because the patient has had an MI and has HFrEF (LVEF 20% [0.20]), beta-blocker therapy (carvedilol) should be continued indefinitely (D is correct). Three years of therapy would only be required if the LVEF were normal (C is incorrect). Although there is some debate about only 1 year of beta-blocker therapy in patients with ACS and normal LVEF, guidelines do not recommend durations of beta-blocker therapy less than 3 years (A and B are incorrect).

15. **A.** Because the patient does not have ST-elevation on the ECG, there is no indication for fibrinolytic therapy with alteplase (A is correct). Aspirin, enoxaparin, and ticagrelor would all be plausible therapies in this patient; avoidance would be unnecessary (B, C, and D are incorrect).