SECTION I

Ischemic Heart Disease

EDITOR

Venu Menon

CHAPTER 1

Christopher M. Huff

Acute Myocardial Infarction

I. EPIDEMIOLOGY. Acute myocardial infarction (MI) is the leading cause of death in North America and Europe. Each year, an estimated 785,000 Americans will sustain a new MI, and another 470,00 will have a recurrent MI. An American has an acute MI every 25 seconds, and someone dies of an MI every minute. In 2007, coronary heart disease caused one out of every six deaths. The incidence and mortality with acute MI have declined dramatically over the last 30 years, with the advent of the coronary care unit, fibrinolytic therapy, catheter-based reperfusion, and statin therapy. The aging of the population in advanced economies, as well as the global increased incidence of diabetes and obesity, will however, increase the sequelae of atherosclerotic coronary artery disease in the future (1).

II. PATHOPHYSIOLOGY. In most patients, coronary plaque rupture is the initiating event of acute MI. Rupture of the fibrous cap of a coronary atheroma exposes the underlying subendothelial matrix to formed elements of circulating blood, leading to activation of platelets, thrombin generation, and thrombus formation. Erosion of a coronary plaque without rupture can also lead to thrombus formation and is estimated to cause up to 25% of MIs. Acute coronary syndrome (ACS) is a dynamic process that involves cyclical transitioning among complete vessel occlusion, partial vessel occlusion, and reperfusion. Occlusive thrombus in the absence of significant collateral vessels most often results in acute ST-segment elevation myocardial infarction (STEMI). The pathophysiology of STEMI and non–ST-segment elevation myocardial infarction (NSTEMI) is similar, and this explains the substantial overlap in ACSs with regard to ultimate outcome, extent of necrosis, and mortality rates. The recognition of ST-segment elevation is particularly important because it generally mandates the need for emergent reperfusion therapy.

III. DEFINITION. A 2007 expert consensus document (2) redefined acute MI as the detection of a rise and/or fall in cardiac troponin with at least one value above the 99th percentile of the upper reference limit (URL) utilizing an assay with < 10% coefficient of variation at the level of detection, together with evidence of ischemia. Ischemia was defined as any symptom of ischemia, electrocardiographic changes suggestive of new ischemia, development of pathologic Q waves on electrocardiogram (ECG), or imaging evidence of infarction. Included in the definition were sudden cardiac death (SCD) with evidence of myocardial ischemia (new ST elevation, left bundle branch block [LBBB], or coronary thrombus) and biomarker elevation > 3× URL for post–percutaneous coronary intervention (PCI) patients or > 5× URL for post–coronary artery bypass grafting (post-CABG) patients. Documented stent thrombosis was recognized in this new definition as well (Table 1.1). Established MI was defined as any one criterion that satisfies the following: development of new pathologic Q waves on serial ECGs, imaging evidence of MI, or pathologic findings of healed or healing MI.

TABLE 1.1 Clinical Classification of Different Types of Myocardial Infarction

Type 1	Spontaneous MI related to ischemia from a coronary plaque rupture or dissection
Type 2	MI due to ischemia resulting from increased oxygen demand or decreased supply
Type 3	Sudden cardiac death with symptoms of ischemia, new ST elevation, or LBBB or coronary thrombus
Type 4a	MI associated with PCI
Type 4b	MI associated with stent thrombosis
Type 5	MI associated with CABG

CABG, coronary artery bypass grafting; LBBB, left bundle branch block; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Adapted from Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *J Am Coll Cardiol.* 2007;50:2173–2175.

IV. CLINICAL DIAGNOSIS. In any patient with a clinical history of chest pain suspected to be of cardiac origin, an ECG should be obtained within 10 minutes of presentation and interpreted promptly to determine eligibility for reperfusion therapy. If the **ECG demonstrates acute ST-segment elevation or new LBBB, emergent reperfusion treatment with primary PCI or fibrinolysis is indicated**. During this evaluation period, a targeted medical history and physical examination should be performed. If the patient's history is compatible with cardiac ischemia and the ECG does not meet the criteria for reperfusion therapy, the patient may have unstable angina or NSTEMI. These syndromes are discussed in Chapter 2.

A. Signs and symptoms

1. The classic symptoms are severe, **crushing substernal chest pain** described as a squeezing or constricting sensation with frequent radiation to the left arm, often associated with an impending sense of doom. The discomfort is similar to that of angina pectoris, but it is typically more severe, of longer duration (usually > 20 minutes), and is not relieved with rest or nitroglycerin. Peak intensity is usually not instantaneous, as it would be with pulmonary embolism or aortic dissection.
   a. The chest discomfort may radiate to the neck, jaw, back, shoulder, right arm, and epigastrium. Pain in any of these locations without chest pain is possible. Myocardial ischemic pain localized to the epigastrium is often misdiagnosed as indigestion. Acute MI can occur without chest pain, especially among postoperative patients, the elderly, and those with diabetes mellitus.
   b. If the pain is sudden, radiates to the back, and is described as tearing or knife-like, aortic dissection should be considered.
2. Associated symptoms may include diaphoresis, dyspnea, fatigue, light-headedness, palpitations, acute confusion, indigestion, nausea, or vomiting. Gastrointestinal symptoms are especially common with inferior infarction.

B. Physical examination. In general, the physical examination does not add much to the diagnosis of acute MI. However, the examination is extremely important in excluding other diagnoses that may mimic acute MI, in risk stratification, in the diagnosis of impending heart failure, and in serving as a baseline examination to monitor for mechanical complications of acute MI that may develop.

1. **Risk stratification**, which aids in treatment decisions and counseling patients and families, is based in part on age, heart rate, and blood pressure and on the presence or absence of pulmonary edema and a third heart sound.
2. The **mechanical complications** of mitral regurgitation and ventricular septal defect are often heralded by a new systolic murmur (see Chapter 3). Early diagnosis of these complications relies on well-documented examination findings at baseline and during the hospital course.

V. DIFFERENTIAL DIAGNOSIS. The differential diagnosis of ST elevation includes conditions with comorbid ischemia such as acute aortic dissection involving the root, conditions with ST elevation but no ischemia such as left ventricular (LV) hypertrophy or early repolarization abnormality, and conditions with chest pain but no ischemia such as myopericarditis (Table 1.2). The most common differential diagnostic considerations are discussed in the following text.

A. Pericarditis. Chest pain that is worse when the person is supine and improves when the person is sitting upright or slightly forward is typical of pericarditis. Care must be taken in excluding acute MI, however, because pericarditis can complicate acute MI. The electrocardiographic abnormalities of acute pericarditis may also be confused with acute MI. Diffuse ST-segment elevation is the hallmark of acute pericarditis, but this finding may be seen in acute MI that involves the left main coronary artery or a large "wraparound" left anterior descending artery. PR-segment depression, peaked T waves, or electrocardiographic abnormalities out of proportion to the clinical scenario may favor the diagnosis of pericarditis. The ST-segment elevations in pericarditis are often concave, whereas the ST-segment elevations in acute MI are usually convex. Reciprocal ST depression does not occur in pericarditis, except in leads aVR and V_1. Early T-wave inversion is not a feature of acute pericarditis. Echocardiography may be useful, not in evaluating pericardial effusion, which may occur in either condition, but in documenting the lack of wall motion abnormalities in the setting of ongoing pain and ST elevation.

B. Myocarditis. As with pericarditis, the symptoms and electrocardiographic findings of myocarditis may be similar to those of acute MI. Echocardiography is less useful in differentiating this syndrome from acute MI, because segmental LV dysfunction may be encountered in either condition. A complete history often reveals a more insidious onset and associated viral syndrome with myocarditis.

TABLE 1.2 Differential Diagnostic Considerations for ST-Segment Elevation Myocardial Infarction

Comorbid ischemia	ST elevation but no ischemia	Chest pain but no ischemia
Aortic dissection	Early repolarization	Aortic dissection
Systemic arterial embolism	Left ventricular hypertrophy	Myopericarditis
Hypertensive crisis	Left bundle branch block	Pleuritis
Aortic stenosis	Hyperkalemia	Pulmonary embolism
Cocaine use	Brugada syndrome	Costochondritis
Arteritis		Gastrointestinal disorders

Adapted from Christofferson RD. Acute ST-elevation myocardial infarction. In: Shishehbor MH, Wang TH, Askari AT, et al., eds. *Management of the Patient in the Coronary Care Unit.* New York: Lippincott Williams & Wilkins; 2008.

C. **Acute aortic dissection.** Sharp, tearing chest pain that radiates through the chest to the back is typical of aortic dissection (see Chapter 26). This type of radiation pattern should be investigated thoroughly before administration of antithrombotic, antiplatelet, or fibrinolytic therapy. Proximal extension of the dissection into either coronary ostium can account for acute MI. A chest radiograph may reveal a widened mediastinum. Transthoracic echocardiography may reveal a dissection flap in the proximal ascending aorta. If it does not, a more definitive diagnosis should be obtained with transesophageal echocardiography (TEE), computerized tomography (CT), or magnetic resonance imaging (MRI).

D. **Pulmonary embolism.** Shortness of breath associated with pleuritic chest pain but without evidence of pulmonary edema suggests pulmonary embolism. Echocardiography helps to rule out wall motion abnormalities and may identify right ventricular (RV) dilatation and dysfunction in the setting of pulmonary embolism.

E. **Esophageal disorders.** Gastroesophageal reflux disease, esophageal motility disorders, and esophageal hyperalgesia can cause chest pain, the character of which is very similar to cardiac ischemic pain. These disorders can often coexist in patients with coronary disease, thereby complicating the diagnosis. A workup for coronary disease should precede evaluation of esophageal disorders. Symptoms that may be suggestive but not diagnostic of chest pain of an esophageal origin include postprandial symptoms, relief with antacids, and lack of radiation of pain.

F. **Acute cholecystitis** can mimic the symptoms and ECG findings of inferior acute MI, although the two can coexist. Tenderness in the right upper quadrant, fever, and an elevated leukocyte count favor cholecystitis, which can be diagnosed by means of hepatobiliary iminodiacetic acid (HIDA) scanning.

VI. LABORATORY EXAMINATION (Fig. 1.1)

A. **Troponins.** Troponin T and troponin I assays are particularly useful in the diagnosis and management of unstable angina and NSTEMI because of their high sensitivity, ability to be used and interpreted rapidly at bedside, and nearly universal availability. Currently, the lag time between occlusion and detectable elevations in serum levels limits their usefulness in the diagnosis of acute STEMI; however, the development of high-sensitivity troponin T assays may allow for more rapid detection of myocardial necrosis. Also, data have suggested that a single troponin T concentration measured 72 hours after acute MI may be predictive of MI size, independent of reperfusion (3). Troponin elevation in the absence of ischemic heart disease can be found in congestive heart failure (CHF), aortic dissection, hypertrophic cardiomyopathy, pulmonary embolism, acute neurologic disease, cardiac contusion, or drug toxicity.

B. **Creatine kinase (CK).** An elevated level of CK is rarely helpful in making the diagnosis of acute MI for a patient with ST-segment elevation. Because it usually takes 4 to 6 hours to see an appreciable rise in CK levels, an initial normal value does not exclude recent complete occlusion. CK and CK-MB (creatine kinase myocardial band) levels can be elevated in the presence of pericarditis and myocarditis, which may cause diffuse ST-segment elevation. CK levels are more helpful in gauging the size and timing of acute MI than in making the diagnosis. CK levels peak at 24 hours, but the peak CK level is believed to occur earlier among patients who undergo successful reperfusion. False-positive results of CK elevation occur in a variety of settings, including skeletal muscle disease or trauma (e.g., rhabdomyolysis).

C. **Myoglobin.** Damaged cardiac myocytes rapidly release this protein into the bloodstream. Peak levels occur between 1 and 4 hours, allowing for early diagnosis of acute MI. However, myoglobin lacks cardiac specificity, thereby limiting its clinical utility. Studies have indicated that it might play a role in risk stratification after reperfusion therapy (4).

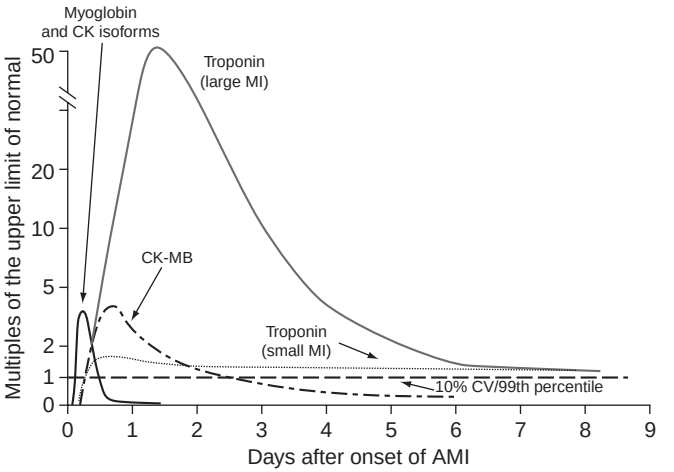


FIGURE 1.1 Timing of biomarker release after acute myocardial infarction. AMI, acute myocardial infarction; CK, creatine kinase; CK-MB, creatine kinase myocardial band; CV, coefficient of variation. (Reprinted from Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction—executive summary. *J Am Coll Cardiol.* 2007;50:652–726, with permission from Elsevier.)

VII. DIAGNOSTIC TESTING

A. Electrocardiography

1. **Definitive electrocardiographic diagnosis** of acute MI requires ST elevation of 1 mm or more in two or more contiguous leads, often with reciprocal ST depression in the contralateral leads. In leads V_2–V_3, 2 mm of ST elevation in men and 1.5 mm in women are required for accurate diagnosis.
2. **ECG subsets.** ST-segment elevations can be divided into subgroups that may be correlated with the infarction-related artery and risk of death. These five subgroups are listed in Table 1.3 and illustrated in Figure 1.2.
3. **Left bundle branch block**
   a. **New LBBB in the setting of symptoms consistent with acute MI** may indicate a large, anterior wall acute MI involving the proximal left anterior descending coronary artery and should be managed as acute STEMI.
   b. **In the absence of an old ECG or in the presence of LBBB at baseline**, the diagnosis of acute STEMI can be made with > 90% specificity on the basis of the criteria listed in Table 1.4 and illustrated in Figure 1.3.
   c. **Right bundle branch block (RBBB) may** complicate interpretation of ST elevation in leads V_1 through V_3. RBBB does not, however, obscure ST-segment elevation.

B. Echocardiography

may be helpful in the evaluation of LBBB of undetermined duration in that the lack of regional wall motion abnormality in the presence of continuing symptoms makes the diagnosis of acute MI unlikely. It is worth noting that abnormal septal motion is often observed in the setting of LBBB even in the absence of ischemia.

TABLE 1.3 Acute Myocardial Infarction: Electrocardiogram Subsets and Correlated Infarct-Related Artery and Mortality

Category	Anatomy of occlusion	ECG findings	30-Day mortality rate (%)[a]	1-Year mortality rate (%)
1. Proximal LAD	Proximal to first septal perforator	ST↑ V_1–V_6, I, aVL and fascicular or bundle branch block	19.6	25.6
2. Mid-LAD	Proximal to large diagonal but distal to first septal perforator	ST↑ V_1–V_6, I, aVL	9.2	12.4
3. Distal LAD or diagonal	Distal to large diagonal or diagonal itself	ST↑ V_1–V_4, or I, aVL, V_5, V_6	6.8	10.2
4. Moderate to large inferior (posterior, lateral, right ventricular)	Proximal RCA or left circumflex	ST↑ II, III, aVF, and any of the following: (a) V_1, V_3R, V_4R (b) V_5, V_6 (c) R > S in V_1, V_2	6.4	8.4
5. Small inferior	Distal RCA or left circumflex branch	ST↑ II, III, aVF only	4.5	6.7

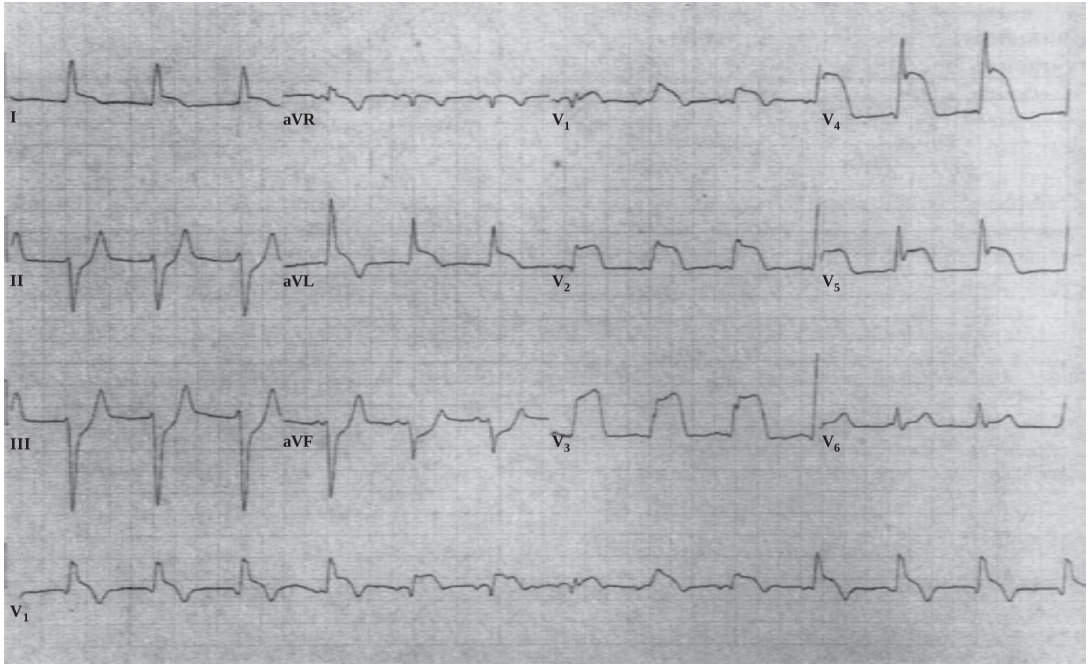
ECG, electrocardiogram; LAD, left anterior descending (coronary artery); ↑, increased; RCA, right coronary artery.

[a]Mortality rate based on GUSTO I cohort population in each of the 5 year categories, all receiving reperfusion therapy.

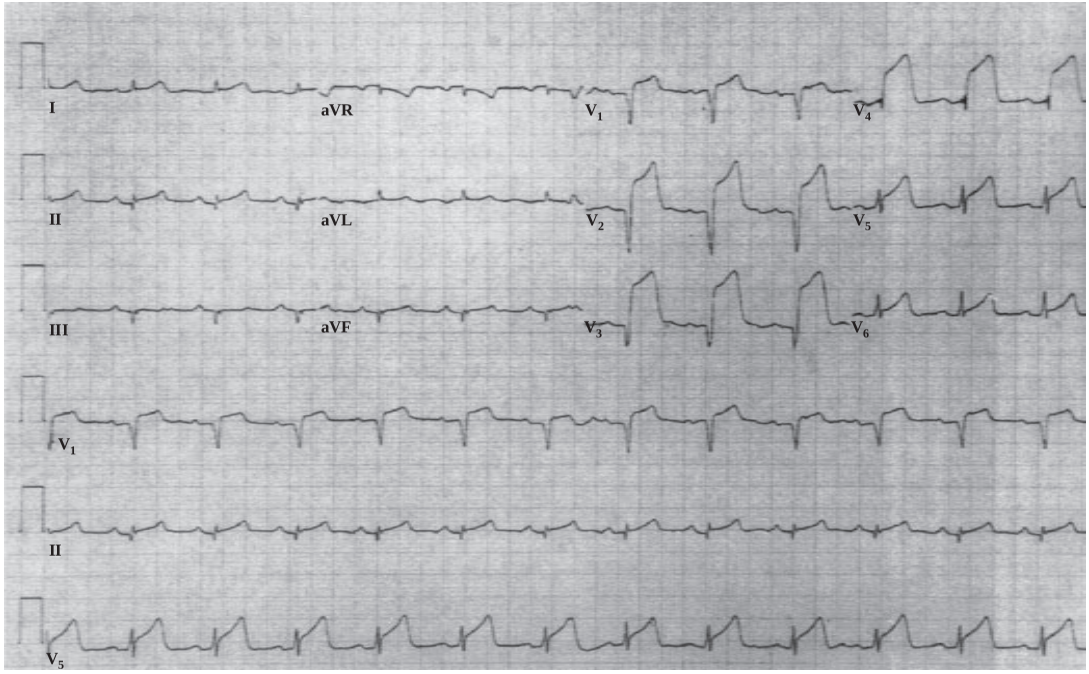
From Topol EJ, Van de Werf FJ. Acute myocardial infarction: early diagnosis and management. In: Topol EJ, ed. *Textbook of Cardiovascular Medicine*. New York: Lippincott-Raven; 1998, with permission.

VIII. RISK STRATIFICATION. It is possible and useful to estimate the risk of death of a patient with acute MI. The estimate can aid in making treatment decisions and recommendations and in counseling patients and families. Five simple baseline parameters have been reported to account for > 90% of the prognostic information for 30-day mortality. These characteristics are given in descending order of importance: age, systolic blood pressure, Killip classification (Table 1.5), heart rate, and location of MI (Table 1.3, Fig. 1.2) (5). In addition, various risk models have been created to improve risk prediction.

A. The Thrombolysis in Myocardial Infarction (TIMI) risk score incorporates eight variables obtained from the history, physical examination, and ECG (Table 1.6). In patients treated with fibrinolysis, a TIMI score of 9 or greater predicts a 30-day mortality of approximately 35%. In patients with a TIMI score of 0 or 1, the 30-day mortality rate is < 2%. The strongest predictor of poor prognosis is advanced age (where age ≥ 75 years receives 3 points and age 65 to 74 years receives 2 points). Other variables that predict a poor prognosis include hypotension, Killip class II–IV at presentation, tachycardia, history of diabetes or hypertension, anterior ST elevation (also complete LBBB), low body weight, and a time to treatment of > 4 hours.



A



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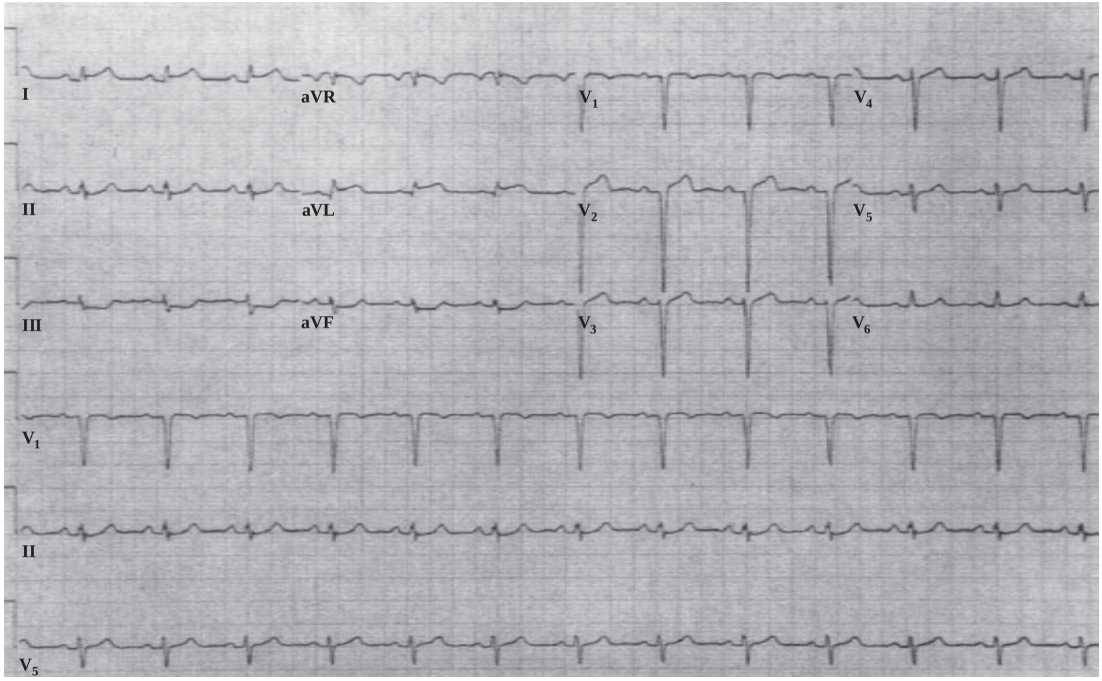

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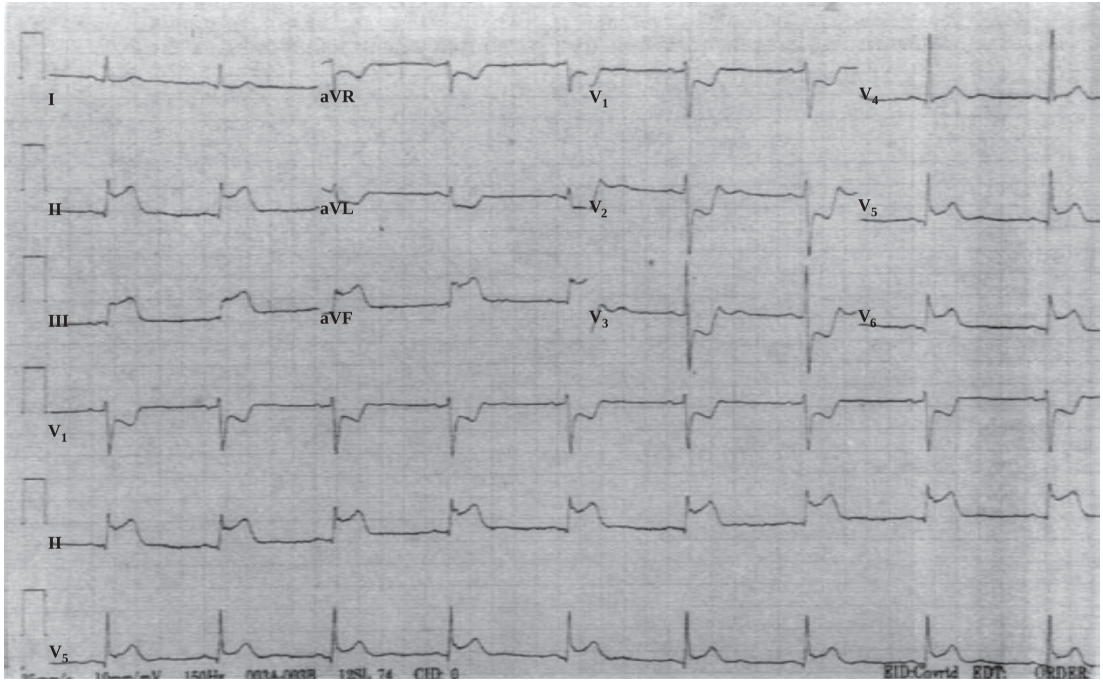

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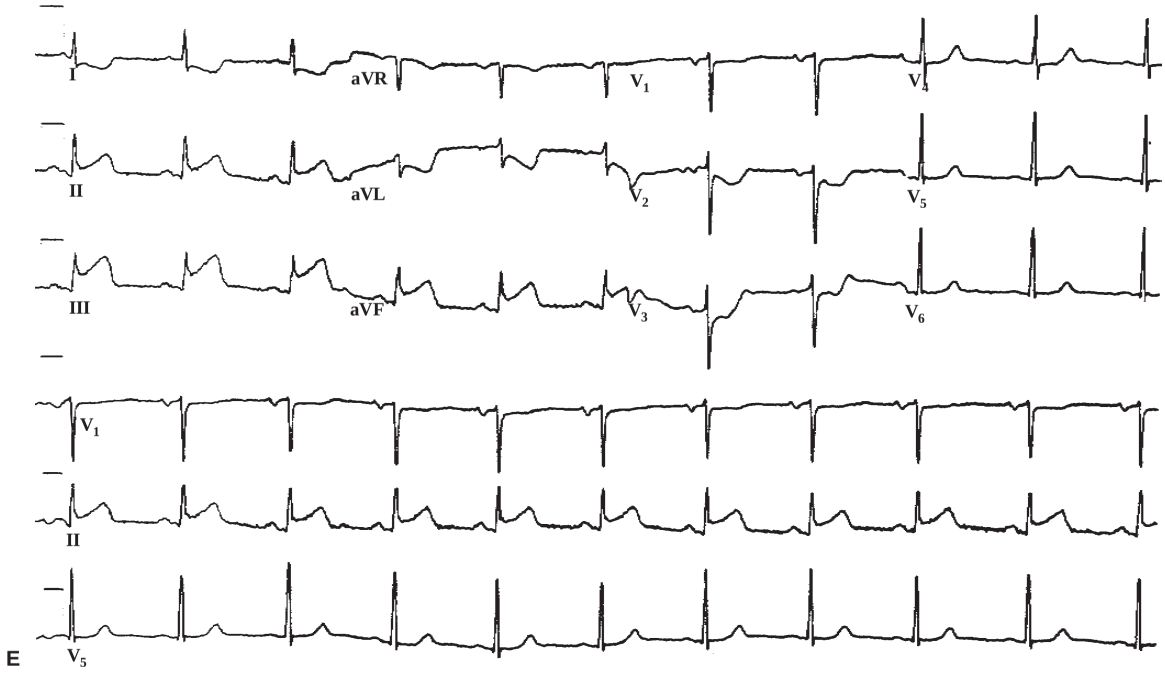

FIGURE 1.2 Electrocardiographic subsets of acute myocardial infarction (MI). **A:** Large anterior MI with conduction disturbance (proximal left anterior descending [LAD] coronary artery). **B:** Anterior MI without conduction disturbance (mid-LAD). **C:** Lateral MI (distal LAD, diagonal branch, or left circumflex branch). **D:** Large inferior MI with reciprocal changes (proximal right coronary artery [RCA]). **E:** Small inferior MI (distal RCA). (From Topol EJ, Van de Werf FJ. Acute myocardial infarction: early diagnosis and management. In: Topol EJ, ed. *Textbook of Cardiovascular Medicine*. New York: Lippincott-Raven; 2002, with permission.)".

TABLE 1.4 Electrocardiographic Criteria for the Diagnosis of Acute Myocardial Infarction in the Presence of Left Bundle Branch Block

Criterion	Score[a]
ST-segment elevation ≥ 1 mm concordant with QRS	5
ST-segment depression ≥ 1 mm in leads V_1, V_2, or V_3	3
ST-segment elevation ≥ 5 mm discordant with QRS	2

[a]Point scores for each criterion met are added. Total point score of 3 yields ≥ 90% specificity and an 88% positive predictive value.

Adapted from Sgarbossa EB, Pinski SL, Barbagelata A, et al. Electrocardiographic diagnosis of evolving acute myocardial infarction in the presence of left bundle branch block. *N Engl J Med.* 1996;334:481–487.

B. The Global Registry of Acute Coronary Events (GRACE) score is used to predict in-hospital mortality in patients with ACS. Risk is calculated based on Killip class, heart rate, systolic blood pressure, creatinine level, age, presence or absence of cardiac arrest at admission, presence or absence of cardiac biomarkers, and ST-segment deviation. Patients with a score of ≤ 60 have a ≤ 0.2% probability of in-hospital mortality, whereas patients with a score of ≥ 250 have a ≥ 52% probability of in-hospital mortality.

IX. THERAPY

A. Prior to reperfusion

1. **Aspirin.** Immediate administration of aspirin is indicated for all patients with acute MI, unless there is a clear history of true aspirin allergy (not intolerance). Aspirin therapy conveys as much mortality benefit as streptokinase (SK), and the combination provides additive benefit (6). The dose should be four 81 mg chewable tablets (for more rapid absorption) or one 325 mg nonchewable tablet. If oral administration is not possible, a rectal suppository can be given. If true aspirin allergy is present, clopidogrel monotherapy is the best alternative. In STEMI patients who undergo PCI, aspirin should be continued indefinitely. According to the 2011 ACCF/AHA/SCAI PCI guidelines, after PCI it is reasonable to use 81 mg of aspirin as opposed to higher maintenance doses (16).
2. **Oxygen.** Supplemental oxygen by means of nasal cannula should be given to all patients with suspected MI. Administration through a face mask or endotracheal tube may be necessary for patients with severe pulmonary edema or cardiogenic shock.
3. **Nitroglycerin.** It is worthwhile to give sublingual nitroglycerin (0.4 mg) to determine whether the ST-segment elevation represents coronary artery spasm while arrangements for reperfusion therapy are being initiated. Patients should be questioned about recent use of a phosphodiesterase inhibitor (PDE) because administration of nitroglycerin within 24 hours of a PDE may cause life-threatening hypotension. A meta-analysis performed before the age of routine reperfusion suggested a mortality benefit with intravenous nitroglycerin (8), although routine use of oral nitrates after MI had no benefit in two large randomized trials in the modern era. Nitroglycerin can be useful in the management of acute MI complicated by CHF, ongoing symptoms, or hypertension. A 30% reduction in systolic blood pressure can be expected with appropriately

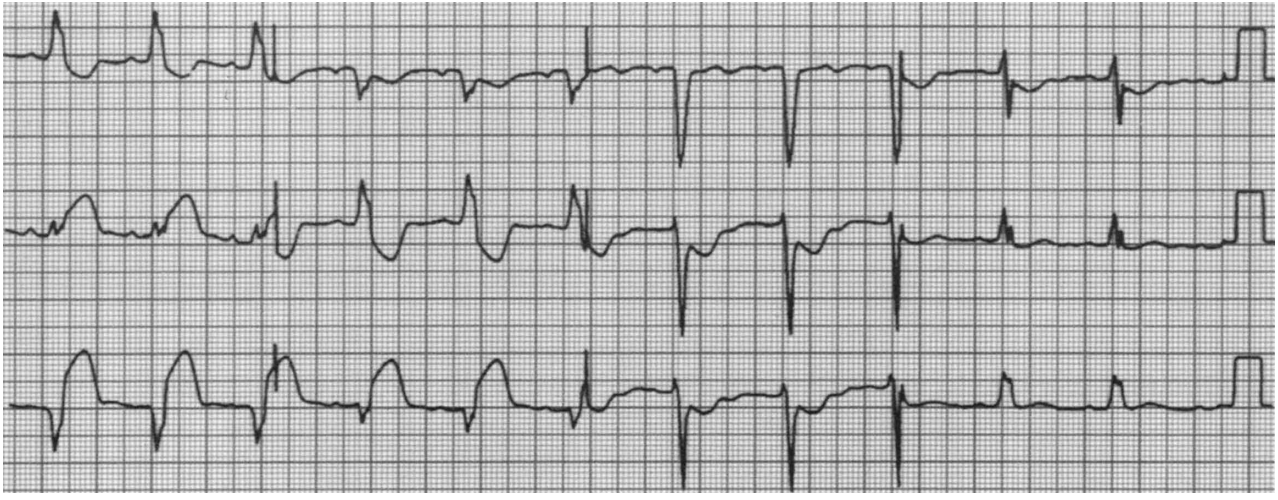

FIGURE 1.3 Electrocardiogram displays all of the criteria for the diagnosis of acute myocardial infarction (MI) in the setting of left bundle branch block (LBBB): ST-segment elevation > 1 mm, concordant with QRS in lead II (5 points); ST-segment depression > 1 mm in leads V_2 and V_3 (3 points); and ST-segment elevation > 5 mm, discordant with QRS in leads III and VF (2 points). A score of 10 points indicates an extremely high likelihood of inferior MI. (From Sgarbossa EB, Wagner G, 1997, with permission.)

TABLE 1.5 30-Day Mortality Based on Hemodynamic (Killip) Class

Killip class	Characteristics	Patients (%)	Mortality rate (%)
I	No evidence of CHF	85	5.1
II	Rales, ↑ JVD, or S_3	13	13.6
III	Pulmonary edema	1	32.2
IV	Cardiogenic shock	1	57.8

CHF, congestive heart failure; ↑, increased; JVD, jugular venous distention; S_3, third heart sound.

Adapted from Lee KL, Woodlief LH, Topol EJ, et al. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021 patients. GUSTO-I Investigators. *Circulation.* 1995;91:1659-1668.

TABLE 1.6 TIMI Risk Model for Prediction of Short-Term Mortality in ST-Segment Elevation Myocardial Infarction Patients

History	
Age 65–74 years	2 points
Age ≥ 75 years	3 points
Angina or DM/HTN	1 point
Physical examination	
HR > 100 bpm	2 points
SBP < 100 mm Hg	3 points
Killip class II–IV	2 points
Weight < 67 kg	1 point
Presentation	
Anterior ST elevation or LBBB	1 point
Time to treatment > 4 h	1 point
TIMI risk score = total points (0–14)	

DM, diabetes mellitus; HR, heart rate; HTN, hypertension; LBBB, left bundle branch block; SBP, systolic blood pressure; TIMI, thrombolysis in myocardial infarction.

Adapted from 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.

aggressive dosing (10 to 20 μg/min with 5 to 10 μg/min increases every 5 to 10 minutes). Intravenous therapy can be continued for 24 to 48 hours, after which time patients with heart failure or residual ischemia can transition to oral or topical therapy with an appropriate nitrate-free interval to avoid tachyphylaxis.

4. **Platelet $P2Y_{12}$ receptor antagonists** should be used routinely in all patients with STEMI regardless of whether or not PCI is performed (9). Currently, the three agents recommended for treatment of STEMI are clopidogrel, prasugrel, and ticagrelor. Clopidogrel and prasugrel are thienopyridines that irreversibly inhibit the platelet adenosine diphosphate $P2Y_{12}$ receptor, and Ticagrelor is a reversible direct inhibitor of this same receptor. In patients in whom PCI is planned, a loading dose should be given prior to or at the time of PCI. The recommended loading dose of clopidogrel is 600 mg. This is largely based on results of a meta-analysis that included more than 25,000 patients undergoing PCI. The meta-analysis demonstrated that when compared to 300 mg, a 600 mg clopidogrel loading dose reduces MACE without an increase in major bleeding. (10). The recommended loading dose of prasugrel is 60 mg (9). Prasugrel is considered to be superior to clopidogrel in onset of action and potency of platelet inhibition; in addition, its metabolism is not influenced by cytochrome P450 genetic polymorphisms. The TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction) investigators compared efficacy and safety of prasugrel versus clopidogrel in patients with moderate- to high-risk ACS undergoing PCI. The primary end point was a composite of death due to cardiovascular causes, nonfatal MI, or nonfatal stroke. Patients who received prasugrel had a significant reduction in the primary end point compared with patients who received clopidogrel (9.9% vs. 12.1%; hazard ratio [HR] 0.81; 95% confidence interval [CI], 0.73 to 0.90; $p < 0.001$). This difference was primarily driven by a reduction in nonfatal MI (7.3% for prasugrel vs. 9.5% for clopidogrel; HR 0.76; 95% CI, 0.67 to 0.85; $p < 0.001$). The risk of TIMI major bleeding was higher with the use of prasugrel (2.4% vs. 1.8%; HR 1.32; 95% CI, 1.03 to 1.68; $p = 0.03$), though the net clinical benefit end point, which included all-cause mortality, ischemic events, and major bleeding events, still favored the use of prasugrel (11). Based on subgroup analysis, diabetics derived a greater benefit with prasugrel as compared with clopidogrel, whereas post hoc analysis showed that patients 75 years of age or older or patients with a body weight of < 60 kg derived no net clinical benefit from prasugrel. Post hoc analysis also showed net harm in patients treated with prasugrel who had a history of a transient ischemic attack or stroke, and therefore prasugrel should be avoided in these patients (11). Ticagrelor is given as a 180 mg loading dose. Platelet inhibition with ticagrelor occurs faster and is more potent than clopidogrel. The efficacy and safety of ticagrelor was compared to clopidogrel in the PLATO (Platelet Inhibition And Patient Outcomes)trial. At one year, patients who received ticagrelor had a significant reduction in the composite endpoint of death from vascular causes, MI, or stroke, without an increase in major bleeding. Of note, patients who receive ticagrelor should not be treated with high dose aspirin, which has been associated with worse outcomes in these patients (12). Currently, guidelines do not endorse one agent over another except in patients who have received fibrinolysis. In these patients, clopidogrel is the thienopyridine of choice, at a loading dose of 300 mg if fibrinolysis was performed within 24 hours of administration (13). This is based on results of the CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy—Thrombolysis in Myocardial Infarction) trial, which showed pretreatment with clopidogrel to be safe and effective without increased bleeding among patients treated with fibrinolytic therapy, with many receiving subsequent PCI (-57%). The composite end point of cardiovascular death, reinfarction or revascularization, was reduced from 14.1% to 11.6% ($p = 0.03$) by clopidogrel pretreatment (9,13). In patients receiving a stent (BMS or drug-eluting stent [DES]), thienopyridine therapy should be continued for at least 1 year (9).

The maintenance dose of clopidogrel and prasugrel is 75 mg daily and 10 mg daily, respectively. The maintenance dose for prasugrel is 90 mg twice a day. An important consideration is the increased risk of major bleeding during surgery. It is currently recommended that clopidogrel and ticagrelor be held for 5 days and prasugrel be held for 7 days prior to CABG, unless the need for urgent revascularization outweighs the risk of potential excessive bleeding (9).

5. **Parenteral anticoagulants.** Unless there is a contraindication, all STEMI patients should receive antithrombotic therapy. Traditionally, this has been accomplished with unfractionated heparin (UFH). The dose of UFH is 60 U/kg as a bolus (maximum 4,000 U), followed by 12 U/kg/h infusion (maximum 1,000 U/h) to achieve a partial thromboplastin time of 45 to 65 seconds (7). Based on the GUSTO I (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial, heparin should be given as an adjunct to patients who receive thrombolysis with alteplase, but should not be given to patients who receive streptokinase unless the patient has recurrent ischemia or there is another indication for anticoagulant therapy (14). The use of UFH as adjunctive therapy with reteplase and tenecteplase (TNK) has been validated in GUSTO III and ASSENT 2 (Assessment of the Safety and Efficacy of a New Thrombolytic), respectively. Low-molecular-weight heparin (LMWH) is an alternative to UFH and should be preferred in patients undergoing fibrinolysis. The ASSENT 3 trial tested the efficacy of various antithrombotic regimens in conjunction with weight-based TNK. TNK plus enoxaparin was superior to TNK plus UFH in reducing the composite end point of death, in-hospital reinfarction, or in-hospital refractory ischemia (15). Similarly, the ExTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment - Thrombolysis in Myocardial Infarction) trial randomized STEMI patients undergoing fibrinolysis to either enoxaparin throughout the index hospitalization or UFH for 48 hours. The primary end point was death or nonfatal MI at 30 days. The enoxaparin group had a significant reduction in the primary end point, most of which was due to a significant reduction in the rate of reinfarction (3.0% vs. 4.5%). The enoxaparin group was also less likely to undergo urgent revascularization (2.1% vs. 2.8%). It is worth noting that duration of therapy differed between the two groups. Although UFH was only administered for 48 hours, LMWH therapy was continued for a mean of 7 days (16). Patients undergoing PCI after treatment with LMWH may need additional dosing in the cardiac catheterization laboratory, depending on the time at which the last dose was administered. If the last dose was within 8 hours, no additional enoxaparin should be given. If the last dose was given 8 to 12 hours earlier, an intravenous dose of 0.3 mg/kg should be given. If it has been > 12 hours since that last dose, an additional 1 mg/kg dose should be administered subcutaneously. LMWH should be avoided in patients > 75 years old or in patients with significant renal insufficiency (22). The 2009 focused update of the ACC/AHA STEMI guidelines added bivalirudin as an acceptable anticoagulant in patients undergoing primary PCI (9). The 2011 ACCF/AHA/SCAI PCI guideline confirmed this with a class I recommendation for bivalirudin during PCI (17). This is primarily based on results of the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial. The HORIZONS-AMI trial randomized 3,600 patients to either bivalirudin and provisional glycoprotein (GP) IIb/IIIa inhibitor or UFH and planned GP IIb/IIIa inhibitor prior to primary PCI. The primary end point was the 30-day rate of the combined outcome of net adverse clinical events, including major bleeding, death, reinfarction, target vessel revascularization (TVR), and stroke. Patients in the bivalirudin group

had a significant reduction in the primary end point (9.2% vs. 12.1%; relative risk [RR] 0.76; 95% CI, 0.63 to 0.92; $p = 0.005$) primarily due to decreased major bleeding (4.9% vs. 8.3%; $p = 0.001$). The benefit was maintained at 1 year (18). Fondaparinux is a synthetic pentasaccharide factor Xa inhibitor that has also been studied in acute MI. The OASIS-6 (Organization for the Assessment of Strategies for Ischemic Syndromes) trial evaluated fondaparinux with fibrinolytics and appeared to demonstrate benefit versus placebo/UFH in terms of death and reinfarction at 30 days (9.7% vs. 11.2%; HR – 0.86; 95% CI, 0.77 to 0.98; p = 0.008) without an increased risk of bleeding (19). However, in the primary PCI subset, there was no benefit and a significant increase in guiding catheter thrombosis, which has limited its widespread use. Accordingly, current ACC/AHA guidelines recommend that patients treated with fondaparinux receive additional anticoagulation with an anti-IIa agent prior to proceeding with PCI.

B. Reperfusion therapy. The primary goal in the management of acute MI is to institute reperfusion therapy as quickly as possible. All patients with ST-segment elevation or new LBBB MI who seek treatment within 12 to 24 hours from onset of continuous symptoms should be considered for immediate reperfusion therapy. Persistent ischemic symptoms after 12 hours may indicate a stuttering course of occlusion, spontaneous reperfusion, and reocclusion and may indicate potential continued benefit for early therapy.

1. **Benefit.** The benefit of reperfusion therapy has been well documented in the management of acute MI, regardless of age, gender, and most baseline characteristics. However, the patients who derive the most benefit are those treated earliest and those at highest risk, such as those with anterior MI.
2. **Time to treatment is paramount.** Patients treated in the first hour have the highest mortality benefit. **There is an inverse relationship between time to treatment and survival benefit**. This relationship appears more consistent with fibrinolytic therapy than with direct PCI. After 12 hours of continuous symptoms, there is little net benefit to pharmacologic reperfusion with fibrinolytics. The therapeutic window for PCI extends beyond that of fibrinolysis, but is not infinite (20,21). The Occluded Artery Trial (OAT) suggests that stenting of an occluded infarct-related artery > 72 hours after the initial event is not associated with benefit and may be harmful (21). Currently, the AHA recommends against PCI of an occluded infarct-related artery > 24 hours after STEMI if the patient is hemodynamically stable and does not have signs of severe ischemia (22).
3. **Fibrinolysis versus direct PCI.** After it has been determined that a patient is a candidate for reperfusion therapy, the decision to use fibrinolytic or direct PCI therapy must be made quickly.
   a. If facilities for immediate coronary angiography and PCI are available within 90 minutes of first medical contact, this is the preferred therapy. Pooled data from several large trials show a significant (22%) reduction in short-term mortality for patients treated with primary angioplasty (23). This benefit was durable because there were significant reductions in the incidence of death, nonfatal MI, and recurrent ischemia at long-term follow-up. PCI is also associated with a reduction in the incidence of intracerebral hemorrhage compared with fibrinolytic therapy.
   b. If facilities for immediate coronary angiography and direct PCI are not available, fibrinolytic therapy, unless contraindicated, should be instituted within 30 minutes of first medical contact. There is some controversy regarding the use of primary PCI with prolonged transfer times. Several trials, including the DANAMI-2 (Danish Multicenter Randomized Study on Thrombolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction) (24), the Air-PAMI (Air-Primary Angioplasty in

Myocardial Infarction) (25), and the PRAGUE (Primary Angioplasty in Patients Transferred from a General Community Hospital to Specialized PTCA Units) (26), have investigated the benefit of on-site fibrinolysis compared with transfer to tertiary centers for direct PCI. These studies have found improved outcomes in patients randomized to a transfer strategy and direct PCI even after taking into account the increased time for patient transfer. For example, patients in DANAMI-2 randomized to transfer for PCI had a significantly lower 30-day incidence of death, MI, or stroke (8.5% vs. 14.3%; $p = 0.002$) despite a median time from randomization to balloon inflation of 112 minutes. According to current guidelines, if a patient presents with STEMI at a PCI-capable facility and can undergo PCI within 90 minutes of first medical contact, this is the preferred approach. Conversely, if the patient presents to a hospital without PCI capability and cannot receive PCI within 120 minutes of first medical contact, fibrinolytics should be administered within 30 minutes of hospital presentation (17,22). This assumes that there are no contraindications to fibrinolysis (Table 1.7).

c. If a contraindication to fibrinolytic therapy exists or there is some question of the diagnosis, arrangements should be made for transfer to a PCI facility.

TABLE 1.7 Contraindications and Cautions for Use of Thrombolytic Agents to Manage Myocardial Infarction

Absolute contraindications
Previous hemorrhagic stroke at any time; ischemic stroke within 3 mo
Known intracranial neoplasm, structural cerebral vascular lesion, or closed head injury within 3 mo
Active bleeding or bleeding diathesis (excluding menses)
Suspected aortic dissection
Relative contraindications
Severe, uncontrolled hypertension at presentation (blood pressure > 180/110 mm Hg) or history of chronic severe hypertension
History of ischemic stroke > 3 mo, dementia, or known intracerebral pathologic condition not covered in contraindications
Current use of anticoagulants, the risk increases with increasing INR
Traumatic or prolonged (> 10 min) CPR or major surgery (< 3 wk)
Noncompressible vascular punctures
Recent (within 2–4 wk) internal bleeding
For streptokinase or anistreplase: prior exposure (> 5 d prior) or prior allergic reaction
Pregnancy
Active peptic ulcer

CPR, cardiopulmonary resuscitation; INR, international normalized ratio.

Adapted from Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *J Am Coll Cardiol.* 2004;44:E1–E211.

d. Because of the relative lack of efficacy of lytic therapy among patients with cardiogenic shock or prior bypass operations, such patients are especially well suited for primary PCI.

4. Primary PCI. Once the decision has been made to perform reperfusion with primary PCI, the patient should be moved to the cardiac catheterization laboratory and undergo angiography as rapidly as possible. After the culprit lesion has been identified, reperfusion should be achieved with standard PCI techniques (see Chapter 65).

a. Platelet GP IIb/IIIa inhibitors. Several clinical trials, including RAPPORT (ReoPro and Primary PTCA Organization and Randomized Trial) and ADMIRAL (Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up), have documented the benefits of abciximab in improving clinical outcomes after primary PCI with or without stenting in patients with STEMI (27,28). Despite these trials, the emergence of potent platelet ADP $P2Y_{12}$ receptor inhibtors has sparked controversy regarding the benefit of GP IIb/IIIa treatment in STEMI patients receiving dual, oral antiplatelet therapy. Three major trials have evaluated the efficacy of GP IIb/IIIa therapy in STEMI patients receiving dual, oral antiplatelet therapy. The Bavarian Reperfusion AlternatiVes Evaluation-3 (BRAVE-3) study looked at 800 STEMI patients who received aspirin plus 600 mg of clopidogrel and either abciximab or placebo during PCI. The primary end point was infarct size measured by single photon emission computed tomography prior to hospital discharge. The study also compared 30-day major adverse cardiovascular events (MACE) between the two groups. Compared with placebo, abciximab offered no additional benefit in terms of reducing infarct size or MACE (28,29). On-TIME 2 was a randomized control trial in Europe that compared outcomes in STEMI patients undergoing PCI who were treated with aspirin and 600 mg of clopidogrel plus either high-dose tirofiban or placebo. Patients in the high-dose tirofiban group had improved ST-segment resolution at 1 hour, but there was no significant difference in TIMI grade 3 flow or 30-day MACE (30). Lastly, in the HORIZONS-AMI trial, patients undergoing primary PCI for STEMI were randomized to either UFH plus a GP IIb/IIIa or bivalirudin with provisional GP IIb/IIIa therapy. All patients received aspirin and thienopyridine therapy prior to PCI. At 30 days, net adverse clinical events were higher in patients treated with a GP IIb/IIIa, primarily due to increased bleeding (18).

The timing of GP IIb/IIIa therapy has also been questioned. The FINESSE (Facilitated Intervention with Enhanced Speed to Stop Events) trial compared half-dose reteplase with abciximab, abciximab alone, or placebo (primary PCI) in patients undergoing PCI for STEMI. Although more patients with fibrinolytic plus GP IIb/IIIa therapy had an open artery on arrival to the catheterization laboratory, the composite primary end point of death or complications of MI at 90 days was no different among the various strategies (9.8% half-dose fibrinolytic + GP IIb/IIIa inhibitor, 10.5% GP IIb/IIIa inhibitor alone, and 10.7% placebo; p = NS), suggesting no benefit to upstream GP IIb/IIIa therapy (31). In addition, bleeding rates were higher with half-dose fibrinolytic + GP IIb/IIIa inhibitor (31).

Meta-analyses have been performed to compare the efficacy of small molecule GP IIb/IIIa inhibitors with abciximab in STEMI patients undergoing PCI. Results show no statistically significant difference in 30-day mortality, reinfarction, major bleeding, TIMI grade 3 flow, or ST-segment resolution between eptifibatide, tirofiban, and abciximab (32,33).

Based on all available data, if a patient has no contraindication to dual, oral antiplatelet therapy, it is reasonable to reserve the use of GP IIb/IIIa

therapy until coronary anatomy has been defined. Current ACC/AHA guidelines reflect this practice, as GP IIb/IIIa administration during PCI carries a class IIa recommendation, while upstream use is classified as class III (17). Also according to current guidelines, abciximab, tirofiban, and eptifibatide are considered equivalent options for GP IIb/IIIa therapy in patients undergoing PCI for STEMI (9).

b. **Thrombus aspiration.** The use of aspiration catheters has been shown to improve ST-segment resolution and myocardial blush and more recently has been associated with improved clinical outcomes. TAPAS (Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study) was a single-center, randomized, clinical trial that compared manual thrombus aspiration before PCI with conventional balloon angioplasty and stenting in patients with STEMI (34). Unless contraindicated, all patients were treated with aspirin, 600 mg of clopidogrel, UFH, and abciximab. Complete resolution of ST-segment elevation occurred in significantly more patients who received aspiration thrombectomy when compared with patients who underwent conventional balloon angioplasty and PCI (56.6% vs. 44.2%; $p < 0.001$). In addition, a TIMI myocardial blush grade of 0 or 1 occurred in 17.1% of patients who received aspiration thrombectomy compared with 26.3% of patients who received conventional PCI ($p < 0.001$) (34). Although death, reinfarction, and TVR rates did not differ at 30 days, at 1 year there was a significant reduction in the rates of cardiac death (3.6% vs. 6.7%; $p = 0.02$) and cardiac death or nonfatal reinfarction (5.6% vs. 9.9%; $p = 0.009$) in the thrombus aspiration group (34,35). Based on current guidelines, thrombus aspiration is considered reasonable during PCI in patients with STEMI who have a high clot burden and short ischemic times (9).

c. **Distal embolic protection devices (EPDs)** have failed to show any benefit in multiple trials and may in fact increase infarct size. The major criticism of these trials is the exclusion of patients with large thrombus burden. Regardless of this caveat, these devices are not routinely recommended for acute PCI of native coronary arteries. If the culprit vessel is a saphenous vein bypass graft, an EPD should be used, as it has been shown to reduce a 30-day composite outcome of death, MI, emergency CABG, and target-lesion revascularization (TLR).

d. **Coronary stenting.** The early benefit of angioplasty over thrombolytic therapy is attenuated with more extended follow-up. In the GUSTO IIb expanded previously trial in which use of accelerated tissue plasminogen activator (tPA) was compared with angioplasty alone (percutaneous transluminal coronary angioplasty, PTCA), the reduction in rates of death and nonfatal MI at 30 days (13.7% tPA vs. 9.6% PTCA) dwindled, and by 6 months, the difference (16.1% for tPA vs. 14.1% for PTCA) had lost statistical significance (36). This loss of effect may be at least partially caused by restenosis of the target lesion that was managed directly with angioplasty. Although coronary stents are known to reduce rates of restenosis during elective PCI, it was once believed that stents should not be placed in thrombus-laden lesions, such as those associated with acute MI, because of risk of in-stent thrombosis. However, clinical trials with adequate antiplatelet therapy have shown stenting to be safe. The STENT-PAMI (STENT-Primary Angioplasty in Myocardial Infarction) (37) study found that coronary stenting significantly reduced the need for TVR at 6 months (7.7% vs. 17.0%; $p < 0.001$). These findings were confirmed in the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) (38) trial, which found that coronary stenting significantly reduced the incidence of restenosis at 6 months (40.8% vs. 22.2%; $p < 0.0001$),

independent of abciximab use. Based on several meta-analyses, there does not appear to be a difference between DES and BMS in terms of mortality, MI, or risk of stent thrombosis (39–41). There is, however, a reduction in TVR with DES (39–41). This was also seen in the HORIZONS-AMI trial, which randomized > 3,000 patients to DES or BMS in a 3:1 ratio. At 12 months, there was no difference in the composite end point of death, reinfarction, stroke, or stent thrombosis; however, DES patients had a decreased rate of ischemia-driven TVR and TLR (5.8% vs. 8.7% and 4.5% vs. 7.5%, respectively) (18,42). Accordingly, patients with the highest risk of in-stent restenosis such as diabetics and patients with long, smaller diameter coronary lesions derive the greatest benefit from DES. In 2009, the ACC/AHA guidelines were updated to include DES as an alternative to BMS in patients undergoing primary PCI for STEMI (9). As mentioned by the ACC/AHA writing group members, the greatest challenge in determining if a STEMI patient is a candidate for DES is deciding in an emergent situation if the patient is a candidate for prolonged dual-antiplatelet therapy. The ideal candidate for a DES should not have social or financial barriers to prolonged dual-antiplatelet therapy, should have no surgical procedures scheduled within the next year, and should be at low risk for bleeding complications (9).

5. **Fibrinolytic therapy.** The lifesaving capability of early fibrinolytic therapy has been well established, beginning with the GISSI 1 (Gruppo Italiano per lo Studio della Sopravivenza nell'Infarto Miocardico) trial (43) in 1986. Pooled data show a relative reduction in mortality of 18% and an absolute reduction of nearly 2%. Even more dramatic long-term mortality benefit may be the result of preservation of normal LV function.
   a. **Contraindications.** As discussed previously (Table 1.7), the only **absolute contraindications to fibrinolytic therapies are recent cerebrovascular accident (CVA), hemorrhagic CVA, intracranial neoplasm, active internal bleeding, and suspected aortic dissection**. The presence of one of these or one or more of the relative contraindications would favor PCI, even if it meant delaying reperfusion.
   b. **Choice of agent**
      (1) **Alteplase (tPA).** The GUSTO I previously expanded trial showed that use of accelerated alteplase significantly reduced 30-day mortality rate by 15% relative to SK plus subcutaneous or intravenous heparin (14). This mortality reduction correlated with significantly higher rates of TIMI 3 flow at 90 minutes compared with SK (54% vs. 31%; $p < 0.001$). The benefit was initially challenged because of the high cost of alteplase (approximately US $2,200 per episode of MI) compared with SK (approximately US $300). For alteplase, this corresponds to a cost of US $32,678 per year of life saved, less than that of the well-accepted standard of hemodialysis for end-stage renal disease (44). The benefit was seen across all subgroups, although the patients at highest risk derived the most benefit. The accelerated protocol consisted of an intravenous bolus dose of 15 mg followed by 0.75 mg/kg (up to 50 mg) over 30 minutes and then 0.5 mg/kg over 60 minutes. Alteplase is considered a fibrin-specific agent because of its relative selectivity for clot-bound fibrin.
      (2) **Reteplase.** The first of the third-generation fibrinolytic agents approved for use in the United States, reteplase, is a less fibrin-specific mutation of alteplase. Reteplase has a longer half-life than alteplase and can be administered in a double bolus (10 mg each, 30 minutes apart). The GUSTO III trial (45) showed no mortality benefit of reteplase over alteplase, but its ease of use may help to reduce time to administration.

(3) **Tenecteplase**, another third-generation fibrinolytic, is characterized by its improved fibrin specificity, enhanced resistance to plasminogen activator inhibitor 1, and decreased plasma clearance. These properties allow it to be administered as a single bolus. The ASSENT 2 trial found no mortality difference between TNK and tPA at 30 days (46). However, TNK was associated with significantly less noncerebral bleeding and improved mortality in patients treated for > 4 hours after symptom onset. The weight-adjusted dose of TNK is 30 to 40 mg (ASSENT 1).

(4) **Streptokinase.** This first-generation nonfibrin-specific lytic is a reasonable alternative to second- or third-generation agents if newer agents are not available or cannot be used because of limited financial resources. Because of the possible development of antibodies, SK should not be administered to a patient who has received it in the past. Because the overall rate of intracerebral hemorrhage is lower with SK (0.5%) than with tPA (0.7%), some cardiologists advocate its use in the care of high-risk patients, such as elderly patients with a history of a cerebrovascular event or severe hypertension. SK is a nonfibrin-specific agent capable of lysing circulating and clot-bound plasminogen to plasmin. This process results in substantial systemic fibrinogenolysis, fibrinogenemia, and elevation in fibrin degradation products.

c. **Bleeding complications after fibrinolysis.** The most serious **complication** of fibrinolytic therapy is **intracerebral hemorrhage, which occurs in approximately 0.5% to 0.7% of patients receiving such therapy. The major risk factors for intracranial hemorrhage include age (> 75 years), hypertension, low body weight, female gender, and coagulopathy** (e.g., prior Coumadin use). The diagnosis must be considered if a patient has severe headache, visual disturbances, new neurologic deficit, acute confusional state, or seizure. If the clinical suspicion is high, fibrinolytic, antithrombin, and antiplatelet therapy should be interrupted while emergency CT or MRI is performed and neurosurgical consultation is obtained. Surgical evacuation may be lifesaving. Even with prompt recognition and treatment, the mortality rate is higher than 60%; elderly patients (> 75 years) have a mortality rate higher than 90%. There is controversy regarding the risk of fibrinolytic therapy in elderly patients. An observational study (47) from the Medicare database found that patients older than 75 years had an increased risk of death at 30 days with fibrinolytic therapy (RR = 1.38; 95% CI, 1.12 to 1.71; $p = 0.003$). However, an updated meta-analysis of nine randomized trials (48,49) found that the risk reduction with fibrinolysis in patients older than 75 years was 16% (odds ratio = 0.84; 95% CI, 0.72 to 0.98; $p < 0.05$). There appears to be a decreasing relative benefit with fibrinolysis in the elderly, but an absolute gain in lives saved. The only randomized trial to specifically study management of STEMI in the elderly found that patients treated with PCI had significantly lower 30-day and 1-year mortality rates than patients treated with fibrinolysis (49). However, the ExTRACT-TIMI 25 study more recently indicates that fibrinolytic therapy may be safe in the elderly if a reduced dose of enoxaparin is used (16). Gastrointestinal, retroperitoneal, and access site bleeding may complicate fibrinolytic therapy but are usually not life-threatening if promptly recognized and managed. In any case, the best treatment of acute STEMI in elderly patients appears to be primary PCI.

d. **Prehospital fibrinolysis.** Early administration of fibrinolytic therapy by emergency services has been shown to potentially reduce infarct size but lacks solid randomized trial data advocating its routine use. It has also been found to reduce time to treatment (50,51), but this did not translate

into a reduction in mortality. Although a meta-analysis (52) of prehospital fibrinolytic trials did find a 17% reduction of in-hospital mortality, it remains to be seen whether this strategy can improve long-term outcomes in clinical practice.

6. **Combination fibrinolytic therapy with GP IIb/IIIa inhibitors (without PCI)**
   a. **Rationale.** Sustained tissue-level reperfusion occurs in only 25% of patients treated with fibrinolytic therapy. Platelets have paradoxically increased activity after fibrinolysis and are important mediators in the tendency for vessel reocclusion. Aspirin is pathway specific and, therefore, a relatively weak antiplatelet agent. GP IIb/IIIa inhibitors, however, are potent antiplatelet agents that block the final common pathway of platelet aggregation, and for this reason, they have been studied in combination with half-dose fibrinolysis.
   b. **Clinical trials.** GUSTO V found that the addition of abciximab to half-dose reteplase did not reduce mortality at 30 days or 1 year compared with full-dose reteplase, but it did reduce reinfarctions and complications after MI (53). ASSENT 3 also found comparable reductions in reinfarction with the combination of half-dose TNK and abciximab (15).
   c. **Contraindications.** GUSTO V found that the rate of intracranial hemorrhage in elderly patients (> 75 years) treated with combination therapy was almost twice that of standard lytic therapy (2.1% vs. 1.1%; $p = 0.07$). ASSENT 3 confirmed this finding. Age older than 75 years is, therefore, an additional contraindication for combination lytic therapy. No increase in intracranial hemorrhage was seen in younger patients.
7. **Rescue percutaneous revascularization** is defined as the use of PCI when fibrinolytic therapy has proved unsuccessful. Despite the proven mortality benefit, > 30% of patients who received lytic therapy have TIMI 0 to 1 flow at 90 minutes, whereas patency at 90 minutes has been shown to correlate with long-term survival (54). If reperfusion is not clearly evident 90 minutes after initiation of lytic therapy, particularly among patients with large acute MI, the decision to perform emergency angiography and mechanical reperfusion should be made promptly. Patients in cardiogenic shock, with severe CHF, or with compromising arrhythmias after lytic therapy should undergo immediate coronary angiography and should not await clinical assessment of reperfusion.
   a. **Clinical determination of successful reperfusion.** It can be difficult to determine clinically whether a patient has successful reperfusion with fibrinolytic therapy. Resolution of chest pain is an inaccurate measure of reperfusion, because the pain may be blunted by narcotic analgesia or the partial denervation that is known to occur among some patients with MI. Serial assessment of 12-lead ECGs is a more reliable indicator of reperfusion, although it is also suboptimal. An accelerated idioventricular rhythm (AIVR) is fairly specific for reperfusion, but arrhythmias other than AIVRs are not reliable indicators because a variety of ventricular and supraventricular arrhythmias may be observed in patients with nonreperfused infarction-related artery. The complete resolution of chest pain and electrocardiographic changes (defined as > 70% resolution of ST-segment elevation), accompanied by a run of AIVR, is highly specific for successful reperfusion, but it occurs in < 10% of patients receiving lytic therapy. Resolution of ST-segment elevation by > 70% is correlated with effective tissue-level reperfusion, and this finding has been correlated with better clinical outcomes and angiographic reperfusion.
   b. **Benefit.** It has been shown in the RESCUE (Randomized Evaluation of Salvage Angioplasty with Combined Utilization of Endpoints) trial (55) that patients with anterior MI who have unsuccessful thrombolysis (TIMI 0 or

1 flow) have a significant benefit from rescue angioplasty. In addition, the Rapid Early Action for Coronary Treatment (REACT) trial demonstrated that among patients with failed reperfusion with lytics, treatment with rescue angioplasty with or without PCI is associated with an ~50% reduction in death, reinfarction, stroke, and severe heart failure (56). The Grupo de Análisis de la Cardiopatía Isquémica Aguda I (GRACIA I) trial evaluated an early invasive strategy (within 24 hours) versus an ischemia-guided approach among patients with STEMI treated with fibrinolytic therapy. This trial primarily demonstrated a reduction in revascularization events with the early invasive approach, although a trend was seen toward fewer deaths and reinfarcts. Based on the above data, an early angiography strategy (within 24 hours) may also be considered a reasonable approach in all patients who receive lytic therapy. However, this approach should be differentiated from the facilitated PCI strategy described later.

8. **Facilitated PCI** refers to the use of an initial pharmacologic regimen to improve vessel patency rates prior to planned PCI. This method has been proposed as a way to manage patients with acute MI who present to hospitals without 24-hour catheterization laboratory facilities. Various facilitated PCI strategies have been proposed, including high-dose heparin, early GP IIb/IIIa inhibitors, full-dose or reduced-dose fibrinolytics, and combination fibrinolytics and GP IIb/IIIa inhibitors. Theoretical advantages include earlier time to reperfusion, improved hemodynamic stability, smaller infarct size, greater procedural success, and improved survival, albeit at increased risk for bleeding complications. The ASSENT 4 PCI previously expanded trial was the largest study to evaluate full-dose fibrinolytic therapy (TNK) plus PCI versus primary PCI alone. The trial was terminated prematurely because of higher in-hospital mortality rates (6% vs. 3%; $p = 0.01$) and higher primary composite end points (death, shock, and heart failure within 90 days) with full-dose fibrinolytics plus PCI versus primary PCI alone (18.6% vs. 13.4%; $p = 0.0045$) (57). As discussed previously, the FINESSE trial randomized STEMI patients undergoing PCI to half-dose reteplase with abciximab, abciximab alone, or placebo (primary PCI). Although more patients with fibrinolytic plus GP IIb/IIIa inhibitor had an open artery on arrival to the catheterization laboratory, the composite primary end point of death or complications of MI at 90 days was no different among the various strategies (9.8% half-dose fibrinolytic + GP IIb/IIIa inhibitor, 10.5% GP IIb/IIIa inhibitor alone, and 10.7% placebo; p = NS), the bleeding rates being higher with the half-dose fibrinolytic plus GP IIb/IIIa inhibitor. Finally, a large meta-analysis of multiple smaller trials confirmed that primary PCI is superior to facilitated PCI (58).
9. **Pharmacoinvasive Strategy.** Though it is clear that routine fibrinolysis prior to transfer for PCI in all patients who present with AMI (facilitated PCI) results in worse outcomes, fibrinolysis is still necessary to achieve early reperfusion in some patients who present to non-PCI-capable facilities. More recent data suggest that high risk patients (Table 1.8) who receive fibrinolytic therapy benefit from immediate transfer for PCI. The CARESS-in-AMI (Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction) trial (59) randomized patients presenting to a non-PCI-capable facility, who received half-dose fibrinolytics and abciximab, to either immediate transfer for PCI or rescue PCI. Patients who were transferred immediately for PCI had a significant reduction in the primary endpoint of death, reinfarction, or refractory ischemia at 30 days (59). In addition, the TRANSFER-AMI (Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction) study showed that high-risk patients benefit from this pharmacoinvasive strategy. This trial looked at 1,059 high-risk patients with STEMI who presented to a non–PCI-capable facility within 12 hours of symptom onset (60). All patients

received fibrinolysis with TNK and were then randomized to immediate transfer for PCI or rescue PCI dictated by continued chest pain, < 50% resolution of ST elevation, or hemodynamic instability. The primary end point was 30-day composite of the first occurrence of death, MI, recurrent ischemia, new or worsening heart failure, and cardiogenic shock. The primary end point was significantly less common in the pharmacoinvasive group compared with the group who received rescue PCI (11% vs. 17.2%; RR 0.64; 95% CI, 0.47 to 0.87; $p = 0.004$) (60). Based on the CARESS-in-AMI and TRANSFER-AMI trials, the ACC/AHA now recommends abandoning the use of the terms "facilitated" and "rescue" and rather decide on transfer for PCI based on the patient's level of risk (9). High-risk patients (Table 1.8) who receive fibrinolysis as the primary reperfusion strategy should be transferred to a PCI-capable facility as soon as possible. PCI can then be performed immediately or as needed. For low-risk patients, this management strategy is a class IIb recommendation (9).

10. **The late open artery hypothesis** postulates that benefit in terms of improved ventricular function, increased electrical stability, and provision of collaterals can be gained by late patency of occluded infarct arteries. However, OAT failed to show benefit of angioplasty for late total occlusion within 3 to 28 days after MI (21). Criticism of this trial includes exclusion of high-risk patients with New

TABLE 1.8 ACC/AHA Definition of High-Risk Patients with Acute Myocardial Infarction

Defined in CARESS-in-AMI

(1) STEMI patients with one or more of the following:
- – Extensive ST-segment elevation
- – Previous MI
- – New-onset LBBB
- – Killip class > II or EF ≤ 35% for inferior MI

(2) Anterior MI with ≥ 2 mm or more ST elevation in two or more leads

Defined in TRANSFER-AMI

(1) ≥ 2 mm ST elevation in two anterior leads or ST elevation ≥ 1 mm in inferior leads with at least
- – SBP < 100 mm Hg
- – HR > 100 bpm
- – Killip class II–III
- – ≥ 2 mm ST-segment depression in anterior leads
- – ≥ 1 mm of ST elevation in right-sided lead V_4 indicative of RV infarct

EF, ejection fraction; HR, heart rate; LBBB, left bundle branch block; MI, myocardial infarction; RV, right ventricular; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction; UFH, unfractionated heparin.

Adapted from Kushner FG, Hand M, King SB, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update). *J Am Coll Cardiol.* 2009;54:2205–2241.

York Heart Association (NYHA) class III or IV heart failure, rest angina, clinical instability, multivessel disease (left main or three-vessel disease), or severe inducible ischemia on stress testing. Regardless of these concerns, this study has led to a new **class III recommendation against PCI of a totally occluded artery > 24 hours after STEMI in asymptomatic patients without the previously noted high-risk criteria** (22).

11. **Emergency coronary bypass surgery** may be the treatment of choice for patients in whom the intent is to perform direct or rescue percutaneous mechanical reperfusion but who are found to have a critical left main stem lesion or severe three-vessel disease unapproachable with percutaneous revascularization. Studies of this strategy are fairly encouraging, especially when patients can be taken to the operating room early in the course of infarction, before severe myocardial necrosis has occurred. RV infarction is a relative contraindication to bypass surgery because it complicates the discontinuation of cardiopulmonary support.
12. **PCI in hospitals without surgical backup.** The C-PORT (Atlantic Cardiovascular Patient Outcomes Research Team) trial (61) found a reduced 6-month composite outcome of death, MI, and stroke in patients with acute MI randomized to primary PCI versus fibrinolytic therapy (12.4% vs. 19.9%; $p = 0.03$), even when PCI was performed in hospitals without surgical backup. All the community hospitals involved in this study underwent a formal "PCI development program." Based on current PCI guidelines, it is reasonable to perform primary PCI at a facility that does not have surgical backup if there is a proven plan in place for rapid transfer to another hospital capable of performing cardiac surgery. This plan must involve the ability to use hemodynamic support if needed during transfer.

C. Adjuvant therapy

1. **β-Blockers.** Extensive data from the era before reperfusion established the usefulness of β-blockers in reducing recurrent ischemia, arrhythmias, and mortality. Several small randomized trials performed in the fibrinolytic reperfusion era confirmed the anti-ischemic and antiarrhythmic benefits, although short-term mortality was not affected. As a result, prior recommendations have stated that β-blockers should be administered to all patients within the first 24 hours of acute MI, unless contraindicated by severe reactive airway disease, hypotension, bradycardia, or cardiogenic shock. However, more recent data from the PCI era have shown no difference in mortality and no difference in the composite end point of death, reinfarction, or ventricular fibrillation arrest (62). The COMMIT/CCS-2 (Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study) trial, a large ($n = 22{,}929$) randomized controlled trial found that the metoprolol group had more ventricular fibrillation arrest (2.5% vs. 3.0%; $p = 0.001$) and shock (5.0% vs. 3.9%; $p < 0.001$). The incidence of shock was most notable in patients with Killip class II and III heart failure. This has led to a change in guidelines recommending more judicious use of early (< 24 hours) β-blockers, avoiding use in patients with significant signs of heart failure, low cardiac output, risk of cardiogenic shock, or other relative contraindications to their use (22).
   a. **For ongoing ischemia with tachycardia or hypertension**, after rapid evaluation of ventricular function, intravenous metoprolol can be given (5 mg every 5 minutes until the desired blood pressure and pulse are achieved). Patients who tolerate the intravenous loading can begin moderate oral doses (12.5 to 50 mg of metoprolol, two to four times daily). The dose should be subsequently titrated upward to the maximally tolerated dose (200 mg of sustained-release metoprolol, once daily). Use of β-blockers should be avoided in patients with tachycardia of unclear origin, as these

agents can decompensate heart failure in patients with compensatory tachycardia.

2. **Angiotensin-converting enzyme (ACE) inhibitors** can be started orally in the first 24 hours for all patients without hypotension, acute renal failure, or other contraindications. These medications were shown to reduce mortality in the GISSI 3 (62) and ISIS 4 (International Study of Infarct Survival) (63) trials. ACE inhibitors should be continued indefinitely in patients with LV dysfunction or clinical CHF, because these patients have been shown to derive a mortality benefit. In addition, the Heart Outcomes Prevention Evaluation (HOPE) study (64) found that high-risk patients, including those with prior MI but normal LV function, still had long-term benefit from ramipril. Intravenous formulations of these agents should not be used because they have not demonstrated benefit and may increase mortality. Rather, a graded oral regimen is advised. Angiotensin-receptor blockers remain a viable option for ACE inhibitor–intolerant patients.
3. **Calcium channel blockers.** Evidence for a potential increase in mortality has limited the use of calcium channel blockers in the care of patients with acute MI. They are indicated for the management of supraventricular tachyarrhythmia, cocaine-induced MI, or relief of postinfarction angina unresponsive to β-blockade. Otherwise, these agents should be avoided. Short-acting agents, such as nifedipine, are contraindicated because of their reflex sympathetic activation. Verapamil and diltiazem should be avoided in patients with LV dysfunction or CHF. Amlodipine is an effective antianginal agent and appears safe to use for this indication in patients with CHF.
4. **Magnesium.** There was once considerable enthusiasm for the routine use of intravenous magnesium in patients with MI, based on the findings of LIMIT 2 (Leicester Intravenous Magnesium Intervention Trial), which observed a 24% reduction in mortality compared with placebo. The larger ISIS 4 and MAGIC (Magnesium in Coronaries) trials failed to duplicate this benefit, however, and enthusiasm has waned. Some have speculated that the lack of effect in ISIS 4 was because of delayed administration or low control group mortality. In the modern era, magnesium is not routinely used other than to replete serum magnesium levels that are lower than 2.0 μg/dL or for the management of *torsade de pointes* (1 to 2 g over 5 minutes).
5. **Aldosterone antagonists.** The use of aldosterone-blocking agents has been shown to be beneficial in post-MI patients. RALES (Randomized Aldactone Evaluation Study) found a reduction in all-cause mortality with the use of aldactone in patients with ischemic cardiomyopathy and NYHA class III or IV heart failure. However, the only randomized trial to address the use of such agents among patients with ventricular dysfunction after STEMI is EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study), where eplerenone was found to reduce death, cardiovascular death, and hospitalization for heart failure.
6. **Diabetes control.** The DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) study found a significantly lower mortality rate at 1 year compared with standard therapy (8.6% vs. 18.0%; $p = 0.020$) in diabetic patients treated with aggressive blood glucose reduction with an insulin infusion during hospitalization, followed by multidose subcutaneous insulin injections. However, a small trial (OASIS-6 GIK) and a large (> 20,000 patients) randomized trial (CREATE-ELCA) failed to show any benefit to glucose–insulin–potassium (GIK) infusions. As a result, it appears prudent to institute sound glucose control, but it is not necessary to aggressively pursue glucose control with GIK infusions. Current guidelines suggest insulin therapy

to achieve and maintain blood glucose levels < 180 mg/dL while avoiding hypoglycemia (9).

7. **Antiarrhythmics.** The use of lidocaine or other antiarrhythmic agents is not warranted for the prophylactic suppression of ventricular tachycardia (VT) and fibrillation. Although lidocaine may decrease tachyarrhythmias, there is no survival benefit. There is also evidence to suggest an increase in mortality related to an increased incidence of bradycardia and asystole. In addition, there is evidence that "high-dose" amiodarone may actually increase mortality. Antiarrhythmic therapies are discussed in more detail in Chapter 21.
8. **Intraaortic balloon pump (IABP).** In the treatment of patients with cardiogenic shock, IABP counterpulsation is the preferred means of augmenting systolic pressure because use of an IABP decreases afterload and oxygen requirements while increasing diastolic coronary flow. IABP is contraindicated in the care of patients with marked aortic regurgitation, because it may worsen the regurgitation and cause rapid hemodynamic deterioration (see Chapter 63).
9. **Inotropic agents.** In general, these agents should be avoided whenever possible because of their tendency to increase myocardial oxygen demand and their associated risk of tachycardia and arrhythmias. If IABP counterpulsation proves insufficient, intravenous inotropic support may be warranted, but its use should be guided by means of pulmonary arterial catheter monitoring whenever possible.
   a. **Patients with hypotension accompanied by a pulmonary capillary wedge pressure (PCWP) < 15 mm Hg** should be managed with rapid infusion of boluses of normal saline solution, as should patients with inferior MI who have concomitant RV infarction.
   b. **After intravascular volume has been repleted** and the PCWP is > 15 mm Hg, dopamine may be indicated at doses up to 20 μg/kg/min if hypotension or signs of heart failure persist. Norepinephrine may be used as second-line therapy. The benefits of improved cerebral and systemic perfusion pressure by an increase in inotropy usually come at the cost of increased afterload and myocardial oxygen demand from vasoconstriction.
   c. **Dobutamine** can be useful when PCWP is > 18 mm Hg in the setting of mild to moderate hypotension (70 to 90 mm Hg) or when nitroglycerin or nitroprusside is contraindicated because of the risk of inducing hypotension. Use of PDEs such as milrinone, which have combined vasodilating and inotropic actions, is problematic because of their arrhythmogenicity and their tendency to increase myocardial oxygen consumption. Use of these drugs to maintain adequate systemic pressure and forward output is acceptable if the other therapies have failed. The main goal, however, should be to avoid these agents or reduce the need for them in terms of absolute dose and duration.
10. **Implantable cardioverter–defibrillators (ICDs).** Posited to reduce the risk of sudden death following acute MI, ICDs were routinely implanted an average of 18 days following the index MI event in patients with reduced ventricular function and autonomic dysfunction (DINAMIT trial) (65). Although there was a decrease in cardiovascular death, this study failed to demonstrate any reduction in all-cause mortality. The Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) evaluated the benefit of delayed ICD insertion in patients with prior MI (66). The trial enrolled 1,232 patients with a history of MI at least 1 month prior to enrollment (90 days if bypass surgery was performed) and a left ventricular ejection fraction (LVEF) of ≤ 30%. Patients were randomized to prophylactic ICD insertion or standard medical therapy. At an average follow-up of 20 months, prophylactic insertion of an ICD significantly reduced all-cause

mortality (14.2% vs. 19.8% for standard therapy; HR 0.69; 95% CI, 0.51 to 0.93; $p = 0.016$) (66). According to current ACC/AHA guidelines, an ICD should be inserted in patients with ventricular fibrillation or hemodynamically significant sustained VT that occurs 48 hours after acute MI, assuming there is no recurrent ischemia or MI (67). Patients with an EF ≤ 35% and NYHA class II or III heart failure secondary to an MI that occurred at least 40 days prior should also receive an ICD (67). In addition, patients who are 40 days post-MI with NYHA class I heart failure and an EF ≤ 30% are candidates for ICD insertion (67). Lastly, any patient with a prior MI, nonsustained VT, EF ≤ 40%, and inducible ventricular fibrillation or sustained VT during an electrophysiological study should receive an ICD (67). Patients who have received CABG should have their LVEF and NYHA functional class reassessed 90 days after the procedure to determine ICD candidacy.

11. **Wearable cardioverter–defibrillators.** Patients who are considered at risk for SCD but do not meet the above criteria, such as patients waiting for reassessment of LVEF after CABG, can be given the option of a wearable cardiac defibrillator as a bridge to ICD implantation or recovery of LVEF. The efficacy of wearable cardioverter–defibrillators was evaluated by a two-component trial consisting of the WEARIT and BIROAD studies (68). The WEARIT study enrolled 177 patients with an LVEF < 30% and NYHA class III or IV heart failure. The BIROAD study enrolled 112 patients with a recent MI or CABG who were considered high risk for SCD but did not meet criteria for or refused ICD implantation. During the 901 patient-month observation period, there were six successful and two unsuccessful defibrillations (68). Both unsuccessful defibrillation attempts were due to the device being worn incorrectly (68). During the study, there were six instances of SCD. Five cases were secondary to the device not being worn and in one case the device was being worn incorrectly (68). While wearable cardioverter–defibrillators are currently not recognized in the ACC/AHA guidelines, there appears to be a benefit in select patients.
12. **Anticoagulation for large anterior wall MIs.** Historical teaching (not based on randomized data) has advocated anticoagulating patients for 6 weeks after a large anterior wall MI, with the goal of preventing LV thrombus development. However, in the era of primary PCI with coronary stenting, this recommendation would necessitate treatment with aspirin, clopidogrel, and coumadin, placing patients at fairly high risk for bleeding. Some clinicians recommend anticoagulation only if there is objective evidence of LV thrombus by echocardiography. Others still recommend empiric anticoagulation, but with a slightly lower target international normalized ratio (1.5 to 2.0).

X. ACUTE MI ASSOCIATED WITH COCAINE ABUSE.

The pathophysiologic process and management of acute MI associated with cocaine use differ from those of classic MI.

A. Pathophysiology

1. **The underlying pathophysiologic factor** in acute MI associated with cocaine abuse is believed to be coronary spasm or thrombus formation caused by α-adrenergic stimulation. This can occur in a normal segment of artery or be superimposed on mild to moderate atherosclerosis. Atherosclerosis is accelerated by chronic cocaine use.
2. **Increased oxygen demand** caused by β-adrenergic stimulation of heart rate and contractility also contributes to the onset of ischemia.

B. Clinical presentation.

Chest pain caused by infarction after cocaine ingestion typically occurs within 3 hours, although it can vary from minutes to days, and depends on the route of administration (median of 30 minutes with intravenous cocaine,

90 minutes with crack smoking, and 135 minutes with nasal inhalation). More than 80% of persons with infarction are also cigarette smokers. Studies with animals have demonstrated a synergistic effect between cigarette smoking and cocaine use.

C. Therapy

1. The **initial management** of ST-segment elevation associated with cocaine use includes the routine administration of aspirin, oxygen, and heparin. Aggressive use of sublingual and intravenous nitroglycerin or intravenous calcium channel blockers is advised in an effort to relieve coronary spasm. Intravenous benzodiazepines should also be given, as they not only relieve cocaine induced chest pain but also improve cardiac hemodynamics (69).
2. **β-Blockers are contraindicated in patients with cocaine-induced acute MI.** Although they block undesirable β-adrenergic effects, these agents allow unopposed α-adrenergic stimulation and have been associated with increased mortality in nonrandomized analyses.
3. **Reperfusion therapy must be considered if vasodilator therapy is unsuccessful** in relieving symptoms and ST-segment changes.
4. **Immediate angiography and mechanical revascularization as appropriate** may be even more beneficial in cocaine-induced MI patients. Many patients who use cocaine have contraindications to thrombolysis, such as severe hypertension or persistent vasospasm without thrombosis, which is not amenable to thrombolytic therapy.

XI. POSTOPERATIVE ACUTE MI

A. Etiology and pathophysiology. Acute MI following noncardiac operations most commonly occurs on the third or fourth postoperative day. Conventional theory was that MI was caused by a combination of increased oxygen demand and arterial shear stress associated with the increased adrenergic drive that accompanies pain and ambulation in the postoperative period. Intravascular volume shifts caused by redistribution of fluids, intravenous administration of fluids, and decreased enteral intake all contribute to the risk of postoperative MI. It is apparent that there is a postoperative inflammatory state associated with hypercoagulability, marked by an increase in fibrinogen and other acute-phase reactants. Recent data would indicate that perioperative management of patients with DESs may be problematic, as risk of stent thrombosis may be speculated to be increased in this milieu, whereas antiplatelet therapies are discontinued to reduce bleeding risks.

B. Therapy. Management is complicated by limitations on the use of fibrinolytic agents and anticoagulant therapies. Therapy relies more heavily on the intravenous use of β-blockers and urgent angiography and mechanical reperfusion. The optimal antiplatelet or anticoagulation regimen for recent (< 1 year) DES patients undergoing noncardiac surgery is not known.

XII. SIMPLIFIED REPERFUSION STRATEGY.

The wealth of data regarding reperfusion strategies and adjunctive therapies in acute MI detailed previously may lead to confusion regarding the optimal approach. Based on guideline recommendations, a simplification of the STEMI management strategy can be achieved.

A. For patients presenting with acute MI where primary PCI is available, a reasonable strategy would involve prehospital administration of aspirin, parenteral anticoagulation, and a platelet $P2Y_{12}$ receptor inhibitor, as well as nitrates and β-blocker therapy if not contraindicated, and immediate transfer to the catheterization laboratory. The decision for GP IIb/IIIa therapy and whether coronary stenting should be performed with BMS or DES should be left at the discretion of the interventional cardiologist. If the patient does not have decompensated heart failure or renal failure, assessment of ventricular function should be performed, allowing risk stratification

and initiation of additional adjunctive therapies such as statins, ACE inhibitors, and aldosterone antagonists.

B. For patients presenting to a hospital where primary PCI is not available, but immediate transfer (medical contact to balloon time < 120 minutes) to a PCI facility is available, a similar strategy is employed, with initiation of aspirin, platelet $P2Y_{12}$ receptor antagonist, anticoagulation, nitrates, and β-blockers prior to transfer, although patients at high risk with potentially longer transfer times may benefit from the addition of GP IIb/IIIa inhibitor or half-dose fibrinolytics plus GP IIb/IIIa inhibitor prior to transfer.

C. If anticipated transfer times will exceed the medical contact-to-PCI time of 120 minutes, then fibrinolytic therapy should be instituted in eligible patients within 30 minutes of medical contact. The choice of UFH or enoxaparin remains operator dependent, with either option reasonable. Among patients receiving fibrinolytics, immediate transfer to a PCI facility is preferable, and early angiography (< 24 hours) is recommended. Full-dose fibrinolytics followed by immediate transfer for coronary angiography should be performed in any patient with cardiogenic shock, severe CHF, or ventricular arrhythmia causing hemodynamic compromise, provided that the patient is a suitable candidate for revascularization.

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CHAPTER 2

James E. Harvey

Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction

I. INTRODUCTION.

Unstable angina (UA) and **non–ST-segment elevation myocardial infarction (NSTEMI)** remain leading causes of morbidity and mortality in the United States, accounting for more than 1.5 million hospital admissions in the year 2004 alone. These conditions are part of a continuum of acute coronary syndromes (ACSs) that range from UA and NSTEMI to ST-segment elevation myocardial infarction (STEMI). **The clinical presentation of non–ST-elevation acute coronary syndrome (NSTE-ACS) can be variable**, ranging from **progressive exertional angina** to **postinfarction angina**. Because **NSTEMI is distinguished from UA by the presence of elevated serum levels of cardiac biomarkers**, serial measurements in patients presenting with ACS should be performed. With improvements in the diagnosis and risk stratification of patients with UA and NSTEMI, therapeutic approaches to NSTE-ACS have continued to evolve.

II. CLINICAL PRESENTATION

A. Risk factors

1. **Clinical characteristics indicative of high risk.** Symptoms may include an **acceleration of ischemic symptoms within the preceding 48 hours, angina at rest (> 20 minutes), congestive heart failure (S_3 gallop, pulmonary edema, and rales), known reduced left ventricular (LV) function, hypotension, new or worsening mitral regurgitation murmur, age > 75 years, diffuse ST-segment changes on an electrocardiogram (ECG, ≥ 0.5 to 1 mm), and the presence of elevated serum cardiac biomarkers (typically creatine kinase myocardial band [CK-MB], troponin T, or troponin I)**. Patients at intermediate or low risk have angina of short duration, have no ischemic ST-segment changes on ECG, are negative for cardiac biomarkers, and are hemodynamically stable (Table 2.1).
2. **Electrocardiogram.** The initial ECG can help risk-stratify patients with UA. Ideally, this should be performed within 10 minutes of arrival to the emergency department (ED). Patients with ST-segment deviation (i.e., ST-depression or transient ST-elevation) ≥ 0.5 mm or with pre-existing left bundle branch block (LBBB) are at increased risk for death or myocardial infarction (MI) at 1 year after presentation. ST-segment elevation ≥ 0.5 mm in lead aVR raises the possibility of left main or three-vessel coronary artery disease (CAD). **T-wave inversions alone are generally not predictive of adverse ischemic events**.
3. **NSTEMI.** NSTEMI predicts a poorer prognosis among patients with NSTE-ACS. Multivariate predictors of NSTEMI in patients with ACS include **prolonged chest pain** (> 60 minutes), **ST-segment deviations** (depression or transient elevation), and **new or recent onset of angina** (in the past month). Elevations in the levels of troponin I or troponin T, contractile proteins released

TABLE 2.1 Risk Stratification of Patients with Unstable Angina

High risk[a]	Intermediate risk	Low risk
One of the following must be present:	No high-risk feature but must have one of the following:	No high- or intermediate-risk features present
Accelerating tempo of ischemic symptoms in preceding 48 h	Prior MI, peripheral or cerebrovascular disease	
Prolonged ongoing rest pain (> 20 min): moderate or high likelihood of CAD	Prolonged rest pain (> 20 min) that resolves	Increased frequency or duration of angina
Pulmonary edema: most likely caused by ischemia	Rest angina (> 20 min or relieved with rest or sublingual NTG)	Angina provoked by less exertion
Rest angina with dynamic ST changes ≥ 0.5 mm	Nocturnal angina	New-onset angina (within 2 wk to 2 mo)
New or worsening rales, S_3, or MR murmur	New-onset, severe angina within 2 wk with moderate or high likelihood of CAD	
Hypotension, bradycardia, tachycardia		
Bundle branch block, new or presumed new	T-wave changes	Normal or unchanged ECG
Sustained ventricular tachycardia	Pathologic Q waves or resting ST depression (< 1 mm) in multiple lead groups	
Positive serum cardiac biomarkers	Slightly elevated CK-MB, troponin T, troponin I (e.g., troponin T 0.01 ng/mL but < 0.1 ng/mL)	Normal cardiac markers
	Age older than 70 y	

CAD, coronary artery disease; CK-MB, creatine kinase myocardial band; ECG, electrocardiogram; MI, myocardial infarction; MR, mitral regurgitation; NTG, nitroglycerin.

[a]Risk stratification involves considering clinical characteristics and ECG findings to make early triage decisions.

from necrotic cardiac myocytes, are independently predictive of morbidity and mortality among patients with UA (discussed later). According to the European Society of Cardiology/American College of Cardiology (ESC/ACC), troponin elevations in this clinical setting are, by definition, NSTEMI.

4. **Clinical risk classification systems.** Numerous scores have been derived to facilitate risk assessment and guide medical therapy in patients with NSTE-ACS. It is important to note that these scores can also be used to determine which patients may benefit most from early invasive therapy as opposed to a more conservative approach. The **Braunwald classification system** risk-stratifies patients with UA at presentation (Table 2.2). Braunwald defined UA according to the **characteristics of anginal pain** and the **underlying cause**. Patients with

TABLE 2.2 Braunwald Classification of Unstable Angina

Class	Characteristics[a]
I	**Exertional angina**
	New onset, severe, or accelerated
	Angina of < 2 mo duration
	More frequent angina
	Angina precipitated by less exertion
	No rest angina in the last 2 mo
II	**Rest angina, subacute**
	Rest angina within the last month but none within 48 h of presentation
III	**Rest angina, acute**
	Rest angina within 48 h of presentation
	Clinical circumstances
A	**Secondary unstable angina**
	Caused by a noncardiac condition, such as anemia, infection, thyrotoxicosis, or hypoxemia
B	**Primary unstable angina**
C	**Postinfarction unstable angina**
	Within 2 wk of documented myocardial infarction

[a]This classification can be used for risk stratification. Clinical characteristics at presentation and severity of angina are considered.

increasing Braunwald class have been shown to have increasing risk of recurrent ischemia and death at 6 months. Vital clinical characteristics not included in this classification were age, the presence of comorbid conditions (e.g., diabetes mellitus and renal insufficiency), electrocardiographic criteria, and the presence of positive cardiac markers.

The thrombolysis in myocardial infarction (TIMI) UA risk score, based on the TIMI IIB and ESSENCE trials, incorporates **the combination of age, clinical characteristics, ECG changes, and cardiac markers for risk stratification** (Table 2.3). A higher risk score correlated with an increase in the incidence of death, new or recurrent MI, and recurrent ischemia requiring revascularization. The GRACE prediction score, which incorporates nine clinical variables derived from the medical history and clinical findings on initial presentation and during hospitalization, can be used to estimate the in-hospital and 6-month outcomes for patients hospitalized with any form of ACS. Other risk stratification scores based on the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial and the GUSTO IV–ACS trial (Table 2.4) have also been described. Together, these various clinical risk stratification systems help identify high-risk patients likely to benefit most from more aggressive therapy.

TABLE 2.3 Thrombolysis in Myocardial Infarction Risk Score

Score	Incidence of death, new or recurrent MI, and recurrent ischemia requiring revascularization (%)
0/1	4.7
2	8.3
3	13.2
4	19.9
5	26.2
6/7	40.9

Scoring system

One point when risk factor is present, zero points if absent (a total of seven points are possible): Age > 65 y

- Presence of more than three risk factors for coronary artery disease
- Prior coronary stenosis ≥ 50%
- Presence of ST-segment deviation on admission electrocardiogram
- More than two episodes of angina within the past 24 h
- Prior use of aspirin in past 7 d
- Elevated cardiac markers

B. Demographics. Compared with STEMI, patients with **UA/NSTEMI** tend to be **older** and have a higher incidence of **cardiac risk factors or comorbid conditions (e.g., diabetes, hypertension, and hypercholesterolemia)** and a greater likelihood of **prior MI and revascularization procedures** (i.e., percutaneous coronary intervention [PCI] and coronary artery bypass grafting [CABG]).

C. Signs and symptoms. Chest pain due to UA may be rest pain or may be triggered with minimal exertion and can be new onset or increased in severity and frequency or precipitated with less effort than prior angina. Compared with stable angina, **chest pain in UA** is usually more **severe and protracted**, often requiring several doses of sublingual nitroglycerin or extended periods of rest for relief. UA or NSTEMI cannot be differentiated on the basis of chest pain characteristics or ECG abnormalities alone. **The only way this determination can be made is with evidence of myocardial necrosis by measurement of cardiac biomarkers**.

D. Differential diagnosis. It is vitally important to determine the probability that the chest pain or presenting symptom(s) are caused by ACS resulting from obstructive CAD. The exclusion of other diagnoses that mimic angina such as costochondritis, pneumonia, or pericarditis, as well as other life-threatening conditions such as aortic dissection, pneumothorax, and pulmonary embolus, is essential. Hypertensive urgency or emergency, thyrotoxicosis, systemic infection, anemia due to blood loss, and other precipitating causes of myocardial ischemia and secondary UA should also be sought.

TABLE 2.4 GUSTO Risk Score

Risk score	30-Day mortality rate (%)
0–5	0.4
6–10	2.8
11–15	8.7
16–19	25.0
20–22	41.7

Scoring system	
Points are assigned based on the following criteria:	
Age (y)	Points
50–59	2
60–69	4
70–79	6
80+	8
Clinical history	
Prior heart failure	2
Prior stroke/TIA	2
Prior MI/revasc./chronic angina	1
Vitals and laboratory values	
Heart rate ≥ 90 beats/min	3
Elevated troponin and CK-MB	3
Creatinine > 1.4 mg/dL	2
CRP (μg/L) > 20	2
10–20	1
Anemia	1

CK-MB, creatine kinase myocardial band; CRP, C-reactive protein; GUSTO, Global Utilization of Strategies to Open Occluded Arteries; MI, myocardial infarction; revasc., revascularization; TIA, transient ischemic attack.

E. Physical findings. Physical examination alone is insufficient for the diagnosis of UA. **Signs of heart failure** (elevated jugular venous pressure, S_3), impaired myocardial performance (S_4), or peripheral vascular disease (i.e., bruits over major vessels) may be present. These findings predict a higher likelihood of significant CAD.

III. PATHOPHYSIOLOGY. The pathophysiology of ACS encompasses a complex interplay of plaque erosion or rupture, platelet activation and aggregation leading to thrombus formation, endothelial dysfunction, vasospasm, and vascular remodeling.

A. Plaque rupture. UA, NSTEMI, and STEMI share a common initiating event: atheromatous plaque fissure or rupture. Plaque rupture exposes thrombogenic components stimulating platelet deposition, activation, and aggregation at the site

of injury, followed by activation of the coagulation cascade and thrombus formation. Factors contributing to plaque instability include lymphocyte and macrophage activation and increased inflammation. Ruptured plaques or culprit lesions in patients, even when medically stabilized, tend to progress in comparison with stable lesions. Follow-up angiography of 85 patients with UA who were medically stabilized 8 months after initial presentation revealed that 25% of culprit lesions progressed in disease severity (usually to complete occlusion), compared with 7% of nonculprit lesions. This progression of disease correlated with future cardiac events.

B. Thrombus formation. Exposure of circulating platelets to subendothelial contents results in platelet adhesion, aggregation, and, ultimately, thrombus formation. With platelet activation, the glycoprotein (GP) IIb/IIIa receptor on the platelet surface undergoes a conformational change, facilitating further platelet activation and aggregation. This markedly increases thrombin production, further expanding and stabilizing the thrombus.

C. Vasospasm can be induced by the local production of vasoactive substances released from the subendothelial matrix or propagating thrombus or it can occur as a primary phenomenon. Severe localized spasm of a coronary artery segment (i.e., Prinzmetal's angina) may also result in ACS. This vasospasm frequently occurs at sites of unstable plaque and is thought to contribute to thrombus formation. Even angiographically normal coronary arteries with underlying endothelial dysfunction may be subject to vasospasm.

D. Multiple lesions. Although a single culprit lesion is often found at angiography, multiple culprit lesions are not uncommon in patients presenting with UA/NSTEMI, attesting to the global nature of the disease. In a substudy of patients with NSTEMI, **multiple apparent culprit lesions were found in 14% of patients**, whereas a single culprit lesion was found in 49%. An intravascular ultrasound study of patients with NSTEMI undergoing angiography and possible PCI revealed an average of 2.1 plaque ruptures per patient, with 79% of patients having a lesion in a location different from that of the culprit lesion.

E. Secondary causes. UA can also result from a supply–demand mismatch of oxygen delivery to the myocardium. With stable obstructive coronary lesions, precipitants of UA include **increased myocardial oxygen demand** (i.e., tachycardia, severe hypertension, cocaine use, hyperthyroidism, fever, or sepsis) and **decreased oxygen supply** (i.e., anemia or hypoxemia).

IV. INITIAL EVALUATION AND MANAGEMENT

A. Initial triage and clinical assessment recommendations

1. Patients with symptoms suggestive of ACS should be instructed to call 911 immediately. It is recommended that the patient be transported to the hospital by ambulance rather than by friends or relatives.
2. Prehospital emergency service providers should give 162 to 325 mg of aspirin to patients who have symptoms suggestive of ACS, unless it is contraindicated. The patient should be instructed to chew the aspirin rather than swallow it whole so as to facilitate rapid absorption.
3. Patients who have been prescribed nitroglycerin should be instructed to take only one dose in response to chest pain. If the symptoms have not improved or are worsening within 5 minutes, then the patient should call 911 immediately before taking additional nitroglycerin. If the patient is known to have chronic stable angina and the chest pain is significantly improving after taking a dose of nitroglycerin, it is appropriate to instruct the patient to take additional doses of nitroglycerin every 5 minutes for a total of three doses and then call 911 if symptoms have not completely resolved.

4. Patients with suspected ACS who have had anginal symptoms at rest for greater than 20 minutes, hemodynamic instability, or recent syncope should be referred immediately to the ED.

B. Early risk stratification recommendations

1. Patients who present with suspected ACS should be quickly assessed and should undergo early risk stratification for adverse cardiovascular events. This should include a history and physical examination focused on high-risk features of ACS (prolonged chest pain at rest, syncope, signs of CHF, etc.), an ECG, and laboratory biomarkers of cardiac injury, preferably troponin I or T.
2. **A 12-lead ECG should be performed immediately upon arrival at the ED, with the standard being within 10 minutes of arrival for patients with symptoms suggestive of ACS.**

   Common ECG findings in UA/NSTEMI include ST-segment depression, transient ST-segment elevation, and T-wave inversion. However, approximately 20% of patients with an NSTEMI confirmed by cardiac enzymes have no ischemic ECG changes. Moreover, a "normal" ECG pattern is not sufficient to rule out ACS in patients with chest pain (> 4% of patients presenting with chest pain and normal ECG patterns are diagnosed with UA). Persistent ST-segment elevation of ≥ 1 mm in two or more contiguous leads or new LBBB suggests acute STEMI and should be considered for emergency reperfusion therapy (see Chapter 1). As previously mentioned, ST-segment elevation ≥ 0.5 mm in lead aVR raises the possibility of left main or three-vessel CAD. T-wave inversions are the least specific of ECG changes in ACS. However, new, deep, symmetric T-wave inversions of ≥ 2 mm across the precordium in patients presenting with UA (Wellens' syndrome) often correspond to acute ischemia, usually related to a severe proximal left anterior descending artery stenosis. In this setting, revascularization often results in improved ventricular function and normalization of the ECG.

   a. Older classification systems recognized NSTEMI as non–Q-wave MI because myocardial necrosis occurs without ECG evidence of transmural injury. Because of the inability to determine the transmural extent of myocardial injury based on the presence or absence of ST-segment elevation, NSTEMI has become the preferred terminology.
   b. Analysis of 1,473 UA or NSTEMI patients in the **TIMI III trial** revealed transient ST-segment elevation in 10%, ST-segment depression in 33%, T-wave inversion in 46%, and no ischemic ECG changes in 9%.
3. **In patients in whom the initial ECG is not diagnostic** but the anginal symptoms persist, serial ECGs should be performed in 15- to 30-minute intervals. This is done in order to detect the development of ST-segment depression or elevation. Posterior circulation ischemia/infarction should be suspected and the use of posterior ECG leads and echo imaging should be considered.
4. Cardiac biomarkers should be measured in all patients presenting with symptoms suggestive of ACS. The preferred and recommended biomarker is a cardiac-specific troponin (troponin I or T). Patients with negative cardiac biomarkers within 6 hours of symptom onset should have the biomarkers remeasured at 8 to 12 hours after the onset of symptoms.

   a. **Troponins.** Cardiac troponin I and T are contractile proteins found only in cardiac myocytes and are the preferred assays to document the presence of cardiac necrosis. Many clinical trials have used troponin levels for diagnosis and prognosis in ACS. Serum levels of troponins I and T typically rise within 3 to 12 hours after myocardial necrosis and remain elevated afterward for much longer than creatine kinase (CK; 10 to 14 days). Although troponins are more sensitive and specific for myocardial injury than CK and CK-MB, elevated troponin levels can be seen in other nonischemic cardiac conditions

(advanced heart failure and acute pericarditis) and in the setting of renal insufficiency. In the setting of NSTE-ACS, troponins have important prognostic significance beyond that specified by clinical criteria, with elevated levels portending a worse prognosis. In the **GUSTO IIb** trial of patients with UA, the 30-day mortality rate for patients with an elevated troponin T level (> 0.1 ng/mL) was 11.8%, compared with 3.9% for patients with normal troponin levels. Elevated troponin levels in the setting of NSTE-ACS have also been associated with increased likelihood of multivessel disease, high-risk culprit lesions, and intracoronary thrombus visible at the time of angiography.

b. Creatine kinase. Among the most commonly used biochemical markers for the evaluation of patients with suspected ACS are CK and the MB isoenzyme of CK, measured serially every 6 to 8 hours for the first 24 hours. Total CK levels **peak at 12 to 24 hours** after the onset of symptoms, and **CK-MB levels peak at 10 to 18 hours** after the onset of symptoms. The CK-MB isoenzyme is more specific and more sensitive than the total CK measurement for documenting myocardial necrosis. Although a low level of CK and CK-MB is usually found in normal patients, values above the upper limit of normal for a given laboratory suggest the presence of myocardial necrosis. **Many nonischemic conditions, such as pericarditis, skeletal muscle injury, and renal failure**, can cause elevations of total CK levels or, less likely, an increase in CK-MB.

5. The initial evaluation should include consideration and appropriate evaluation of noncoronary causes of the unexplained symptoms (see Section **II.D**).

C. Recommendations for immediate management and triage. The initial management of patients with suspected ACS is dependent on the predicted risk of adverse cardiovascular outcomes. Patients can be initially categorized as low, intermediate, or high risk depending on the historical and clinical findings (Table 2.1). The use of risk stratification models such as the TIMI (Table 2.3), GRACE, and PURSUIT risk scores can also assist in determining which patients are at increased risk.

Patients with probable or possible ACS whose initial 12-lead ECG and cardiac biomarker levels are normal should be monitored on telemetry. Repeat ECGs and repeat cardiac biomarker measurements should be performed at scheduled intervals 6 to 8 hours apart.

1. In **low- and intermediate-risk patients** (Table 2.1) whose serial ECGs and cardiac biomarkers are normal, a conservative strategy may be considered and a **cardiac stress test** should be performed in the ED or monitoring facility. For low-risk patients, it is also appropriate to consider performing the stress test as an outpatient within 72 hours. The optimal time for testing may be determined at the discretion of the physician and in consideration of the patient's wishes. For such patients who are referred for outpatient stress testing, the initiation of antiplatelet and anti-ischemic pharmacotherapy (nitroglycerin and β-blockers) should be strongly considered.
2. **High-risk patients** (Table 2.1) and low-risk patients who have a positive stress test with high-risk features should be admitted to the hospital for inpatient management. Patients with active ongoing ischemia or hemodynamic or electrical instability should be admitted to the intensive care unit.
3. **Noninvasive stress testing.** Stress testing has been thought to be contraindicated in the evaluation of patients with UA because of the concern for acute occlusion with increased cardiac workloads in the presence of unstable plaques. However, patients at low or even intermediate risk who remain pain free for at least 12 to 24 hours and without any symptoms of heart failure can safely undergo functional testing. Intermediate-risk patients include those with age > 70 years; slightly elevated cardiac biomarkers (e.g., troponin T > 0.01 ng/mL but

< 0.1 ng/mL); T-wave changes; pathologic QS; minimal resting ST-depression (< 1 mm) on ECG; rest angina or present with atypical symptoms; and prior history of MI, CABG, peripheral or cerebrovascular disease, or aspirin use.

a. Patients who have **normal myocardial perfusion scan** without fixed or reversible perfusion defects can be safely **discharged** from the hospital and followed up on an outpatient basis. However, **cardiac catheterization** should be considered for patients found to have high-risk features on stress testing because they are at increased risk for adverse ischemic events.

b. If patients are unable to exercise, **pharmacologic stress testing** can be performed instead with dobutamine or a vasodilator such as adenosine or regadenoson. However, no large-scale studies using these modalities for stress testing have been performed in this patient population.

V. EARLY HOSPITAL CARE. The mainstay of treatment for ACS is directed at anti-ischemic therapy and antithrombotic (antiplatelet and anticoagulation) therapy. In clinical practice, the choice of specific antithrombotic therapy is partly determined by whether an initial conservative or an initial invasive approach is planned.

A. Anti-ischemic therapy. All patients admitted to the hospital with ACS should have their activity limited to bed or chair rest to help maintain minimal myocardial demand. Continuous ECG monitoring (telemetry) is recommended, and supplemental oxygen should be provided for patients who are in respiratory distress or have an oxygen saturation < 90%. The following anti-ischemic medications should also be considered.

1. **Nitrates.** Despite a lack of randomized clinical trial data, nitrates remain the mainstay of treatment for patients with UA with chest pain or spontaneous ischemia.

   a. **Dosing.** Sublingual nitroglycerin or nitroglycerin spray (0.4 mg) should be administered immediately and repeated every 5 minutes (three times) to relieve anginal discomfort. If angina persists, intravenous nitroglycerin may be started (at 10 to 20 μg/min). Intravenous nitroglycerin can be quickly titrated (5 to 10 μg/min increases every 5 to 10 minutes) to relieve angina. Caution must be exercised as it may cause profound hypotension. Topical (nitroglycerin transdermal patch, 0.2 to 0.6 mg/h, or nitropaste, 1 to 2", replaced every 6 hours) or oral (isosorbide dinitrate, 10 to 40 mg orally three times daily, or isosorbide mononitrate, 30 to 120 mg orally each day) nitrates can also be used in patients to prevent recurrent anginal symptoms. Tolerance to nitrates is dose and interval dependent and can occur within 24 hours of initiation, requiring higher doses of nitrates. After symptoms are controlled, changing from intravenous to topical or oral formulations with nitrate-free intervals can limit this phenomenon.

   b. **Contraindications.** Contraindications are known **hypersensitivity to nitrates and hypotension. Sildenafil (Viagra) use** within the prior 24 hours has been associated with hypotension, MI, and death.

2. **β-Blockers.** β-Blockers may relieve myocardial ischemia by lowering myocardial oxygen demand through its effects on blood pressure, heart rate, and contractility. A meta-analysis of 4,700 patients with UA and impending MI showed that β-blockers reduced the risk of MI, but no clear effect on mortality was seen. The goals of therapy are a resting heart rate of usually 50 to 60 beats/min and relief of angina. Cardioselective β-blockers (e.g., metoprolol and atenolol) are typically used to minimize side effects.

   a. **Dosing.** Patients with ongoing anginal pain or persistent hypertension can initially be treated with intravenous β-blockers. Intravenous metoprolol can be given in 5-mg increments every 5 to 10 minutes until the desired heart rate and blood pressure response is achieved. Oral metoprolol therapy can

then be started at a dose of 25 to 50 mg every 6 to 12 hours and can be subsequently titrated as necessary.

b. **Contraindications.** Contraindications to β-blocker therapy include **advanced atrioventricular block, active bronchospasm, cardiogenic shock, hypotension, baseline bradycardia,** and **congestive heart failure**.

3. **Calcium channel blockers.** Calcium channel blockers have diverse physiologic effects, including vasodilation, decreased or slowed atrioventricular conduction, and negative inotropy and chronotropy. A meta-analysis of calcium channel blocker trials in the management of UA showed no effect on death or nonfatal MI. However, short-acting nifedipine increased the risk of MI or recurrent angina compared with metoprolol. Diltiazem may reduce adverse events among patients with UA with normal LV function. However, patients with LV dysfunction or pulmonary congestion on physical examination are reported to have worse outcomes when treated with diltiazem.

   a. **Indications.** Calcium channel blockers are recommended for patients with UA, but **only in patients with contraindications to β-blockers or when β-blockers and nitrates fail to fully relieve symptoms of ischemia**. Calcium channel blockers are preferred in patients with variant angina or cocaine-induced vasospasm.

   b. **Contraindications.** Contraindications to calcium channel blockers include LV dysfunction or signs and symptoms of congestive heart failure, hypotension, or atrioventricular conduction abnormalities.

4. **Angiotensin-converting enzyme (ACE) inhibitors.** In patients with LV dysfunction, ACE inhibitors improve survival and ventricular remodeling. The effects of ACE inhibitors in the care of patients with UA or NSTEMI are less well defined. However, **if patients have LV dysfunction, ACE inhibitors should be added to existing medical therapy**. Moreover, in the long term, ACE inhibitors should be considered in every patient with UA/NSTEMI, especially given the overall favorable data for their use in patients with CAD.

B. **Initial conservative versus initial invasive strategy.** Two approaches to managing patients with NSTE-ACS have evolved. Based on a host of factors, including an overall assessment of patient risk, a decision to pursue either an early invasive strategy or an initial conservative strategy needs to be made early in the management of NSTE-ACS (Table 2.5). Overall, patients selected to have early invasive therapy will have coronary angiography performed within 24 hours of admission, or sooner, depending on the clinical situation. Those patients elected to a conservative strategy are managed with optimal medical therapy and undergo angiography only in select circumstances such as development of recurrent symptoms or objective evidence of ischemia while on appropriate medical therapy. There have been several studies comparing these two strategies. Bavry et al. performed a contemporary meta-analysis of seven randomized trials evaluating an early invasive versus a conservative approach in the management of patients with NSTE-ACS. In this pooled analysis of 8,375 patients, there was a 25% relative reduction in all-cause mortality at 2 years with use of early invasive as compared with conservative therapy (4.9% vs. 6.5%, $p = 0.001$). Early invasive therapy also reduced the incidence of nonfatal MI and rehospitalization for UA by 17% and 31%, respectively.

1. The 2011 UA/NSTEMI ACC/AHA guidelines provide specific treatment strategies for the following patient populations:

   a. Patients who have **refractory angina despite medical therapy, hemodynamic instability, or electrical instability** are recommended to undergo an **early invasive strategy**.

   b. For patients who are **initially stabilized but are at high risk for adverse events**, it is reasonable to undergo an **early invasive strategy *or* an initially**

TABLE 2.5 Initial Management Strategy in NSTE-ACS: Early Invasive versus Conservative (Selective Invasive) Approach

Early invasive	Conservative
Hemodynamic instability	Low risk score (e.g., TIMI, GRACE, and PURSUIT)
Arrhythmia instability	Physician or patient preference in low- to intermediate-risk patient
High risk score (e.g., TIMI, GRACE, and PURSUIT)	
Elevated troponin T or I	
Refractory angina despite aggressive medical therapy	
Prior PCI within 6 mo or prior CABG	
Signs or symptoms of congestive heart failure	
New or worsening mitral regurgitation	
Left ventricular function < 40%	

CABG, coronary artery bypass grafting; GRACE, Global Registry of Acute Coronary Events; NSTE-ACS, non–ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; PURSUIT, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; TIMI, thrombolysis in myocardial infarction.

conservative strategy. This includes patients who are troponin positive. The decision of which strategy to employ should be based upon both physician and patient preference.

c. For patients who are **not at high risk**, it is reasonable to proceed with a **delayed invasive approach**.

d. **Women with low-risk features** are recommended to proceed with a **conservative strategy**.

e. For patients with **extensive comorbid conditions** (e.g., cancer and liver or pulmonary failure), **an early invasive strategy is not recommended**. This is particularly true when the risks of revascularization are likely to outweigh the benefits.

f. It is **not recommended to proceed with an early invasive strategy** in patients with **acute chest pain and a low likelihood of ACS**.

g. Patients who are **not willing to undergo coronary revascularization should not undergo an early invasive strategy**.

2. **Randomized trials.** The following is a summary of the randomized trials that have compared an early invasive versus an early conservative approach in different patient populations.

a. Two earlier trials performed prior to the current era of antiplatelet therapy and coronary stenting were the **TIMI IIIB** and **VANQWISH** trials. Both of these trials showed similar long-term outcomes (death or MI) between early invasive and conservative treatment strategies; however, there was an increase in early mortality associated with invasive therapy in the VANQWISH study,

and these two trials were excluded from the recent meta-analysis, since both are noncontemporary.

b. In the **FRISC II** trial, patients with UA/NSTEMI were randomized in a factorial design to an early invasive or conservative strategy and to dalteparin or placebo. An early invasive strategy was associated with a reduction in the rate of death or MI at 6 months (9.4% vs. 12.1%, $p = 0.031$) and reduced symptoms of angina and rehospitalization, regardless of treatment with dalteparin.

c. In the **TACTICS-TIMI 18** trial, patients with UA/NSTEMI treated with aspirin, heparin, and tirofiban were randomized to an early invasive or a conservative strategy. Patients assigned to an **early invasive approach underwent catheterization within 4 to 48 hours**, with revascularization as appropriate. Patients assigned to the conservative arm underwent cardiac catheterization only if there was objective evidence of recurrent ischemia or abnormal stress test. An early invasive strategy was associated with a reduction in the composite of death, nonfatal MI, or rehospitalization for ACS at 6 months (15.9% vs. 19.4%, $p = 0.025$), as well as a reduction in the incidence of death or nonfatal MI at 6 months (7.3% vs. 9.5%, $p < 0.05$).

d. In the **RITA 3** trial, an early invasive strategy for moderate-risk patients with UA/NSTEMI was associated with a decreased rate of death, MI, or refractory angina compared with conservative therapy at 4 months (9.6% vs. 14.5%, $p = 0.001$). This was caused primarily by a reduction in refractory angina. These results suggest that even in moderate-risk patients, an early invasive strategy may be preferred. The RITA 3 investigators also reported a meta-analysis of trials comparing an early invasive versus a conservative approach, with an association between the early invasive approach and a decreased incidence of death or nonfatal MI at 1 year (relative risk [RR] = 0.88, 95% confidence interval [CI]: 0.78 to 0.99).

e. In the **ISAR-COOL** trial, patients with UA/NSTEMI treated with intensive medical therapy (aspirin, heparin, clopidogrel [600-mg loading dose], and tirofiban) were randomized to immediate invasive therapy (median time of 2.4 hours) versus delayed invasive therapy after a "cooling off" period (median time of 86 hours). Those who had early intervention had a significant reduction in death or MI at 30 days compared with those who had a "cooling off" period (5.9% vs. 11.6%, $p = 0.04$).

f. In the **ICTUS** trial, 1,200 patients with NSTE-ACS with elevated troponins were randomized to either early invasive therapy (angiography within 24 to 48 hours) or initial conservative strategy with selective invasive therapy. There was no difference in the primary composite end point of death, MI, or rehospitalization for ACS at 1 year between the two groups (22.7% vs. 21.2%, $p = 0.33$). The aggressive medical therapies and high rates of revascularization (47%) in the initial conservative strategy group are two among many potential explanations for the findings of this trial.

g. In the **TIMACS** trial, patients with NSTEMI presenting within 24 hours of onset of symptoms were randomized to undergo angiography as soon as possible (within 24 hours) or after a minimum delay of 36 hours. These patients received contemporary medical therapy including acetylsalicylic acid (ASA), clopidogrel (>80%), heparin or fondaparinux, and GP IIb/IIIa inhibitors (23%). Overall, there was a nonsignificant trend toward a reduction in death, new MI, or stroke at 6 months for patients who received an early invasive strategy (11.3% for delayed angiography vs. 9.6% in the early intervention, $p = 0.15$). However, there was a significant reduction in the secondary end point of death, MI, or refractory ischemia for patients randomized to an early invasive strategy (12.9% vs. 9.5%, $p = 0.003$) that was primarily driven

by a decrease in refractory ischemia. Interestingly, patients who were in the highest tertile of risk according to the GRACE score were the most likely to benefit from an early invasive strategy. Overall, this study supports an early invasive strategy for patients presenting with UA/NSTEMI, particularly for those among the highest tertile of risk according to the GRACE scale.

h. The **ABOARD** trial assessed whether a very aggressive strategy of emergent intervention (analogous to primary PCI for STEMI) would benefit patients presenting with UA/NSTEMI versus delayed angiography and intervention. Immediate angiography and intervention did not decrease the rate of the primary outcome of median troponin I release (2.1 ng/mL for the invasive strategy vs. 1.7 ng/mL for the delayed strategy) nor did it show a trend toward improved outcomes in the secondary end point of death, MI, or urgent revascularization at 1 month (13.7% for early invasive management vs. 10.2% for the conservative approach, $p = 0.31$).

C. Antiplatelet and anticoagulant therapies. There are many different antiplatelet and antithrombotic agents currently available for the treatment of ACS. As such, the decision of which combination of medications to use and when to administer them can be challenging. In general, the decision of which agents to use depends on (1) whether an early invasive strategy is used and (2) what post-angiography management strategy is employed. Regardless of which strategy is chosen, all patients presenting with ACS should receive a loading dose of aspirin (162 to 325 mg) to be chewed and swallowed; if the patient is aspirin intolerant, then a loading dose of clopidogrel (300 to 600 mg) should be given. The antiplatelet and anticoagulant therapies available for each of the following strategies are listed below. The specific doses, adverse effects, and pharmacokinetics of these agents are then listed separately.

1. **Initial conservative strategy.** After receiving aspirin, patients who undergo an initial conservative strategy should receive an **anticoagulant** and be started on **clopidogrel** therapy. Enoxaparin and fondaparinux are the anticoagulants of choice; unfractionated heparin (UFH) is an acceptable alternative. Of note, if fondaparinux is used and an invasive strategy is ultimately employed, then another anticoagulant with factor IIa activity (UFH) must be coadministered to prevent catheterization-associated thrombosis.
2. **Initial invasive strategy.** After receiving aspirin, patients who undergo an initial invasive strategy should receive **anticoagulation with enoxaparin, UFH, or bivalirudin**. Before proceeding with catheterization, it is recommended to administer a **second antiplatelet agent**. These agents include clopidogrel or ticagrelor. Prasugrel may also be utilized after angiographic definition. A GP IIb/IIIa inhibitor such as eptifibatide or tirofiban may be considered.
3. **Once angiography is performed, the appropriate subsequent therapy depends on the management plan.**
   a. For patients undergoing **CABG surgery**, it is recommended to **continue aspirin therapy**. If clopidogrel therapy has been started, it should be discontinued 5 days prior to CABG. GP IIb/IIIa inhibitors should be discontinued 4 hours prior to CABG. Although ticagrelor is a reversible $P2Y_{12}$ inhibitor, bleeding rates were similar to clopidogrel following CABG when discontinued 5 days prior to surgery. Bleeding rates following CABG were greater with prior exposure to prasugrel compared with clopidogrel in the TRITON–TIMI 38 trial and the risk persisted for up to 7 days from last drug exposure. UFH can be continued until CABG; however, enoxaparin should be discontinued 12 to 24 hours prior to CABG and bivalirudin should be discontinued 3 hours prior to CABG.
   b. **Percutaneous coronary intervention.** All patients undergoing PCI should be on dual antiplatelet therapy. Routine GP IIb/IIIa inhibitor prior to PCI is not warranted and may be used adjunctive to PCI in selective cases.

c. **Medical therapy.** If the catheterization reveals no significant obstructive CAD, then the antiplatelet and anticoagulant therapy is to be continued at the discretion of the physician. If catheterization reveals significant CAD that is to be medically managed, then it is recommended to continue aspirin therapy and to load with clopidogrel therapy if not done so prior to catheterization. GP IIb/IIIa therapy should be discontinued. UFH should be continued for 48 hours; enoxaparin or fondaparinux should be continued for the duration of the hospitalization. Bivalirudin should be continued for 72 hours.

4. **Aspirin.** Despite being a relatively weak inhibitor of platelet aggregation, aspirin has a significant effect on mortality in UA. There are several pathways that lead to platelet activation, of which aspirin blocks only the cyclooxygenase-derived thromboxane A_2 pathway. Aspirin therapy for UA/NSTEMI has been studied in five major clinical trials at doses ranging from 75 to 325 mg/d. Overall, treatment with aspirin reduced the combined end point of death or nonfatal MI by 50%.
   a. **Pharmacokinetics.** The onset of aspirin's antiplatelet effect is quite rapid, with substantial inhibition of thromboxane A_2 production within 15 minutes, translating into measurable platelet inhibition within 60 minutes. It should be given as soon as patients present with ACS. Because aspirin's inhibition of cyclooxygenase is irreversible, its antiplatelet effect is durable, lasting 7 to 10 days.
   b. **Dosing.** Unless contraindicated (e.g., active bleeding and documented hypersensitivity to aspirin), an initial dose of 162 to 325 mg of nonenteric-coated aspirin (chewed and swallowed) should be given to all patients with suspected UA. Those patients allergic or intolerant to aspirin should receive clopidogrel as soon as possible. For patients who undergo PCI, aspirin at 162 to 325 mg/d is recommended for at least 1 month after bare-metal stent (BMS), 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation followed by 81 to 162 mg/d indefinitely thereafter. Subsequent daily aspirin doses can be reduced, with the preferred dose for secondary prevention being 81 to 162 mg daily; this should be continued indefinitely.
5. **Ticlopidine.** Ticlopidine was the first commercially available thienopyridine. Ticlopidine and the other thienopyridines inhibit adenosine diphosphate–induced platelet aggregation. Compared with placebo, ticlopidine reduced rates of death or MI at 6 months among patients with UA to a degree similar to that of aspirin. Ticlopidine is associated with a 1% to 5% increase in neutropenia and is thus no longer recommended as a first-line thienopyridine in patients who present with UA/NSTEMI. It is now reserved for patients in whom clopidogrel or prasugrel is not tolerated or contraindicated.
   a. **Pharmacokinetics.** Ticlopidine's onset of action is delayed, usually taking 2 to 3 days for maximum antiplatelet effect.
   b. **Side effects.** Ticlopidine can cause neutropenia (1% to 5% of patients) and is rarely associated with thrombotic thrombocytopenic purpura (TTP).
   c. **Dosing.** Ticlopidine is given as a loading dose of 500 mg followed by 250 mg twice daily.
6. **Clopidogrel.** Clopidogrel was the second commercially available thienopyridine and is the most extensively studied member of this group. In the CURE trial, patients with UA or NSTEMI had a lower rate of cardiovascular death, nonfatal MI, or stroke when treated with aspirin and clopidogrel versus aspirin alone (9.3% vs. 11.4%, $p < 0.001$). Patients treated with this combination experienced lower rates of refractory ischemia, heart failure, or revascularization. However, an increased rate of major bleeding (3.7% vs. 2.7% for aspirin) was seen in

patients receiving clopidogrel, predominantly in those undergoing CABG. In a substudy of the CURE trial, PCI-CURE, pretreatment with clopidogrel resulted in lower rates of cardiovascular death, nonfatal MI, or urgent target-vessel revascularization at 30 days (4.5% vs. 6.4%) in patients with UA/NSTEMI undergoing PCI. Long-term treatment with clopidogrel resulted in lower rates of cardiovascular death, nonfatal MI, or revascularization, without a significant increase in major bleeding. The benefit of clopidogrel pretreatment in PCI was further confirmed in the CREDO trial in which patients receiving a 300-mg loading dose plus 1 year of 75 mg daily maintenance therapy of clopidogrel had a 26.9% relative reduction in death, nonfatal MI, or stroke at 1 year compared with those receiving only 1 month of maintenance therapy without any loading dose of clopidogrel.

a. **Pharmacokinetics.** Clopidogrel is a prodrug that is metabolized to a pharmacologically active metabolite. Clopidogrel has a shorter onset of action than ticlopidine when 300 mg is given, with antiplatelet activity being detected within 2 hours after administration. Loading with 600 mg has been shown to have an even more rapid onset of action.
b. **Side effects.** Clopidogrel is generally well tolerated. Rarely, it can cause an allergic reaction typically resulting in diffuse urticaria. There have also been case reports of TTP with clopidogrel therapy.
c. **Dosing.** The conventional loading dose for clopidogrel has been 300 mg; however, recent evidence demonstrates a more rapid and heightened platelet inhibitory response, resulting in decreased ischemic events after PCI with use of a 600-mg loading dose of clopidogrel. The CURRENT OASIS-7 trial found that patients presenting with ACS who ultimately undergo PCI have a lower rate of cardiovascular death, MI, and stroke when loaded with 600 mg versus 300 mg. This decrease in ischemic end points came at the cost of an increase in major bleeding. Clopidogrel maintenance therapy is 75 mg daily.

7. **Prasugrel.** Prasugrel is the most recently commercially available thienopyridine. In preclinical studies, prasugrel has been shown to have a more potent antiplatelet effect than clopidogrel. The TRITON–TIMI 38 trial evaluated the efficacy of prasugrel versus clopidogrel in patients presenting with ACS with planned PCI. In this study of 13,608 patients, use of prasugrel as compared with clopidogrel resulted in a significant reduction in the primary efficacy end point of death from cardiovascular causes, nonfatal MI, or nonfatal stroke (9.9% vs. 12.1%, $p < 0.001$). However, the salutary benefits in reduction of ischemic events with prasugrel came at the expense of an increase in late bleeding events, including a significant increase in rates of both major bleeding (2.4% vs. 1.1%, $p = 0.03$) and fatal bleeding (0.4% vs. 0.1%, $p = 0.002$). It is an absolute contraindication to use prasugrel in patients with a history of transient ischemic attack or stroke and a relative contraindication in patients ≥ 75 years of age or < 60 kg due to the absence of a net favorable benefit or even a harmful effect in these patient subgroups.

a. **Pharmacodynamics.** Like clopidogrel, prasugrel is a prodrug and is rapidly metabolized to a pharmacologically active metabolite and inactive metabolites. After a 60-mg loading dose of prasugrel is given, 90% of patients achieve ≥ 50% inhibition of platelet aggregation within 1 hour, with maximum achieved platelet inhibition being approximately 80%. The mean steady-state inhibition of platelet aggregation with prasugrel is 70% after 3 to 5 days of treatment. Platelet aggregation returns to baseline 5 to 9 days after discontinuation of therapy.
b. **Side effects.** Similar to clopidogrel, prasugrel is generally well tolerated. Allergic reactions to prasugrel are rare; however, bleeding-related complications such as epistaxis or easy bruising are not uncommon.

c. **Dosing.** The loading dose for prasugrel is 60 mg followed by a maintenance dose of 10 mg/d.

8. **Ticagrelor.** Ticagrelor is a recently FDA-approved reversible non-thienopyridine $P2Y_{12}$ receptor antagonist. Unlike clopidogrel and prasugrel, ticagrelor is not a prodrug and does not require bioactivation. In the PLATO trial involving patients presenting with ACS, there was a significant 1.9% reduction in major adverse cardiac events and a significant 1.4% reduction in death for patients who were randomized to receive ticagrelor versus clopidogrel. This came at the cost of an increase in nonprocedural bleeding in patients who were randomized to ticagrelor. In addition, dyspnea was noted in 14% of patients taking ticagrelor.
   a. **Dosing.** The loading dose of ticagrelor is 180 mg followed by a maintenance dose of 80 mg twice daily. Ticagrelor was not FDA approved at the time of the 2011 UA/NSTEMI guidelines, and so it is not currently included in the recommendations.
9. **Heparin.** UFH in combination with aspirin reduces the incidence of ischemic events in patients with UA. A meta-analysis of six trials in patients with UA demonstrated that treatment with aspirin plus UFH reduced the incidence of death or nonfatal MI by 33% compared with treatment with aspirin alone, although this difference did not quite reach statistical significance. The treatment effect of heparin may also wane after therapy is discontinued.
   a. **Duration of therapy.** Although the optimal length of therapy with UFH is unknown, studies have suggested that therapy must be continued for at least 3 to 7 days to achieve clinical benefit. Currently, heparin is discontinued after angiography and PCI are performed.
   b. **Rebound ischemia.** Rebound ischemia is thought to result from the accumulation of thrombin during UFH administration and the ensuing platelet aggregation. Studies have shown that this rebound ischemia can be attenuated with the concomitant use of aspirin.
   c. **Recommendations.** Intravenous UFH can be used for anticoagulant therapy in patients with NSTE-ACS undergoing either an invasive or conservative treatment strategy unless contraindicated (e.g., active bleeding, known hypersensitivity, and history of heparin-associated thrombocytopenia).
   d. **Dosing.** Initially, heparin should be given as a weight-adjusted bolus (60 U/kg), followed with an infusion (15 U/kg/h). The activated partial thromboplastin time (aPTT) should be monitored every 6 hours until it stabilizes between 50 and 70 seconds and monitored subsequently every 12 to 24 hours thereafter. Standardized heparin nomograms have simplified and streamlined the initial orders for UFH and the subsequent adjustment of dosing based on aPTT levels.
10. **Low-molecular-weight heparin (LMWH).** The advantages of LMWH compared with UFH include increased bioavailability, a fixed dosing regimen, more effective thrombin inhibition, lower rates of heparin-induced thrombocytopenia, and cost savings because serial aPTT levels do not have to be monitored.
   a. **Comparison with heparin.** A meta-analysis of 12 trials involving 17,157 patients with UA/NSTEMI that compared the use of several different LMWHs with UFH found no significant benefit with LMWHs compared with UFH (odds ratio [OR] = 0.88, 95% CI: 0.69 to 1.12, $p = 0.34$). In the **ESSENCE** trial, however, patients with UA/NSTEMI had a lower rate of death, MI, or recurrent angina at 30 days when treated with the LMWH, enoxaparin, than with UFH (19.8% vs. 23.3%, $p = 0.016$). Patients treated with enoxaparin also underwent fewer revascularization procedures and experienced similar rates of major bleeding. Similarly, in the **TIMI IIB** study, patients with UA/NSTEMI treated with enoxaparin had a lower rate of death, MI, or urgent revascularization at 43 days compared with those treated

with UFH (17.3% vs. 19.7%, $p = 0.048$). Enoxaparin has been shown to be superior to UFH in this patient population and may be used instead of UFH, unless CABG is anticipated within 24 hours. In the **SYNERGY** trial of 9,978 high-risk patients with NSTE-ACS treated with an invasive therapeutic approach, enoxaparin was found to be noninferior but not superior to UFH. The rate of death or MI at 30 days was 14% in the enoxaparin group and 14.5% in the UFH group ($p = 0.396$). There was an increase in major bleeding per the TIMI criteria in those patients randomized to enoxaparin as compared with UFH (9.1% vs. 7.6%, $p = 0.008$). Post hoc analysis suggested that crossover from enoxaparin to UFH may have partly been the reason for this excess bleeding risk associated with enoxaparin.

b. **Dosing. Enoxaparin** is administered as a 1 mg/kg dose given subcutaneously (SQ) every 12 hours. No routine laboratory values have to be followed. However, in certain clinical settings (e.g., renal insufficiency and severe obesity), an anti-Xa level can be measured. The therapeutic anti-Xa level has yet to be determined in patients with UA/NSTEMI or in patients undergoing PCI, but the commonly accepted therapeutic range is 0.5 to 1.0 anti-Xa units/mL.

c. **Recommendations.** In patients with NSTE-ACS who may undergo either a conservative or an early invasive therapy, enoxaparin is an acceptable agent for anticoagulation.

11. **Direct thrombin inhibitors (DTIs).** DTIs inhibit clot-bound thrombin more effectively than UFH and are not inactivated by plasma proteins or platelet factor 4. Hirudin is an older generation DTI that is no longer used clinically and has been supplanted by its synthetic derivative, bivalirudin.

    a. **Bivalirudin (previously Hirulog).** Bivalirudin is a synthetic derivative of hirudin, with a shorter half-life, that reversibly inhibits thrombin. In the **ACUITY** trial of 13,819 patients with UA/NSTEMI, the clinical efficacy of bivalirudin plus GP IIb/IIIa inhibition was noninferior to heparin plus GP IIb/IIIa inhibition, with 30-day rates of ischemia of 7.7% versus 7.3%, respectively.

        (1) **Recommendations.** Current guidelines recommend bivalirudin as a possible choice for anticoagulant therapy in conjunction with GP IIb/IIIa inhibition or a thienopyridine prior to angiography in patients presenting with NSTE-ACS with a planned invasive therapeutic approach. Bivalirudin is not recommended in those patients determined to undergo an initial conservative approach with medical therapy.

12. **Factor Xa inhibitors.** Fondaparinux is a heparin pentasaccharide analog that selectively inhibits factor Xa in the coagulation cascade. In comparison with UFH, fondaparinux has decreased binding to plasma proteins along with dose-independent clearance with a longer half-life. These properties translate into more predictable and sustained anticoagulation, which permits fixed-dose, once-daily administration.

    a. **Comparison with enoxaparin.** The **OASIS-5** trial evaluated the efficacy of fondaparinux versus enoxaparin in 20,078 patients with UA/NSTEMI. Patients receiving fondaparinux (2.5 mg SQ once daily) had a similar rate of the combined end point of death, MI, or refractory ischemia at 9 days as those randomized to enoxaparin (1.0 mg/kg SQ twice daily). The use of fondaparinux was associated with a lower rate of major bleeding at 9 days as compared with enoxaparin (2.2% vs. 4.1%, $p < 0.001$). However, in this trial, there was an increased incidence of catheter-associated thrombus noted, and the trial protocol was changed to allow for use of open-label UFH, which initially was not allowed during PCI.

    b. **Dosing.** The dosing of fondaparinux for UA/NSTEMI is 2.5 mg SQ once daily. Fondaparinux is renally cleared and its use is contraindicated in those patients with a creatinine clearance (CrCl) < 30 mL/min.

c. **Recommendations.** Fondaparinux can be used for anticoagulant therapy in those patients selected to undergo a conservative medical approach. It is the preferred therapy in patients with increased risk of bleeding being managed with medical therapy. For patients who undergo angiography and PCI, adjuvant UFH is recommended, given the increased rates of catheter-associated thrombus with fondaparinux in the **OASIS-5** trial.

13. GP IIb/IIIa inhibitors

Background. Platelet aggregation requires the activation of GP IIb/IIIa receptors on the platelet surface. The GP IIb/IIIa receptors of adjacent platelets bind fibrinogen molecules that allow cross-linking of the platelets, which subsequently initiates thrombus formation. Blocking the GP IIb/IIIa receptor inhibits platelet aggregation and reduces thrombus formation. **Abciximab**, the Fab fragment of a murine monoclonal antibody to the human GP IIb/IIIa receptor, binds this receptor tightly and inhibits platelet aggregation for days after the drug infusion is discontinued. In addition to its affinity for the GP IIb/IIIa receptor, abciximab inhibits other receptors, including the vitronectin receptor on endothelial cells and the MAC-1 receptor on leukocytes. **Eptifibatide** is a cyclic peptide inhibitor derived from snake venom, with rapid onset and a short half-life. Because of its short half-life, continuous drug infusion is required to sustain maximal inhibition of platelet aggregation. **Tirofiban** may also be utilized.

Use in UA during PCI. Abciximab and eptifibatide have been approved by the FDA for use as adjunctive therapy during PCI. Tirofiban has been approved for the treatment of UA, with continuation of its use into the catheterization laboratory.

a. **Abciximab** was studied in patients with UA undergoing high-risk percutaneous transluminal coronary angioplasty (PTCA) in the Evaluation of 7E3 for the Prevention of Ischemic Complications (**EPIC**) trial. In 489 patients, abciximab lowered major ischemic event rates (12.8% for placebo vs. 4.8% for abciximab, $p = 0.012$) at 30 days, primarily because of a reduced rate of death or MI. This benefit was maintained at long-term follow-up (3 years). In the Evaluation in PTCA to Improve Long-term Outcome with abciximab Glycoprotein IIb/IIIa blockade (**EPILOG**) trial, treatment with abciximab in addition to heparin was associated with a significant reduction in the rate of death, MI, or urgent revascularization at 30 days (11.7% vs. 5.2% in the low-dose heparin group, $p < 0.001$), expanding the benefit to low- and intermediate-risk patients undergoing PCI. In the EPILOG trial, a lower, weight-adjusted dosing algorithm of heparin resulted in similar major and minor bleeding rates between abciximab and placebo. In the c7E3 Fab Antiplatelet Therapy for Unstable Refractory Angina (**CAPTURE**) study, abciximab given 18 to 24 hours before PCI reduced the rate of death, MI, and urgent intervention (10.8% vs. 15.4%, $p = 0.017$). Patients treated with abciximab also had a higher rate of thrombus resolution and improved procedural success. Results from the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (**EPISTENT**) trial demonstrated that when **stents and abciximab** are used together, the rate of adverse ischemic events and long-term (1-year) mortality is lower than that with stents alone. Abciximab (bolus of 0.25 mg/kg abciximab is followed by 12-hour infusion at 10 μg/min) is commonly used during PCI in patients with ACS.

b. **Tirofiban.** In the Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (**RESTORE**) trial, patients presenting with ACS who underwent PCI within 72 hours of presentation were treated with heparin and aspirin with the addition of tirofiban or placebo. Treatment with tirofiban resulted in a reduction in the short-term rate of death, MI, or revascularization for failed PTCA or recurrent ischemia without an increase in major bleeding. In the Platelet Receptor Inhibition in Ischemic Syndrome

Management (**PRISM**) trial, treatment with tirofiban (the dose used was a 0.6 μg/kg/min bolus for 30 minutes, followed by an infusion of 0.15 μg/kg/min) in patients with UA resulted in a 32% decrease in the rate of death, MI, or refractory ischemia at 48 hours (3.8% vs. 5.6%, $p = 0.01$). The composite end point, however, was not significantly different at 30 days, although the mortality was reduced (3.6% vs. 2.3%). Notably, very few patients underwent PCI during the treatment period (1.9%). In the Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (**PRISM-PLUS**) trial, tirofiban in addition to heparin was associated with a decreased rate of death, MI, or refractory ischemia compared with heparin alone at 7 days (12.9% vs. 17.9%, $p = 0.004$), at 30 days (18.5% vs. 22.3%, $p = 0.03$), and at 6 months (27.7% vs. 32.1%, $p = 0.02$).

c. **Eptifibatide** was evaluated in the **PURSUIT** trial. Eptifibatide treatment (180 μg/kg bolus followed by an infusion of 1.3 or 2.0 μg/kg/min) in patients with UA/NSTEMI was associated with a decreased rate of death or nonfatal MI at 30 days compared with placebo (14.2% vs. 15.7%, $p = 0.04$), although with an increased rate of bleeding.

d. **Use independently of PCI.** Eptifibatide and tirofiban have been approved for use in the care of patients with UA as a primary medical therapy whether PCI is performed or not. A pooled analysis of the **CAPTURE**, **PURSUIT**, and **PRISM-PLUS** trials revealed that during the study medication infusion, treatment with a GP IIb/IIIa inhibitor resulted in a reduction of death or nonfatal MI of 34% in patients with UA/NSTEMI, suggesting an early benefit during medical treatment that may be independent of its effect during PCI. However, in the **GUSTO IV–ACS** trial, patients with UA/NSTEMI treated with abciximab bolus and infusion for 24 or 48 hours received no benefit in addition to conventional therapy with aspirin and heparin, with the 30-day incidence of death or MI being similar across groups (8.0% placebo, 8.2% for 24-hour infusion, and 9.1% for 48-hour infusion). Medical management was encouraged during the first 48 hours, and only 1.6% of patients underwent PCI while on the study drug. In patients not likely to be treated with an early invasive strategy, abciximab has shown no benefit using the dosing protocol described in that trial.

e. **Recommendations. The benefit of GP IIb/IIIa inhibitors is predominantly in patients who subsequently undergo PCI.** However, in the contemporary era with newer anticoagulant therapies and use of higher loading doses of clopidogrel (600 mg), there is less clarity regarding the utility of adjuvant GP IIb/IIIa inhibition with PCI. The **ISAR-REACT 2** trial randomized 2,022 patients with NSTE-ACS undergoing PCI to abciximab or placebo in addition to pretreatment with a 600-mg loading dose of clopidogrel. Overall, there was a 25% reduction in death, MI, or urgent target-vessel revascularization noted in those patients who received abciximab. However, this benefit was observed solely in those patients with elevated troponin levels. Also, the **ACUITY** trial suggests that GP IIb/IIIa inhibition is unnecessary in those patients who have received bivalirudin plus clopidogrel pretreatment with a loading dose of at least 300 mg at least 6 hours prior to angiography. For patients with UA/NSTEMI undergoing an **early invasive strategy**, the ACC/American Heart Association (AHA) guidelines state that either a GP IIb/IIIa inhibitor or clopidogrel can be used upstream in lower risk patients, whereas combination therapy with both is favorable in patients with high-risk features, with early recurrent ischemic discomfort, or having a delay to angiography. If PCI is likely to be performed and there is no expected delay to angiography, then abciximab can be used upstream for

GP IIb/IIIa inhibition. Otherwise, eptifibatide or tirofiban is the preferred GP IIb/IIIa inhibitor of choice.

f. Subgroups that benefit from GP IIb/IIIa inhibitors

(1) Troponin-positive status. Several studies have shown that the benefit of these agents resides primarily with patients presenting with elevated cardiac troponins. In the **CAPTURE** trial, patients with UA with an elevated troponin T level had a greater reduction in the rate of death or nonfatal MI with abciximab therapy than patients with a normal troponin T level. This continues to be true in the contemporary era of dual antiplatelet therapy with aspirin and clopidogrel, as discussed earlier with the results of the **ISAR-REACT 2** trial. Therefore, elevated troponin levels continue to identify patients at higher risk for adverse cardiac events who may benefit particularly from therapy with GP IIb/IIIa inhibitors.

(2) Diabetics. In a meta-analysis of diabetic patients with ACS, the use of GP IIb/IIIa inhibitors was associated with decreased mortality at 30 days (6.2% vs. 4.6%, $p = 0.007$). In diabetic patients with ACS undergoing PCI, treatment with GP IIb/IIIa inhibitors was associated with a more marked benefit (mortality rate: 4.0% vs. 1.2%, $p = 0.002$). In this same analysis, GP IIb/IIIa inhibitors did not confer the same improvement in mortality to nondiabetic patients (3.0% vs. 3.0%). These data suggest that diabetic patients, in particular, benefit from the use of these agents, when undergoing PCI during the initial hospitalization.

g. Oral GP IIb/IIIa inhibitors. Oral GP IIb/IIIa inhibitors have not been shown to be beneficial and may increase mortality. The reason for this dichotomy between the benefit seen with intravenous GP IIb/IIIa inhibitors and the detriment seen with oral inhibitors is not entirely clear. One possible explanation is that the oral agents, in contrast to the intravenous GP IIb/IIIa inhibitors, have partial agonist activity, which actually leads to an increase in fibrinogen binding and platelet aggregation on administration.

14. Fibrinolytic agents. Although fibrinolytic therapy has decreased mortality and improved LV function among patients with STEMI, the use of these agents is associated with worse outcomes in patients with UA and NSTEMI. A meta-analysis of fibrinolytic therapy in the management of UA demonstrated an increase in death or nonfatal MI in patients receiving fibrinolytics (9.8% for fibrinolytics vs. 6.9% for placebo). The lack of efficacy of fibrinolytic agents in these patients may result from the prothrombotic milieu induced by exposure of clot-bound thrombin after fibrin cleavage. Plasmin generation increases, and platelets are activated, perpetuating this prothrombotic state. Fibrinolytic agents would not be expected to dramatically improve coronary blood flow in UA because of the nonocclusive nature of thrombi in these patients.

VI. HOSPITAL DISCHARGE AND POSTDISCHARGE CARE. The risk of progression to MI or the development of recurrent MI or death is highest during the first two months after UA/NSTEMI. Thus, although patients with UA usually receive definitive therapy during hospitalization, close follow-up care after hospital discharge is imperative. There are no guidelines regarding noninvasive stress testing of patients without symptoms who have undergone percutaneous or surgical revascularization for UA. If anginal symptoms recur after hospital discharge, stress testing or cardiac catheterization can be performed, depending on the clinical presentation. Follow-up must include lifestyle alteration, risk factor modification, and secondary prevention. An exercise regimen in stable patients, smoking cessation efforts, and dietary changes have all been shown to improve outcomes. Hypertension, dyslipidemia, and diabetes mellitus must be diagnosed and aggressively treated. Antianginals (i.e., nitrates, β-blockers, and possibly calcium antagonists) should be used for symptom relief. Patients must be reassured and educated about their

acceptable level of activity. **The long-term use of aspirin, clopidogrel, β-blockers, statins/cholesterol-lowering regimens, and/or ACE inhibitors should not be neglected**. Specific recommendations regarding a secondary prevention postdischarge medication regimen are listed below:

A. **Anti-ischemic medications** that were required to control symptoms during the hospitalization should be continued after discharge in patients who did not undergo coronary revascularization, had an unsuccessful revascularization, or had recurrent angina after revascularization. This will often require additional titration of the anti-ischemic medications (see Section **VI.A**). All patients should be given clear instructions about what symptoms to look for that are suggestive of worsening myocardial ischemia. In addition, all patients should be given **sublingual or spray nitroglycerin** and instructions on how to use it.

B. **Aspirin 75 to 162 mg daily should be continued indefinitely for all patients who have had UA/NSTEMI**. Patients who have undergone PCI with a BMS should be given ASA 162 to 325 mg daily for at least 1 month after stent implantation. Patients who have undergone PCI with a drug-eluting stent (DES) should be given ASA 162 to 325 mg daily for at least 3 months after sirolimus-eluting stent implantation and at least 6 months after paclitaxel-eluting stent implantation, after which daily ASA at 75 to 162 mg should be continued indefinitely. For post-PCI patients in whom there is concern for a risk of bleeding, an initial lower dose of ASA at 75 to 162 mg/d is acceptable. For patients in whom ASA is contraindicated or not tolerated, clopidogrel 75 mg daily (preferred) or ticlopidine (if not contraindicated) should be given indefinitely.

C. **Thienopyridine therapy.** In patients with UA/NSTEMI who underwent PCI with a DES or BMS, clopidogrel, ticagrelor, or prasugrel therapy should be continued for at least 12 months and further continuation beyond 15 months may be considered. In patients in whom the risk of bleeding outweighs the expected benefits of prolonged thienopyridine therapy, early discontinuation can be considered, especially in patients who have received a BMS. UA/NSTEMI patients who were treated medically without PCI should be given clopidogrel 75 mg daily for at least 1 month, and ideally up to 1 year. Although there are currently no data proving that performing **platelet function testing** on patients on thienopyridine therapy results in improved outcomes, it is considered reasonable to do so if the results of testing would alter management.

D. **β-Blockers** should be given indefinitely to all UA/NSTEMI patients unless contraindicated. Patients recovering from UA/NSTEMI with moderate or severe LV dysfunction should be gradually titrated onto adequate β-blocker therapy. **Calcium channel blockers** (other than short-acting dihydropyridine calcium channel blockers) are recommended for ischemic symptoms when β-blockers are not successful, are contraindicated, or are not tolerated.

E. **ACE inhibitors** should be given indefinitely to all patients with UA/NSTEMI and heart failure, left ventricular ejection fraction (LVEF) < 40%, hypertension, or diabetes mellitus unless contraindicated. An ACE inhibitor is also reasonable in UA/NSTEMI patients in the absence of these conditions. **Angiotensin receptor blockers** should be given to patients who are intolerant of ACE inhibitors and have heart failure with an LVEF < 40%.

F. **Aldosterone receptor antagonists** should be given to post-UA/NSTEMI patients who do not have significant renal dysfunction (CrCl > 30 mL/min), do not have hyperkalemia (K ≤ 5 mEq/L), are already on an adequate dose of ACE inhibitor, and have heart failure or diabetes mellitus with an LVEF < 40%. In the **EPHESUS** trial, 6,642 patients post-MI (3 to 14 days) with an LVEF ≤ 40% along with either symptomatic heart failure or diabetes mellitus were randomized to oral eplerenone (starting dose of 25 mg, titrated to maximum of 50 mg/d) or placebo in addition to optimal medical therapy. In those individuals randomized to eplerenone as compared with placebo, there was a significant reduction in overall mortality (14.4% vs. 16.7%,

$p = 0.008$), cardiovascular mortality (12.3% vs. 14.6%, $p = 0.005$), and cardiovascular mortality or hospitalization for cardiovascular events (26.7% vs. 30%, $p = 0.002$) at mean follow-up of 16 months. There is an increased risk of hyperkalemia with use of this agent, particularly in those patients with abnormal renal function. In the **EPHESUS** study, there was a significant increase in the risk of serious hyperkalemia (serum potassium ≥ 6.0 mmol/L) in patients using eplerenone as compared with those in the placebo group (5.5% vs. 3.9%, $p = 0.002$). Eplerenone should not be used in those patients with severe renal insufficiency.

G. Statin therapy should be given to all patients with UA/NSTEMI, regardless of baseline low-density lipoprotein cholesterol (LDL-C) levels. LDL-C levels should be lowered to ≤ 100 mg/dL and to levels ≤ 70 mg/dL if feasible.

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (i.e., **statins**) have been shown to be integral in primary and secondary prevention of CAD. Early initiation of statin therapy has beneficial effects in patients with NSTE-ACS as well. In the **MIRACL** study involving 3,086 patients with UA/NSTEMI, treatment with atorvastatin 24 to 96 hours after presentation was associated with a decreased rate of death, nonfatal MI, cardiac arrest, or recurrent ischemia at 16 weeks (14.8% vs. 17.4%, RR = 0.84, 95% CI: 0.70 to 1.00, $p = 0.048$), primarily because of reduced recurrent symptomatic ischemia requiring hospitalization. The **PROVE IT–TIMI 22** trial demonstrated the salutary effects of aggressive lipid-lowering therapy in patients with ACS. In this study, 4,162 patients with ACS were randomized to pravastatin 40 mg daily (standard therapy) or atorvastatin 80 mg daily (intensive therapy) and followed for a mean of 24 months. There was a significant 16% reduction in the rate of death, MI, UA requiring rehospitalization, revascularization, and stroke at 2 years in those randomized to more intensive lipid-lowering therapy compared with standard lipid therapy (22.4% vs. 26.3%, $p = 0.005$). Further analysis from this trial demonstrated an early clinical benefit, which correlated with concomitant reductions in C-reactive protein levels, at 30 days with use of intensive lipid-lowering therapy. These early benefits from statin therapy are likely caused by the "pleiotropic" or nonlipid-lowering effects of statins such as their anti-inflammatory, antioxidant, and antithrombotic properties. Statins' anti-inflammatory effects are likely responsible for beneficial effects in the periprocedural MI reduction seen in patients with NSTE-ACS treated with PCI. In the **ARMYDA-ACS** study of patients with NSTE-ACS undergoing PCI, pretreatment (12 hours prior to PCI) with atorvastatin 80 mg as compared with placebo resulted in a significant reduction in death, MI, or unplanned revascularization at 30 days (5% vs. 17%, $p = 0.01$), which was driven entirely by the reduction in periprocedural MI rates (5% vs. 15%, $p = 0.04$).

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CHAPTER 3

Michael P. Brunner
Venu Menon

Complications of Acute Myocardial Infarction

I. INTRODUCTION. **In-hospital mortality after acute myocardial infarction (MI) is primarily caused by circulatory failure from severe left ventricular (LV) dysfunction and/or other acute complications of MI.** These complications can be broadly classified as **mechanical, arrhythmic, embolic, and inflammatory (e.g., pericarditis)**.

II. MECHANICAL COMPLICATIONS. Mechanical complications of acute MI include ventricular septal rupture (VSR), acute mitral regurgitation (MR), ventricular free wall rupture, ventricular pseudoaneurysm, and ventricular aneurysm.

A. Ventricular septal rupture

1. **Clinical presentation.** VSR occurred in 1% to 2% of patients after acute MI in the prethrombolytic era and accounted for 5% of the periinfarction mortality. The incidence has dramatically decreased in the postthrombolytic era. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries 1 (GUSTO-1) trial, the incidence of VSR was approximately 0.2%, occurring with equal frequency in anterior and non-anterior locations. VSR is more likely to occur in patients who are **older, female, and hypertensive and have no prior history of smoking.** It commonly occurs in the setting of a **first MI, in the background of delayed or absent reperfusion therapy.** Angiography usually reveals an **absence of collateral circulation to the infarct zone**. VSR may develop as early as 24 hours after MI but is usually seen 2 to 5 days after MI. Fibrinolytic therapy is not associated with increased risk of VSR but may accelerate rupture in vulnerable subjects, accounting for the "early hazard" observed with treatment over placebo in randomized clinical trials.
   a. **Signs and symptoms.** Patients with post-MI VSR may appear relatively comfortable early in the disease course. Recurrence of angina, pulmonary edema, hypotension, and shock may develop abruptly later in the course. Alternatively, precipitous onset of hemodynamic compromise characterized by hypotension, biventricular failure, and a new murmur may be the initial manifestation.
   b. **Physical findings.** The diagnosis should be suspected when a new **pansystolic murmur** develops, especially in the setting of worsening hemodynamic profile and biventricular failure. For this reason, it is important that **all patients with MI have a well-documented cardiac examination** at presentation and frequent evaluations thereafter. This assumes critical importance as systems struggle to achieve optimal door-to-balloon times.
      (1) The murmur is usually best heard at the **lower left sternal border**; it is accompanied by a **thrill in 50% of the cases**. In patients with a large

TABLE 3.1 Differential Diagnosis of a New Systolic Murmur after Acute Myocardial Infarction

Differentiating features	Ventricular septal rupture	Acute mitral regurgitation
Location of MI	Anterior = nonanterior	Inferoposterior > anterior
Location of murmur	Lower left sternal border	Cardiac apex
Intensity	Loud	Variable; may be faint
Thrill	50% of patients	Rare
RV failure	More likely	Less likely
Pulmonary edema	Less likely	More likely
V waves in PCWP	Present or absent	Almost always present
V waves in PA tracing	Absent	Present
O_2 step-up in PA	Almost always present	Present or absent

MI, myocardial infarction; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; RV, right ventricular.

VSR and severe heart failure or cardiogenic shock, the murmur may be of low intensity or inaudible, but **the absence of a murmur does not rule out VSR**.

(2) Several features differentiate the murmur of VSR from that of acute MR (Table 3.1). The murmur may radiate to the base and the apex of the heart. A third heart sound (S_3), loud P_2, and signs of tricuspid regurgitation may be present.

2. **Histopathology.** The defect usually occurs at the myocardial infarct border zone, located in the **apical septum with anterior MI** and in the **basal posterior septum with inferior MI**. A VSR almost always occurs in the setting of a transmural MI. The defect may not always be a single large defect; a meshwork of serpiginous channels can be identified in 30% to 40% of patients. Multiple fenestrations are especially common with inferior MIs.
3. **Diagnostic testing**
   a. **An electrocardiogram** (ECG) may show atrioventricular (AV) node or infranodal conduction abnormalities in approximately 40% of patients.
   b. **Echocardiography**
      (1) **Transthoracic echocardiography is the test of choice** for the diagnosis of VSR. It is important for the clinician to interrogate the area of interest with color Doppler ultrasound. Lowering the Nyquist limit will enable definition and help define the size of the defect. The echocardiogram will also provide insight into the feasibility of utilizing temporizing percutaneous closure devices in this setting.
         (a) **Basal VSR** is best visualized in the parasternal long axis with medial angulation, the apical long axis, and the subcostal long axis.
         (b) **Apical VSR** is best visualized in the apical four-chamber view.
      (2) In some cases, **transesophageal echocardiography** may help in determining the extent of the defect and assessing suitability for potential percutaneous closure.
      (3) Echocardiography may help determine the size of the defect and the magnitude of the left-to-right shunt by comparing flow across the pulmonary valve with flow across the aortic valve.

(4) An assessment of right ventricular (RV) and LV function is key to prognostication and management as they remain important determinants of mortality.

c. **Right heart catheterization.** Pulmonary artery (PA) catheterization with oximetry measurement can help diagnose VSR by demonstrating an oxygen saturation step-up in the RV and PA. The **location of the increase is significant** because there have been case reports of enhanced oxygen saturation in the peripheral PA due to acute MR. Diagnosis involves fluoroscopically guided measurement of the oxygen saturation in the superior and inferior venae cavae; high, mid, and low right atrium (RA); base, mid, and apical levels of the RV; and the PA.

(1) Normal oxygen saturations for these chambers are 64% to 66% in the superior vena cava (SVC), 69% to 71% in the inferior vena cava (IVC), 64% to 67% in the RA, 64% to 67% in the RV, and 64% to 67% in the PA.

(2) An oxygen step-up at the level of the RV is characteristically seen with VSR. A left-to-right shunt across the ventricular septum typically results in a **5% or greater** increase in oxygen saturation between the RA and the RV or PA.

(3) **Shunt fraction is calculated as follows:**

$$Q_p/Q_s = (Sa_{O_2} - Mv_{O_2})/(Pv_{O_2} - Pa_{O_2})$$

In this equation, Q_p is pulmonary flow; Q_s is systemic flow; Sa_{O_2} is peripheral arterial oxygen saturation; Mv_{O_2} is mixed venous oxygen saturation; Pv_{O_2} is pulmonary venous oxygen saturation; and Pa_{O_2} is pulmonary arterial oxygen saturation. Mv_{O_2} is calculated by multiplying the SVC oxygen saturation by three, adding the IVC oxygen saturation, and then dividing the sum by four. Pv_{O_2} is generally assumed to be equal to the peripheral oxygen saturation. **Qp/Qs ≥ 2 suggests the presence of a considerable shunt. In the acute MI setting, any VSR should be considered for urgent surgical repair, regardless of the shunt fraction.**

(4) For a patient with an intracardiac shunt, **cardiac output measured by means of the thermodilution technique is inaccurate; the Fick method should be used.** The key to measurement of accurate systemic flow in the presence of a shunt is that the oxygen content measured in the PA will be abnormally elevated and must be measured in the chamber immediately **proximal** to the shunt (i.e., the RA or the SVC and IVC in the case of VSR). The Fick equation is normally calculated as follows:

$$\text{Cardiac output} = O_2 \text{ consumption}/([Sa_{O_2} - Pa_{O_2}] \times \text{Hgb} \times 1.34 \times 10)$$

d. **Left heart catheterization.** Ventriculography performed after angiography or percutaneous intervention (PCI) may reveal VSR if the suspicion is high. Visualization is best in the left anterior oblique projection with cranial angulation.

e. **Cardiac MRI and CT** are additional imaging modalities that can be utilized. However, the studies are more difficult to perform in hemodynamically unstable patients and do not play a significant role in this setting.

4. **Therapy**

a. **Priority of therapy.** Urgent surgical closure is the treatment of choice (AHA/ACC class I recommendation), especially when the patient's condition is stable because hemodynamic deterioration in this setting is unpredictable. Although initial reports suggested that delaying surgery to allow healing of friable tissue improved surgical mortality, it was likely that lower mortality

was simply a result of selection bias. The mortality rate for patients with VSR treated medically is 24% at 72 hours and 75% at 3 weeks.

b. Vasodilators can decrease left-to-right shunt and increase systemic flow by means of reducing systemic vascular resistance (SVR); however, a greater decrease in pulmonary vascular resistance may actually increase shunting. The vasodilator of choice is **intravenous nitroprusside**, which is started at 0.5 to 0.8 μg/kg/min and titrated to a mean arterial pressure (MAP) of 70 to 80 mm Hg.

c. An **intraaortic balloon pump (IABP)** should be inserted as early as possible as a bridge to a surgical procedure, unless there is marked aortic regurgitation. IABP counterpulsation decreases SVR, decreases shunt fraction, increases coronary perfusion, and maintains blood pressure. After insertion of an IABP, vasodilators can be tailored with hemodynamic monitoring.

d. Surgical therapy

(1) Cardiogenic shock and multisystem failure are associated with high surgical mortality, further supporting earlier operations on these patients before complications develop. Mortality in patients with cardiogenic shock and VSR was 81% in the SHOCK (SHould we emergently revascularize Occluded coronaries for Cardiogenic shocK?) trial registry (1).

(2) Surgical mortality is high among patients with **basal septal rupture associated with inferior MI** (70% compared with 30% in patients with anterior infarcts) because of the greater technical difficulty and the need for concomitant mitral valve repair in these patients, who often have coexisting MR. RV dysfunction due to infarction and/or pressure and volume overload further increases the risk profile of these subjects.

e. Percutaneous therapy. Although surgical closure remains the treatment of choice for VSR, emerging data suggest that **percutaneous closure** may be a viable treatment for high-risk surgical patients and patients in whom surgical closure has failed. In a series of 29 patients treated with percutaneous VSR closure at a median time of 1 day after MI, mortality at 30 days in patients treated with successful device placement was 36% and 86% without and with cardiogenic shock, respectively. At a median follow-up of 730 days, mortality was 36% and 93%, respectively. In our institution, a percutaneous approach is utilized for temporary palliation and as a bridge to surgical repair only in patients considered too high risk to undergo surgery.

B. Acute MR. The incidence of acute MR after MI was 13% to 39% in large registries such as GUSTO-1 and SHOCK. Fibrinolytic agents decrease the overall incidence, but rupture may occur earlier in the post-MI period. MR, even if clinically silent, is a predictor of poor prognosis in MI. Multiple mechanisms may account for acute MR. These include dilation of the mitral valve annulus as a result of LV dilation; papillary muscle dysfunction with a concomitant ischemic regional wall motion abnormality near the insertion of the posterior papillary muscle; and partial or complete rupture of the chordae or papillary muscle. Severe MR caused by papillary muscle rupture is a life-threatening complication of acute MI. Historical reports indicate that papillary muscle rupture occurs between days 2 and 7. However, the SHOCK registry revealed a median time to papillary muscle rupture of 13 hours. Acute severe MR accounted for 7% of the cases of cardiogenic shock and 5% of mortality after acute MI in the SHOCK registry.

1. Clinical presentation

a. Signs and symptoms. These are variable and depend on the anatomy of the papillary muscle involved, the mechanism of valvular dysfunction, and the extent of injury. Complete transection of the papillary muscle is rare and usually results in immediate cardiogenic shock and death. Patients with partial or complete rupture of one or more heads of the papillary muscle lose

significant leaflet support. The resultant torrential MR can result in pulmonary edema and severe respiratory distress.

b. **Physical findings.** A new **pansystolic murmur that is audible at the cardiac apex with radiation to the axilla or the base of the heart suggests acute MR**. In posterior papillary muscle rupture, the murmur radiates to the left sternal border and may be confused with the murmur of VSR or aortic stenosis. The intensity of the murmur does not predict the severity of the MR. The **murmur may often be quiet, soft, or absent** in patients with poor cardiac output or in persons with elevated left atrial pressure due to the rapid equilibration of pressures. Resting tachycardia and mechanical ventilation can also make murmur recognition challenging.

2. **Pathophysiology.** Papillary muscle rupture is **more common with an inferior MI** because the posteromedial papillary muscle receives blood supply from the posterior descending artery, whereas the anterolateral papillary muscle has dual blood supply from the left anterior descending (LAD) and circumflex arteries. Papillary muscle rupture is more likely to occur in patients with a **first MI**, and in many patients the **infarct size may be relatively small. The discordance between the degree of hemodynamic instability and the extent of myocardium in jeopardy is often a clue to the underlying condition**.

3. **Diagnostic testing**
   a. An **ECG** usually shows evidence of recent inferior or posterior MI.
   b. A **chest radiograph** may demonstrate pulmonary edema. In some patients, focal pulmonary edema may be seen in the right upper lobe because of flow directed at the right pulmonary veins.
   c. **Transthoracic echocardiography** with Doppler and color flow imaging is the diagnostic modality of choice.
      (1) The **mitral valve leaflet is usually flail** with severe MR.
      (2) Color Doppler imaging is useful in differentiating papillary muscle rupture with severe MR from VSR after MI.
   d. **Transesophageal echocardiography. Transthoracic echo may underestimate the degree of acute MR**. Rapid equalization of pressure, resting tachycardia, and poor acoustic windows may contribute to this finding. An eccentric jet in this setting should lead to the performance of **transesophageal echocardiography** to quantify the severity and elucidate the mechanism of MR.
   e. **PA catheterization.** Hemodynamic monitoring with a PA catheter may reveal large V waves in the pulmonary capillary wedge pressure (PCWP) tracing. However, patients with VSR may also have large V waves because of increased pulmonary venous return in a normal-sized and normally compliant left atrium. Among patients with severe MR and reflected V waves in the PA tracing, **oxygen saturation in the PA may be higher** than that in the RA, complicating differentiation from VSR. There are two methods for differentiating MR from VSR:
      (1) Prominent V waves in the PA tracing before the incisura are almost always associated with acute severe MR (Fig. 3.1).
      (2) Blood for oximetry is obtained with fluoroscopy to ensure sampling from the main PA rather than distal branches.

4. **Therapy**
   a. **Priority of therapy.** Papillary muscle rupture should be identified early. Patients should receive **aggressive medical therapy** and consideration for **emergent surgical repair**.
   b. **Vasodilator therapy** is beneficial in the treatment of patients with acute MR. **Intravenous nitroprusside** decreases SVR, reduces regurgitant fraction, and increases stroke volume and cardiac output. Nitroprusside is started at 0.5 to 0.8 μg/kg/min and is titrated to an MAP of 70 to 80 mm Hg.

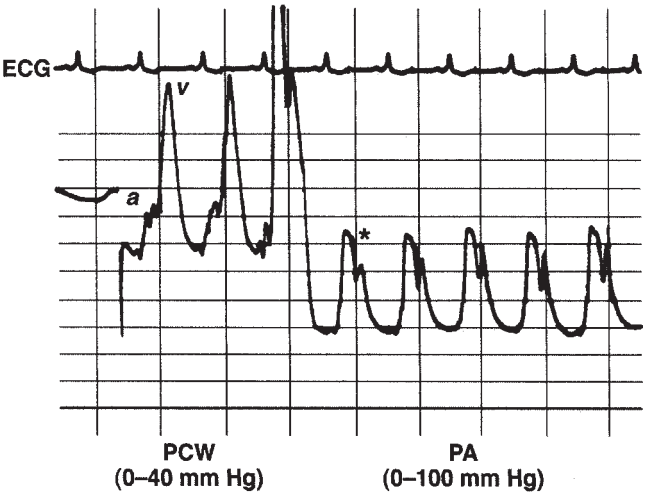

FIGURE 3.1 Giant V waves on the pulmonary capillary wedge (PCW) tracing can be transmitted to the pulmonary artery (PA) pressure, producing a notch (*asterisk*) on the PA downslope. (Adapted from Kern M. *The Cardiac Catheterization Handbook.* 2nd ed. St. Louis, MO: Mosby-Year Book; 1991.)

c. **Intraaortic balloon pump.** Vasodilator therapy is contraindicated in patients with significant **hypotension** and an IABP should be inserted promptly. An IABP decreases LV afterload, improves coronary perfusion, and increases forward cardiac output. Patients with hypotension can often be given vasodilators after insertion of an IABP to improve hemodynamic values.

d. **Percutaneous therapy.** Improvement in hemodynamic values and reduction in MR has been reported after PCI in patients with severe MR caused by papillary muscle ischemia rather than rupture. However, this is a relatively rare clinical presentation. **PCIs have no role in true papillary muscle rupture**.

e. **Surgical therapy should be considered immediately for patients with papillary muscle rupture.**

(1) The prognosis is very poor among patients treated medically. Even though perioperative mortality (20% to 25%) is higher than that for elective surgical treatment, surgical therapy should be considered for every patient.

(2) **Coronary angiography** should be performed before surgical correction, because revascularization is associated with improved short- and long-term mortality.

C. **Ventricular free wall rupture**

1. **Clinical presentation.** The incidence of ventricular free wall rupture after MI in the reperfusion era is < 1%. However, ventricular free wall rupture accounts for approximately **10% of mortality after MI**. In the SHOCK registry, in-hospital mortality associated with ventricular rupture was > 60%. Rupture occurs in the

first 5 days in 50% of patients and within 2 weeks in 90% of patients. Ventricular free wall rupture occurs in the setting of a transmural MI. Risk factors include advanced age, female sex, first MI, and poor coronary collateral vessels.

a. Signs and symptoms

(1) Acute course. With acute rupture, patients develop tamponade, electromechanical dissociation, and sudden death. Sudden onset of chest pain with straining or coughing may suggest the onset of myocardial rupture.

(2) Subacute course. Some patients may have a contained rupture and present subacutely with pain suggestive of pericarditis, nausea, and hypotension. In a large retrospective analysis of post-MI patients, 2.6% of patients were found to have sustained subacute ventricular free wall rupture. Immediate bedside echocardiography may reveal localized pericardial effusion or pseudoaneurysm.

b. Physical findings. Jugular venous distention, pulsus paradoxus, diminished heart sounds, and a pericardial rub suggest subacute rupture. New to-and-fro murmurs may be heard in patients with subacute rupture or pseudoaneurysm.

2. Pathophysiology

a. Ventricular free wall rupture constitutes part of the "early hazard" of thrombolytic therapy. Mortality among patients who receive thrombolytic agents is higher for the first 24 hours and is partially attributable to ventricular rupture. Nevertheless, the overall incidence of ventricular free wall rupture is not greater in patients treated with thrombolytics. The incidence of ventricular free wall rupture is lower in patients treated with primary angioplasty compared with thrombolytics. Rupture most commonly occurs at the anterior or lateral wall, although any wall may be involved.

b. There are **three distinct types of ventricular free wall rupture** (Fig. 3.2):

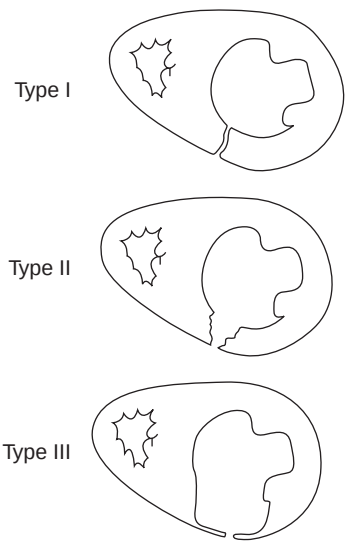

FIGURE 3.2 Morphologic classification of ventricular free wall rupture. (Reprinted with permission from Becker AE, van Mantgem JP. Cardiac tamponade. A study of 50 hearts. *Eur J Cardiol.* 1975;3:349-358.)

(1) **Type I** generally occurs within the first 24 hours and is a slitlike full-thickness rupture characterized by abrupt onset of symptoms (this rupture type increases with thrombolytics).
(2) **Type II** occurs as a result of erosion of the myocardium at the site of infarction. The rupture progresses more slowly and symptoms may be subacute.
(3) **Type III** occurs late and is characterized by expansion of the infarct zone with marked wall thinning and then rupture through the subsequent aneurysmal segment. It has been postulated that type III rupture occurs as a result of dynamic left ventricular outflow tract (LVOT) obstruction and the resultant increased wall stress. Type III rupture occurs less frequently in patients treated with thrombolytics.

3. **Diagnostic testing.** There may not be time for diagnostic testing in the treatment of patients with acute ventricular free wall rupture.
   a. In addition to evidence for new MI, an **ECG** may show junctional or idioventricular rhythm, low-voltage complexes, and tall precordial T waves. A large proportion of patients have transient bradycardia immediately preceding rupture.
   b. **Transthoracic echocardiography** reveals findings of **cardiac tamponade** in patients with a subacute course: RA and RV diastolic collapse, dilated IVC (i.e., IVC plethora), and marked respiratory variation in mitral (> 25%) and tricuspid (> 40%) inflow. Visualization of ventricular free wall rupture may be improved with echocardiographic contrast agents.
   c. **Cardiac catheterization.** Hemodynamic evaluation with a PA catheter may reveal **equalization of the RA pressure, RV diastolic pressure, PA diastolic pressure, and PCWP** consistent with pericardial tamponade. During left heart catheterization, analysis of the arterial waveform may reveal significant **respiratory variations in the systolic blood pressure (pulsus paradoxus)**. Ventriculography performed in the right anterior or left anterior oblique orientation may allow visualization of the rupture.
   d. **Cardiac MRI and CT** can be utilized in hemodynamically stable patients but are usually not available for critical decision making.
4. **Therapy.** Reperfusion therapy has reduced the overall incidence of cardiac rupture.
   a. **Priority of therapy.** The goal is to rapidly identify the problem and perform emergency surgical treatment.
   b. **Medical therapy** has little role in the treatment of these patients, except for aggressive supportive care in anticipation of surgical correction.
   c. **Percutaneous therapy**
      (1) **In the setting of hemodynamic extremis, immediate pericardiocentesis** should be performed in patients with tamponade as soon as the diagnosis is made and while arrangements are being made for transport to the operating room.
      (2) If the index of suspicion is high and the patient's condition is unstable, pericardiocentesis should be attempted without waiting for diagnostic test results.
      (3) An indwelling catheter should be clamped and left in the pericardial cavity and connected to a drainage bag during transfer to the operating room so that continued decompression of the pericardial cavity with recurrent hemodynamic compromise can be achieved.
   d. **Surgical therapy.** Emergency thoracotomy with surgical repair is the definitive therapy and is the **only chance for survival among patients with acute ventricular free wall rupture**.

D. Ventricular pseudoaneurysm (i.e., contained rupture)

1. **Clinical presentation.** Ventricular pseudoaneurysm is **more likely to occur with inferior MI than with anterior MI** (2).
   a. **Signs and symptoms.** Pseudoaneurysms may remain clinically silent and be discovered during routine investigation. However, patients may present with chest pain, dyspnea, recurrent tachyarrhythmia, and sudden cardiac death.
   b. **Physical findings.** Systolic, diastolic, or to-and-fro murmurs related to flow of blood across the narrow neck of the pseudoaneurysm during systole and diastole may be appreciated.
2. **Pathophysiology.** Ventricular pseudoaneurysm is caused by contained rupture of the LV free wall.
   a. The **outer walls of a true ventricular aneurysm are formed by infarcted myocardium and scar**, whereas the **outer walls of a pseudoaneurysm are formed by the pericardium and mural thrombus**. A pseudoaneurysm may remain small or undergo progressive enlargement.
   b. Ventricular pseudoaneurysms communicate with the body of the ventricle through a **narrow neck, the diameter of which is < 50% of the diameter of the fundus**.
3. **Diagnostic testing**
   a. A **chest radiograph** may show cardiomegaly with an abnormal bulge on the cardiac border.
   b. An **ECG** may demonstrate persistent ST-segment elevation, as with true aneurysms.
   c. **Ventriculography is the most reliable method of diagnosis**.
   d. **Echocardiography, cardiac MRI, and cardiac CT** may be utilized in evaluation as well. Echocardiographic contrast agents may increase the diagnostic accuracy.
4. **Therapy.** Spontaneous rupture may occur without warning in approximately one-third of patients with a pseudoaneurysm. **Surgical resection is recommended for patients with or without symptoms, regardless of the size of the pseudoaneurysm, to minimize the risk of death**.

E. Ventricular aneurysm

1. **Clinical presentation.** The incidence of ventricular aneurysm after MI in the reperfusion era is approximately 15% and occurs **more commonly with anterior MI than with inferior or posterior MI**.
   a. **Signs and symptoms**
      (1) **Acute aneurysm.** Acute development of a large ventricular aneurysm can result in severe LV dysfunction and cardiogenic shock. Patients with an acute MI that involves the apex of the LV, particularly those with transmural anteroapical infarcts, are at greatest risk. Acute aneurysms expand during systole. This expansion wastes contractile energy generated by normal myocardium and puts the entire ventricle at a mechanical disadvantage.
      (2) **Chronic aneurysms** persist > 6 weeks after MI, are less compliant than acute aneurysms, and rarely expand during systole. Patients with chronic aneurysms may experience heart failure, ventricular arrhythmias, mural thrombus, and systemic embolism, but they frequently have no symptoms.
   b. **Physical findings.** A dyskinetic segment of the ventricle may be apparent during inspection or may be felt during palpation. The apical impulse may be displaced to the left of the midclavicular line due to cardiac enlargement. An S_3 or S_4 gallop may be appreciated due to LV dilation and stiffening. A systolic murmur of MR may occur due to changes in LV geometry.
2. **Pathophysiology.** Infarct expansion and progressive LV dilation are consequences of absent or ineffective coronary reperfusion. The aneurysmal segment initially consists of necrotic tissue and is later replaced by fibrous scar tissue.

3. **Diagnostic testing**
   a. **ECG**
      (1) **Acute aneurysm.** The ECG reveals evidence of ST-segment elevation MI, which may persist despite evidence of reperfusion.
      (2) **Chronic aneurysm.** ST-segment elevation that persists > 6 weeks occurs in patients with chronic ventricular aneurysms.
   b. **Chest radiography** may reveal a localized bulge in the cardiac silhouette.
   c. **Transthoracic echocardiography** is the diagnostic **test of choice** and accurately depicts the aneurysmal segment. It may also reveal the presence of a mural thrombus. Echocardiography is useful in differentiating a true aneurysm from a pseudoaneurysm. True aneurysms have a wide neck, whereas pseudoaneurysms have a narrow neck in relation to the diameter of the aneurysm.
   d. Cardiac **MRI and CT** may also be utilized to characterize ventricular aneurysm.
4. **Therapy**
   a. **Medical therapy**
      (1) **Acute aneurysm.** LV failure caused by acute aneurysm is managed with **intravenous vasodilators** and **IABP** therapy. **Angiotensin-converting enzyme (ACE) inhibitors** have been shown to reduce infarct expansion and progressive LV remodeling. Because infarct expansion starts early, ACE inhibitors should be initiated within the first 24 hours of the onset of acute MI if blood pressure allows.
      (2) **Chronic aneurysm.** Heart failure associated with chronic aneurysm formation is managed with afterload reduction, namely with ACE inhibitors.
      (3) **Anticoagulation**
         (a) Anticoagulation with **warfarin sodium** should be prescribed (AHA/ACC class I indication) to patients found to have a LV mural thrombus or embolic phenomenon. Patients are initially treated with intravenous heparin with a target partial thromboplastin time (PTT) of 50 to 65 seconds. Warfarin is started simultaneously. Patients should be treated with warfarin to a target international normalized ratio (INR) of 2 to 3 for at least 3 months and then indefinitely if the risk of bleeding is not excessive. Novel oral anticoagulants such as dabigatran etexilate and rivaroxaban have not been approved for this indication at this time.
         (b) It is reasonable (AHA/ACC class IIa indication) to prescribe prophylactic anticoagulation to patients with LV dysfunction and extensive regional wall motion abnormalities that do not have a mural thrombus.
         (c) Patients with MI requiring dual antiplatelet therapy because of PCI need to have the benefits of anticoagulation weighed against an **increase in bleeding risk with triple therapy**.
   b. **Surgical therapy.** Patients with refractory heart failure and/or refractory ventricular arrhythmias should be considered for aneurysmectomy. Surgical resection may be followed by conventional closure or newer techniques (e.g., inverted T closure and endocardial patch) to maintain LV geometry.

F. LV failure and cardiogenic shock. Please refer to Chapter 4 for further discussion.

G. RV failure. Mild RV dysfunction is common after **MI of the inferior or inferoposterior wall**; however, hemodynamically significant RV impairment occurs in only 10% of patients. The **proximal right coronary artery** (RCA) is commonly involved. Extensive, irreversible RV damage is unusual because the RV has lower oxygen requirements due to its smaller muscle mass, is perfused during systole and

diastole, and often receives extensive left to right collateral blood flow. Most patients with RV infarction who survive the acute phase spontaneously improve after 48 to 72 hours.

1. **Clinical presentation**
   a. **Signs and symptoms.** The triad of **hypotension, jugular venous distention, and clear lung fields** is highly specific (but has poor sensitivity) for RV infarction. Patients with severe RV failure have symptoms of a low cardiac output state, including diaphoresis; cool, clammy extremities; and altered mental status. Patients often are hypotensive and oliguric. The use of **nitrates or β-blockers during routine MI treatment may precipitate profound hypotension** and provide the first clue of RV involvement. Table 3.2 lists causes of hypotension among patients with inferior wall MI.
   b. **Physical findings.** Patients with RV failure without concomitant LV failure may have elevated jugular venous pressure (JVP) and a RV S_3 with clear lungs. The combination of JVP > 8 cm H_2O and **Kussmaul's sign** (i.e., failure of JVP to decrease with inspiration) is sensitive and specific for severe RV failure. Elevated right-sided pressures can occasionally result in **right-to-left shunting** through a patent foramen ovale. This should be considered in patients with RV infarction and hypoxia. Table 3.3 lists the clinical findings associated with an RV infarction.
2. **Pathophysiology.** RV involvement depends on the location of the RCA occlusion. Marked dysfunction occurs only if occlusion is proximal to the acute marginal branch. The degree of RV involvement also depends on the presence of left to right collateralization and the extent of diastolic reverse perfusion through the thebesian veins.
3. **Diagnostic testing**
   a. An **ECG** usually shows **inferior ST-segment elevation**. ST-segment elevation in **V_4R** in the setting of suspected RV infarction has a positive predictive value of 80%. RV infarction is also suggested by ST-segment elevation that is greater in lead III than lead II. ST-segment elevation exceeding 1 mm may be seen in V_1 and occasionally in V_2 and V_3 (Fig. 3.3).
   b. A **chest radiograph** is usually normal and there is no evidence of pulmonary congestion.
   c. **Transthoracic echocardiography** is the diagnostic **study of choice** for RV infarction. It may demonstrate RV dilation and severe RV dysfunction and usually shows LV inferior wall dysfunction. It is also useful in

TABLE 3.2 Causes of Hypotension in Patients Presenting with Inferior Myocardial Infarction

Right ventricular infarction
Left ventricular failure
Bradyarrhythmia
Acute severe mitral regurgitation
Ventricular septal rupture
Bezold-Jarisch reflex

TABLE 3.3 Clinical Findings Associated with Right Ventricular Infarction

Hypotension
Elevated jugular venous pressure
Kussmaul's sign
Abnormal jugular venous pressure pattern (y ≥ x descent)
Tricuspid regurgitation
Right-sided S_3 and S_4
Pulsus paradoxus
High-grade atrioventricular block

differentiating RV infarction from other syndromes that can mimic it, such as cardiac tamponade.

d. Pulmonary artery catheterization. Hemodynamic monitoring with a PA catheter usually reveals **high RA pressures with low PCWP**. Acute RV failure results in underfilling of the LV and a low cardiac output state. The PCWP is usually low unless concomitant, severe LV dysfunction is present. In some patients, RV dilation can cause decreased LV performance resulting from ventricular interdependence. As the RV dilates, the septum flattens or bows into the LV and restricts ventricular filling. RA pressure > 10 mm Hg and RA pressure to PCWP ratio ≥ 0.8 strongly suggests RV infarction.

4. Therapy

a. Medical therapy

(1) Fluid administration. Management of RV infarction involves volume loading to increase preload and cardiac output. Some patients may require several liters in 1 hour. **Hemodynamic monitoring is crucial** because overzealous fluid administration in a patient with severe RV dilation can further decrease LV preload and cardiac output. Excessive fluid administration can cause the ventricular septum to shift toward the LV and impede LV filling. The target central venous pressure is approximately 15 mm Hg.

(2) Inotropes. When volume loading fails to increase cardiac output, the use of inotropes is indicated. Administration of **dobutamine** increases cardiac index and RV ejection fraction and is superior to afterload reduction with nitroprusside.

b. Percutaneous therapy

(1) Patients who undergo successful **reperfusion** of the RV have improved RV function and decreased 30-day mortality rates.

(2) AV sequential pacing may markedly improve the condition of a patient with RV infarction and bradyarrhythmia or loss of sinus rhythm. **A longer AV delay of approximately 200 milliseconds and a heart rate of 80 to 90 beats per minute are usually optimal for these patients.**

(3) An IABP may be beneficial, especially in cases of concomitant LV dysfunction.

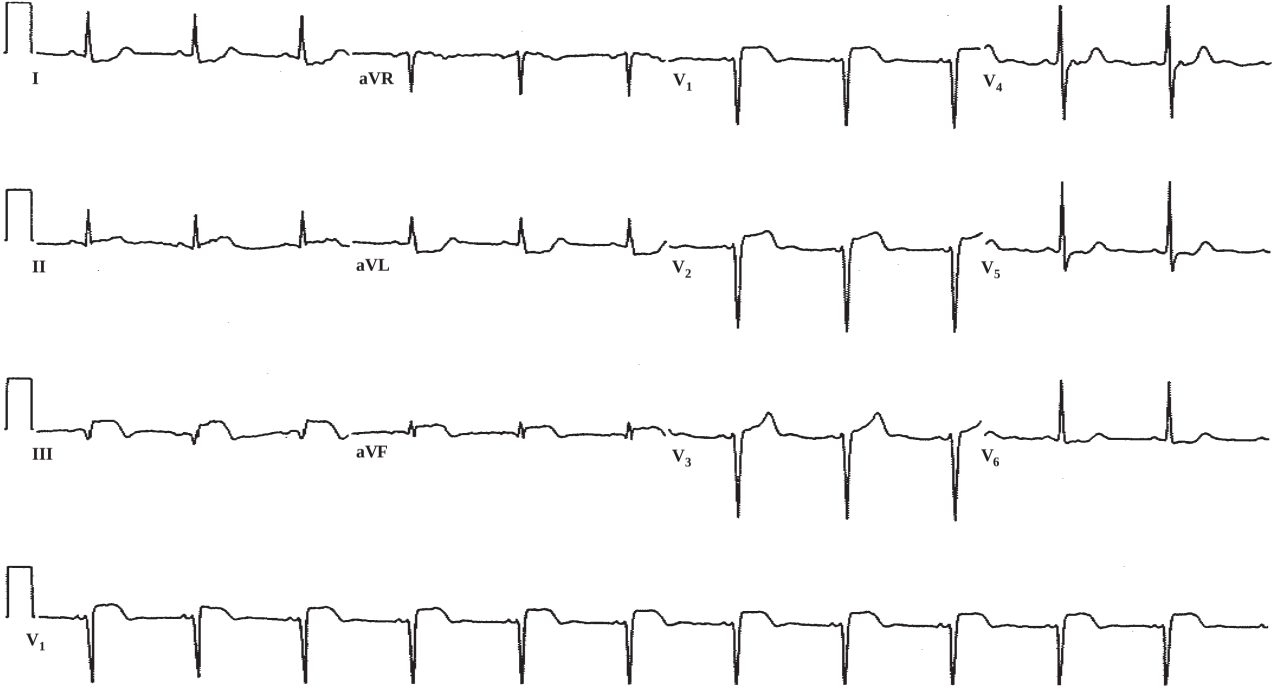

FIGURE 3.3 Electrocardiogram demonstrating acute inferior myocardial infarction with right ventricular involvement.

c. **Surgical therapy**
   (1) **Pericardiectomy** may be considered in the care of patients with refractory shock as it reverses the septal impingement on LV filling.
   (2) An **RV assist device** is indicated in the care of patients who remain in cardiogenic shock despite the foregoing measures.

H. Dynamic LVOT obstruction. Dynamic LVOT obstruction is an **uncommon complication** of acute anterior MI. Although this complication has been cited only in case reports, it may be an underappreciated and underreported complication.

1. **Clinical presentation**
   a. **Signs and symptoms.** Patients may have respiratory distress, diaphoresis, and cool, clammy extremities in addition to the typical signs and symptoms of acute MI. Patients with severe obstruction may appear to be in cardiogenic shock, with severe orthopnea, dyspnea, and oliguria in addition to altered mental status from cerebral hypoperfusion.
   b. **Physical findings** frequently include a new systolic ejection murmur heard best at the left upper sternal border with radiation to the neck. A new systolic murmur can be heard at the apex with radiation to the axilla, as a result of systolic anterior motion (SAM) of the mitral leaflet. An S_3 gallop, pulmonary rales, hypotension, and tachycardia may also occur.
2. **Pathophysiology.** The dynamic LVOT obstruction that may occur as a complication of acute anterior MI is related to compensatory hyperkinesis of the basal and mid segments of the LV. The increased contractile force of these regions decreases the cross-sectional area of the LVOT. The resultant increase in velocity of blood through the outflow tract can produce decreased pressure below the mitral valve and cause anterior mitral valve leaflet displacement toward the septum (i.e., Venturi effect). This results in further outflow tract obstruction and MR. It has been postulated that this complication can play a role in ventricular free wall rupture. LVOT obstruction leads to increased end-systolic intraventricular pressure, which leads to increased stress of the weakened, necrotic infarcted zone.
3. **Diagnostic testing. Transthoracic echocardiography** is the diagnostic test of choice and helps evaluate the hyperkinetic segments, the LVOT obstruction, and the presence of systolic SAM of the mitral leaflet.
4. **Medical therapy** is focused on decreasing myocardial contractility and heart rate while expanding intravascular volume and increasing afterload modestly.
   a. **β-Blockers** should be added slowly and with careful monitoring of the heart rate, blood pressure, and cardiac output.
   b. **Intravenous hydration** should be initiated with several small (250 mL) boluses of normal saline to increase preload and decrease LVOT obstruction and SAM. The patient's hemodynamic and respiratory status should be monitored closely during this therapeutic intervention.

III. ARRHYTHMIC COMPLICATIONS. Arrhythmias are a common complication after acute MI and are associated with significant mortality. Please refer to Chapters 21 through 25 and 41 for further discussion.

IV. EMBOLIC COMPLICATIONS. The contemporary incidence of LV mural thrombus after acute MI is approximately 5% and the incidence of systemic embolism in patients with LV mural thrombus is approximately 13%. The incidence of mural thrombus in patients with a **large anterior wall MI** is approximately 10%. Other factors associated with LV mural thrombus include **decreased LV ejection fraction, wall motion abnormalities, and LV aneurysm**.

A. **Clinical presentation**
   1. **Signs and symptoms.** The most common clinical presentation of an embolic complication is stroke, although patients may have limb ischemia, renal infarction, and intestinal ischemia. Most episodes of systemic embolization occur in the first 2 weeks after acute MI.
   2. **Physical findings.** The physical findings depend on the site of embolism.
      a. Patients with stroke present with neurologic deficits.
      b. Embolism to the peripheral circulation results in limb ischemia and cold, pulseless, and painful extremities.
      c. Renal infarctions may cause hematuria and flank pain.
      d. Mesenteric ischemia causes abdominal pain and bloody diarrhea.
   3. **Diagnostic testing**
      a. **Transthoracic echocardiography** is the initial diagnostic test of choice to evaluate for LV mural thrombus. Echocardiographic contrast agents may increase the diagnostic accuracy.
      b. **Cardiac MRI** has similar specificity but may be more sensitive than echocardiography in the detection of an LV mural thrombus.

B. **Therapy** with anticoagulation is outlined above in the management of ventricular aneurysm.

V. INFLAMMATORY COMPLICATIONS

A. **Early pericarditis.** The incidence of early pericarditis after acute MI is approximately 10%. The inflammation usually develops 24 to 96 hours after MI.
   1. **Clinical presentation.** Early pericarditis occurs in patients with transmural MI. A transient pericardial friction rub may be audible in some patients before symptoms become prominent.
      a. **Signs and symptoms**
         (1) Patients report progressive, severe chest pain that lasts for hours. The **pain is postural**: worse when the patient is supine and alleviated if the patient sits up and leans forward. The pain is usually pleuritic in nature and is worsened with deep inspiration, coughing, and swallowing.
         (2) **Radiation of pain to the trapezius ridge** is nearly pathognomonic for acute pericarditis and does not occur in patients with ischemic pain. The pain may also radiate to the neck and less frequently to the arm or back.
      b. **Physical findings.** The presence of a pericardial friction rub is pathognomonic for acute pericarditis; however, it can be evanescent.
         (1) The rub is best heard at the left lower sternal edge with the diaphragm of the stethoscope.
         (2) The rub has three components: one component each in atrial systole, ventricular systole, and ventricular diastole. In about 30% of patients, the rub is biphasic, and in 10% it is uniphasic.
         (3) The development of pericardial effusion may cause fluctuations in the intensity of the rub, although the rub may still be heard despite substantial pericardial effusion.
   2. **Etiology and pathophysiology.** Pericarditis typically results from an area of localized pericardial inflammation overlying the infarcted myocardium. The inflammation is fibrinous in nature. The development of an evanescent pericardial rub correlates with a larger infarct and hemodynamic derangements.

3. **Diagnostic testing**
   a. An **ECG** is the most useful test in the diagnosis of pericarditis; however, evolving electrocardiographic changes may make the diagnosis difficult for patients who have had MI. Unlike ischemia, in which the changes are limited to a particular territory, pericarditis produces generalized electrocardiographic changes.
      (1) The ST-segment elevation seen with pericarditis is a concave upward or saddle-shaped curve.
      (2) In pericarditis, T waves become inverted after the ST segment becomes isoelectric, whereas in acute MI, T waves may become inverted when the ST segment is still elevated.
      (3) Four phases of electrocardiographic abnormality have been described in association with pericarditis (Table 3.4).
   b. **Chest radiography** is of limited value in the diagnosis of pericarditis.
   c. **Echocardiography** may reveal pericardial effusion, which strongly suggests pericarditis, although the absence of effusion does not rule out the diagnosis.
4. **Therapy**
   a. **Aspirin** is used to manage post-MI pericarditis and doses as high as 650 mg every 4 to 6 hours may be needed.
   b. **Nonsteroidal antiinflammatory agents and corticosteroids should not be used to treat these patients**. These agents may interfere with myocardial healing and contribute to infarct expansion.
   c. **Colchicine** may be beneficial. Colchicine 0.6 mg every 12 hours plus conventional therapy with aspirin decreases symptom recurrence in patients with idiopathic pericarditis.

B. **Late pericarditis (i.e., Dressler's syndrome).** The incidence of Dressler's syndrome is between 1% and 3%. The syndrome occurs 1 to 8 weeks after MI. The pathogenesis is unknown, but an autoimmune mechanism has been suggested.
1. **Clinical presentation.** Patients may present with chest discomfort that suggests pericarditis, pleuritic pain, arthralgia, malaise, fever, pericardial friction rub, elevated leukocyte count, and an elevated sedimentation rate. Echocardiography may reveal a pericardial effusion.
2. **Therapy** is similar to that for early post-MI pericarditis: aspirin, colchicine, and avoidance of nonsteroidal antiinflammatory drugs and corticosteroids. However, if > 4 weeks have elapsed since the MI, nonsteroidal antiinflammatory agents and corticosteroids may be indicated for severe symptoms.

TABLE 3.4 Electrocardiographic Changes of Pericarditis

Stage I	ST elevation, upright T waves
Stage II	ST elevation resolves, upright to flat T waves
Stage III	ST isoelectric, inverted T waves
Stage IV	ST isoelectric, upright T waves

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CHAPTER 4

Michael P. Brunner
Venu Menon

Cardiogenic Shock Complicating Acute Myocardial Infarction

I. INTRODUCTION. Left ventricular (LV) dysfunction is common after acute myocardial infarction (MI), and the severity of dysfunction correlates with the extent of myocardial injury. Cardiogenic shock is estimated to **complicate 3% to 8% of cases of acute MI** (1–3). **The mortality associated with cardiogenic shock in patients with acute MI had historically approached 80%** (1,4). Despite advancements in coronary reperfusion, **the contemporary mortality associated with MI complicated by cardiogenic shock remains at 40% to 70%** (3,5,6). **Prior MI, older age, female sex, diabetes, and anterior infarction** are risk factors for the development of cardiogenic shock after MI.

II. CLINICAL PRESENTATION. Cardiogenic shock is a clinical condition in which **inadequate tissue perfusion is the consequence of cardiac dysfunction**. It is characterized by a **reduction in cardiac output despite adequate filling pressures**. Criteria typically used to define cardiogenic shock include **systolic blood pressure < 90 mm Hg** for at least 30 minutes or need for vasopressor or intra-aortic balloon support to maintain systolic blood pressure > 90 mm Hg, **pulmonary capillary wedge pressure (PCWP) > 15 mm Hg, and cardiac index < 2.2 L/min/kg/m^2**.

A. Symptoms. Patients in cardiogenic shock from LV failure typically present with **respiratory distress**. **Confusion** may occur due to inadequate tissue perfusion.

B. Physical findings

1. **Hypotension, tachycardia, confusion, diminished urine output (<30 mL/h), and cool, mottled, and cyanotic extremities** typically characterize the clinical presentation of cardiogenic shock. Peripheral pulses are often diminished in cardiogenic shock due to decreased pulse pressure **(pulsus parvus)**. In a failing left ventricle the strength of every other beat may alternate, a phenomenon known as **pulsus alternans**. A **dyskinetic segment of the ventricle** may be apparent during inspection or may be felt during palpation. An **S_3 gallop** may be heard in patients with poor LV function.
2. Patients with acute mechanical complications of MI such as ventricular septal rupture, acute mitral regurgitation, ventricular free wall rupture, ventricular pseudoaneurysm, ventricular aneurysm, right ventricular failure, and dynamic outflow tract obstruction may present with additional physical findings as discussed in Chapter 3.
3. Cardiogenic shock due to LV failure may cause pulmonary congestion and inspiratory rales. However, **a significant proportion of patients in the SHOCK (SHould we emergently revascularize Occluded coronaries for Cardiogenic shocK?) registry had no pulmonary congestion** (7). Neither auscultation nor chest radiograph detected pulmonary edema in 28% of the patients.
4. A select group of patients may exhibit **preshock**. This clinical entity is characterized by signs of hypoperfusion with resting tachycardia but not frank hypotension due to a compensatory increase in systemic vascular resistance. On right heart catheterization, these patients have an ineffective cardiac index and are at high risk for in-hospital mortality.

III. RISK STRATIFICATION

A. In the prereperfusion era, **Killip and Kimball** classified **four subsets of patients on the basis of clinical presentation and physical findings** at the onset of MI (4). They reported an 81% in-hospital mortality in patients with cardiogenic shock (Killip class IV). In the fibrinolytic era, the 30-day mortality rate for patients in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries 1 (GUSTO-1) trial that presented with cardiogenic shock was 58% (Table 4.1) (8). The presence of resting tachycardia and pulmonary congestion identifies patients at highest risk even in the current reperfusion era.

B. In a classic study performed in the prereperfusion era, **Forrester** classified **four hemodynamic subsets of patients on the basis of PCWP and cardiac index** (Table 4.2) and determined the associated mortality in acute MI (9).

C. Right heart catheterization hemodynamic parameters including stroke volume, cardiac output, and cardiac index are strong predictors of in-hospital mortality in patients presenting with MI complicated by cardiogenic shock. In the SHOCK registry, the **cardiac power index** (mean arterial pressure × cardiac index/451) in W/m^2 was the strongest independent hemodynamic correlate of in-hospital mortality (10).

D. The SHOCK trial investigators have also published a **severity scoring system** to predict in-hospital mortality in patients with acute MI complicated by cardiogenic

TABLE 4.1 30-Day Mortality Based on Hemodynamic (Killip) Class in the GUSTO-1 Trial

Killip class	Characteristics	Patients (%)	Mortality rate (%)
I	No evidence of CHF	85	5
II	Rales, ↑ JVD, or S_3	13	14
III	Pulmonary edema	1	32
IV	Cardiogenic shock	1	58

CHF, congestive heart failure; ↑, increased; JVD, jugular venous distention.

Adapted from Fox AC, Glassman E, Isom OW. Surgically remediable complications of myocardial infarction. *Prog Cardiovasc Dis.* 1979;107:852-855.

shock (11). Age, shock on admission, clinical evidence of end-organ hypoperfusion, anoxic brain damage, systolic blood pressure, prior coronary artery bypass grafting, anterior MI location, and creatinine > 1.9 mg/dL are the risk factors utilized in a multivariable model. In patients with hemodynamic monitoring, age, end-organ hypoperfusion, anoxic brain damage, stroke work, and left ventricular ejection fraction < 28% are the variables considered.

IV. ETIOLOGY. Table 4.3 outlines the various etiologies of cardiogenic shock complicating acute MI. Patients with acute MI and cardiogenic shock typically have significant **left main** and **severe three-vessel coronary artery disease** and commonly have substantial involvement of the **left anterior descending artery** (12). Autopsy studies have revealed that at least 40% of the LV is affected in most patients presenting with cardiogenic shock complicating acute MI (13). Forty percent of patients have a history of prior MI. If the previous MI was large, even a small, acute MI in a nonanterior location may cause shock. **In the SHOCK registry, LV failure (79%), severe mitral regurgitation (7%), ventricular septal rupture (4%), right ventricular failure (3%), and ventricular free wall rupture (1%) were the leading causes of cardiogenic shock in acute MI** (6). **Bradyarrhythmias and tachyarrhythmias** related to acute MI can also cause cardiogenic shock. **Medications** administered for acute MI such as β-blockers, angiotensin-converting enzyme inhibitors, and morphine can cause iatrogenic shock by inducing hypotension.

TABLE 4.2 Forrester Classification

Subset	PCWP	Cardiac index	Mortality rate
I	<18	>2.2	3
II	>18	>2.2	9
III	<18	<2.2	23
IV	>18	<2.2	51

PCWP, pulmonary capillary wedge pressure.

TABLE 4.3 Causes of Cardiogenic Shock Complicating Acute Myocardial Infarction

Left ventricular failure
Right ventricular failure
Ventricular septal rupture
Acute mitral regurgitation
Ventricular aneurysm
Ventricular free wall rupture
Cardiac tamponade
Dynamic left ventricular outflow tract obstruction
Arrhythmia
Iatrogenic (e.g., β-blocker related)

In the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), early β-blocker use was associated with an increased risk of developing cardiogenic shock, especially when used within the first day of admission (14). **Occult bleeding** resulting from antiplatelet and anticoagulation therapies in acute MI can also result in hypotension and circulatory collapse.

V. PATHOPHYSIOLOGY. Ineffective cardiac output in the setting of cardiogenic shock results in hypotension and tachycardia. A compensatory increase in systemic vascular resistance may occur through peripheral vasoconstriction in an effort to maintain blood pressure and tissue perfusion. However, this classic paradigm has been challenged. Data from the SHOCK registry revealed that many patients with cardiogenic shock instead had low systemic resistance, similar to patients with septic shock (15). It has been postulated that a systemic inflammatory response-like syndrome with a low systemic vascular resistance may be encountered in up to one-fifth of patients with acute MI complicated by cardiogenic shock (16). Figure 4.1 provides an overview of the pathophysiology of cardiogenic shock caused by acute MI and the expansion of the paradigm to include the contribution of inflammatory mediators.

VI. LABORATORY EXAMINATION. Decreased mixed venous oxygen saturation, lactic acidosis, and elevated creatinine and liver transaminase levels are common.

VII. DIAGNOSTIC STUDIES

A. Electrocardiogram. Patients with cardiogenic shock resulting from LV failure usually have extensive electrocardiographic abnormalities consistent with massive infarction, severe diffuse ischemia, or evidence of a large, prior MI. Extensive ST-segment deviations are common. Both ST-elevation MI and non–ST-elevation MI can manifest as cardiogenic shock.

B. Chest radiography may reveal pulmonary congestion.

C. Hemodynamic monitoring with an **arterial line** and **pulmonary artery (PA) catheter** is helpful in monitoring the patient's hemodynamic status and may also identify complications of acute MI, including right ventricular infarction, acute mitral regurgitation, and ventricular septal rupture. In GUSTO-1, mortality among patients ($n = 995$) presenting with acute MI and cardiogenic shock that were managed with

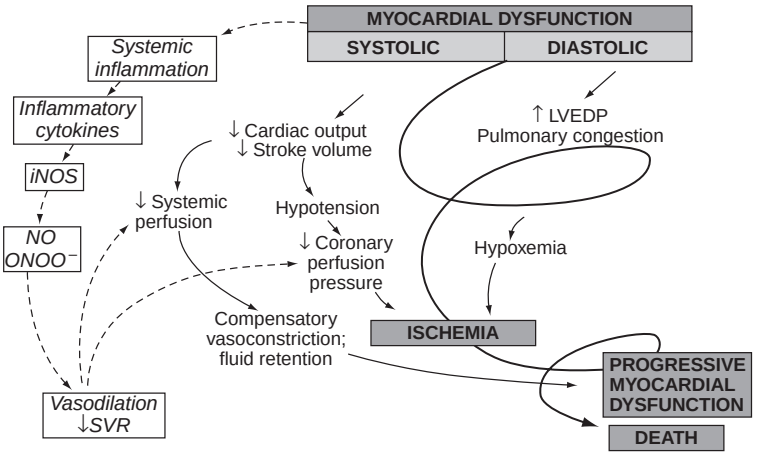

FIGURE 4.1 Expansion of the pathophysiologic paradigm of cardiogenic shock to include the potential contribution of inflammatory mediators. LVEDP, left ventricular end diastolic pressure; NO, nitric oxide; iNOS, inducible nitric oxide synthase; $ONOO^-$, peroxynitrite; SVR, systemic vascular resistance. (Reprinted with permission from Hochman JS, Ohman EM. Pathophysiology. In: *Cardiogenic Shock*. Oxford: Wiley-Blackwell; 2009.)

PA catheters (45.2%) was less than among those (n = 1,406) that were not managed with PA catheters (63.4%) (17). However, the difference in part may be attributable to survivor bias as well as confounding.

D. Transthoracic echocardiography may help determine the etiology of shock as well as the extent of myocardial injury. It can identify the complications of acute MI that contribute to cardiogenic shock. It may also draw attention to additional causes of cardiogenic shock such as aortic dissection, cardiac tamponade, or pulmonary embolism.

VIII. THERAPY

A. Priority of therapy. Early revascularization is critically important in the management of patients presenting with acute MI and cardiogenic shock. The benefits of this strategy were proven in the SHOCK trial (18). Early revascularization saved 13 lives per 100 treated at 1 year compared with a strategy of medical stabilization and delayed revascularization. This strategy should be strongly considered in all patients aged < 75 years in the absence of contraindications; select older patients with good premorbid functional status also derived a similar benefit from this approach. Consequently, patients with acute MI complicated by cardiogenic shock should undergo prompt angiography for defining coronary anatomy. Subsequent revascularization should be guided by clinical presentation, extent of disease, and concomitant valvular function.

B. Percutaneous coronary intervention (PCI) of the infarct-related artery should be attempted emergently in this population. With the adoption of PCI, there has been a marked decline in the mortality of patients with acute MI complicated by cardiogenic shock. Persistence of shock following successful PCI of the infarct-related artery may be an indication to consider multivessel intervention, especially when remote ischemia in noninfarct distributions is suspected.

C. Coronary artery bypass grafting. Emergency surgical revascularization should be considered in the care of patients with severe multivessel disease or substantial left main coronary artery stenosis. It is also indicated when there is a significant concomitant valvular disease that is contributing to hemodynamic instability. Despite sicker patients with more extensive coronary artery disease being referred for coronary artery bypass grafting, mortality due to surgery in the SHOCK Trial and Registry was comparable to that of PCI. However, at many centers, there is reluctance to operate on patients in cardiogenic shock and early reperfusion is generally performed utilizing PCI.

D. Adjunctive support

1. An **intra-aortic balloon pump** (IABP) should be inserted as soon as possible in a patient with cardiogenic shock to ensure hemodynamic stability and protect end-organ perfusion. IABP support reduces afterload, improves cardiac output, and decreases the myocardial oxygen requirement by means of reduction in wall stress. An IABP is also beneficial in MI because diastolic augmentation may increase coronary perfusion in vessels that do not have a flow-limiting stenosis. Contraindications to placement include the presence of significant peripheral vascular disease, aortic dissection, and more than moderate aortic insufficiency. There are no randomized controlled trials to support the placement of an IABP in this setting. One must, however, remember that the IABP was an integral component of the early revascularization strategy observed in the SHOCK trial.
2. **Transvenous pacing.** Patients with inadequate heart rate due to bradyarrhythmia or chronotropic incompetence may require temporary pacing to increase the heart rate and augment cardiac output. **Atrial pacing** maintains atrioventricular synchrony and normal LV contraction and is preferable to ventricular pacing if atrioventricular conduction is intact.

E. Medical therapy

1. **Vasopressors.** Patients may need vasopressors to maintain an effective mean arterial pressure. **Dopamine** is started at 3 μg/kg/min and titrated to a maximal dose of 20 μg/kg/min. **Norepinephrine** is started at 2 μg/min and titrated to a maximal dose of 30 μg/min. Dopamine may be associated with higher mortality in cardiogenic shock than norepinephrine when titrated to maintain an effective mean arterial pressure (19).
2. **Inotropic agents.** Patients with severe LV failure and cardiogenic shock may require temporary support with an inotropic agent.
   a. **Dobutamine** has a positive inotropic action comparable to that of dopamine and may decrease afterload. Dobutamine is started at a dose of 2.5 μg/kg/min and increased to a maximal dose of 40 μg/kg/min.
   b. **Milrinone**, a phosphodiesterase inhibitor with inotropic and vasodilator action, may be beneficial in some patients, especially those with right ventricular dysfunction. Milrinone is given as a 50-μg/kg bolus over 10 minutes, followed by an infusion of 0.375 to 0.75 μg/kg/min. The bolus may be omitted in the care of patients with low blood pressure. Patients without adequate blood pressure may not tolerate milrinone.
   c. **Levosimendan** is an intravenous agent that increases inotropy by binding cardiac troponin C and sensitizing myofilaments to calcium. It is currently approved for use in some countries in Europe and South America but is not available for use in the United States.
3. **Vasodilators** such as **nitroglycerin** and **sodium nitroprusside** can play an important role in the management of post-MI LV failure by means of preload and afterload reduction. However, in the setting of cardiogenic shock, their use may be limited by refractory hypotension.
4. Table 4.4 summarizes the hemodynamic effects of medications used in the management of cardiogenic shock.

TABLE 4.4 Hemodynamic Effects of Medications Used to Manage Cardiogenic Shock

Medication	Preload	Afterload	Inotropy	Chronotropy
Dopamine (3–10 μg/kg/min)	0	–	++++	++
Dopamine (>10 μg/kg/min)	0	+++	+++	+++
Norepinephrine (2–300 μg/min)	0	++++	+	++
Epinephrine (0.05–1 μg/kg/min)	0	+++	+++	+++
Phenylephrine (0.5–15 μg/kg/min)	0	++++	0	–
Dobutamine (2.5–25 μg/kg/min)	–	–	++++	+++
Milrinone (0.375–0.75 μg/kg/min)	– –	– –	+++	+
Nitroglycerin (2.5–300 μg/min)	– – –	–	0	+
Nitroprusside (0.3–10 μg/kg/min)	– – –	– – –	0	+

0, no effect; –, decrease; +, increase.

IX. MANAGEMENT OF REFRACTORY SHOCK AFTER CORONARY REVASCULARIZATION

A. Triage. Patients that remain in cardiogenic shock despite coronary revascularization are best served by transfer to a facility that can provide additional adjunctive hemodynamic therapies. In addition, the facility should have an active cardiac transplant program and full-time availability of interventional cardiology, electrophysiology, cardiothoracic surgery, and neurology services.

B. Decision making. The prognosis for patients that remain in cardiogenic shock after coronary revascularization is extremely poor. However, there are patients that do ultimately recover their LV function and survive. It is often impossible to predict which patients will do well and which patients will succumb to their illness. In our institution, we often consider additional adjunctive hemodynamic therapies as a bridge to decision making.

C. Additional adjunctive hemodynamic support

1. **Percutaneous ventricular assist device (pVAD).** Traditional mechanical circulatory support from an IABP may prove insufficient in certain patients, and consideration may be given to more aggressive support with a percutaneous assist device, especially if shock persists after coronary revascularization.
   - **(a)** The **TandemHeart** (Fig. 4.2) device provides left atrial to femoral artery bypass flow at rates of up to 5.0 L/min with percutaneous access and can serve as a bridge to recovery or more definitive therapy. Limited case series from isolated centers suggest that the TandemHeart device is able to rapidly reverse the terminal hemodynamic compromise seen in patients with severe cardiogenic shock refractory to IABP and/or high-dose vasopressor support (20).
   - **(b)** The **Impella** intracardiac axial flow ventricular assist device can provide either 2.5 or 5.0 L/min support. Our experience has been that the Impella 2.5 L/min device does not provide much additional benefit beyond that of an IABP, whereas the 5.0 L/min device provides substantial adjunctive support. Currently, the Impella 5.0 L/min device requires surgical cut-down for vascular access.

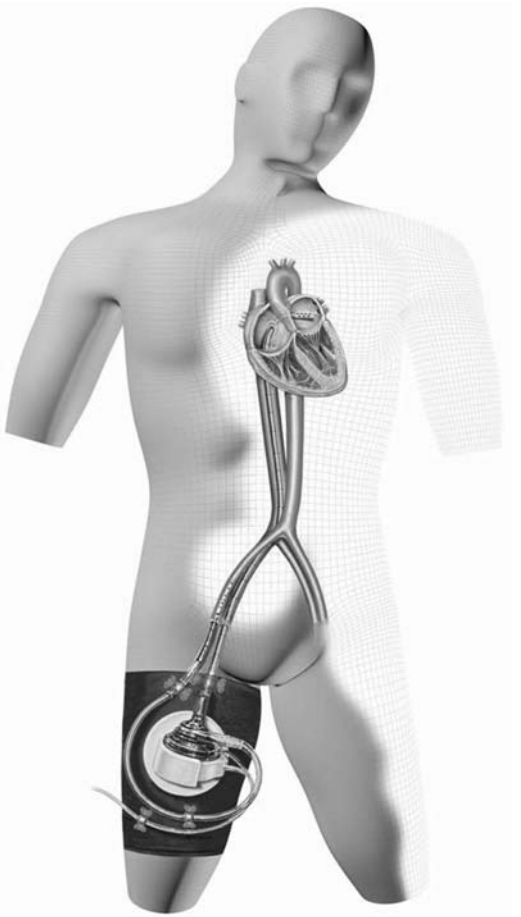

FIGURE 4.2 The TandemHeart percutaneous left ventricular assist device. (Reprinted with permission from CardiacAssist, Inc.)

2. **Extracorporeal membrane oxygenation (ECMO).** ECMO is an established therapy that can be implemented expeditiously in experienced hands. It provides hemodynamic support and as an additional advantage can support oxygenation if the lung function is compromised. We often use ECMO in our institution as a bridge in deciding whether to use more long-term therapy such as an implanted left ventricular assist device (LVAD).
3. **Left ventricular assist device.** Surgical LVAD therapy is often utilized in advanced LV failure as a destination therapy or as a bridge to transplant. In patients presenting with acute MI complicated by cardiogenic shock, LVAD therapy is a consideration. However, other temporizing measures such as pVAD or ECMO are often considered first.

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CHAPTER 5

Willis M. Wu
Venu Menon

Post–Myocardial Infarction Risk Stratification and Management

I. INTRODUCTION. More than 1.5 million patients will have an acute coronary syndrome (ACS) in the United States each year. At least 1 million will have evidence of myocardial infarction (MI), for which mortality and morbidity remain considerable. Although patient outcomes have improved, well-documented therapies are still often underprescribed. Besides identifying patients with MI, the goals of the physician must be to successfully stratify patients according to risk, implement medical interventions, and initiate risk factor modification during the initial hospitalization.

II. RISK STRATIFICATION. Post-MI risk stratification identifies patients at high risk for subsequent cardiovascular events who will benefit from revascularization.

A. Age is the most important predictor of mortality after MI. The average age of patients with first MI is approximately 65 years. Although older patients are at greatest risk and may benefit most, they receive less aggressive treatment compared with younger patients, who have the lowest overall mortality.

B. Assessment of left ventricular (LV) function

1. **LV function** is the second most important predictor of mortality after MI. An inverse relation exists between left ventricular ejection fraction (LVEF) and mortality. Mortality is greatest for patients with an LVEF < 40%.
2. Assessment of LV function is indicated for all patients diagnosed with MI. Echocardiography is often utilized to assess LV function because it is readily available, is relatively inexpensive, and can assess concomitant valvular function as well as mechanical complications of MI. Left ventriculography performed during diagnostic catheterization, or ascertained by radionuclide ventriculography, and cardiac magnetic resonance may also be utilized to evaluate LV function. Availability, local expertise, and cost are important considerations when deciding which procedure to use.

C. Other indicators. Biomarkers are useful in further risk-stratifying patients after MI. **Cardiac troponin** elevation identifies high-risk patients and incremental increases in troponin levels predict higher mortality in patients with ACS. Elevated serum levels of high-sensitivity **C-reactive protein** and **B-type natriuretic peptide may also provide prognostic information**. New **ST-segment changes**, both elevation and depression, portend higher risk of death, heart failure, recurrent ischemia, and severe coronary artery disease (CAD). **Electrical instability**, such as ventricular arrhythmias and atrial fibrillation, are associated with increased risk. Anterior MI, renal insufficiency, poor glycemic control, and anemia are also associated with worse outcomes.

D. Risk models. Various models utilize a combination of the aforementioned risk factors to quantitate a predictive score of patient risk for subsequent cardiac events

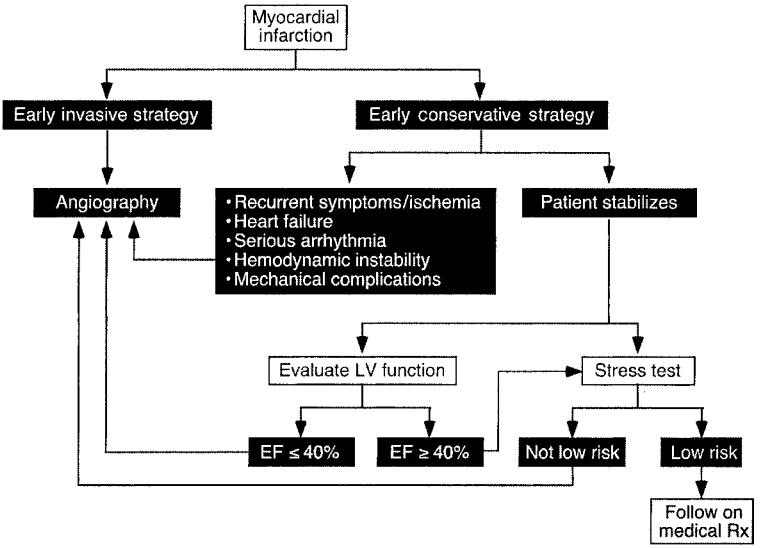

FIGURE 5.1 Post–myocardial infarction risk stratification. LV, left ventricular; EF, ejection fraction.

and mortality. Examples include Thrombolysis in Myocardial Infarction (TIMI), Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio (GISSI), and the Global Registry of Acute Coronary Events (GRACE).

E. Assessment of residual ischemia (Fig. 5.1). The extent of CAD and the presence of residual ischemia are two strong predictors of mortality among patients who have had an MI. For this reason, post-MI patients who have not undergone angiography should undergo stress testing before discharge or shortly thereafter (preferably within 3 to 7 days post-MI). Non–ST-elevation ACS patients at low or intermediate risk who do not have ongoing ischemia or heart failure for at least 12 to 24 hours are also candidates for submaximal stress testing. Because of increasing availability of percutaneous revascularization and growing implementation of a pharmaco-invasive strategy for ST-elevation MI (STEMI) patients who receive thrombolytics, most patients with STEMI undergo angiographic definition. Stable STEMI patients who have not undergone catheterization should undergo stress testing to assess for ischemia 2 to 3 days after the index event.

1. **Submaximal exercise stress testing is optimal for noninvasive risk stratification.** This test provides considerable prognostic information, assesses functional capacity and efficacy of medical therapy, and can guide cardiac rehabilitation after discharge. Patients who achieve at least 3 metabolic equivalents (METs) of the task have a good prognosis. Inability to achieve 3 METs, hypotension during exercise, or marked ST-segment depression or elevation is an indication for coronary angiography.
2. **Stress imaging with echocardiography** or **radionuclide imaging is** recommended in patients who have uninterpretable electrocardiograms (e.g., baseline ST-T changes, LV hypertrophy, intraventricular conduction delays, paced rhythm, or digoxin-related effects). Addition of either imaging modality increases both the sensitivity and specificity of detecting CAD. Patients with

severe resting or exercise-induced LV dysfunction or evidence of extensive ischemia (large perfusion defect, multiple moderate perfusion defects, wall motion abnormalities at low-dose dobutamine or low heart rate, and stress-induced LV dilation) are considered high risk and should undergo coronary angiography.

3. **Dobutamine, adenosine, and dipyridamole** are pharmacologic agents used safely in conjunction with imaging for post-MI stress testing if a patient cannot exercise (see Chapter 6).

III. THERAPY AFTER MI

A. Coronary angiography

1. Indications

a. Coronary angiography is indicated in patients with STEMI as well as in those with non-STEMI who are at high risk for clinical events, recurrent angina or ischemia on medical therapy, or high-risk findings on noninvasive stress testing.

b. An **"early invasive strategy" utilizing coronary angiography** is the preferred approach for patients at high risk for clinical events, including a high-risk score, elevated troponin, congestive heart failure, mechanical complications, and electrical or hemodynamic instability.

c. **Patients with a history of prior revascularization,** either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), should generally be referred for angiography.

d. Coronary angiography to identify potential bypass targets is generally preferred prior to open heart surgery if a patient has surgical anatomy or has a mechanical complication post-MI requiring surgical intervention. Such complications of MI include ventricular septal rupture, LV aneurysm, and acute mitral regurgitation due to papillary muscle rupture. In rare instances when hemodynamic instability precludes angiography, the surgeon may bypass all or selected coronary arteries.

2. **Contraindications.** Catheterization should not be performed on patients who are ineligible for surgical or percutaneous revascularization because of severe comorbid conditions or who do not consent to angiography because of personal preference.

3. **Controversy.** Low-risk, asymptomatic patients who have sustained an uncomplicated MI generally have a good long-term prognosis and may not need to undergo angiography. These patients presumably are those without high-risk features on noninvasive stress testing who will receive aggressive medical therapy and risk factor modification.

4. **PCI.** A new era of PCI therapy that includes novel anticoagulants, antiplatelet agents, and newer generation drug-eluting stents continues to significantly enhance the options and outcomes for post-MI patients undergoing revascularization.

B. CABG after MI can be divided into two categories: emergent and elective.

1. **Emergent CABG.** The indications and management considerations for emergent CABG are discussed in Chapter 1.

2. **Elective CABG.** CABG has been shown to provide a survival benefit for patients with left main (> 50% stenosis) or extensive three-vessel CAD. Surgical revascularization remains preferable for patients with severe LV dysfunction, diabetes, or two-vessel disease with proximal left anterior descending involvement and either high-risk noninvasive stress test results or LV dysfunction. However, the Arterial Revascularization Therapies Study (ARTS) demonstrated no significant difference in mortality, MI, or stroke among patients with multivessel disease and normal to moderately decreased LV function randomized to CABG versus PCI. The Synergy between Percutaneous Coronary Intervention with Taxus and

Cardiac Surgery (SYNTAX) trial evaluated PCI versus CABG for three-vessel or left main disease and nearly 30% of the patients had ACS. This trial demonstrated equivalent cumulative rates of major adverse cardiac or cerebrovascular events in the low (0 to 22) and intermediate (22–32) SYNTAX score patients, though there was a higher rate of adverse events in the high (≥33) SYNTAX score patients who underwent PCI. Target vessel revascularization was higher in the PCI group but stroke rate was higher in the CABG group.

3. **Operative risk.** No prospective, randomized trials have been performed to determine the optimal timing of elective CABG after MI. Most data suggest that CABG 3 to 7 days after MI is associated with a low operative mortality similar to that of elective bypass in patients without recent infarction. **Operative risk increases** among patients with LV dysfunction, advanced age, and multiple comorbid conditions (e.g., diabetes mellitus, chronic obstructive pulmonary disease, and chronic renal insufficiency). Emergent CABG and reoperations on patients with prior open heart surgery are associated with a higher operative mortality. If initiated previously, **clopidogrel** should be held for at least **5 days** prior to surgery and **prasugrel** for at least **7 days** prior to decrease perioperative bleeding risk. Ticagrelor is a reversible inhibitor of the adenosine diphosphate (ADP) receptor $P2Y_{12}$ that is more rapid acting and potent than clopidogrel. There was initial hope that the use of ticagrelor in patients with ACS undergoing urgent bypass surgery could reduce the time from cessation of antiplatelet agents to the time of surgery to just 2 or 3 days, given the more rapid reversal of platelet inhibition. However, results from the Study of Platelet Inhibition and Patient Outcomes (PLATO) demonstrated no difference in TIMI major bleeding or transfusion rates in patients with ACS who stopped clopidogrel 5 days prior to CABG compared with those who stopped ticagrelor 24 to 72 hours before surgery. Bleeding rates were equivalent even when surgery occurred 1 to 3 days after discontinuation of antiplatelets. Therefore, current ACC/AHA guidelines recommend **withholding ticagrelor for at least 5 days** prior to elective open heart surgery.

IV. SECONDARY PREVENTION

A. Smoking cessation is mandatory. Smoking doubles the rate of reinfarction and death after MI, causes coronary artery spasm, and reduces the effectiveness of β-blocker therapy. The risk reduction attributed to smoking cessation is rapid and nearly equals that of post-MI patients who never smoked in only 3 years. Half of all patients who stop smoking after MI will begin smoking again within 6 to 12 months. Many approaches to smoking cessation have been attempted, including pharmacologic therapy, formal smoking cessation programs, hypnosis, and abstinence.

1. **Nicotine substitutes** can be delivered by a variety of vehicles, including transdermal patches, chewing gum, nasal spray, and inhalers. These systems can deliver 30% to 60% of the nicotine of cigarettes. Although nicotine substitutes are not recommended for the acute phase of MI, use of these agents is safe in later phases. Patients who start smoking again should discontinue the use of nicotine substitutes.
2. **Pharmacotherapy. Bupropion** appears to be an effective aid in smoking cessation. The dose is doubled after 3 days and it is then taken twice daily for 7 to 12 weeks. Patients set a goal to stop smoking 1 to 2 weeks into therapy. **Varenicline**, a partial agonist of nicotine receptors, provides nicotine stimulation while blocking cigarette nicotine effects. In a head-to-head trial, varenicline was more effective than bupropion at the 12-week time period, but data suggest no significant difference in rates of abstinence at 1 year. In addition, the FDA issued a communication in 2011 warning that varenicline may increase the risk of cardiovascular events.

3. **Recommendations.** Physicians can aid patients in their effort to stop smoking by using a stepped approach with education and a firm recommendation to quit smoking, devising a plan, and reinforcing the need to quit. Patients who are likely to relapse are older, less educated, or heavy smokers. Formal smoking cessation programs have been shown to have high rates of patient abstinence. Coinhabitants should also stop smoking to increase the likelihood of success.

B. Lipid management

1. **Low-density lipoprotein (LDL).** Most patients with acute MI have abnormal lipid profiles. Several large, secondary prevention trials have demonstrated that lowering of lipids can reduce the incidence of future mortality, reinfarction, and stroke.
   a. **Diagnostic testing.** All patients who have had an MI should have a complete lipid panel (e.g., total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides (TG) determined during hospitalization.
   b. **Diet.** Current ACC/AHA guidelines recommend that all patients should start the AHA step II diet (< 7% of total calories as saturated fat and < 200 mg/d cholesterol). However, adherence to step II diet is low.
   c. **Therapy.** The National Cholesterol Education Program III **(NCEP III)** recommends a target LDL cholesterol level < 100 mg/dL, with a goal of < 70 mg/dL in very high risk patients (e.g., post-MI). Given the results of the Heart Protection Study (HPS), a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, or **statin, should be initiated in all patients irrespective of LDL levels,** owing to potential benefits in addition to lipid lowering, including anti-inflammatory and antithrombotic effects. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) and Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trials demonstrate that **early initiation of aggressive lipid-lowering statin therapy** during an ACS is associated with a **reduction in major cardiovascular events, including death**. Long-term compliance with statins is improved by in-hospital initiation of therapy (77% vs. 40%). Other therapies include bile acid sequestrants, niacin, gemfibrozil, moderate alcohol consumption (particularly red wine), and exercise. These may be used in conjunction with statin therapy.
2. **HDL.** Low HDL cholesterol level is an independent risk factor for MI. The NCEP III recommends an HDL level of at least 40 mg/dL. Consideration can be given to therapy with exercise, niacin, or gemfibrozil. An earlier trial, the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE), compared the use of a cholesteryl ester transfer protein (CETP) inhibitor torcetrapib plus statin versus statin alone and demonstrated increased HDL levels but significantly more adverse cardiovascular events and death from all causes in the torcetrapib group. A more recent trial with a newer drug anacetrapib, the Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib (DEFINE) study, has corroborated the beneficial effect on HDL and LDL but without an increase in cardiovascular side effects. Randomized clinical trials are currently evaluating the role of CETP inhibitors in event reduction.
3. **Triglycerides.** Hypertriglyceridemia may be an independent risk factor for CAD, commonly accompanied by low HDL levels or diabetes. Patients with TG levels above 200 mg/dL should be counseled to achieve non-HDL levels below 130 mg/dL. Fenofibrate or gemfibrozil can be added when TG levels exceed 200 mg/dL, particularly if a low HDL level is concurrent. Fibrates and high doses of statins can increase the risk of myopathy and should be avoided if possible. Omega-3 fatty acids may also be beneficial. Niacin can also be

considered for treatment of hypertriglyceridemia, but results from the recent Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial challenge the efficacy of extended-release niacin in preventing cardiovascular events. In this trial, even though extended-release niacin, when added to statin therapy, was able to decrease TG levels from 164 to 122 mg/dL, decrease LDL from 74 to 62 mg/dL, and raise HDL from 35 to 42 mg/dL, there was no difference in the primary end point (mean follow-up period of 3 years) consisting of a composite of cardiovascular outcomes.

C. Diabetes management. The American Diabetes Association recommends treating glucose levels with the goal of lowering the hemoglobin A1c to below or around 7% with the intent of decreasing micro- and macrovascular events. However, the concept of "intensive" glucose control has been challenged recently by trials demonstrating adverse events associated with this strategy in both the inpatient and outpatient settings. The Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial enrolled critically ill patients in an ICU setting and demonstrated increased mortality in the group randomly assigned to maintaining target glucose levels between 81 and 108 mg/dL versus a target glucose level of 180 mg/dL or less in the comparison group. Likewise, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, a large randomized study of over 10,000 outpatients, was discontinued due to excess mortality in the intensive therapy group assigned to achieve a hemoglobin A1c < 6% compared with the standard therapy group whose target A1c was between 7% and 7.9%.

D. Antiplatelet therapy

1. All patients who have had an MI should take **aspirin** upon presentation and continue indefinitely unless there are absolute contraindications. Aspirin therapy after MI results in a mortality reduction of 25 lives per 1,000 patients treated. Aspirin reduces the rates of vascular mortality, nonfatal stroke, and nonfatal MI. Doses of at least 75 to 162 mg daily are recommended for all patients presenting with ACS. Patients receiving dual antiplatelet therapy (e.g., aspirin plus thienopyridines) have fewer side effects, such as bleeding, at lower aspirin doses.
2. **Thienopyridines** (i.e., ticlopidine, clopidogrel, prasugrel, and ticagrelor) inhibit platelets via adenosine diphosphate antagonism. Clopidogrel is favored over ticlopidine because of a greater incidence of hematologic dyscrasia associated with ticlopidine. In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, the combination of clopidogrel and aspirin was given early for ACS without ST-segment elevation, thereby reducing cardiovascular death, MI, stroke, in-hospital ischemia, and revascularization, with benefit seen at 1 year of therapy. The Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY) trial and Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) demonstrated the benefit of clopidogrel in patients with ST-elevation MI with reperfusion via lytics or PCI. Prasugrel is a more potent and more rapid inhibitor of ADP than clopidogrel, and the Trial to Assess Improvements in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-TIMI (TRITON-TIMI) 38 trial demonstrated a reduction in the composite end point of death from all causes, nonfatal MI, or urgent target vessel revascularization with use of prasugrel compared with clopidogrel. Absolute contraindications to prasugrel use include prior stroke or transient ischemic attack. Patients with elevated risk of bleeding with prasugrel include those above age 75 years and those who weigh < 60 kg, and caution should be taken before prescribing this drug to these patients. Ticagrelor is the first reversible inhibitor of the $P2Y_{12}$ receptor and its action is more rapid and potent than that of clopidogrel. The PLATO trial demonstrated the superiority of ticagrelor over clopidogrel in reducing a composite of death from vascular causes, MI, or stroke in patients with ACS. It was also able

to demonstrate a greater reduction in the secondary end point of death from any cause using ticagrelor versus clopidogrel. Opinions vary as to whether to withhold thienopyridine loading prior to arrival in the catheterization lab in patients who are likely to require CABG because of an increased risk of bleeding and possible delay in surgery. If a patient requires urgent surgery, then clopidogrel and ticagrelor should be held for at least 24 hours to reduce the risk of major bleeding.

3. **Adding other medications,** such as sulfinpyrazone and dipyridamole, has not been shown to be more efficacious than aspirin alone and is not recommended for patients who have had an MI.

E. Warfarin sodium

1. **Patients** with a large anterior MI and LV thrombus treated with warfarin are at decreased risk for embolic stroke. Randomized trials do not exist, but many physicians recommend 6 weeks of warfarin therapy for this group of patients. This may assist in stabilization and endothelialization of the thrombus.
2. Data for the routine use of warfarin in conjunction with aspirin for secondary prevention of reinfarction are conflicting. The Combination Hemotherapy and Mortality Prevention (CHAMP) study and the Coumadin Aspirin Reinfarction Study (CARS) trial found no benefit from the addition of warfarin to standard aspirin therapy. However, combination therapy with aspirin and warfarin decreased infarct-related artery reocclusion and recurrent events in the Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis (APRICOT 2) trial. The routine use of warfarin after MI is currently not recommended except for other established indications for anticoagulation, such as atrial fibrillation or prosthetic heart valves. Patients with concomitant use of dual antiplatelet agents for coronary disease are at significant risk for bleeding and hence this therapy should be used judiciously in these patients.

F. β-Blockers

1. **Indications.** β-Blockers are anti-ischemic, antihypertensive, and antiarrhythmic and they reduce LV wall stress. Mortality reduction results from decreased risk of sudden death, non–sudden cardiac death (SCD), and nonfatal infarction. Overall, the use of β-blockers reduces post-MI events by approximately 20%.
   a. **The beneficial effects of β-blockers are greatest among patients who are at high risk,** such as patients with anterior infarction, complex ventricular ectopy, advanced age, and LV dysfunction. In the COMMIT trial, metoprolol given at presentation significantly reduced reinfarction and ventricular fibrillation in patients with acute MI who were hemodynamically stable; mortality benefit was not significant and this was probably the result of a net hazard during days 0 to 1 for patients presenting with New York Heart Association (NYHA) class III or IV heart failure. Several studies have found that only 50% of patients who sustain an MI actually receive β-blockers. **β-Blockers should be started as soon as possible in hemodynamically stable patients with MI** and should be continued indefinitely. Moderate LV dysfunction and compensated congested heart failure are not contraindications to β-blocker treatment.
   b. **β-Blockers** without intrinsic sympathomimetic activity, such as carvedilol, metoprolol, propranolol, timolol, and atenolol, appear to have the greatest benefit. Reduction in heart rate seems to be important in achieving a mortality benefit.
2. **Contraindications.** Relative contraindications include second- or third-degree heart block, severe asthma, severe chronic obstructive pulmonary disease, severe or decompensated congestive heart failure, heart rate < 60 beats/min, hypotension with systolic blood pressure < 120 mm Hg, or other signs of a low-output state. In patients with heart rate > 100 beats/min, cardiogenic shock should be

ruled out by history and examination before administering β-blockers. Diabetes is not an absolute contraindication; however, the dose of the β-blocker may have to be reduced or discontinued if hypoglycemic episodes are frequent or severe.

G. Angiotensin-converting enzyme (ACE) inhibitors

1. **Indications.** Ventricular remodeling can be attenuated by ACE inhibitors, reducing ventricular dilation and development of congestive heart failure. During infarction, the expression of ACE increases within the myocardium. Several large randomized clinical trials have demonstrated that ACE inhibitors reduce mortality. These trials include Survival and Ventricular Enlargement (SAVE), Acute Infarction Ramipril Efficacy (AIRE), and Trandolapril Cardiac Evaluation (TRACE). The greatest benefit was found among patients with large areas of infarction, anterior infarction, and infarction that impaired LV function. **ACE inhibitor therapy should be considered in all patients after an acute MI** in the absence of contraindications. Therapy should be continued indefinitely in the setting of LV dysfunction (ejection fraction [EF] < 40%), heart failure, hypertension, or diabetes, although the ACC/AHA guidelines give class IIa recommendation for indefinite therapy in all patients after MI regardless of LV function or comorbidities. Angiotensin receptor blockers (ARBs) may be substituted if ACE inhibitors are not tolerated. The Valsartan in Acute Myocardial Infarction (VALIANT) trial evaluated post-MI patients with clinical signs of heart failure and low EF (< 35% by echo or angiography or < 40% by radionuclide ventriculography). Even though this study did not support superiority of valsartan therapy, it demonstrated noninferior mortality outcomes between groups treated with valsartan, captopril, or the two combined. However, adverse events including hypotension and medication dose reductions due to renal causes were more frequent in the valsartan and valsartan plus captopril groups. Cough, rash, and taste disturbances were more commonly reported in the captopril group.
2. **Side effects** include cough, worsening renal function, hypotension, and angioedema. Adverse events, especially renal impairment and hypotension, may be worse when ACE inhibitors and ARBs are used concomitantly, as was shown in the Ongoing Telmisartan Alone and in Combination with Rampril Global End Point Trial (ON TARGET) and VALIANT trials.

H. Aldosterone antagonists

1. **Indications.** The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial demonstrated that eplerenone, when added to optimal medical therapy in post-MI patients with an EF of 40% or less, reduced the risk of death from any cause as well as the risk for a combination of death from cardiovascular causes and hospitalization for cardiovascular events. Optimal medical therapy included ACE inhibitors, ARBs, β-blockers, and coronary reperfusion.
2. **Contraindications.** Because of its diuretic property and effect on the renin–angiotensin–aldosterone neurohormonal system, eplerenone should not be used in patients with renal dysfunction (creatinine > 2.5 mg/dL) or hyperkalemia (serum potassium > 5.0 mmol/L).

I. Calcium channel blockers. The preferred agent after ACS is a β-blocker unless truly contraindicated. Calcium channel blockers are reserved for patients with **refractory angina** and not recommended for routine use after MI by the ACC/AHA guidelines. Longer acting preparations should be used if necessary, whereas short-acting dihydropyridine antagonists should be avoided.

1. **Indications.** The use of calcium channel blockers should be limited to patients with refractory angina or rapid atrial arrhythmias or to patients with clear contraindications to the use of β-blockers.
2. **Contraindications.** Calcium channel blockers should be avoided in patients with congestive heart failure or high-degree atrioventricular block after an MI.

Short-acting dihydropyridine antagonists, such as nifedipine, may increase the risk of death or infarction after MI. Short-acting nifedipine may be especially harmful to patients with hypotension or tachycardia and can induce coronary steal or reflex sympathetic activation, which increases myocardial oxygen demand. Verapamil and diltiazem are contraindicated in the care of patients with LV dysfunction or congestive heart failure after MI. These agents may be useful in patients with contraindications to β-blockers who do not have LV dysfunction or congestive heart failure. Few data are available for the effect of the second-generation agents, amlodipine and felodipine, on survival after MI.

J. Estrogen replacement therapy. The Heart and Estrogen/Progestin Replacement Study (HERS) found no benefit from hormone replacement therapy as secondary prevention for coronary disease, as the therapy was associated with an early increase in death and MI. The Women's Health Initiative (WHI) also observed an increased risk of cardiovascular events and breast cancer with hormone replacement therapy. Initiation of estrogen for primary and secondary prevention of cardiovascular disease is not recommended and should be discontinued at the time of MI.

K. Antioxidants. Previous epidemiologic studies suggested that vitamin E, vitamin C, and β-carotene were associated with a lower incidence of CAD, but more recent studies failed to corroborate these findings. The HPS did not demonstrate a mortality or cardiovascular benefit from antioxidant therapy. Several other large randomized trials have failed to show either primary or secondary benefit for other similar vitamin supplementation strategies. The ACC/AHA guidelines, therefore, do not support the use of vitamin C or vitamin E, β-carotene, or folate with or without B_6 and B_{12}, for primary or secondary prevention.

V. PREVENTION OF SCD AFTER MI

A. Risk stratification for SCD

1. **All patients are at risk** for SCD after MI, with the greatest risk encountered during the first year (3% to 5%), most commonly due to ventricular arrhythmias.
2. **Reduced LV function (< 40%)** remains the best predictor of mortality. Measurement of LV function soon after MI may reflect myocardial stunning, so echocardiography should be re-measured again at the time of possible implantable cardioverter defibrillator (ICD) implantation, usually 40 days after MI for primary prevention or 3 months if reperfused after MI, via either PCI or CABG.
3. Many studies have found that patients who have more than six premature ventricular contractions per hour have a 60% relative increased risk for SCD. Patients with ventricular fibrillation or sustained ventricular tachycardia more than 48 hours after MI also are at increased risk. Monomorphic ventricular tachycardia is a manifestation of scar-related reentrant ventricular tachycardia.
4. Various techniques have been tested to identify patients at increased risk for SCD, but none is sensitive enough to be recommended for routine use. Signal-averaged ECG, heart rate variability, QT-interval dispersion, and baroreflex sensitivity are noninvasive tests, with each test having a low (< 30%) positive predictive value. Repolarization alternans (T-wave alternans) appears to have a higher sensitivity and specificity for inducible ventricular arrhythmia during electrophysiologic testing. Still invasive electrophysiologic testing has a low predictive value for future cardiac events. Consequently, **these modalities are not recommended for routine post-MI risk stratification**.

B. Therapy

1. The only medications proven to reduce risk for SCD are **β-blockers**. All patients should receive β-blockers after an MI unless absolutely contraindicated.
2. **Other medications. Amiodarone** has multiple antiarrhythmic effects, but is primarily classified as a class III agent. Trials of amiodarone in the care of

patients who have had an MI with LVEF < 40% have shown conflicting results, although a significant reduction in mortality has not been demonstrated. Amiodarone is still the preferred antiarrhythmic therapy for symptomatic or sustained ventricular arrhythmias in post-MI patients. Lidocaine is sometimes used as an alternative to amiodarone, but it should not be administered without documented ventricular tachycardia. Likewise, the prophylactic use of sotalol after MI has been associated with increased mortality. The use of type IC antiarrhythmic agents (i.e., encainide, flecainide, and propafenone) after MI is contraindicated.

3. **Implantable cardioverter-defibrillator. Early implantation of an ICD after MI has not been shown to be beneficial.** The Defibrillator IN Acute Myocardial Infarction Trial (DINAMIT) found no mortality benefit despite a reduction in arrhythmogenic death when ICDs were implanted within 40 days after MI despite LVEF < 35%. The Immediate Risk-Stratification Improves Survival (IRIS) trial enrolled patients at increased risk for sudden death within 31 days of an MI. Such patients were those with an EF = 40% and a heart rate > 90 beats/min or those with evidence of nonsustained ventricular tachycardia on ECG or holter monitor, or both. Overall mortality was not reduced in those in whom an ICD was implanted compared with the group treated with medical therapy. On the contrary, the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) investigators and others demonstrated a survival benefit in patients with LV dysfunction and previous MI receiving a prophylactic ICD (see Chapter 23). The Multicenter Unsustained Tachycardia (MUST) trial noted improved survival with ICD implantation in patients who had inducible ventricular arrhythmias with electrophysiologic (EP) study. Therefore, class I indications for ICD therapy post-MI include patients with ischemic cardiomyopathy EF < 35% with NYHA class II or III symptoms at least 40 days post-MI, ischemic cardiomyopathy EF < 30% with NYHA class I symptoms at least 40 days post-MI, and ischemic cardiomyopathy EF < 40% with inducible ventricular fibrillation or sustained ventricular tachycardia on EP study. Patients who undergo either percutaneous or surgical revascularization after MI should have an assessment of LV function after 3 months to help determine the appropriateness of ICD implantation.

VI. THERAPY AND PREVENTION AFTER HOSPITAL TREATMENT

A. **Cardiac rehabilitation programs** seek to improve the biopsychosocial aspects of patients after MI by addressing the benefits of exercise, weight loss, proper diet, smoking cessation, and good mental health. Both randomized data and meta-analyses have demonstrated a mortality benefit associated with cardiac rehab in patients after MI.

1. Formal rehabilitation programs use **exercise and patient education** to help patients modify their lifestyles. The benefits of cardiac rehabilitation include improvement in a patient's commitment to treatment, increased functional capacity, and reduced likelihood of readmission for recurrent ischemia. The **social support** offered is associated with a 25% reduction in both cardiac and all-cause mortality. Depression after MI is common, and patients must be screened during follow-up. Depression is also an independent risk factor for mortality, possibly by decreasing commitment to therapy and exercise. There are limited data regarding the safety and efficacy of antidepressant medications in the post-MI setting. In a small study, sertraline was found to be safe and efficacious for the treatment of major depressive disorder after ACS.
2. **Home programs and family care.** Although cardiac rehabilitation has been shown to have many benefits, less than one-half of patients who have had an MI participate in formal programs. Home programs may be helpful, but they do not provide the social network found in group rehabilitation programs. Because most cardiac arrests after MI occur within 18 months after discharge, family members should be encouraged to learn basic cardiopulmonary resuscitation.

B. Soon after receiving the diagnosis of MI, patients should be counseled regarding **lifestyle modification** to improve weight control, diet, exercise, lipid control, blood pressure, and smoking cessation.

1. Optimal control of hypertension and diabetes should be achieved. The Diabetes Control and Complication Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) determined the need for strict glucose control of insulin and non–insulin-dependent diabetes. Improvement in serum glucose levels decreases the progression of microvascular complications. In both trials, a trend toward decreased microvascular events among the groups that received aggressive treatment was observed.
2. **Weight reduction.** Among adults in the United States, approximately two-thirds of the population, or nearly 130 million persons, are overweight (i.e., body mass index > 25 kg/m^2). Patients should be encouraged to achieve (or maintain) an ideal body weight. All patients should begin an AHA step II diet to achieve lipid goals. Fewer than 50% of patients comply with step II diet, and many patients will need additional pharmacologic therapy to manage hyperlipidemia.
3. **Resumption of daily activities**
   a. At discharge, all patients who have had an MI should receive information regarding resumption of sexual activity, driving, work, and exercise.
   b. **Sexual activity** can be resumed within a week for most patients. Oral phosphodiesterase inhibitors **are absolutely contraindicated in patients on concomitant nitrate therapy. Nitrates should not be used** within 24 hours of sildenafil and 48 hours of tadalafil. Vardenafil has a similar half-life as sildenafil and thus similar precautions should be taken. **Driving** can also be resumed within a week. Most patients who have had an MI who do not have symptoms can **return to work** within 2 weeks.
   c. A patient's performance on an **exercise test** can be used to generate an activity prescription. Patients who can perform at least 5 METs on a submaximal exercise test without marked ST-segment depression or development of angina have a good long-term prognosis.
   d. Because of the lowered oxygen tension in most commercial aircraft (pressurized to 7,500 to 8,000 feet), only patients in stable condition should **travel by plane** within the first 2 weeks after MI. They should carry sublingual nitroglycerin and request a wheelchair for transportation.

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CHAPTER 6

Amar Krishnaswamy
Samir R. Kapadia

Stable Angina

I. INTRODUCTION. Angina pectoris, derived from the Greek "ankhon" (strangling) and the Latin "pectus" (chest), is the term used to describe the syndrome of chest discomfort resulting from myocardial ischemia. Angina is characterized as stable or unstable on the basis of symptom pattern.

A. Anginal symptoms are defined as stable if there is no substantial change in symptoms over several weeks. Symptoms of stable angina can fluctuate from time to time, depending on myocardial oxygen consumption, emotional stress, or change in ambient temperature. In general, the clinical definition of stable angina pectoris closely correlates with the stability or quiescence of an atherosclerotic plaque and decreased clinical risk.

B. Angina is said to be unstable when the symptom pattern worsens abruptly (increase in frequency and duration) without an obvious cause of increased myocardial oxygen consumption. Similarly, the onset of rest angina in a patient for whom angina was previously provoked by some degree of exertion may signal an unstable syndrome.

C. For some patients with new-onset angina that has been stable over a few weeks, clear distinction between stable and unstable angina is not possible. These patients can be considered to be in an intermediate stage between unstable and stable angina.

II. CLINICAL PRESENTATION. For most patients with chest pain, the diagnosis of angina pectoris can be made with careful history taking. The presence of risk factors for coronary artery disease (CAD), such as hypertension, diabetes mellitus, smoking, family history, hyperlipidemia, claudication, and advanced age, increases the likelihood that the chest pain is being caused by myocardial ischemia.

A. Signs and symptoms. The constellation of symptoms characteristic of angina pectoris includes the following four cardinal features.

1. **Location.** Discomfort is commonly located in the retrosternal area with radiation to the neck, shoulders, arms, jaws, epigastrium, or back. In some instances, it involves these areas without affecting the retrosternal area.
2. **Relation to a trigger.** Symptoms are typically triggered by physical activity, emotional stress, exposure to cold, consumption of a heavy meal, or smoking.
   a. Some patients will experience the resolution of angina despite continued exertion, which is known as the walk-through phenomenon. Others may experience the warm-up phenomenon, in which an initial exertion produces angina but a similar second exertion does not reproduce anginal symptoms. These circumstances probably result from the recruitment of collateral coronary flow during the initial episode of ischemia.
   b. Decubitus angina, which is a less common manifestation, occurs with a change in posture and is believed to be caused by a shift in blood volume. Nocturnal angina, which occurs at night, is frequently associated with nightmares and tachyarrhythmias.
3. **Character.** Most patients describe angina as a vague chest discomfort. They describe it as a squeezing, burning, tight, choking, heavy, and occasionally hot or cold sensation. Many patients do not perceive angina as pain per se. Some patients may experience dyspnea, profound fatigue, weakness, lightheadedness, nausea, diaphoresis, altered mental status, or syncope in the absence of any chest discomfort. These symptoms are often referred to as anginal equivalents. Noncardiac causes of chest pain (gastrointestinal, respiratory, musculoskeletal, etc.) may be indicated by fleeting chest pain, unrelenting chest pain not affected by activity, antecedent chest trauma, association with food intake, location inferior to the umbilicus, pleurisy, etc.
4. **Duration.** The chest pain associated with ischemia typically lasts 3 to 5 minutes. Ischemic pain usually does not last more than 30 minutes without causing myocardial infarction (MI). Chest pain triggered by emotional distress tends to last longer than that triggered by exercise. Chest pain that lasts < 1 minute is unlikely to be of cardiac origin, especially when it is not associated with other typical symptoms or findings.
5. It should be stressed that women may present with symptom constellations that may be atypical in location or quality in comparison to the symptoms described by men or manifest as anginal equivalents such as nausea or dyspnea.
6. Chest pain is defined as "typical angina" if it consists of characteristic substernal discomfort, is provoked by stress, and is relieved by rest or nitroglycerin. It is considered "atypical" if it involves two or less of the previously mentioned criteria.
7. **Classification.** Various classifications are available to assess the severity and to predict the outcome among patients with angina. The Canadian Cardiovascular Society classification is the most popular one (Table 6.1). Other classification systems include the Specific Activity Scale, the Duke Activity Status Index, and the Braunwald classification.

B. Physical findings. For patients with a history of chest pain, physical examination helps identify risk factors for CAD and occult cardiac abnormalities.

1. **The signs associated with a high risk for CAD** include elevated blood pressure or manifestations of hypertensive vascular disease such as retinal arteriopathy, signs of hyperlipidemic conditions including corneal arcus or xanthelasma, and evidence of carotid or other peripheral vascular disease.

TABLE 6.1 Classification of Angina

CCS class	Definition	Comment
I	Ordinary physical activity does not cause angina	Angina only with extraordinary exertion at work or recreation
II	Slight limitation of ordinary activity	Angina with walking more than two blocks on a level surface or climbing more than one flight of stairs at a normal pace
III	Marked limitation of ordinary physical activity	Walking one to two blocks on a level surface or climbing one flight of stairs at a normal pace
IV	Inability to carry on any activity without discomfort	Angina at rest or with minimal activity or stress

CCS, Canadian Cardiovascular Society.

2. **Physical examination** performed during an episode of chest pain may reveal rales, an S_3 or S_4 gallop, or a systolic murmur from ischemic mitral regurgitation, all of which generally disappear with resolution of symptoms.

C. Baseline electrocardiogram (ECG)

1. A baseline ECG is **useful for the initial screening** of CAD, although about 60% of patients with chest pain have a normal ECG. Presence of a Q wave or persistent ST depression is associated with an unfavorable outcome. The ECG can also demonstrate other abnormalities, such as left ventricular (LV) hypertrophy, bundle branch block, and preexcitation syndromes.
2. Information obtained from the ECG is **useful in the assessment of chest pain** and helps to stratify patients who are at risk for an adverse event.
3. ECG at the time of chest pain can also **help identify the cause of the chest pain**. Transient changes in the T-wave, ST-segment, or conduction patterns point toward a cardiac source of the chest pain. A normal ECG does not exclude ischemia as being the etiology of chest pain.

III. DIAGNOSTIC TESTING. For a patient with stable CAD, investigations are aimed at risk stratification and management of symptoms and unfavorable outcomes.

A. Stress testing. The basic principle of stress testing is to provoke ischemia or produce coronary vasodilation, followed by functional assessment with different systems to detect ischemia. Stress tests can be categorized according to the methods used to provoke and detect myocardial ischemia. The sensitivity and specificity of each test to identify coronary stenosis vary according to the study population, definition of disease, definition of a positive test result, protocol used for the stress testing, and experience of the interpreter. The following is a brief overview of noninvasive cardiac testing. **For a thorough discussion on noninvasive imaging and stress modalities, please refer to the specific chapters**.

1. **Methods to induce ischemia.** Exercise is the most physiologically sound and useful method for inducing ischemia. An exercise test is considered adequate if 85% or more of age-predicted maximum heart rate (220 – age) is achieved. Exercise testing provides an objective assessment of functional capacity, which provides useful prognostic information. Pharmacologic testing, with dobutamine or adenosine/adenosine derivatives (i.e., dipyridamole), can be used for patients who cannot exercise adequately.

2. **Methods to assess ischemia**
   a. **Stress ECG.** Exercise ECG provides useful diagnostic information about the patients with normal baseline ECGs who are at intermediate risk for CAD. Stress ECG is also used to create an exercise prescription in patients with stable angina. The sensitivity and specificity of stress ECG are poor among patients with an abnormal baseline ECG, LV hypertrophy, ventricular pacing, left bundle branch block (LBBB), or intraventricular conduction disturbance and among patients taking digitalis or other medications that affect conduction and depolarization. Electrocardiographic changes during dipyridamole or adenosine infusion have high specificity but poor sensitivity. Electrocardiographic changes during dobutamine infusion have sensitivity and specificity similar to those of exercise ECG.
   b. **Echocardiographic imaging.** Stress echocardiography is an economical test with good specificity for identifying the location and extent of ischemic territories. This is assessed by the induction of regional wall motion abnormalities with stress or dilation of the left LV cavity with stress (which may indicate global ischemia). If the patient is unable to exercise, a dobutamine stress test can be performed. A biphasic response with dobutamine, in which contractility initially increases with lower doses of dobutamine and then decreases with higher doses, is diagnostic of ischemia. Augmentation of contractility in hypokinetic segments may indicate the presence of hibernating myocardium in a specific coronary distribution. At some medical centers, dipyridamole and adenosine stress tests are performed with echocardiographic imaging. This method is less sensitive in detecting underlying CAD. Results of stress echocardiography are difficult to interpret in some patients with a hypertensive response to exercise and in some patients with severe mitral or aortic regurgitation. Preexisting wall motion abnormalities may further complicate image interpretation.
   c. **Radionuclide imaging.** Single-positron emission computed tomography (SPECT) can be performed after injection with thallium 201 or technetium (Tc) 99m–labeled radiopharmaceuticals. Positron emission tomography (PET) can be performed utilizing rubidium 82 or 13N ammonia tracers. PET imaging provides greater spatial resolution and diagnostic accuracy in comparison with SPECT imaging. Injection of fluorine 18–labeled deoxyglucose (FDG) allows assessment of myocardial viability in patients with resting perfusion defects. The sensitivity and specificity of nuclear testing are decreased among patients with severe obesity, balanced three-vessel disease, and LBBB.

B. **Echocardiography** provides useful information in the overall assessment of suspected stable angina.
   1. Regional wall motion abnormalities involving the left ventricle are commonly caused by CAD and may represent resting ischemia or prior MI. Any impairment in LV systolic function, LV hypertrophy, and presence of substantial mitral regurgitation are associated with heightened clinical risk and poor outcome. LV systolic function may guide the choice of medical therapy versus revascularization.
   2. Echocardiography is the test of choice to quantify aortic stenosis or the presence of hypertrophic cardiomyopathy.

C. **Magnetic resonance imaging (MRI)**
   1. Ischemic evaluation using pharmacologic stress (dobutamine or adenosine) and cardiovascular magnetic resonance can also be utilized to evaluate myocardium in jeopardy. MRI uses gadolinium as a contrast medium to evaluate regional wall motion abnormalities and ejection fraction, as well as segmental myocardial perfusion (when using adenosine). MRI can also provide direct visualization of the

coronary arteries, although computed tomography (CT) angiography is much better for this application.

2. Delayed-phase gadolinium imaging also provides information on the location and transmurality of myocardial scar.
3. The weaknesses include increased cost, lack of portability, and unsuitability for use in the growing population of patients with pacemakers and defibrillators.

D. Electron beam computed tomography (EBCT)

1. EBCT is a noninvasive method of obtaining cross-sectional images of the heart and allows quantification of coronary artery calcification. The test is rapid and provides a "calcium score." This test does not provide sufficient detail to accurately quantify and grade stenosis due to atherosclerotic lesions. An increasing calcium score correlates strongly with heightened risk of cardiovascular events and abnormal findings should lead to further risk factor modification and cardiovascular risk assessment.

E. Multidetector computed tomography

1. **Strengths.** Coronary computed tomography angiography (CCTA) allows for the evaluation of the epicardial coronary tree using a noninvasive approach. The sensitivity of CCTA for assessing coronary stenosis approaches 97% with a specificity of 86% when using a 64-slice technology. With technologic advances allowing a greater number of slices to be acquired in current practice, the accuracy of this study is expected to increase. Importantly, the negative predictive value of CCTA is 99%, with an optimal study and appropriate patient selection. Severe coronary artery calcification or previous coronary stent placement may significantly detract from image quality, rendering the evaluation of specific coronary segments uninterpretable. Larger stents may be grossly evaluated for patency but accurate quantification for in-stent restenosis in anatomical locations distal to the left main coronary artery (LMCA) is not always feasible.

F. Coronary angiography

1. **Strengths.** Coronary angiography is the standard for anatomic assessment of coronary arterial stenosis and provides important prognostic information.
   a. Patients with > 75% stenosis involving at least one coronary artery have a lower survival rate than patients with 25% to 50% or < 25% stenosis. Even for mild stenosis, risk for MI is markedly higher than for no stenosis.
   b. The severity of lesions demonstrated with angiography is not predictive of plaque stability; two-thirds of patients with acute MI have stenosis of > 50% diameter at the site of plaque rupture before MI. It is possible, however, to assess plaque instability on the basis of angiographic characteristics or morphologic features of the lesion.
      (1) Eccentric lesions with narrow necks, overhanging edges, or scalloped borders (type II plaques) are more unstable than concentric lesions with smooth borders (type I plaques).
      (2) Lesion roughness (i.e., irregular borders) is predictive of plaque instability and heightens the risk of future infarction.
      (3) The morphologic characteristics of the plaque help in judging the feasibility and risk of percutaneous or surgical intervention.
   c. Ventriculography performed at the time of selective coronary angiography adds an important dimension to risk stratification by providing an index of LV systolic function and regional wall motion characteristics as well as the presence and degree of mitral regurgitation.
2. **Indications.** In the management of stable angina, use of angiography is variable. An American College of Cardiology and American Heart Association (ACC/AHA) task force classified the indications for coronary angiography into three categories. The relevant indications in the context of stable angina are presented in Table 6.2.

TABLE 6.2 Indications for Coronary Angiography in Stable Angina

Class I (general agreement among cardiologists)
Severe anginal symptoms (CCS class III or IV) with optimal medical therapy
Stress testing indicators of high-risk coronary disease
Survivors of sudden cardiac arrest
Symptoms of congestive heart failure with angina
Clinical predictors of severe CAD
Class II (frequently used but controversial)
Symptoms of angina and positive stress test
Inadequate information from noninvasive testing
Severe angina that improves to mild/moderate angina with medical therapy
Anginal symptoms and intolerance of medical therapy
Asymptomatic patients with positive stress test
Patients who are unable to be evaluated noninvasively
Patients with an occupation that involves an unusual degree of risk
Patients suspected of ischemic symptoms caused by nonatherosclerotic coronary disease (i.e., vasculitis and radiation coronary disease)
Suspicion of coronary vasospasm with the need for provocative testing
Suspicion of left main or three-vessel coronary disease
Recurrent hospitalization for chest pain and need for definitive coronary evaluation
Patients with intermediate or high probability of CAD and a desire for definitive diagnosis
Class III (unjustified use of angiography)
Mild symptoms that resolve with medical therapy
Patients who would not undergo revascularization
Patients with low probability of CAD and a desire for definitive diagnosis

CAD, coronary artery disease; CCS, Canadian Cardiovascular Society.

3. **Limitations.** Coronary angiography underestimates plaque burden, possibly because of vascular remodeling and the diffuse nature of the disease. Coronary angiography does not depict intraluminal plaque burden and does not show coronary flow reserve. Adjunctive use of intravascular ultrasonography (IVUS) greatly facilitates the investigation of hazy areas on coronary angiograms, which may be caused by calcium, thrombus, severe eccentric lesion, or dissection. The IVUS can also assess positive and negative remodeling, which has been shown to correlate with stable and unstable syndromes.

G. Intravascular ultrasonography allows visualization of the cross-sectional image of coronary arteries. This modality helps to quantitate plaque area, artery size, and luminal stenosis; assess hazy areas on coronary angiograms, questionable areas of stenosis, and extent of stenosis; and sometimes determine the calcium content of a plaque. Hypodense areas in a plaque may correlate with high lipid content, which may indicate fast-growing or potentially unstable plaque. This information can help

assess the need for and options of therapy. This modality does not, however, have a role in routine evaluation of patients with stable angina, due to the invasive nature of the test.

H. Optical coherence tomography (OCT) is a relatively new intracoronary imaging modality that has better resolution than IVUS but provides less depth. It has been used, thus far, almost exclusively as a research tool, but a number of studies are currently ongoing to establish its clinical utility. Potential contributions of OCT include characterization of plaque, better understanding of stent characteristics (degree of apposition and stent endothelialization, etc.), and arterial remodeling. This technique requires injection of contrast medium during imaging (usually totaling 12 to 20 cc per run) and so may be of limited use in patients with chronic kidney disease.

I. Invasive functional assessment. Invasive assessment of the functional significance of an intermediate stenosis can be made by means of coronary blood flow measurement with intracoronary Doppler ultrasound and direct measurement of a pressure gradient across a stenosis.

1. With the help of a small transducer mounted on a guidewire, coronary blood flow can be measured by means of a fixed sample volume and pulsed Doppler.
   - **a.** In the left coronary artery, most coronary flow occurs during diastole. In normal arteries, a ratio of proximal-to-distal flow velocity approaching 1 is considered normal. In the presence of coronary stenosis, coronary blood flow becomes mainly systolic because the diastolic component of the flow is jeopardized first.
   - **b.** Three indices can help identify physiologically important stenoses:
     - **(1)** Diastolic-to-systolic average peak coronary flow velocity ratio of < 1.8 distal to the obstruction
     - **(2)** A proximal-to-distal average peak coronary flow velocity ratio of > 1.7
     - **(3)** Coronary flow reserve (i.e., increase in coronary flow with adenosine, which is administered after intracoronary nitroglycerin) with a less than twofold increase in peak velocity
2. **Direct measurement of pressure gradients** can be accomplished with a transducer mounted on a catheter. Ratio of mean pressure distal and proximal to the lesion after maximum vasodilation (fraction flow reserve or FFR) of < 0.75 to 0.80 indicates a hemodynamically significant lesion. These techniques supplement angiography in determining the functional significance of an intermediate (30% to 70%) angiographic stenosis. In a group of patients with angiographically intermediate stenosis, the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) investigators were able to demonstrate lower rates of mortality and MI (8.4% vs. 23.9%, $p = 0.02$) with less stent placement when a strategy of FFR-guided (vs. angiography-guided alone) percutaneous coronary intervention (PCI) was pursued.

J. Holter monitoring

1. After MI, increased ventricular ectopy is predictive of increased cardiovascular morbidity and mortality. This association is less important among patients with stable angina without prior MI, and routine Holter testing for risk stratification is not indicated. No medical treatment aimed at suppressing ventricular ectopy has been shown to improve outcome.

IV. THERAPY.

The goals of therapy are to prevent cardiovascular morbidity and mortality and to improve quality of life.

A. Therapeutic options. Medical therapy, PCI, and coronary artery bypass grafting (CABG) have all been shown to control symptoms and improve exercise time to ischemia. In an era of rudimentary medical therapy, CABG has been proven to decrease cardiovascular mortality in specific patient subsets. Although PCI has been shown to improve stable anginal symptoms and improve quality of life, a decrease in mortality has not been proven in randomized controlled trials (RCTs).

B. Pharmacologic therapy

1. Platelet inhibitors

a. The Antiplatelet Trialists' Collaboration was a meta-analysis that included approximately 100,000 patients from 174 trials involving antiplatelet therapy. This data set showed that aspirin (acetylsalicylic acid, ASA) reduced the rate of stroke, MI, and death among high-risk patients, including those with stable angina without previous MI. A recent systematic review confirms that, while optimal dosing is controversial, there is general support in the literature for limiting the dose of ASA to 75 to 81 mg daily. Approximately 5% to 10% of patients with CAD have aspirin resistance, defined as a lack of decrease in platelet function associated with aspirin use. Aspirin resistance has been shown to result in higher thrombotic events in people with peripheral vascular disease. Patients who demonstrate increased platelet reactivity despite aspirin therapy have increased risks for stroke, MI, and vascular death compared with aspirin responders.

b. Among patients with true allergy or intolerance to aspirin, clopidogrel has been shown to decrease the frequency of fatal and nonfatal vascular events in peripheral, cerebral, and coronary vessel diseases.

(1) Clopidogrel is a second-line therapy in patients unable to tolerate aspirin. In high-risk patients with prior cardiac surgery or ischemic events, the use of clopidogrel as monotherapy, or in addition to aspirin, is beneficial. In patients receiving bare-metal stenting (BMS) for stable coronary disease, at least 1 month of dual antiplatelet therapy (DAPT; aspirin 81 mg plus clopidogrel 75 mg daily) is recommended. The use and duration of DAPT with clopidogrel and aspirin in the setting of drug-eluting stent (DES) implantation are currently under intense review, with concerns of very late stent thrombosis (ST) on one hand and studies questioning the benefit of extended duration DAP on the other. The most recent ACC/AHA PCI guidelines recommend 12 months of DAPT in patients undergoing DES, though longer duration may be considered (class IIb) in specific high-risk patient/stent subsets. Clopidogrel is usually well tolerated and has few side effects.

(2) In the initial analysis of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, performed on a large group of patients included with either prior cardiovascular events or multiple cardiovascular risk factors, there was no benefit from the use of DAPT over aspirin alone in preventing MI or death. A prespecified analysis of higher risk patients only (such as those with prior MI) did show a decrease in cardiovascular events for the group receiving clopidogrel in addition to aspirin. This suggests that an appropriate group of patients may benefit from prolonged DAPT.

2. Lipid-lowering agents. Among patients with established CAD, secondary prevention with lipid-lowering therapy, specifically statins, has demonstrated marked reduction in risk for subsequent cardiovascular events. Statins are potent inhibitors of 3-hydroxy-3-methylglutaryl coenzyme reductase (HMG-CoA reductase). They are the most effective medical therapy for lowering levels of low-density lipoprotein (LDL) and have also been shown to upregulate nitric oxide (NO) synthase, decrease expression of endothelin-1 mRNA, improve platelet function, and decrease production of detrimental free radicals; all of these promote normal endothelial function.

a. Indications. The Scandinavian Simvastatin Survival Study (4S), Cholesterol and Recurrent Events (CARE), Long-term Intervention with Pravastatin in Ischemic Disease (LIPID), and Heart Protection Study (HPS) trials have provided convincing evidence that in patients with evidence of cardiovascular

disease with normal or elevated cholesterol levels, statins decrease mortality, the rate of MI and stroke, and the need for CABG.

b. Effectiveness. Recent studies have shown that in patients with stable CAD (treating to new targets [TNT]) or post-acute coronary syndrome (ACS) (PROVE IT-TIMI-22), aggressive lipid lowering to an LDL goal of 70 mg/dL decreases the risks of cardiovascular death, MI, and stroke compared with patients treated to an LDL goal of 100 mg/dL. There is also a suggestion that aggressive statin therapy retards and even results in a mild degree of plaque regression as measured by IVUS.

c. Choice of agents. Statins should be the first line of therapy in patients with CAD. The quantification of lipoprotein(a) [Lp(a)], fibrinogen, apolipoprotein (apo A), and apolipoprotein B_{100} (apo B_{100}) is investigational. Bile acid sequestrants primarily reduce LDL cholesterol and should not be used in patients with triglyceride levels higher than 300 mg/dL, because these agents may exacerbate hypertriglyceridemia. Nicotinic acid reduces LDL and triglyceride levels and is the most effective of the available lipid-lowering medications at increasing high-density lipoprotein (HDL) level. It is also the only agent that lowers Lp(a). Fibric acid derivatives are most effective against hypertriglyceridemia; they raise HDL level modestly and have little effect on LDL. They are the first line of treatment in patients with triglyceride levels higher than 400 mg/dL. ω-3 Fatty acids may also be used to treat hypertriglyceridemia that is refractory to niacin and fibric acid therapy. Agents to raise HDL cholesterol, cholesteryl ester transfer protein inhibitors, are currently undergoing intensive clinical evaluation in RCTs and may provide a beneficial treatment adjunct to statin therapy in the future.

(1) Current evidence supports aggressive lowering of LDL cholesterol levels in patients with established coronary disease, or CAD equivalents, to a goal of 70 mg/dL (class IIa). A level of HDL cholesterol > 45 mg/dL and triglycerides < 150 mg/dL are secondary goals of dietary, lifestyle, and pharmacologic therapies.

(2) The side effects of statin therapy, including myositis and hepatitis, are quite rare. The package inserts recommend liver function test evaluation prior to initiation of therapy (or increase in dose) and 3 months thereafter. Blood tests are not necessary for routine follow-up of patients who are stable on these medications and should only be measured based upon clinical suspicion of an untoward effect.

3. Nitrates (Table 6.3)

a. Mechanism of action. Nitrates decrease cardiac workload and oxygen demand by means of reducing preload and afterload of the left ventricle. They also redistribute blood flow to the ischemic subendocardium by means of decreasing LV end-diastolic pressure, vasodilation of epicardial vessels, and improvement of collateral blood flow to ischemic tissue. In an adjuvant role, nitrates may also be weak inhibitors of platelet aggregation.

b. Evidence for effectiveness. Nitrates can decrease exercise-induced myocardial ischemia, alleviate symptoms, and increase exercise tolerance in patients with stable angina.

(1) Adding nitrates to an optimal β-blocker regimen does not improve frequency of anginal episodes, glyceryl trinitrate consumption, exercise duration, or duration of silent ischemia.

(2) In some small studies, the efficacy of nitrates in reducing anginal episodes was increased with concomitant use of angiotensin-converting enzyme (ACE) inhibitors.

(3) No study has shown survival benefit with the use of nitrates to treat patients with chronic stable angina.

TABLE 6.3 Nitrates

Medication	Route of administration	Each dose	Frequency
Nitroglycerin (glyceryl trinitrate, Nitro-Bid, Nitrostat, and Nitro-Dur)	Sublingual tablet	0.15–0.6 mg	As needed
	Sublingual spray	0.4 mg	As needed
	Sustained-release capsule	2.5–9.0 mg	Every 6–12 h
	Ointment (topical)	0.5–2″ (1.25–5 cm)	Every 4–8 h
	Disk (patch)	1 disk (2.5–15 mg)	Every 24 h
	Intravenous	5–400 μg/min	Continuous
	Buccal tablet	1 mg	Every 3–5 h
Isosorbide dinitrate (Isordil, Sorbitrate, and Dilatrate SR)	Sublingual tablet	2.5–10 mg	Every 2–3 h
	Chewable tablet	5–10 mg	Every 2–3 h
	Oral tablet	10–40 mg	Every 6 h
	Sustained-release tablet	40–80 mg	Every 8–12 h
Isosorbide-5-mononitrate (Imdur and Ismo)	Sublingual tablet	10–40 mg	Every 12 h
	Sustained release	60 mg	Every 24 h
Erythrityl tetranitrate (Cardilate)	Sublingual tablet	5–10 mg	As needed
	Tablet	10 mg	Every 8 h

c. **Selection of preparations.** Because nitrates have a fast onset of action, a sublingual tablet or oral spray offers immediate relief of an anginal episode.
   (1) For short-term prophylaxis (up to 30 minutes), nitroglycerin tablets can be used when activities known to precipitate angina are anticipated. Timing and frequency of the doses can be individualized according to the diurnal rhythm of anginal episodes. A nitrate-free interval of about 8 hours is adequate for preventing tolerance.
   (2) Use of long-acting medications and transcutaneous delivery systems improves compliance but still necessitates a nitrate-free interval.

d. **Side effects.** Oral nitrates should be taken with meals to prevent heartburn.
   (1) Headache is common and can be severe. Severity usually decreases with continued use and often can be controlled by decreasing the dose.
   (2) Transient episodes of flushing, dizziness, weakness, and postural hypotension can occur, but these effects are usually abrogated by positioning and by other procedures that facilitate venous return.

e. **Drug interactions**
   (1) Hypotension can occur with the use of other vasodilators, such as ACE inhibitors, hydralazine, or calcium channel blockers. **Concurrent use of PDE5 inhibitors like sildenafil (Viagra) and nitrates can lead to severe hypotension and, therefore, is *absolutely contraindicated*.**

f. **Controversies**
   (1) **Tolerance.** Sustained therapy attenuates the vascular and antiplatelet effects of nitrates. Although the basis for this phenomenon of nitrate tolerance is not completely understood, sulfhydryl depletion, neurohormonal activation, and increased plasma volume are likely involved.

Administration of *N*-acetylcysteine, ACE inhibitors, or diuretics does not consistently prevent nitrate tolerance. Intermittent nitrate therapy is the only way to avoid nitrate tolerance.

(2) **Rebound.** Intermittent use of nitrates is not associated with serious rebound of angina among patients taking maintenance therapy with β-blockers. Dosing to allow for a longer nitrate-free interval is also not associated with rebound.

4. **β-Blockers** (Table 6.4)
   a. **Mechanism of action.** Blocking the β_1-adrenergic receptors in the heart decreases the rate–pressure product and oxygen demand. Decreased tension in the LV wall allows favorable redistribution of blood flow from the epicardium to the endocardium.
      (1) Coronary vasospasm is rare from the β_2-receptor blocking effect, but use of β-blockers should be avoided among patients with known, active vasospasm.
      (2) β-Blockers have a variable degree of membrane-stabilizing effect.
   b. **Evidence for effectiveness.** β-Blockers decrease mortality after MI. The mortality benefit is not proven among patients with stable angina without prior MI, although symptomatic improvement is well documented.
   c. **Side effects.** The most important side effects are related to blockade of β_2-receptors. However, data show that some of the side effects may occur less frequently than previously believed, and potentially lifesaving therapy should be offered to those at greatest risk for adverse events.
      (1) Bronchoconstriction, masking of symptoms caused by hypoglycemic reaction among patients with diabetes, exacerbation of symptoms of peripheral vascular disease, and central nervous system (CNS) side effects such as somnolence, lethargy, depression, and vivid dreaming are well documented. The CNS side effects are thought to be related to the lipid solubility of these compounds.
      (2) Symptomatic bradycardia and precipitation of heart failure are concerns for patients with a diseased conduction system and preexisting heart failure, respectively.
      (3) Decreased libido, impotence, and reversible alopecia can be a problem for some patients.
      (4) β-Blockers adversely alter lipid profile by increasing LDL cholesterol and decreasing HDL cholesterol.
   d. **Drug interactions.** Severe bradycardia and hypotension can occur with concomitant use of some calcium channel blockers.
   e. **Selection of preparations.** Cardioselectivity, lipid solubility, mode of excretion, and frequency of dosing are the main considerations when selecting a particular agent. The major cardiospecific agents (i.e., β1 blockade) include metoprolol, atenolol, bisoprolol, and nebivolol. Of note, nebivolol also induces the endothelial NO pathway and contributes to vasodilation. Intrinsic sympathomimetic activity is not a clinically important factor in the choice of a medication, although benefits in patients with CAD have been decreased with agents having intrinsic sympathomimetic activity.
   f. **Effect on lipids.** The clinical significance of lipid abnormalities associated with β-blockers is unclear. β-Blockers have been associated with a decline in HDL level and a rise in triglycerides level. β-Blockers can improve survival among patients in New York Heart Association (NYHA) class I or II heart failure and angina. The condition of a patient with NYHA class III or IV disease should be stabilized before β-blocker therapy is instituted.
5. **Calcium channel blockers** (Table 6.5)

TABLE 6.4 β-Blockers

Compound	Daily dose (mg)	Frequency	Excretion	Lipid solubility	Intrinsic sympathomimetic activity	Membrane stabilization
Selective β-blockers						
Metoprolol						
Short-acting	50–400	Every 12 h	Liver	Moderate		
Long-acting		Every 24 h			None	Possible
Atenolol	25–200	Every 24 h	Kidney	None	None	None
Acebutolol	200–600	Every 12 h	Kidney	Moderate	Low	Low
Nebivolol	5–40	Every 24 h	Kidney	High	None	
Betaxolol	20–40	Every 24 h	Kidney		Low	
Nonselective β ($\beta_1 + \beta_2$)-blockers						
Propranolol	80–320	Every 4–6 h	Liver			
Long-acting		Every 12 h		High	None	Moderate
Nadolol	80–240	Every 24 h	Kidney	Low	None	None
Timolol	15–45	Every 12 h	Liver	Moderate	None	None
Pindolol	15–45	Every 8–12 h	Kidney	Moderate	Moderate	Possible
Labetalol[a]	600–2,400	Every 6–8 h	Liver	None	None	Possible
Carvedilol[a]						
Short-acting	25–50	Every 12 h	Liver	Moderate	None	Possible
Long-acting	10–80	Every 24 h				

[a]Also a potent α_1-antagonist.

TABLE 6.5 Calcium Channel Blockers

Compound	Each dose (mg)	Frequency	Vasodilation	Sinoatrial node inhibition	Atrioventricular node inhibition	Negative inotrope
Nifedipine	30–120	Every 8 h	5	1	0	1
Nifedipine (Procardia XL)	30–180	Every 24 h				
Diltiazem	30–90	Every 6–8 h	3	5	4	2
Diltiazem (Cardizem CD)	120–300	Every 24 h				
Verapamil	40–120	Every 6–8 h	4	5	5	4
Verapamil (Calan SR and Isoptin SR)	120–240	Every 12 h				
Amlodipine (Norvasc)	2.5–10	Every 24 h	4	1	0	1
Felodipine (Plendil)	5–20	Every 24 h	5	1	0	0
Bepridil (Vascor)	200–400	Every 24 h	4	4	4	5
Isradipine (DynaCirc)	2.5–10	Every 24 h	4	4	0	0
Nicardipine (Cardene)	10–20	Every 8 h	5	1	0	0

0, no activity; 5, most potent effect. Intermediate numbers suggest intermediate potency of effects.

a. **Mechanism of action.** These agents block calcium entry into vascular smooth muscle cells and cardiac cells by inhibiting calcium channels, but they do not affect the regulation of intracellular calcium release. The result is decreased contraction of muscle cells.
   (1) The four types of calcium channels are L, T, N, and P.
   (2) The T-type calcium channels are located in the atria and sinoatrial node and affect the phase I of depolarization.
   (3) The L-type channels contribute to entrance of calcium into the cell during phase III of the action potential.
   (4) The N and P types of channels are present mainly in the nervous system.
   (5) The three main groups of calcium channel blockers are dihydropyridines (e.g., nifedipine), benzothiazepines (e.g., diltiazem), and phenylalkylamines (e.g., verapamil).
   (6) The dihydropyridines bind to the extracellular portion of the L channels at a specific site. They do not bind to the T channels and do not have a negative chronotropic effect. Because of their extracellular site of action, dihydropyridines do not inhibit receptor-induced intracellular calcium release.
   (7) Verapamil binds to the intracellular part of the L channel and inhibits the T channel. Intracellular calcium release is inhibited by verapamil because of its intracellular binding site and reflex sympathetic activation is less effective. Use dependence occurs with verapamil because open channels are needed for transport of the drug into the intracellular binding site. In stable angina, verapamil helps by improving rate–pressure product and by increasing oxygen delivery from coronary vasodilation.

b. **Evidence of effectiveness.** Numerous placebo-controlled, double-blind trials have shown that calcium channel blockers decrease the number of anginal attacks and attenuate exercise-induced depression of ST segments.
   (1) Studies comparing the efficacy of β-blockers and calcium channel blockers in the management of stable angina in which death, infarction, and unstable angina were used as end points showed calcium channel blockers to be as effective as β-blockers.
   (2) Increased mortality caused by short-acting nifedipine among patients with CAD was demonstrated in a retrospective study and meta-analysis. If the use of nifedipine is contemplated, a long-acting preparation in conjunction with β-blocker therapy is the safer approach. The mechanism of increased mortality is unclear, but reflex tachycardia and coronary steal phenomenon are potential explanations.

c. **Side effects.** The most common side effects are hypotension, flushing, dizziness, and headache. Because a negative inotropic effect can precipitate heart failure, the use of calcium channel blockers to treat patients with impaired LV function is relatively contraindicated. Conduction disturbances and symptomatic bradycardia occur with the use of compounds that have a marked inhibitory effect on the sinoatrial and atrioventricular nodes. Bepridil is known to prolong QTc, and QT monitoring is necessary when this medication is used. Lower extremity edema is often seen with the use of dihydropyridine calcium channel blockers and this may necessitate lowering the dose or discontinuation of the medication. The non–dihydropyridine calcium channel blockers are also known to cause constipation.

d. **Drug interactions.** Digitalis levels are increased by the non–dihydropyridine calcium channel blockers verapamil and diltiazem. The use of these drugs is contraindicated in the presence of digitalis toxicity.

e. **Selection of preparations.** Calcium channel blockers have a variable negative inotropic effect.

(1) Amlodipine is most likely to be tolerated by patients with compensated heart failure. In decompensated heart failure, all calcium channel blockers should be avoided. Amlodipine is the only calcium channel blocker approved for angina by the US Food and Drug Administration (FDA).

(2) Patients with conduction disturbances should take agents with minimal effects on the conduction system. Longer acting preparations minimize the risk for precipitation of angina caused by reflex tachycardia.

6. **ACE inhibitors.** The rationale for using ACE inhibitors to manage chronic stable angina comes from post-MI and heart failure trials that demonstrated a significant reduction in ischemic events with the use of ACE inhibitors.
   a. It is possible that ACE inhibitors, by decreasing mainly the preload and, to some extent, afterload, decrease myocardial oxygen demand and help in the management of chronic stable angina. The Heart Outcomes Prevention Evaluation (HOPE) trial in high-risk patients with CAD, stroke, diabetes, and peripheral vascular disease showed that ramipril was associated with a significant reduction in death, MI, and stroke in this population. A recent meta-analysis found that ACE inhibitors reduce the risk of these outcomes even in patients with atherosclerosis who do not have evidence of systolic dysfunction. It is notable that the randomized Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) study evaluating the use of trandolapril in patients with preserved LV function did not find a benefit with respect to death, MI, angina, revascularization, or stroke. Numerous hypotheses to explain these divergent results, including dose effects, difference in medication effects, and the risk level of enrolled patients, have been postulated. Nevertheless, the use of ACE inhibitors is recommended (class I) for patients with abnormal LV function and considered reasonable (class IIa) for patients with normal LV function.
   b. The relative efficacy of different ACE inhibitors for relieving ischemia has not been well studied.
   c. Serious side effects of ACE inhibitors include cough, hyperkalemia, and decreased glomerular filtration rate. They are contraindicated in the care of patients with hereditary angioedema or bilateral renal artery stenosis.
7. **Hormone replacement therapy (HRT).** The lipid profiles of women change unfavorably after menopause. LDL, total cholesterol, and triglyceride levels increase and HDL level decreases. All these changes have an adverse effect on cardiovascular morbidity and mortality. Several large case-controlled and prospective cohort studies suggested that the postmenopausal use of estrogen alone or in combination with medroxyprogesterone acetate has a favorable effect on lipid profile and cardiovascular events. However, both the Women's Health Initiative (WHI) study on primary prevention and the Heart and Estrogen/progestin Replacement Study (HERS) on secondary prevention showed an increased risk of cardiovascular and cerebrovascular events in postmenopausal women receiving HRT. Another randomized trial quantifying coronary atherosclerosis angiographically showed negative results with respect to estrogen use. As a result, it has been postulated that the previously shown benefits might have been caused by the "healthy user" effect, and the use of HRT for primary prophylaxis against cardiovascular events is not recommended.
   a. **Benefits of use.** Although the use of estrogen has shown an increase in cardiovascular events, it is associated with some specific favorable findings. The positive effects of estrogen use include maintenance of normal endothelial function, reduction in levels of oxidized LDL, alteration in vascular tone, maintenance of normal hemostatic profile, a favorable effect on plasma glucose levels, reduction of osteoporotic fractures, and a reduction in menopausal symptoms.

b. **Side effects** include bleeding, nausea, and water retention. Because doses of estrogen are small, these side effects are uncommon. For patients with an intact uterus, routine gynecologic examination is mandatory for cancer surveillance. The risk of breast cancer is also increased with the use of HRT, and routine screening is beneficial.

8. **Antioxidants.** The role of vitamins A, C, and E is unclear in patients with CAD.
   a. The initial observational studies on the role of daily vitamin E supplementation in reducing the risk of cardiovascular events among patients with proven atherosclerotic heart disease appeared promising. However, when vitamin E was tested in a randomized fashion, no benefit in its use was proved. There are also data suggesting that vitamin E may attenuate the effect of statins. Vitamins A, C, and E are not recommended for the secondary prevention of cardiovascular events.
   b. Data are lacking about vitamins A and C. Most of the available information suggests no benefit in taking supranormal doses of these vitamins. Vitamin A does not prevent LDL oxidation, even though it binds to LDL molecules. Because it is water soluble, vitamin C does not bind to the LDL molecule. These two vitamins are not recommended for the prevention of progression of atherosclerosis.
9. **Ranolazine**
   a. Ranolazine has recently been shown to work by inhibiting the late sodium channel in myocytes, which can otherwise remain open in pathologic states such as ischemia and heart failure. By reducing the late sodium entry into myocytes, ranolazine causes reduced sodium-dependent calcium entry into the cytosol. This downstream reduction in intracellular calcium levels is thought to reduce diastolic stiffness, thereby improving diastolic blood flow and reducing ischemia and angina. Earlier studies had suggested that effects of ranolazine were primarily through its impact on fatty acid metabolism; however, the weight of evidence now suggests that late sodium channel inhibition is its primary mechanism.
   b. Numerous randomized studies of ranolazine, with or without background antianginal therapy, have shown a benefit in patients with stable angina with respect to frequency of anginal attacks, exercise duration, time to ST-segment depression on treadmill testing, and use of sublingual nitroglycerin.
   c. **Side effects.** Dizziness, headache, and GI intolerance are the most common side effects noted. Prolongation of the QT interval has been reported, especially in patients with hepatic or liver dysfunction due to decreased metabolism. **Prolonged QT interval** at baseline or during treatment follow-up **is a contraindication** to its use.
   d. **Drug interactions.** Inhibitors of CYP3A4, such as azole antifungals, non–dihydropyridine calcium channel blockers, macrolide antibiotics, protease inhibitors, and grapefruit juice, should not be used concomitantly due to inhibition of ranolazine metabolism.
10. **Newer pharmacologic approaches**
   a. Therapy with direct infusion of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor proteins has been shown to increase collateral blood flow in animal models. Studies are underway to investigate the role of these agents in improving collateral blood flow to the ischemic myocardium of patients with angina. Although early results are encouraging, long-term risks and benefits of such therapy remain largely unknown.
   b. Approaches involving the use of gene therapy to cause overexpression of these endogenous growth factors to control the development of collateral blood vessels have been proposed. These approaches are under investigation.

11. **Enhanced external counterpulsation (EECP)** has become a treatment option for patients with stable angina.
    a. EECP involves the intermittent compression of the lower extremities in an effort to increase diastolic pressure and augment coronary blood flow. Three sets of balloons are wrapped around the lower legs, lower thighs, and upper thighs, with precise cuff inflation and deflation gated with the ECG. The lower cuffs are inflated at the start of diastole, as represented by the beginning of the T wave, and simultaneous deflation of all three chambers is triggered just before systole at the onset of the P wave.
    b. In patients with refractory angina, clinical trials have demonstrated improvements in exercise tolerance, reduction in anginal symptoms, decreased use of nitroglycerin, and improvements in objective measures of ischemia as measured by thallium scintigraphy. These benefits are maintained at 2 years of follow-up.

C. Percutaneous coronary intervention. The effectiveness of PCI to control symptoms in chronic stable angina and to prevent death or MI has been compared with medical management and CABG.

1. **Compared with medical treatment**
    a. The Angioplasty Compared with Medicine (ACME) trial compared PCI with medical therapy in approximately 200 patients with single-vessel and multivessel CADs. Patients with single-vessel CAD showed better symptomatic relief at 6 months with PCI but no difference in mortality or MI. Patients with two-vessel CAD had no significant differences in symptoms, mortality, or MI.
    b. The Medicine, Angioplasty, or Surgery Study (MASS) randomized approximately 200 patients with proximal left anterior descending (LAD) artery disease to medical therapy, PCI, or CABG. This study demonstrated no difference in the primary end point (i.e., death, MI, or refractory angina necessitating revascularization). Patients randomized to CABG had a lower incidence of events compared with the other two groups, driven by a decrease in repeat revascularization procedures.
    c. The Randomized Intervention Treatment of Angina-2 (RITA-2) trial randomized more than 1,000 patients with stable angina to medical therapy or PCI. After 2.7 years of follow-up, the primary end point (i.e., death or MI) was lower in the medically treated group. There was an improvement in angina, exercise capacity, and perceived quality of life in patients who underwent PCI. There was also a higher incidence of revascularization in the medically treated group.
    d. The study on Optimal Medical Therapy (OMT) with or without PCI for Stable Coronary Disease (by the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation [COURAGE] Trial Research group) evaluated patients with severe angiographic disease of one or more vessels, and either classic symptoms or documented ischemia on provocative testing. Compared with aggressive medical therapy, an initial strategy of PCI with BMS did not reduce the primary endpoint of death or major adverse cardiovascular events including symptom relief. Notable limitations to the interpretation of this study include the fact that the OMT group had stringent follow-up to achieve the high rates of medical adherence, one-thirds of patients in the medical therapy group crossed over to PCI (but were included in the OMT group as intention-to-treat analysis), and almost 80% of patients had no or minimal angina. Furthermore, it should be stressed that all patients were enrolled after angiography had been performed.
    e. In a substudy of patients enrolled in COURAGE on the basis of positive stress imaging, investigators found that PCI in addition to OMT was

superior in reducing ischemia than OMT alone. Furthermore, the degree of residual ischemia was related to future risk of death or MI. The adequately powered ISCHEMIA trial has been funded by the National Heart, Lung, and Blood Institute to address this issue.

f. The Occluded Artery Trial (OAT) tested the hypothesis that routine PCI of totally occluded arteries 3 to 28 days after MI in high-risk but asymptomatic patients would improve outcomes. In the 2,166 patients studied, there was no statistically significant difference in long-term cardiac events between the PCI and the medical therapy groups, although the PCI group had more rapid relief of angina.

g. The use of DES in comparison to BMS has significantly decreased the risk of in-stent restenosis and the need for target vessel revascularization, thereby improving quality of life, providing freedom from angina, and reducing the risk of repeat procedures. Acknowledging the slightly greater risk of ST with DES compared with BMS, the absolute risk of ST even with DES is quite low. Therefore, their use in appropriate situations is still highly considered in patients without bleeding issues, upcoming surgery, or financial constraints to long-term antiplatelet therapy.

2. Compared with CABG

a. The Emory Angioplasty versus Surgery Trial (EAST) randomized approximately 400 patients with multivessel disease to PCI or CABG. After 8 years of follow-up, there was no difference in the combined end point of mortality, Q-wave MI, and large thallium perfusion defect. In patients with proximal LAD artery disease or diabetes, there was a nonsignificant trend toward improved survival with CABG.

b. The Bypass Angioplasty Revascularization Investigators (BARI) conducted the largest trial comparing PCI with CABG in the management of multivessel disease. In this trial, there was no difference in survival between patients randomized to PCI or CABG at 7 years of follow-up, although the subgroup of patients with diabetes had a better survival rate with CABG than with PCI (76.4% vs. 55.7%).

c. The Arterial Revascularization Therapies Study (ARTS) randomized 1,200 patients with multivessel disease to CABG or BMS placement. After 1 and 5 years of follow-up, there was no difference in mortality, MI, or stroke. Outcomes were similar for patients with stable and unstable angina. Among diabetic patients, however, mortality was greater for those who received PCI. There was a greater incidence of repeat revascularization in the PCI group, although the use of DES in ARTS 2 (compared with the historic CABG group from ARTS 1) shows a similar 1-year rate of revascularization between PCI and CABG groups.

d. The surgery or stenting (SoS) study compared almost 1,000 patients with multivessel disease in the setting of ACS or non-ACS presentation. There was an increased mortality and need for repeat revascularization in the PCI group, which could not be attributed to a diabetic population.

e. In the BARI 2 Diabetes (BARI 2D) trial published more recently, investigators compared prompt revascularization (PCI or CABG as deemed appropriate) and OMT in a group of patients with type 2 diabetes mellitus and CAD. The primary outcome of death was not significantly different in the two groups, nor was the rate of major cardiovascular events (the major secondary end point including death, MI, and stroke). When stratified by revascularization strategy, patients in the CABG group had greater freedom from major cardiovascular events (77.6% vs. 69.5%, $p = 0.01$); this finding was not significant in patients undergoing PCI. Notably, however, this trial was not designed to compare CABG and PCI as revascularization strategies.

f. The recently reported SYNergy between PCI with TAXus and cardiac surgery (SYNTAX) was a pivotal trial randomizing patients with three-vessel disease or left main trunk (LMT) stenosis to multivessel PCI versus CABG. The primary end point of death, stroke, MI, and repeat revascularization favored CABG (12.3% vs. 17.6%, $p = 0.002$). The secondary end point which included death, stroke, and MI was not different between the two groups (7.7% vs. 7.6%, $p = 0.98$). The primary end point favoring CABG was therefore driven primarily by increased rates of repeat revascularization in the PCI group (13.5% vs. 5.9%, $p < 0.001$), though notably the rate of stroke was also significantly lower in the PCI group (2.2% vs. 0.6%, $p = 0.003$).

g. The other major take-home point of the SYNTAX trial was the formulation of the SYNTAX score, which received a class I indication for evaluation of LMT or multivessel disease in the most recent ACC/AHA PCI guidelines. The SYNTAX score grades coronary anatomy on the basis of lesion location, complexity, and functional impact and is a helpful tool for assessing patients at the individual level when discussing options of CABG versus PCI. In the trial, outcomes were assessed by SYNTAX score tertile: patients with a low (0 to 22) or intermediate (23 to 32) score had no difference between the two modes of revascularization for the primary outcome. In patients with a score > 32, however, CABG was favored for the primary outcome (10.9% vs. 23.4%, $p < 0.001$).

h. In patients with LMT stenosis, guidelines had long recommended CABG as the treatment of choice. However, in the modern era of stent placement, PCI of "unprotected" LMT stenosis has gained favor. The 2011 ACC/AHA PCI Guidelines revised the previous class III recommendation for unprotected LMT PCI to class IIa.

Small studies have shown that the mortality difference between PCI and CABG in similarly matched groups of patients is negligible. Furthermore, recent studies comparing the experience of DES implantation in LMT with BMS placement have shown a marked decrease in the need for repeat revascularization.

i. In the prespecified subgroup of patients undergoing unprotected LMT PCI versus CABG in the SYNTAX trial, the primary outcome was similar between the two groups. As in the main study population, stroke was higher in the CABG group (2.7 vs. 0.3%, $p = 0.009$) and repeat revascularization was higher in the PCI group (11.8 vs. 6.5%, $p = 0.02$). Given the clinical equipoise that surrounds unprotected LMT revascularization, the EXCEL (Evaluation of Xience Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial is currently underway. The investigators plan to randomize 2,500 patients with LMT stenosis and a SYNTAX score < 32 to PCI versus CABG.

j. At present, strong consideration is given to CABG in the group of patients with multivessel disease and diabetes, LV dysfunction, or LMT disease who are able to undergo open heart surgery. In the general population with multivessel or LMT disease, however, there is a paucity of evidence showing a survival advantage to CABG over PCI, and recent trials with modern treatment practices (including DES implantation, aggressive antiplatelet therapy, off-pump coronary artery bypass procedures, and use of arterial grafts) have shown favorable comparisons between the two treatment strategies. For patients who are able to undergo either of the treatments, an educated decision should be made by the patient, the cardiologist, and a cardiac surgeon.

3. **Revascularization methods.** For details of PCI strategy and equipment, please refer **Chapter 65**.

D. Coronary artery bypass grafting

1. **Compared with medical treatment.** Compared with medical treatment, CABG improves the survival rate among patients with high-risk stable angina. The benefit is most profound in patients with three-vessel CAD, impaired LV function, or substantial LMCA stenosis.
   a. This information is derived from the Coronary Artery Surgery Study (CASS), European Coronary Surgery Study (ECSS), and Veterans Administration Cooperative Study (VACS). These trials were completed before generalized awareness grew regarding the benefits of medical management with β-blockers, ACE inhibitors, antiplatelet agents, or lipid-lowering medications.
   b. Surgical techniques have also changed significantly, with greater use of arterial conduits including internal mammary artery (IMA) grafts, minimally invasive surgery, and improved techniques of cardiac tissue preservation and anesthesia.
2. **Venous or arterial grafts.** There are different techniques of CABG. The use of minimally invasive bypass surgery involving the left internal mammary artery (LIMA) in patients with isolated LAD artery stenosis has not shown any difference in the rate of mortality, MI, or stroke in comparison to PCI but has shown a decrease in the need for repeat revascularization. With open sternotomy, in which the use of LIMA is well studied, mammary arterial grafting has better long-term outcome compared with vein graft conduits. Given the success of the (LIMA) graft, other arterial conduits have been used, such as the right internal mammary artery (RIMA), the radial artery, and the right gastroepiploic artery.
   a. Twenty percent of venous grafts are nonfunctional at 5 years and only 60% to 70% are functional after 10 years. In contrast, > 90% of LIMA to LAD artery grafts are patent 20 years after the operation.
   b. **Internal mammary artery** grafts have a better patency rate at 10 years when used for LAD lesions (95%) than for circumflex (88%) or right coronary artery (76%) lesions. The patency rates are higher for LIMA compared with RIMA and for in situ grafts compared with free grafts.
   c. Patient survival is better with an IMA graft than when only saphenous venous grafts are used. This survival benefit persists for up to 20 years.
   d. The use of bilateral IMA grafts appears promising, with evidence that the use of RIMA in addition to LIMA improves survival in comparison to LIMA plus saphenous vein grafting. The use of RIMA is technically difficult, however, and has, therefore, not been widespread.
   e. The radial artery graft was introduced into clinical practice around the year 1970 and initially had mixed results. However, at approximately 1 year, 92% of the grafts are patent and at 5 years 80% to 85% of grafts are open. The right gastroepiploic arterial graft has been in use for approximately 15 years, and a 5-year angiographic patency rates of 92% has been reported.
3. **Previous CABG.** Little information is available on the treatment of patients who have already undergone bypass surgery and have stable angina. Although another bypass operation may be offered to these patients, direct comparison with medical treatment in this patient population has not been made. The use of multiple arterial grafts at the time of first CABG reduces the need for reoperation.
4. **Compared with PCI.** This is discussed in Section **IV.C**.

E. Other forms of revascularization

Percutaneous and intraoperative transmyocardial revascularization are potential treatments for patients with coronary disease not amenable to PCI or CABG. Some reports suggest improvement in symptoms, a decrease in perfusion defects, and improvement in contractile function after these procedures but no survival benefit

has been reported. This procedure should be reserved as palliation for patients with medically refractory angina and no other revascularization option, but it has generally fallen out of favor in recent years.

Promotion of ancillary blood vessels by means of injection of blood vessel–promoting agents such as VEGF at the time of surgical or percutaneous coronary revascularization is currently under investigation. So far, the results of this form of intervention have been mixed. Smaller studies targeting improvement in perfusion and exercise tolerance suggest some benefit in the active treatment group. However, two, somewhat larger, studies have recently been terminated early due to lack of benefit at interim analysis.

F. Lifestyle modification

1. Exercise

a. Rationale. Exercise conditions the skeletal muscles, which decreases total body oxygen consumption for the same amount of workload. Exercise training also lowers heart rate for any level of exertion, which decreases the oxygen demand on the myocardium for any workload. Some evidence shows that higher physical activity and exercise can decrease cardiovascular morbidity and mortality.

b. Recommendation. For secondary prevention, aerobic and isotonic exercises with a goal of achieving a sustained heart rate of approximately 70% to 85% of the maximum predicted heart rate at least 3 or 4 times per week has been shown to improve survival. For beginners, a supervised exercise or rehabilitative program, in which 50% to 70% of maximal predicted heart rate is achieved, is also helpful. Isometric exercises are not recommended because they increase myocardial oxygen demand substantially.

2. Diet. A low-fat diet that includes cereals and grains, skimmed dairy products, fruits and vegetables, fish, and lean meats should be recommended and this is effective in providing cardiovascular risk reduction in patients with CAD. These are also integral components of the "Mediterranean Diet," which has been shown to reduce cardiovascular risk. A multidisciplinary approach to the care of patients with CAD that includes a nutritionist/dietician can be quite helpful in personalizing patients' eating habits.

3. Smoking cessation. Cigarette smoking is associated with progression of atherosclerosis, increased myocardial demand due to an α-adrenergic increase in coronary tone, and adverse effects on hemostatic values, all of which can lead to worsening of stable angina. Smoking cessation decreases cardiovascular risk among patients with established CAD, including patients who have undergone CABG. Physician counseling is the best approach to achieve this goal and adjunctive therapies include nicotine replacement patches, gum, or sprays, or medications such as bupropion and varenicline.

4. Psychological factors. Anger, hostility, depression, and stress are shown to adversely affect CAD. Results of small, nonrandomized trials show that biofeedback and various relaxation techniques can help modify these factors.

V. RECOMMENDED APPROACH TO STABLE ANGINA

A. The following approach is suggested for the treatment of patients with stable angina.

1. It is reasonable to risk stratify patients with stable angina using stress testing with imaging, such as nuclear isotope imaging or echocardiography.

a. LV systolic function should be assessed with echocardiography to guide therapy and to identify patients with moderate LV systolic dysfunction.

b. Patients with small perfusion defects or small wall–motion abnormalities, high threshold for ischemia, normal LV systolic function, and clear symptoms should be treated with medication.

2. If symptoms continue after medical therapy is maximized, angiography should be planned. Coronary angiography should also be performed for patients with evidence of impaired perfusion involving multiple territories, a low threshold for ischemia, and moderate LV systolic dysfunction.
3. **Single-vessel disease.** If a patient has single-vessel CAD that does not involve the LMT or supply a large myocardial territory, medical management with risk factor modification is the appropriate first step.
   a. If patients cannot tolerate medical treatment or have symptoms despite maximum medical therapy, revascularization therapy should be offered.
4. Among patients with **multivessel CAD**, medical treatment remains an alternative for patients who have normal LV systolic function, mild symptoms, and relatively smaller areas of myocardium at risk.
   a. The decision for multivessel PCI versus CABG in this group of patients should be made on an individual basis, taking into consideration the angiographic anatomy, LV function, patient comorbidities, surgical risk, and patient preference.
   b. Any doubt regarding viability of the myocardium at risk should be addressed with appropriate diagnostic studies before revascularization.
5. In patients with "unprotected" LMT stenosis, the previous recommendations of CABG in all patients who are able to undergo surgery have recently been revised. PCI for severe LMT disease may be appropriate in select patients.
6. Regardless of treatment strategy, aggressive risk factor modification, including use of lipid-lowering agents, lifestyle modification, and aspirin therapy, is an essential component of management.

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CHAPTER 7

Gus Theodos

Other Ischemic Syndromes: Silent Ischemia and Syndrome X

SILENT ISCHEMIA

I. INTRODUCTION. Silent ischemia represents an underappreciated manifestation of coronary artery disease (CAD), occurring in up to 20% to 40% of patients with stable and unstable coronary syndromes. It is estimated that 195,000 silent first myocardial infarctions (MIs) occur each year, which assumes that 21% of MIs are silent. By definition, patients are asymptomatic, lacking typical or atypical anginal symptoms. Silent ischemia may be documented by a variety of diagnostic modalities, including resting electrocardiogram (ECG), ambulatory ECG (AECG), nuclear scintigraphy, and echocardiography.

II. CLINICAL PRESENTATION. Patients may be loosely categorized into three groups, collectively representing a continuum of silent ischemia.

A. Type I have **asymptomatic** ischemia with no known CAD history with **asymptomatic** MI patterns. Clinicians may discover evidence of subclinical MI from a resting ECG or a preoperative stress test. In the Framingham study, 12.5% of patients with MI had an unrecognized "silent" infarction. Patients may also present with arrhythmias or sudden death from subsequent scar. These patients are considered to have an ineffective "anginal warning system."

In addition, a subset of this group includes patients with **asymptomatic** ischemia without a history of infarction. Silent ischemia is often discovered by stress tests after referral for aggressive primary screening. This type of screening may occur in patients with diabetes, strong family histories, or a high-risk electron beam computed tomography (EBCT) result. Given the increasingly technological nature of medical culture, the prevalence of these patients is likely to rise. AECG is rarely used as a primary screening modality. The American College of Cardiology and American Heart Association (ACC/AHA) guidelines consider the use of AECG for ischemia monitoring in asymptomatic individuals as a class III recommendation.

B. Type II have **symptomatic** MIs but subsequent **asymptomatic** ischemic syndromes. Ischemia is often missed because of a lack of symptoms. Patients in this category are most often encountered after a positive stress test or the rarely ordered AECG. Type II patients may have an abnormal **pain threshold.**

C. Type III encompass the largest patient population with silent ischemia. These patients with known CAD have both **symptomatic** and **asymptomatic** ischemia. Between 20% and 40% of patients with chronic anginal symptoms have silent ischemia. About 75% of ischemic episodes are silent and only 25% are symptomatic.

III. DIAGNOSTIC TESTING. Most patients with silent ischemia are either never identified or identified retrospectively. In the Asymptomatic Cardiac Ischemic Pilot (ACIP) study, patients with frequent silent ischemic events were found to be at increased risk for advanced

coronary disease, including high-risk coronary anatomy such as three-vessel disease. Currently, testing to detect ischemia in asymptomatic patients is controversial. The ACC/AHA guidelines consider the use of exercise ECG testing (without imaging) in asymptomatic patients with possible myocardial ischemia on AECG or severe coronary calcification on EBCT as a *class IIb recommendation*. The use of exercise plus imaging stress testing (echo and nuclear) in asymptomatic patients with a low-risk Duke treadmill score on exercise ECG testing is a *class III recommendation*. In patients with an intermediate- or high-risk Duke treadmill score, it is a *class IIb recommendation.* In *asymptomatic* patients with prior revascularization with high-risk features, periodic stress testing is a *class IIb recommendation*.

IV. MECHANISMS

A. The exact explanation for a lack of symptoms in the face of unequivocal ischemia remains **unknown**. It likely represents abnormal modulation of cardiac **pain perception at different levels in the afferent pathway of the heart**.

B. The association between diabetes and silent ischemia and painless infarction has been attributed to **autonomic neuropathy**. A higher threshold for pain has been related to increased baseline plasma β-endorphin levels and increased age. A potential connection exists between baroreceptor function and pain perception. This may explain the relationships among increased systolic blood pressure, reduced sensitivity to ischemic pain, and the demonstration of anginal relief with carotid sinus stimulation. Results of one study suggested that the gating of afferent signals at the thalamic level is a potential mechanism for silent ischemia. Patients with symptoms had activation of basal frontal, anterior, and ventral cingulate cortices and the left temporal pole. **Cortical activation was limited to the right frontal region in patients with silent ischemia**. It also has been proposed that, among type III patients, asymptomatic ischemia may represent shorter and less severe episodes compared with symptomatic episodes.

V. MANAGEMENT

A. Medications effective in preventing symptomatic ischemia (i.e., nitrates, calcium antagonists, and β-blockers) and in decreasing myocardial O_2 demand are also effective in reducing or eliminating episodes of silent ischemia. In one randomized study, metoprolol was found to be better than diltiazem in reducing the mean number and duration of ischemic episodes. However, the combination of calcium antagonists and β-blockers was more effective than either agent alone. Lipid-lowering therapy has also shown a reduction of ischemia on AECG. The ACC/AHA guidelines currently regard the use of ASA (aspirin), β-blockers, angiotensin-converting enzyme inhibitors, and statins as class I recommendations in asymptomatic patients with evidence of previous MI and class IIa recommendations in patients without history of previous MI. It has also been postulated that ranolazine may also reduce ischemia before symptoms become present.

B. The goal of therapy remains controversial. It is not clear whether therapy should be guided by ischemia or angina. The ACIP study revealed no difference in benefit from either of these approaches. However, 2-year follow-up data from this study demonstrated improved prognosis with initial revascularization compared with angina- or ischemia-guided medical therapy. The Swiss Interventional Study on Silent Ischemia type I (SWISSI I) randomized 54 type I subset patients to treatment with antianginal medications and aspirin versus risk factor modification only. Their findings showed that treatment with the combination of antianginal drug therapy and aspirin appeared to significantly reduce cardiac events, including cardiac death, nonfatal MI, or acute coronary syndrome. In addition, these patients had consistently lower rates of exercise-induced ischemia during follow-up. The SWISSI II study randomized 201 patients with type II silent ischemia to percutaneous coronary intervention (PCI) versus ongoing anti-ischemic medical therapy. The results showed a significant decrease in rates of cardiac death, nonfatal MI, and subsequent

need for revascularization in patients in the PCI group over a 10-year follow-up period. Similarly, in patients with type I silent ischemia, with an ineffective "anginal warning system," it has been suggested that it may be reasonable to treat silent ischemia in a manner equivalent to that for symptomatic ischemia in the general population in terms of revascularization and medical therapy.

VI. PROGNOSIS. Myocardial ischemia, whether symptomatic or asymptomatic, is associated with poorer outcomes among patients with CAD. Patients with frequent and accelerating episodes of ST-segment depression on AECG monitoring are at higher risk for subsequent cardiac events than patients with few or no such episodes. The Copenhagen Holter study examined the significance of ischemic changes on AECG in asymptomatic, healthy individuals between the ages of 55 and 75 years (type I subset). They found that patients with silent ischemia had a threefold higher risk of subsequent cardiac events over a 5-year follow-up period. Circadian effects of asymptomatic ST depression on AECG have been noted with changes being more common in the morning hours; however, nocturnal ST-segment changes have been associated with multivessel CAD or left main narrowing. It has not been proven conclusively, however, that detection of silent ischemia is an independent risk factor for future cardiac events.

VII. CONTROVERSIES

A. Patients with silent ischemia on AECG monitoring represent heterogeneous populations. This may be a marker of unstable, complex coronary plaque or microvascular dysfunction. Results of the angiographic substudy of the ACIP study suggested that most patients with silent ischemia have proximal coronary lesions or complex coronary plaques. This hypothesis has not been tested in a larger population and continues to be investigated.

B. The potential role of **AECG monitoring** for ischemia still needs to be determined to assess its utility compared with more commonly used tests, such as exercise testing with thallium imaging. Different populations should be carefully examined at specific times after their events to answer these questions. Currently, the exercise ECG test remains the most useful and validated screening test for significant CAD.

C. **Medical therapy** should be used to decrease or eliminate ischemia; however, the relative role of medical therapy compared with revascularization in asymptomatic patients with demonstrable ischemia remains unclear.

D. **Coronary artery calcium** scanning to screen asymptomatic patients for CAD is now a *class IIa indication* in those patients with an intermediate (10% to 20%) 10-year risk of cardiac events based on the Framingham risk score or other global risk algorithm and for asymptomatic patients aged 40 years and older with diabetes mellitus.

SYNDROME X

I. INTRODUCTION. Syndrome X is defined as the constellation of effort-induced **anginalike discomfort** in the setting of **angiographically normal coronary arteries** (without inducible spasm on ergonovine provocation testing). This chest pain is usually indistinguishable from traditional ischemic angina caused by obstructive coronary disease and is, therefore, considered a diagnosis of exclusion.

II. PRESENTATION. In the clinical setting, syndrome X is a diagnosis given to patients with persistent **anginal symptoms**, often with abnormal stress testing despite a **normal angiogram** and **negative workup** for noncardiac chest pain. Up to 25% of all coronary angiograms performed in the United States for symptoms of chest pain are normal; yet, most cardiologists do not routinely use ergonovine provocation or intravascular ultrasound to evaluate for variant angina or angiographically silent coronary atherosclerosis in this subset of patients. When intravascular ultrasonography studies have been performed

in these patients, a spectrum of findings ranging from normal vessels to intimal thickening to nonobstructive atheromatous plaque has been reported. Syndrome X has an increased occurrence in women (3:1 preponderance), both premenopausal and postmenopausal. Of note, abnormal cardiac physical examination findings and left ventricular (LV) dysfunction on stress testing are both uncommon in syndrome X.

III. ETIOLOGY AND PATHOPHYSIOLOGY. Syndrome X represents a heterogeneous population and may represent multiple processes with varying causes. **Endothelial dysfunction, microvascular ischemia, and abnormal pain perception have all been implicated in the genesis of this disorder**. Endothelial dysfunction as demonstrated by abnormal coronary flow reserve (CFR), single positron emission computed tomography stress, and positron emission tomography stress testing is common in these patients. In addition, behavioral and psychiatric conditions often coexist. Specific treatment aimed at managing behavioral issues may lead to symptomatic improvement in chest pain in some patients.

IV. DIAGNOSTIC TESTING. Because syndrome X is a **diagnosis of exclusion**, both traditional obstructive coronary atherosclerosis and causes of noncardiac chest pain must be ruled out before a final diagnosis can be made. Multislice computed tomography angiography may play an increasingly important role in avoiding invasive angiography in some of these patients. Laboratory testing for endothelial dysfunction is not widely utilized in the clinical setting. Abnormal CFR in the catheterization laboratory can help confirm abnormalities in microcirculatory control, often accompanied by endothelial dysfunction in patients with syndrome X. C-reactive protein (high-sensitivity CRP) has been shown to correlate with the severity of symptoms and ECG changes in this population.

V. THERAPY. The **primary goal** of the therapy should be **aggressive cardiac risk factor modification,** including lifestyle changes and lipid treatment, although the **ideal treatment regimen is unknown**. β-Blockers have been shown to be very effective in controlling anginal symptoms in this population and are considered superior to calcium channel blockers and nitrates. Other treatments that have provided benefit include tricyclic antidepressants (imipramine), oral aminophylline, and estrogen in postmenopausal women. Given the recent data on estrogens, caution should be exercised when considering estrogen therapy in patients with suspected syndrome X.

VI. PROGNOSIS. The prognosis for patients with angina and normal coronary arteriograms is generally favorable with good long-term outcomes shown in multiple studies. However, subsets of these patients such as patients with persistent anginal symptoms and/or evidence of significant myocardial ischemia on stress testing seem to be at higher risk and have significantly higher event rates, including premature death, MI, and stroke, than the baseline population. These subsets of patients should be treated aggressively with risk factor modification and counseled regarding lifestyle modification.

VII. OTHER. Although not clearly related to syndrome X, **Takotsubo syndrome** (aka LV apical ballooning syndrome and stress-induced cardiomyopathy) is a condition that has been receiving increasing attention. Clinical features include sudden onset of chest pain, ECG changes (often ST elevation) mimicking an acute MI, usually in the setting of severe emotional distress and catecholamine surge. The angiogram shows normal coronary arteries, and diagnosis is made on the typical appearance seen on LV ventriculogram or echocardiogram with basal hyperkinesis and severe apical systolic wall motion abnormality. Most patients recover LV function and require only hemodynamic and pharmacologic support.

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