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PART 6 Disorders of the Cardiovascular System Ischemic Heart Disease Robert P. Giugliano, Elliott M. Antman, Joseph Loscalzo

Ischemic heart disease (IHD) is a condition in which there is an inadequate supply of blood and oxygen to a portion of the myocardium; it typically occurs when there is an imbalance between myocardial oxygen supply and demand. The most common cause of myocardial ischemia is atherosclerotic disease of an epicardial coronary artery (or arteries) sufficient to cause a regional reduction in myocardial blood flow and inadequate perfusion of the myocardium supplied by the involved coronary artery. This chapter focuses on the chronic manifestations and treatment of IHD (sometimes referred to as chronic coronary disease or chronic coronary syndrome), while the subsequent chapters address the acute phases of IHD. ■ ■EPIDEMIOLOGY AND GLOBAL TRENDS IHD causes more deaths and disability and incurs greater economic costs than any other illness in the developed world. IHD is the most common, serious, chronic, life-threatening illness in the United States, where 20.5 million persons have IHD. Although there is regional variation, ~3-4% of the population has sustained a myocardial infarction. Genetic factors, a high-fat and energy-rich diet, smoking, and a sedentary lifestyle are associated with the emergence of IHD. In the United States and Western Europe, IHD is growing among low-income groups, but primary prevention has delayed the disease to later in life across socioeconomic groups. Despite these sobering statistics, it is worth noting that epidemiologic data show a decline in the rate of deaths due to IHD, about half of which is attributable to treatments and half to prevention by risk factor modification. Obesity, insulin resistance, and type 2 diabetes mellitus are increasing and are powerful risk factors for IHD. These trends are occurring in the general context of population growth and as a result of the increase in the average age of the world's population. With urbanization in countries with emerging economies and a growing middle class, elements of the energy-rich Western diet are being adopted. As a result, the prevalence of risk factors for IHD and the prevalence of IHD itself are both increasing rapidly, so that in analyses of the global burden of disease, there is a shift from communicable to noncommunicable diseases, and it is estimated that globally over 200 million people live with IHD. Population subgroups that appear to be particularly affected are men in South Asian countries, especially India and the Middle East. IHD is a major contributor to the number of disability-adjusted lifeyears (DALYs) experienced globally. ■ ■PATHOPHYSIOLOGY Central to an understanding of the pathophysiology of myocardial ischemia is the concept of myocardial supply and demand. In normal conditions, for any given level of a demand for oxygen, the myocardium will control the supply of oxygen-rich blood to prevent under perfusion of

myocytes and the subsequent development of ischemia and infarction. The major determinants of myocardial oxygen demand (MVO₂) are heart rate, myocardial contractility, and myocardial wall tension (stress). An adequate supply of oxygen to the myocardium requires a satisfactory level of oxygen-carrying capacity of the blood (determined by the inspired level of oxygen, pulmonary function, and hemoglobin concentration and function) and an adequate level of coronary blood flow. Blood flows through the coronary arteries in a phasic fashion, with the majority occurring during diastole. About 75% of the total coronary resistance to flow occurs across three sets of arteries: (1) large epicardial arteries (Resistance 1 = R₁), (2) prearteriolar vessels (R₂), and (3) arteriolar and intramyocardial capillary vessels (R₃). In the absence of significant flow-limiting atherosclerotic obstructions, R₁ is trivial; the major determinant of coronary resistance is found in R₂ and R₃ (Fig. 284-1). The normal coronary circulation is dominated and controlled by the heart's requirements for oxygen. This need is met by the ability of the coronary vascular bed to vary its resistance (and, therefore, blood flow) considerably while the myocardium extracts a high and relatively fixed percentage of oxygen. Normally, intramyocardial resistance vessels demonstrate a great capacity for dilation (R₂ and R₃ decrease). The changing oxygen needs of the heart with exercise and emotional stress affect coronary

Section 5 Coronary and Peripheral Vascular Disease
 Segment and size
 Macrocirculation Microcirculation
 Main stimulus for vasomotion Metabolites
 Pressure Flow Exchange Regulation Transport
 Main function Percentage of total resistance to flow
 Epicardial arteries >400 μm
 Small arteries <400 μm
 Arterioles <100 μm
 Capillaries <10 μm

FIGURE 284-1 Macrocirculation and microcirculation across segments and sizes of the arteries. The location and size of the arteries supplying blood to the heart is shown at the top. Vasomotion of the arterial segments occurs in response to the stimuli shown. The main function of each of the arterial segments is shown next, followed by a depiction of the relative resistance to antegrade flow. (Adapted from J Knuuti et al: 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 41:407, 2020/.)

vascular resistance and, in this manner, regulate the supply of oxygen and substrate to the myocardium (metabolic regulation). The coronary resistance vessels also adapt to physiologic alterations in blood pressure to maintain coronary blood flow at levels appropriate to myocardial needs (autoregulation). By reducing the lumen of the coronary arteries, atherosclerosis limits appropriate increases in perfusion when the demand for more coronary flow occurs. When the luminal reduction is severe, myocardial perfusion in the basal state is reduced. Coronary blood flow also can be limited by spasm (see vasospastic angina in Chap. 285), arterial thrombi, and, rarely, coronary emboli as well as by ostial narrowing due to aortitis. Congenital abnormalities such as the origin of the left anterior descending coronary artery from the pulmonary artery may cause myocardial ischemia and infarction in infancy, but this cause is very rare in adults. Myocardial ischemia also can occur if myocardial oxygen demands are markedly increased and particularly when coronary blood flow may be limited, as occurs in severe left ventricular hypertrophy (LVH) due to aortic stenosis. The latter can present with angina that is indistinguishable from that caused by coronary atherosclerosis largely owing to subendocardial ischemia (Chap. 272). A reduction in the oxygen-carrying capacity of the blood, as in extremely severe anemia or in the presence of carboxyhemoglobin, rarely causes myocardial ischemia by itself but may lower the threshold for ischemia in patients with moderate coronary obstruction. Not infrequently, two or more causes of ischemia coexist in a patient, such as an increase in oxygen demand due to LVH secondary to hypertension and a reduction in oxygen supply secondary to coronary atherosclerosis and anemia. Abnormal constriction or failure of normal dilation of the coronary

resistance vessels also can cause ischemia. When it causes angina, this condition is referred to as micro vascular angina. CORONARY ATHEROSCLEROSIS Epicardial coronary arteries are the major site of atherosclerotic disease. The major risk factors for atherosclerosis (high levels of plasma low-density lipoprotein [LDL], cigarette smoking, hypertension, and diabetes mellitus) vary in their relative impact on disturbing the normal functions of the vascular endothelium. These functions include local control of vascular tone, maintenance of an antithrombotic surface, and control of inflammatory cell adhesion and diapedesis. The loss of these defenses leads to inappropriate constriction, luminal thrombus formation, and abnormal interactions between blood cells, especially monocytes and platelets, and the activated vascular endothelium. Functional changes in the vascular milieu ultimately result in the subintimal collections of fat, smooth muscle cells, fibroblasts, and intercellular matrix that define the atherosclerotic plaque. Rather than viewing atherosclerosis strictly as a vascular problem, it is useful to consider it in the context of alterations in the nature of the circulating blood (hyperglycemia; increased concentrations of LDL cholesterol, tissue factor, fibrinogen, von Willebrand factor, coagulation factor VII, and platelet microparticles). The combination of a "vulnerable vessel" in a patient with "vulnerable blood" promotes a state of hypercoagulability and hypofibrinolysis. This is especially true in patients with diabetes mellitus. Atherosclerosis develops at irregular rates in different segments of the epicardial coronary tree and leads eventually to segmental reductions in cross-sectional area, i.e., plaque formation. There is also a predilection for atherosclerotic plaques to develop at sites of increased turbulence in coronary flow, such as at branch points in the epicardial arteries. When a stenosis reduces the diameter of an epicardial artery by 50%, there is a limitation of the ability to increase flow to meet increased myocardial demand. When the diameter is reduced by ~80%, blood flow at rest may be reduced, and further minor decreases in the stenotic orifice area can reduce coronary flow dramatically to cause myocardial ischemia at rest or with minimal stress. Segmental atherosclerotic narrowing of epicardial coronary arteries is caused most commonly by the formation of a plaque, which is subject to rupture or erosion of the cap separating the plaque from the bloodstream. Upon exposure of the plaque contents to blood, two important and interrelated processes are set in motion: (1) platelets are activated and aggregate, and (2) the coagulation cascade is activated, leading to deposition of fibrin strands. A thrombus composed of platelet aggregates and fibrin strands traps red blood cells and can reduce coronary blood flow, leading to the clinical manifestations of myocardial ischemia.

CHAPTER 284 The location of the obstruction influences the quantity of myocardium rendered ischemic and determines the severity of the clinical manifestations. Thus, critical obstructions in vessels, such as the left main coronary artery and the proximal left anterior descending coronary artery, are particularly hazardous. Chronic severe coronary narrowing and myocardial ischemia frequently are accompanied by the development of collateral vessels, especially when the narrowing develops gradually. When well developed, such vessels can by themselves provide sufficient blood flow to sustain the viability of the myocardium at rest but not during conditions of increased demand. Ischemic Heart Disease With progressive worsening of a stenosis in a proximal epicardial artery, the distal resistance vessels (when they function normally) dilate to reduce vascular resistance and maintain coronary blood flow. A pressure gradient develops across the proximal stenosis, and poststenotic pressure falls. When the resistance vessels are maximally dilated, myocardial blood flow becomes dependent on the pressure in the coronary artery distal to the obstruction. In these circumstances, ischemia, manifest clinically by angina or

electrocardiographically by ST-segment deviation, can be precipitated by increases in myocardial oxygen demand caused by physical activity, emotional stress, and/or tachycardia. Changes in the caliber of the stenosed coronary artery resulting from physiologic vasomotion, loss of endothelial control of dilation (as occurs in atherosclerosis), pathologic spasm (vasospastic angina), or small platelet-rich plugs also can upset the critical balance between oxygen supply and demand and thereby precipitate myocardial ischemia. ■ ■EFFECTS OF ISCHEMIA During episodes of inadequate perfusion caused by coronary atherosclerosis, myocardial tissue oxygen tension falls and may cause transient disturbances of the mechanical, biochemical, and electrical functions of the myocardium (Fig. 284-2). Coronary atherosclerosis is a focal process that usually causes nonuniform ischemia. During ischemia, regional disturbances of ventricular contractility cause segmental hypokinesia, akinesia, or, in severe cases, bulging (dyskinesia), which can reduce myocardial pump function. The abrupt development of severe ischemia, as occurs with total or subtotal coronary occlusion, is associated with near instantaneous failure of normal muscle relaxation and then diminished contraction. The relatively poor perfusion of the subendocardium causes more intense ischemia of this portion of the wall (compared with the subepicardial region). Ischemia of large portions of the ventricle causes transient left ventricular (LV) failure, and if the papillary muscle apparatus is involved, mitral regurgitation can occur. When ischemia is transient, it may be associated with angina pectoris; when it is prolonged, it can lead to myocardial necrosis and scarring with or without the clinical picture of acute myocardial infarction (Chap. 286). A wide range of abnormalities in cell metabolism, function, and structure underlie these mechanical disturbances during ischemia. The normal myocardium metabolizes fatty acids and glucose to carbon dioxide and water. With severe oxygen deprivation, fatty acids cannot be oxidized, and glucose is converted to lactate; intracellular pH is reduced, as are the myocardial stores of high-energy phosphates, i.e., ATP and creatine phosphate. Impaired cell membrane function leads to the leakage of potassium and the uptake of sodium by myocytes as well as an increase in cytosolic calcium. The severity and duration of the imbalance between myocardial oxygen supply and demand determine whether the damage is reversible (≤ 20 min for total occlusion in the absence of collaterals) or permanent, with subsequent myocardial necrosis (>20 min). Ischemia also causes characteristic changes in the electrocardiogram (ECG) such as repolarization abnormalities, as evidenced by inversion

Repetitive/progressive manifestations of ischemia Regional wall motion PART 6 Disorders of the Cardiovascular System Decreased segmental perfusion Diastolic dysfunction Micro-infarction/myocardial fibrosis Altered metabolism/abnormal ST segment Decreased subendocardial perfusion Endothelial and microvascular dysfunction Near term Exposure time of mismatch in myocardial oxygen supply/demand FIGURE 284-2 Cascade of mechanisms and manifestations of ischemia. (Reproduced with permission from LJ Shaw et al: Women and ischemic heart disease: Evolving knowledge. J Am Coll Cardiol 54:1561, 2009.) of T waves and, when more severe, displacement of ST segments (Chap. 247). Transient T-wave inversion probably reflects nontransmural, intramyocardial ischemia; transient ST-segment depression often reflects patchy subendocardial ischemia; and ST-segment elevation is thought to be caused by more severe transmural ischemia. Another important consequence of myocardial ischemia is electrical instability, which may lead to isolated ventricular premature beats or even ventricular tachycardia or ventricular fibrillation (Chaps. 261 and 262). Most patients who die suddenly from IHD do so as a result of ischemia-induced ventricular tachyarrhythmias (Chap. 317). ■ ■ASYMPTOMATIC VERSUS SYMPTOMATIC IHD Although the prevalence is decreasing, postmortem studies of accident victims

and military casualties in Western countries show that coronary atherosclerosis can begin before age 20 and is present among adults who were asymptomatic during life. Exercise stress tests in asymptomatic persons may show evidence of silent myocardial ischemia, i.e., exercise-induced ECG changes not accompanied by angina pectoris; coronary angiographic studies of such persons may reveal coronary artery plaques and previously unrecognized obstructions (Chap. 249). Coronary artery calcifications (CACs) may be seen on computed tomography (CT) images of the heart, can be quantified in a CAC score, and may be used as adjunctive information to support a diagnosis of IHD. However, they should not be used as the primary screening modality or as the isolated basis on which to formulate therapeutic decisions. (See further discussion below.) Postmortem examination of patients with such obstructions without a history of clinical manifestations of myocardial ischemia often shows macroscopic scars secondary to myocardial infarction in regions supplied by diseased coronary arteries, with or without collateral circulation. According to population studies, ~25% of patients who survive acute myocardial infarction may not come to medical attention, and these patients have the same adverse prognosis as do those who present with the classic clinical picture of acute myocardial infarction (Chap. 286). Sudden death may be unheralded and is a common presenting manifestation of IHD (Chap. 317). Patients with IHD also can present with cardiomegaly and heart failure secondary to ischemic damage of the LV myocardium that may have caused no symptoms before the development of heart failure; this condition is referred to as ischemic cardiomyopathy. In contrast to the asymptomatic phase of IHD, the symptomatic phase is characterized

Systolic dysfunction Prolonged by chest discomfort due to either angina pectoris or acute myocardial infarction (Chap. 286). Having entered the symptomatic phase, the patient may exhibit a stable or progressive course, revert to the asymptomatic stage, or die suddenly. **STABLE ANGINA PECTORIS** This episodic clinical syndrome is a result of transient myocardial ischemia. Various diseases that cause myocardial ischemia and the numerous forms of discomfort with which it may be confused are discussed in Chap. 15. Males constitute ~70% of all patients with angina pectoris and an even greater proportion of those aged <50 years. It is, however, important to note that descriptions of angina pectoris in women may be different from that in men. ■ ■ **HISTORY** The typical patient with angina is a man >50 years or a woman

“ 60 years of age who complains of episodes of chest discomfort, usually described as heaviness, pressure, squeezing, smothering, or choking and only rarely as frank pain. When the patient is asked to localize the sensation, they typically place a hand over the sternum, sometimes with a clenched fist, to indicate a squeezing, central, substernal discomfort (Levine's sign). Angina is usually crescendo-decrescendo in nature (typically with the severity of the discomfort not at its most intense level at the outset of symptoms), typically lasts 2-5 min, and can radiate to either shoulder and to both arms (especially the ulnar aspects of the forearm and hand). It also can arise in or radiate to the back, interscapular region, root of the neck, jaw, teeth, and epigastrium. Angina is rarely localized below the umbilicus or above the mandible. A useful finding in assessing a patient with chest discomfort is the fact that myocardial ischemic discomfort does not radiate to the trapezius muscles; that radiation pattern is

more typical of pericarditis. Although episodes of angina typically are caused by exertion (e.g., exercise, hurrying, or sexual activity) or emotion (e.g., stress, anger, fright, or frustration) and are relieved by rest, they also may occur at rest and while the patient is recumbent (angina decubitus). The patient may be awakened at night by typical chest discomfort and dyspnea. Nocturnal angina may be due to episodic tachycardia, diminished oxygenation as the respiratory pattern changes during sleep, or expansion of the intrathoracic blood volume that occurs with recumbency; the latter causes an increase in cardiac size (end-diastolic volume), wall

tension, and myocardial oxygen demand that can lead to ischemia and transient LV failure. The threshold for the development of angina pectoris may vary by time of day and emotional state. Many patients report a fixed threshold for angina, occurring predictably at a certain level of activity, such as climbing two flights of stairs at a normal pace. In these patients, coronary stenosis and myocardial oxygen supply are fixed, and ischemia is precipitated by an increase in myocardial oxygen demand; they are said to have stable exertional angina. In other patients, the threshold for angina may vary considerably within any particular day and from day to day. In such patients, variations in myocardial oxygen supply, most likely due to changes in coronary vasomotor tone, may play an important role in defining the pattern of angina. A patient may report symptoms upon minor exertion in the morning yet by midday be capable of much greater effort without symptoms. Angina may also be precipitated by unfamiliar circumstances, a heavy meal, exposure to cold, or a combination of these factors. Exertional angina typically is relieved in 1–5 min by slowing or ceasing activities and even more rapidly by rest and sublingual nitroglycerin (see below). Indeed, the diagnosis of angina should be suspect if it does not respond to the combination of these measures. The severity of angina can be conveniently summarized by the Canadian Cardiac Society functional classification (Table 284-1). Its impact on the patient's functional capacity can be described by using the New York Heart Association functional classification (Table 284-1). Sharp, fleeting chest pain or a prolonged, dull ache localized to the left submammary area is rarely due to myocardial ischemia. However, especially in women and patients with diabetes mellitus, angina pectoris may be atypical in location and not strictly related to provoking factors. In addition, this symptom may exacerbate and remit over days, weeks, or months. Its occurrence can be seasonal, occurring more

TABLE 284-1 Cardiovascular Disease Classification Chart

CANADIAN CARDIOVASCULAR SOCIETY FUNCTIONAL CLASSIFICATION

NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

CLASS I Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain. Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina present with strenuous or rapid or prolonged exertion at work or recreation.

II Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain. Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, or when under emotional stress or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of stairs at a normal pace and in normal conditions.

III Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical

activity causes fatigue, palpitation, dyspnea, or anginal pain. Marked limitation of ordinary physical activity. Walking one to two blocks on the level and climbing one flight of stairs at normal pace. IV Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased. Inability to carry on any physical activity without discomfort— anginal syndrome may be present at rest. Source: Reproduced with permission from L Goldman et al: Comparative reproducibility and validity of systems for assessing cardiovascular functional class: Advantages of a new specific activity scale. *Circulation* 64:1227, 1981.

frequently in the winter in temperate climates. Anginal “equivalents” are symptoms of myocardial ischemia other than angina. They include dyspnea, nausea, fatigue, and faintness and are more common in the elderly and in patients with diabetes mellitus.

Systematic questioning of a patient with suspected IHD is important to uncover the features of an unstable syndrome associated with increased risk, such as angina occurring with less exertion than in the past, occurring at rest, or awakening the patient from sleep. Since coronary atherosclerosis often is accompanied by similar lesions in other arteries, a patient with angina should be questioned and examined for peripheral arterial disease (intermittent claudication [Chap. 292]), stroke, or transient ischemic attacks (Chap. 437). It is also important to uncover a family history of premature IHD (<55 years in first-degree male relatives and <65 years in female relatives) and the presence of diabetes mellitus, hyperlipidemia, hypertension, cigarette smoking, and other risk factors for coronary atherosclerosis. CHAPTER 284 Ischemic Heart Disease The history of typical angina pectoris establishes the diagnosis of IHD until proven otherwise. Given the importance of the history, clinicians should move beyond unstructured interviews with the patient and consider using a validated questionnaire (e.g., Seattle Angina Questionnaire) to establish the presence and severity of IHD. The coexistence of advanced age, male sex, the postmenopausal state, and risk factors for atherosclerosis increases the likelihood of hemodynamically significant coronary disease. A particularly challenging problem is the evaluation and management of patients with persistent ischemic-type chest discomfort but no flow-limiting obstructions in their epicardial coronary arteries. This situation arises more often in women than in men. Potential etiologies include microvascular coronary disease (detectable on coronary reactivity testing in response to vasoactive agents such as intracoronary adenosine, acetylcholine, and nitroglycerin) and abnormal cardiac nociception. Treatment of microvascular coronary disease should focus on efforts to improve endothelial function, including nitrates, beta blockers, calcium antagonists, statins, and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). Abnormal cardiac nociception is more difficult to manage and may be ameliorated in some cases by imipramine. ■ ■ PHYSICAL EXAMINATION The physical examination is often normal in patients with stable angina when they are asymptomatic. However, because of the increased likelihood of IHD in patients with diabetes and/or peripheral or cerebrovascular arterial disease, clinicians should search for evidence of atherosclerotic disease at other sites, such as an abdominal aortic aneurysm, carotid arterial bruits, and diminished arterial pulses in the lower extremities. The physical examination also should include a search for evidence of risk factors for atherosclerosis such as xanthelasmas and xanthomas. Evidence for peripheral and cerebrovascular arterial disease should be sought by evaluating the pulse contour at multiple locations and comparing the blood pressure between the arms and between the arms and the legs (ankle-brachial index). Examination of the

fundi may reveal an increased light reflex and arteriovenous nicking as evidence of hypertension. There also may be signs of anemia, thyroid disease, and nicotine stains on the fingertips from cigarette smoking. Palpation may reveal cardiac enlargement and abnormal contraction of the cardiac impulse (LV dyskinesia). Auscultation can uncover arterial bruits, a third and/or fourth heart sound, and, if acute ischemia or previous infarction has impaired papillary muscle function, an apical systolic murmur due to mitral regurgitation. These auscultatory signs are best appreciated with the patient in the left lateral decubitus position. Aortic stenosis, aortic regurgitation (Chap. 272), pulmonary hypertension (Chap. 294), and hypertrophic cardiomyopathy (Chaps. 266–270) must be excluded, since these disorders may cause angina in the absence of coronary atherosclerosis. Examination during an anginal attack is useful, since ischemia can cause transient LV failure with the appearance of a third and/or fourth heart sound, a dyskinetic cardiac apex, mitral regurgitation, and even pulmonary edema. Tenderness of the chest wall, localization of the discomfort with a single fingertip on the chest, or reproduction of the pain with palpation of the

chest makes it unlikely that the pain is caused by myocardial ischemia. A protuberant abdomen may indicate that the patient has the metabolic syndrome and is at increased risk for atherosclerosis.

■ ■ **LABORATORY EXAMINATION** Although the diagnosis of IHD can be made with a high degree of confidence from the history and physical examination, a number of simple laboratory tests can be helpful. The urine should be examined for evidence of diabetes mellitus and renal disease (including microalbuminuria) since these conditions accelerate atherosclerosis. Similarly, examination of the blood should include measurements of lipids (cholesterol—total, LDL, high-density lipoprotein [HDL]—triglycerides, and lipoprotein (a)), glucose (hemoglobin A1C), creatinine, hematocrit, and, if indicated based on the physical examination, thyroid function. A chest x-ray may be helpful in demonstrating the consequences of IHD, i.e., cardiac enlargement, ventricular aneurysm, or signs of heart failure. These signs can support the diagnosis of IHD and are important in assessing the degree of cardiac damage. Evidence exists that an elevated level of high-sensitivity C-reactive protein (CRP) (specifically, between 1 and 3 mg/L) is an independent risk factor for IHD and may be useful in therapeutic decision-making about the initiation of hypolipidemic treatment. The major benefit of high-sensitivity CRP is in reclassifying the risk of IHD in patients in the “intermediate” risk category on the basis of traditional risk factors. **PART 6 Disorders of the Cardiovascular System** ■ ■ **ELECTROCARDIOGRAM** A 12-lead ECG recorded at rest may be normal in patients with typical angina pectoris, but there may also be signs of an old myocardial infarction (Chap. 247). Although repolarization abnormalities, i.e., ST-segment and T-wave changes, as well as LVH and disturbances of cardiac rhythm or intraventricular conduction, are suggestive of IHD, they are nonspecific, since they also can occur in pericardial, myocardial, and valvular heart disease or, in the case of the former, transiently with anxiety, changes in posture, drugs, or esophageal disease. The presence of LVH is a significant indication of increased risk of adverse outcomes from IHD. Of note, even though LVH and cardiac rhythm disturbances are nonspecific indicators of the development of IHD, they may be contributing factors to episodes of angina in patients in whom IHD has developed as a consequence of conventional risk factors. Dynamic ST-segment and T-wave changes that accompany episodes of angina pectoris and disappear thereafter are more specific. ■ ■ **STRESS TESTING** Electrocardiographic The most widely used test for both the diagnosis of IHD and the estimation of risk and prognosis involves recording of the 12-lead ECG before, during, and after exercise, usually on a treadmill (Fig. 284-3). The test

consists of a standardized incremental increase in external workload (Table 284-2) while symptoms, the ECG, and arm blood pressure are monitored. Exercise duration is usually symptom-limited, and the test is discontinued upon evidence of chest discomfort, severe shortness of breath, dizziness, severe fatigue, ST-segment depression >0.2 mV (2 mm), a fall in systolic blood pressure >10 mmHg, or the development of a ventricular tachyarrhythmia. This test is used to discover any limitation in exercise performance, detect typical ECG signs of myocardial ischemia, and establish their relationship to chest discomfort. The ischemic ST-segment response generally is defined as flat or downsloping depression of the ST segment >0.1 mV below baseline (i.e., the PR segment) and lasting longer than 0.08 s (Fig. 284-2). Upsloping or junctional ST-segment changes are not considered characteristic of ischemia and do not constitute a positive test. Although T-wave abnormalities, conduction disturbances, and ventricular arrhythmias that develop during exercise should be noted, they are also not diagnostic. Negative exercise tests in which the target heart rate (85% of maximal predicted heart rate for age and sex) is not achieved are considered nondiagnostic. In interpreting ECG stress tests, the probability that coronary artery disease (CAD) exists in the patient or population under study (i.e., pretest probability) should be considered. A positive result on exercise indicates that the likelihood of CAD is 98% in males who are

“ 50 years with a history of typical angina pectoris and who develop chest discomfort during the test. The likelihood decreases if the patient has atypical or no chest pain by history and/or during the test. The incidence of false-positive tests is significantly increased in patients with low probabilities of IHD, such as asymptomatic men age <40 or premenopausal women with no risk factors for premature atherosclerosis. It is also increased in patients taking cardioactive drugs, such as digitalis and antiarrhythmic agents, and in those with intraventricular conduction disturbances, resting ST-segment and T-wave abnormalities, ventricular hypertrophy, or abnormal serum potassium levels. Obstructive disease limited to the circumflex coronary artery may result in a false-negative stress test since the posterolateral portion of the heart that this vessel supplies is not well represented on the surface 12-lead ECG. Since the overall sensitivity of an exercise stress ECG is only $\sim 75\%$, a negative result does not exclude CAD, although it makes the likelihood of three-vessel or left main CAD extremely unlikely. A medical professional should be present throughout the exercise test. It is important to measure total duration of exercise, the times to the onset of ischemic ST-segment change and chest discomfort, the external work performed (generally expressed as the stage of exercise), and the internal cardiac work performed, i.e., by the heart rate–blood pressure product. The depth of the ST-segment depression and the time needed for recovery of these ECG changes are also important. Because the risks of exercise testing are small but real—estimated at one fatality and two nonfatal complications per 10,000 tests—equipment for resuscitation should be available. Modified (heart rate-limited rather than symptom-limited) exercise tests can be performed safely in patients as early as 6 days after uncomplicated myocardial infarction (Table 284-2). Contraindications to exercise stress testing include rest angina within 48 h, unstable rhythm, severe aortic stenosis, acute myocarditis,

uncontrolled heart failure, severe pulmonary hypertension, and active infective endocarditis. The normal response to graded exercise includes progressive increases in heart rate and blood pressure. Failure of the blood pressure to increase or an actual decrease with signs of ischemia during the test is an important adverse prognostic sign, since it may reflect ischemia-induced global LV dysfunction. The development of angina and/or severe (>0.2 mV) ST-segment depression at a low workload, i.e., before completion of stage II of the Bruce protocol, and/or ST-segment depression that persists >5 min after the termination of exercise increases the specificity of the test and suggests severe IHD and a high risk of future adverse events. Cardiac Imaging (See also Chap. 248) When the resting ECG is abnormal (e.g., preexcitation syndrome, >1 mm of resting ST-segment depression, left bundle branch block, paced ventricular rhythm), information gained from an exercise test can be enhanced by stress myocardial radionuclide perfusion imaging after the intravenous administration of thallium-201 or 99m-technetium sestamibi during exercise (or with pharmacologic) stress. Contemporary data also suggest positron emission tomography (PET) imaging (with exercise or pharmacologic stress) using N-13 ammonia or rubidium-82 as another technique for assessing perfusion. Images obtained immediately after cessation of exercise to detect regional ischemia are compared with those obtained at rest to confirm reversible ischemia and regions of persistently absent uptake that signify infarction. A sizable fraction of patients who need noninvasive stress testing to identify myocardial ischemia and increased risk of coronary events cannot exercise because of peripheral vascular or musculoskeletal disease, exertional dyspnea, or deconditioning. In these circumstances, an intravenous pharmacologic challenge is used in place of exercise. For example, adenosine can be given to create a coronary "steal" by temporarily increasing flow in nondiseased segments of the coronary vasculature at the expense of diseased segments. Alternatively, a graded incremental infusion of dobutamine may be administered to increase $\dot{V}O_2$. A variety of imaging options are available to accompany these pharmacologic stressors (Fig. 284-3). The development of a transient perfusion defect with a tracer such as thallium-201 or 99m-technetium sestamibi is used to detect myocardial ischemia.

Echocardiography is used to assess LV function in patients with chronic stable angina and patients with a history of a prior myocardial infarction, pathologic Q waves, or clinical evidence of heart failure. Twodimensional echocardiography can assess both global and regional wall motion abnormalities of the left ventricle that are transient when due to ischemia. Stress (exercise or dobutamine) echocardiography may cause the emergence of regions of akinesis or dyskinesis that are not present at rest. Stress echocardiography, like stress myocardial perfusion imaging, is more sensitive than exercise electrocardiography. No diagnostic testing mandated Choice of the test based on clinical likelihood, patient characteristics and preference, availability, as well as local expertise Coronary CTA Very high Very low Clinical likelihood of obstructive CAD A FIGURE 284-3 Selecting appropriate testing patients with angina and suspected coronary artery disease (CAD).

On the left of the figure is an algorithm for selecting from among testing options. In patients who are at low risk, in whom prior testing was equivocal, or in whom the diagnosis of is CAD uncertain, noninvasive functional stress testing with imaging for myocardial ischemia or computed tomography angiography (CTA) is reasonable to establish the diagnosis of CAD prior to initiation of treatment. Patients with a high clinical likelihood of CAD, patients with symptoms despite antianginal therapy or with low-level activities, and patients with high-risk features based on the initial clinical evaluation may proceed directly to invasive coronary angiography without further diagnostic testing. (Adapted from J Knuuti et al: 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 41:407, 2020.) Panels A-F are examples of the data obtained with electrocardiogram (ECG) monitoring and specialized imaging procedures. CMR, cardiac magnetic resonance; EBCT, electron beam computed tomography; ECHO, echocardiography; FFR, fractional flow reserve; IHD, ischemic heart disease; iwFR, instantaneous wave-free ration; MIBI, methoxyisobutyl isonitrite; MR, magnetic resonance; PET, positron emission tomography. A. Lead V4 at rest (top panel) and after 4.5 min of exercise (bottom panel). There is 3 mm (0.3 mV) of horizontal ST-segment depression, indicating a positive test for ischemia. (Adapted from BR Chaitman, in E Braunwald et al [eds]: *Heart Disease*, 8th ed, Philadelphia, Saunders, 2008.) B. A 45-year-old avid jogger who began experiencing classic substernal chest pressure underwent an exercise echo study. With exercise, the patient's heart rate increased from 52 to 153 beats/min. The left ventricular chamber dilated with exercise, and the septal and apical portions became akinetic to dyskinetic (red arrow). These findings are strongly suggestive of a significant flow-limiting stenosis in the proximal left anterior descending artery, which was confirmed at coronary angiography. (Modified from SD Solomon, in E Braunwald et al [eds]: *Primary Cardiology*, 2nd ed, Philadelphia, Saunders, 2003.) C. Stress and rest myocardial perfusion single-photon emission computed tomography images obtained with 99m-technetium sestamibi in a patient with chest pain and dyspnea on exertion. The images demonstrate a medium-size and severe stress perfusion defect involving the inferolateral and basal inferior walls, showing nearly complete reversibility, consistent with moderate ischemia in the right coronary artery territory (red arrows). (Images provided by Dr. Marcello Di Carli, Nuclear Medicine Division, Brigham and Women's Hospital, Boston, MA.) D. A patient with a prior myocardial infarction presented with recurrent chest discomfort. On cardiac magnetic resonance (CMR) cine imaging, a large area of anterior akinesia was noted (marked by the arrows in the top left and right images, systolic frame only). This area of akinesia was matched by a larger extent of late gadolinium-DTPA enhancements consistent with a large transmural myocardial infarction (marked by arrows in the middle left and right images). Resting (bottom left) and adenosine vasodilating stress (bottom right) first-pass perfusion images revealed reversible perfusion abnormality that extended to the inferior septum. This patient was found to have an occluded proximal left anterior descending coronary artery with extensive collateral formation. This case illustrates the utility of different modalities in a CMR examination in characterizing ischemic and infarcted myocardium. DTPA, diethylenetriamine penta-acetic acid. (Images provided by Dr. Raymond Kwong, Cardiovascular Division, Brigham and Women's Hospital, Boston, MA.) E. Stress and rest myocardial perfusion PET images obtained with rubidium-82 in a patient with chest pain on exertion. The images demonstrate a large and severe stress perfusion defect involving the mid and apical anterior, anterolateral, and anteroseptal walls and the left ventricular apex, showing complete reversibility, consistent with extensive and severe ischemia in the mid-left anterior descending coronary artery territory (red arrows). (Images provided by Dr. Marcello Di Carli, Nuclear Medicine Division, Brigham and Women's Hospital, Boston, MA.) F. A 58-year-old woman with psoriasis presented with chest discomfort and underwent coronary CT

angiography (CCTA) for further evaluation. There was a large amount of mostly noncalcified plaque resulting in severe (>70%) stenosis of the mid left anterior descending artery (LAD) and the mid-right coronary artery (RCA). There was minimal plaque in the left circumflex (LCx). CCTA data can be used to reconstruct three-dimensional images to aid visualization. In addition, each coronary artery can be visualized en face by creating a short axis along the length of the coronary segment being visualized. In this case, the stenosis of the LAD is seen in the red box (corresponding to the level of the dashed red line) and compared with the proximal normal segment in the green box (corresponding to the level of the dashed green line). (Images provided by Dr. Ron Blankstein, Cardiovascular Division, Brigham and Women's Hospital, Boston, MA.)

in the diagnosis of IHD. Cardiac magnetic resonance (CMR) stress testing is also evolving as an alternative to radionuclide, PET, or echocardiographic stress imaging. CMR stress testing performed with dobutamine infusion can be used to assess wall motion abnormalities accompanying ischemia, as well as myocardial perfusion. CMR can be used to provide more complete ventricular evaluation using multislice magnetic resonance imaging (MRI) studies.

CHAPTER 284 Atherosclerotic plaques become progressively calcified over time, and coronary calcification in general increases with age. For this Ischemic Heart Disease Invasive angiography (with iwFR/FFR) Testing for ischemia (imaging testing preferred)

PART 6 Disorders of the Cardiovascular System FIGURE 284-3 (Continued)

FIGURE 284-3 (Continued) reason, methods for detecting coronary calcium have been developed as a measure of the presence of coronary atherosclerosis. These methods involve CT applications that achieve rapid acquisition of images (electron beam [EBCT] and multidetector [MDCT] detection). Coronary calcium detected by these imaging techniques most commonly is quantified by using the Agatston score, which is based on the area and density of calcification. Coronary CT angiography (CCTA) (Fig. 284-3) is helpful in diagnosing the extent and severity of nonobstructive and obstructive IHD, as well as assessing plaque composition. Thus, CCTA is an attractive option when the pretest likelihood of IHD is intermediate in a young patient (< 65 years) with chest pain or less obstructive IHD is suspected. Stress imaging is the preferred diagnostic test when the goal is assessing the adequacy of ischemia-guided management. ■ ■CORONARY ARTERIOGRAPHY (See also Chap. 249)

This diagnostic method outlines the lumina of the coronary arteries and can be used to detect or exclude serious coronary obstruction. However, coronary arteriography provides no TABLE 284-2 Relation of Metabolic Equivalent Tasks (METs) to Stages in Various Testing Protocols

FUNCTIONAL CLASS	CLINICAL STATUS	BRUCE Modified 3 min Stages	BRUCE 3 min Stages
HEALTHY	DEPENDENT ON AGE, ACTIVITY NORMAL	I	SEDENTARY
HEALTHY II	LIMITED SYMPTOMATIC	III	10.5

1.7

IV 3.5

Note: The standard Bruce treadmill protocol (right-hand column) begins at 1.7 MPH and 10% gradient (GR) and progresses every 3 min to a higher speed and elevation. The corresponding oxygen consumption and clinical status of the patient are shown in the center and left-hand

columns. Abbreviations: GR, grade; MPH, miles per hour. Source: Reproduced with permission from GF Fletcher et al: Exercise standards for testing and training. Circulation 104:1694, 2001.

CHAPTER 284 Ischemic Heart Disease information about the arterial wall, and severe atherosclerosis that does not encroach on the lumen may go undetected. Of note, atherosclerotic plaques characteristically are scattered throughout the coronary tree, tend to occur more frequently at branch points, and grow progressively in the intima and media of an epicardial coronary artery at first without encroaching on the lumen, causing an outward bulging of the artery—a process referred to as remodeling. Later in the course of the disease, further growth causes luminal narrowing. Indications The ISCHEMIA trial informs decision-making about referral for coronary arteriography (with intent to perform revascularization) in patients with stable IHD and an ejection fraction >35% even in the presence of moderate-severe ischemia on noninvasive functional testing. Over the course of 4 years of follow-up, early referral for an invasive strategy was not associated with a reduction in the risk of myocardial infarction or death but was more effective than an initial conservative, medical strategy in relieving angina. Thus, coronary arteriography is indicated in (1) patients with chronic stable angina pectoris who are severely symptomatic despite medical therapy and are O₂ COST

mL/Kg/min METs TREADMILL PROTOCOLS MPH %GR MPH %GR 6.0

6.0

5.5

5.2

5.0

5.0

56.0

52.5

49.0

45.5

4.2

4.2

42.0

38.5

3.4

3.4

35.0

31.5

28.0

24.5

2.5

2.5

21.0

17.5

1.7

1.7

14.0

7.0

1.7

being considered for revascularization, i.e., a percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG); (2) patients with troublesome symptoms that present diagnostic difficulties in whom there is a need to confirm or rule out the diagnosis of IHD; (3) patients with known or possible angina pectoris who have survived cardiac arrest; and (4) patients with angina or evidence of ischemia on noninvasive testing with clinical or laboratory evidence of ventricular dysfunction.

PART 6 Disorders of the Cardiovascular System Examples of other indications for coronary arteriography include the following:

1. Patients with chest discomfort suggestive of angina pectoris but a negative or nondiagnostic stress test who require a definitive diagnosis for guiding medical management, alleviating psychological stress, career or family planning, or insurance purposes.
2. Patients who have been admitted repeatedly to the hospital for a suspected acute coronary syndrome (Chaps. 285 and 286), but in whom this diagnosis has not been established and in whom it is considered clinically important to determine the presence or absence of CAD.

3. Patients with careers that involve the safety of others (e.g., pilots, firefighters, police) who have questionable symptoms or suspicious or positive noninvasive tests and in whom there are reasonable doubts about the state of the coronary arteries.
 4. Patients with aortic stenosis or hypertrophic cardiomyopathy and angina in whom the chest pain could be due to IHD.
 5. Male patients >45 years and females >55 years who are to undergo a cardiac operation such as valve replacement or repair and who may or may not have clinical evidence of myocardial ischemia.
 6. Patients after myocardial infarction, especially those who are at high risk after myocardial infarction because of the recurrence of angina or the presence of heart failure, frequent ventricular premature contractions, or signs of ischemia on the stress test.
 7. Patients in whom coronary spasm or another nonatherosclerotic cause of myocardial ischemia (e.g., coronary artery anomaly, Kawasaki disease) is suspected. Noninvasive alternatives to diagnostic coronary arteriography include CT angiography and CMR angiography (Chap. 248). Important aspects of their use that should be noted include the substantially higher radiation exposure with CT angiography compared to conventional diagnostic arteriography and the limitations on CMR imposed by cardiac movement during the cardiac cycle, especially at high heart rates. ■ ■
- PROGNOSIS** The principal prognostic indicators in patients known to have IHD are age, the functional state of the left ventricle, the location(s) and severity of coronary artery narrowing, and the severity or activity of myocardial ischemia. Angina pectoris of recent onset, unstable angina (Chap. 285), early postmyocardial infarction angina, angina that is unresponsive or poorly responsive to medical therapy, and angina accompanied by symptoms of congestive heart failure all indicate an increased risk for adverse coronary events. The same is true for the physical signs of heart failure, episodes of pulmonary edema, transient third heart sounds, and mitral regurgitation and for echocardiographic or radioisotopic (or roentgenographic) evidence of cardiac enlargement and reduced (<0.40) ejection fraction. Most important, any of the following signs during noninvasive testing indicates a high risk for coronary events: inability to exercise for 6 min, i.e., stage II (Bruce protocol) of the exercise test; a strongly positive exercise test showing onset of myocardial ischemia at low work loads (≥ 0.1 mV ST-segment depression before completion of stage II, ≥ 0.2 mV ST-segment depression at any stage, ST-segment depression for >5 min after the cessation of exercise, a decline in systolic pressure

“ 10 mmHg during exercise, or the development of ventricular tachyarrhythmias during exercise); the development of large or multiple perfusion defects or increased lung uptake during stress radioisotope perfusion imaging; and a decrease in LV ejection fraction during exercise on radionuclide ventriculography or during stress echocardiography. Conversely, patients who can complete stage III of the Bruce

exercise protocol and have a normal stress perfusion scan or negative stress echocardiographic evaluation are at very low risk for future coronary events. The finding of frequent episodes of ST-segment deviation on ambulatory ECG monitoring (even in the absence of symptoms) is also an

adverse prognostic finding. On cardiac catheterization, elevations of LV end-diastolic pressure and ventricular volume and reduced ejection fraction are the most important signs of LV dysfunction and are associated with a poor prognosis. Patients with chest discomfort but normal LV function and normal coronary arteries have an excellent prognosis. Obstructive lesions of the left main (>50% luminal diameter) or left anterior descending coronary artery proximal to the origin of the first septal artery are associated with a greater risk than are lesions of the right or left circumflex coronary artery because of the greater quantity of myocardium at risk. Atherosclerotic plaques in epicardial arteries with fissuring or filling defects indicate increased risk. These lesions go through phases of inflammatory cellular activity, degeneration, endothelial dysfunction, abnormal vasomotion, platelet aggregation, and fissuring or hemorrhage. These factors can temporarily worsen the stenosis and cause thrombosis and/or abnormal reactivity of the vessel wall, thus exacerbating the manifestations of ischemia. The recent onset of symptoms, the development of severe ischemia during stress testing (see above), and unstable angina pectoris (Chap. 285) all reflect episodes of rapid progression in coronary lesions. With any degree of obstructive CAD, mortality is greatly increased when LV function is impaired; conversely, at any level of LV function, the prognosis is influenced importantly by the quantity of myocardium perfused by critically obstructed vessels. Therefore, it is essential to collect all the evidence substantiating past myocardial damage (evidence of myocardial infarction on ECG, echocardiography, radioisotope imaging, or left ventriculography), residual LV function (ejection fraction and wall motion), and risk of future damage from coronary events (extent of coronary disease and severity of ischemia defined by noninvasive stress testing). The larger the quantity of established myocardial necrosis is, the less the heart is able to withstand additional damage and the poorer the prognosis. Risk estimation must include age, presenting symptoms, all risk factors, signs of arterial disease, existing cardiac damage, and signs of impending damage (i.e., ischemia). The greater the number and severity of risk factors for coronary atherosclerosis (advanced age [>75 years], hypertension, dyslipidemia, diabetes, morbid obesity, accompanying peripheral and/or cerebrovascular disease, previous myocardial infarction), the worse the prognosis of an angina patient. Evidence exists that elevated levels of CRP in the plasma, extensive coronary calcification on EBCT (see above), and increased carotid intimal thickening on ultrasound examination also indicate an increased risk of coronary events.

TREATMENT Stable Angina Pectoris Once the diagnosis of IHD has been made, each patient must be evaluated individually with respect to their level of understanding, expectations and goals, control of symptoms, and prevention of adverse clinical outcomes such as myocardial infarction and premature death. The degree of disability and the physical and emotional stress that precipitates angina must be recorded carefully to set treatment goals. The management plan should include the following components: (1) explanation of the problem and reassurance about the ability to formulate a treatment plan, (2) identification and treatment of aggravating conditions, (3) recommendations for adaptation of activity as needed, (4) treatment of risk factors that will decrease the occurrence of adverse coronary outcomes, (5) drug therapy for angina, and (6) consideration of revascularization. Emphasis should be placed on a patient-centric, team-based approach to care, with recognition of the importance of social determinants of health.

EXPLANATION AND REASSURANCE Patients with IHD need to understand their condition and realize that a long and productive life is possible even though they have angina pectoris or have experienced and recovered from an acute

myocardial infarction. Offering results of clinical trials showing improved outcomes can be of great value in encouraging patients to resume or maintain activity and return to work. A planned

program of rehabilitation can encourage patients to lose weight, improve exercise tolerance, and control risk factors with more confidence.

IDENTIFICATION AND TREATMENT OF AGGRAVATING CONDITIONS

A number of conditions may increase oxygen demand or decrease oxygen supply to the myocardium and may precipitate or exacerbate angina in patients with IHD. LVH, aortic valve disease, and hypertrophic cardiomyopathy may cause or contribute to angina and should be excluded or treated. Obesity, hypertension, and hyperthyroidism should be treated aggressively to reduce the frequency and severity of anginal episodes. Decreased myocardial oxygen supply may be due to reduced oxygenation of the arterial blood (e.g., in pulmonary disease or, when carboxyhemoglobin is present, due to cigarette or cigar smoking) or decreased oxygen-carrying capacity (e.g., in anemia). Correction of these abnormalities, if present, may reduce or even eliminate angina pectoris.

ADAPTATION OF ACTIVITY

Myocardial ischemia is caused by a discrepancy between the demand of the heart muscle for oxygen and the ability of the coronary circulation to meet that demand. Most patients can be helped to understand this concept and utilize it in the rational programming of activity. Many tasks that ordinarily evoke angina may be accomplished without symptoms simply by reducing the speed at which they are performed. Patients must appreciate the diurnal variation in their tolerance of certain activities and reducing their energy requirements in the morning, immediately after meals, and in cold or inclement weather. On occasion, it may be necessary to recommend a change in employment or residence to avoid physical stress. Physical conditioning usually improves the exercise tolerance of patients with angina and has substantial psychological benefits. A regular program of isotonic exercise that is within the limits of TABLE 284-3 Energy Requirements for Some Common Activities

Activity	Energy Requirement (METs)
Self-Care	Less than 3
Washing/shaving	3-5
Cleaning windows	3-5
Easy digging in garden	3-5
Heavy shoveling	5-7
Carrying loads upstairs (objects >90 lb)	5-7
Dressing	3-5
Raking	3-5
Level hand lawn mowing	3-5
Carrying objects (60-90 lb)	3-5
Climbing stairs (quickly)	3-5
Light housekeeping	3-5
Power lawn mowing	5-7
Carrying objects (30-60 lb)	3-5
Shoveling heavy snow	5-7
Desk work	3-5
Bed making/stripping	3-5
Driving auto	3-5
Carrying objects (15-30 lb)	3-5
Occupational sitting (clerical/assembly)	3-5
Stocking shelves (light objects)	3-5
Carpentry (exterior)	5-7
Digging ditches (pick and shovel)	5-7
Desk work	3-5
Light welding/carpentry	5-7
Shoveling dirt	5-7
Standing (store clerk)	3-5
Sawing wood	5-7
Recreational	More than 9
Golf (cart)	3-5
Dancing (social)	3-5
Tennis (singles)	3-5
Canoeing	3-5
Squash	3-5
Knitting	3-5
Golf (walking)	3-5
Snow skiing (downhill)	3-5
Mountain climbing	3-5
Ski touring	3-5
Sailing	3-5
Light backpacking	3-5
Vigorous basketball	3-5
Tennis (doubles)	3-5
Basketball	3-5
Stream fishing	3-5
Physical Conditioning	3-5
Walking (2 mph)	3-5
Level walking (3-4 mph)	3-5
Level walking (4.5-5.0 mph)	3-5
Level jogging (5 mph)	3-5
Running more than 6 mph	3-5
Stationary bike	3-5
Level biking (6-8 mph)	3-5
Bicycling (9-10 mph)	3-5
Swimming (crawl stroke)	3-5
Bicycling (more than 13 mph)	3-5
Very light calisthenics	3-5
Light calisthenics	3-5
Swimming, breast stroke	3-5
Rowing machine	3-5
Rope jumping	3-5

Abbreviation: METs, metabolic equivalent tasks. Source: Modified from WL Haskell: Rehabilitation of the coronary patient, in NK Wenger, HK Hellerstein (eds): Design and Implementation of Cardiac Conditioning Program. New York, Churchill Livingstone, 1978.

the individual patient's threshold for the development of angina pectoris and that does not exceed 80% of the heart rate associated with ischemia on exercise testing should be strongly encouraged. Based on the results of an exercise test, the number of metabolic equivalent tasks (METs) performed at the onset of ischemia can be estimated (Table 284-2) and a practical exercise prescription can be formulated to permit daily activities that will fall below the ischemic threshold (Table 284-3).

CHAPTER 284 TREATMENT OF RISK FACTORS A family history of premature IHD is an important indicator of increased risk and should trigger a search for treatable risk factors such as hyperlipidemia, hypertension, and diabetes mellitus. Obesity impairs the treatment of other risk factors and increases the risk of adverse coronary events. In addition, obesity often is accompanied by three other risk factors: diabetes mellitus, hypertension, and hyperlipidemia. The treatment of obesity and these accompanying risk factors is an important component of any management plan. A diet low in saturated and trans-unsaturated fatty acids and a reduced caloric intake to achieve optimal body weight are a cornerstone in the management of chronic IHD. It is especially important to emphasize weight loss and regular exercise in patients with the metabolic syndrome or overt diabetes mellitus. Ischemic Heart Disease Cigarette smoking accelerates coronary atherosclerosis in both sexes and at all ages and increases the risk of thrombosis, plaque instability, myocardial infarction, and death. In addition, by increasing myocardial oxygen needs and reducing oxygen supply, it aggravates angina. Smoking cessation studies have demonstrated important benefits with a significant decline in the occurrence of these adverse outcomes. Noncombustible tobacco in the form of electronic cigarettes (nicotine delivery systems) may also increase the frequency of anginal episodes. The physician's message must be clear and strong and supported by programs that achieve and monitor abstinence from all tobacco product use (Chap. 465). Heavy labor Heavy calisthenics Walking uphill (5 mph) Bicycling (12 mph)

Hypertension (Chap. 288) may coexist with other risk factors for IHD and is associated with an increased risk of adverse clinical events from coronary atherosclerosis as well as stroke. In addition, the LVH that results from sustained hypertension aggravates ischemia. There is evidence that long-term effective treatment of hypertension can decrease the occurrence of adverse coronary events (Chap. 288).

PART 6 Disorders of the Cardiovascular System Diabetes mellitus (Chap. 415) accelerates coronary, cerebrovascular, and peripheral atherosclerosis and is frequently associated with dyslipidemia and increases in the risk of angina, myocardial infarction, and sudden coronary death. Aggressive control of the dyslipidemia (target LDL cholesterol <70 mg/dL) and hypertension (blood pressure <130/80 mmHg), that are frequently found in patients with diabetes mellitus, is highly effective and therefore essential, as described below. Use of either a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or glucagon-like peptide 1 (GLP-1) receptor agonist in patients with IHD and type 2 diabetes is recommended in current guidelines to reduce the risk of major adverse cardiovascular events. DYSLIPIDEMIA The treatment of dyslipidemia is central in aiming for long-term relief from angina, reduced need for revascularization, and reduction in myocardial infarction and death. The control of lipids can be achieved by the combination of a diet low in saturated and trans-unsaturated fatty acids, exercise, and weight loss. Nearly always, HMG-CoA reductase inhibitors (statins) are required and can lower LDL cholesterol (25–50%), raise HDL cholesterol (5–9%), and lower triglycerides (5–30%). A powerful treatment effect of statins on atherosclerosis, IHD, and outcomes is seen regardless of the pretreatment LDL cholesterol level. In patients with IHD on a maximally tolerated statin with an LDL cholesterol \geq 70 mg/dL, addition of ezetimibe is recommended as the next step, followed by a PCSK9 inhibitor (in patients at very high risk) should the LDL cholesterol goal not be achieved. When these therapies are not sufficient or tolerated, bempedoic acid may be considered for further LDL cholesterol reduction. Icosapent ethyl (purified eicosapentaenoic acid), fibrates, and resin-binding agents can be used to lower triglycerides (Chap. 419), but only icosapent ethyl has been shown to reduce cardiovascular risk in the statin

era. Controlled trials with lipid-regulating regimens have shown equal proportional benefit for men, women, the elderly, patients with diabetes mellitus, and smokers. Evidence exists that a high rate of control of LDL over time is associated with a lower cumulative LDL exposure and lower rate of major adverse cardiovascular events. Compliance with the health-promoting behaviors listed above is generally very poor, and a conscientious physician must not underestimate the major effort required to meet this challenge. Many patients who are discharged from the hospital with proven coronary disease do not receive adequate treatment for dyslipidemia. In light of the proof that treating dyslipidemia brings major benefits, physicians need to establish treatment pathways, monitor compliance, and follow up regularly.

RISK REDUCTION IN WOMEN WITH IHD The incidence of clinical IHD in premenopausal women is very low; however, after menopause, the atherogenic risk factors increase (e.g., increased LDL) and the rate of clinical coronary events accelerates to the levels observed in men. Diabetes mellitus, which is more common in women, greatly increases the occurrence of clinical IHD and amplifies the deleterious effects of hypertension, hyperlipidemia, and smoking. Cardiac catheterization and coronary revascularization are underused in women and are performed at a later and more severe stage of the disease than in men. When cholesterol lowering, beta blockers after myocardial infarction, and CABG are applied in the appropriate patient groups, women benefit to the same degree as men.

DRUG THERAPY The commonly used drugs for the treatment of angina pectoris are summarized in Tables 284-4 through 284-6. Pharmacotherapy for IHD is designed to reduce the frequency of anginal episodes,

TABLE 284-4 Nitrate Therapy in Patients with Ischemic Heart Disease

Preparation	Agent	Dose Schedule
Ointment	Nitroglycerin	0.5–2 in. Two or three times daily
Transdermal patch	Nitroglycerin	0.2–0.8 mg/h Every 24 h; remove at bedtime for 12–14 h
Sublingual tablet	Nitroglycerin	0.3–0.6 mg As needed, up to three doses
Spray	Nitroglycerin	5 min apart One or two sprays As needed, up to three doses
Oral sustained release	Isosorbide dinitrate	10–40 mg Two or three times daily
Oral	Isosorbide 5-mononitrate	20 mg Twice daily (given 7–8 h apart)
Oral sustained release	Isosorbide 5-mononitrate	30–240 mg Once daily

5 min apart Spray One or two sprays As needed, up to three doses

5 min apart Isosorbide dinitrate Oral 10–40 mg Two or three times daily Oral sustained release 80–120 mg Once or twice daily (eccentric schedules) Isosorbide 5-mononitrate Oral 20 mg Twice daily (given 7–8 h apart) Oral sustained release 30–240 mg Once daily

aA 10- to 12-h nitrate-free interval is recommended. Source: Reproduced with permission from DA Morrow, WE Boden: Stable ischemic heart disease. In RO Bonow et al (eds): Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 9th ed. Philadelphia, Saunders, 2012.

myocardial infarction, and coronary death. Trial data emphasize how important medical management is when added to the healthpromoting behaviors discussed above. To achieve maximum benefit from medical therapy for IHD, it is frequently necessary to combine agents from different classes and titrate the doses as guided by the individual profile of risk factors, symptoms, hemodynamic responses, and side effects.

NITRATES The organic nitrates are a valuable class of drugs in the management of angina pectoris (Table 284-4). Their major mechanisms of action include systemic venodilation with concomitant reduction in LV end-diastolic volume and pressure, thereby reducing myocardial wall tension and oxygen requirements; dilation of epicardial coronary vessels; and increased blood flow in collateral vessels. When metabolized, organic nitrates release nitric oxide (NO) that binds to guanylyl cyclase in vascular smooth muscle

TABLE 284-5 Properties of Beta Blockers in Clinical Use for Ischemic Heart Disease

Partial Agonist Activity	Usual Dose for Angina	Drugs
Yes	200–600 mg twice daily	Acebutolol β_1
No	50–200 mg/d	Atenolol β_1
No	10–20 mg/d	Bisoprolol β_1
No	10 mg/d	Esmolol (intravenous) β_1
No	50–300 μ g/kg/min	Esmolol (intravenous) β_1

Labetalolb None Yes 200–600 mg twice daily Metoprolol β 1 No 50–200 mg twice daily Nadolol None No 40–80 mg/d Nebivolol β 1 (at low doses) No 5–40 mg/d Pindolol None Yes 2.5–7.5 mg 3 times daily Propranolol None No 80–120 mg twice daily Timolol None No 10 mg twice daily aEsmolol is an ultra-short-acting beta blocker that is administered as a continuous intravenous infusion. Its rapid offset of action makes esmolol an attractive agent to use in patients with relative contraindications to beta blockade. bLabetolol is a combined alpha and beta blocker. Note: This list of beta blockers that may be used to treat patients with angina pectoris is arranged alphabetically. It is preferable to use a sustained-release formulation that may be taken once daily to improve the patient's compliance with the regimen. Source: Data from RJ Gibbons et al: J Am Coll Cardiol 41:159, 2003.

TABLE 284-6 Calcium Channel Blockers in Clinical Use for Ischemic Heart Disease

DURATION OF ACTION	SIDE EFFECTS	DRUGS	USUAL DOSE
Long	Headache, edema	Dihydropyridines Amlodipine	5–10 mg qd
Long	Headache, edema	Felodipine	5–10 mg qd
Medium	Headache, fatigue	Isradipine	2.5–10 mg bid
Short	Headache, dizziness, flushing, edema	Nicardipine	20–40 mg tid
Immediate release:		Nifedipine	30–90 mg daily orally
Slow release:			

30–180 mg orally Short Hypotension, dizziness, flushing, nausea, constipation, edema Nisoldipine 20–40 mg qd Short Similar to nifedipine Nondihydropyridines Diltiazem Immediate release: 30–80 mg 4 times daily Short Hypotension, dizziness, flushing, bradycardia, edema Slow release:

120–320 mg qd Long Verapamil Immediate release: 80–160 mg tid Short Hypotension, myocardial depression, Slow release: 120–480 mg qd Long heart failure, edema, bradycardia aMay be associated with increased risk of mortality if administered during acute myocardial infarction. Note: This list of calcium channel blockers that may be used to treat patients with angina pectoris is divided into two broad classes, dihydropyridines and nondihydropyridines, and arranged alphabetically within each class. Among the dihydropyridines, the greatest clinical experience has been obtained with amlodipine and nifedipine. After the initial period of dose titration with a shortacting formulation, it is preferable to switch to a sustained-release formulation that may be taken once daily to improve patient compliance with the regimen. Source: Data from RJ Gibbons et al: J Am Coll Cardiol 41:159, 2003. cells, leading to an increase in cyclic guanosine monophosphate, which causes relaxation of vascular smooth muscle. Nitrates also exert antithrombotic activity by NO-dependent activation of platelet guanylyl cyclase, impairment of intraplatelet calcium flux, and platelet activation. The absorption of these agents is rapid and complete through mucous membranes. For this reason, nitroglycerin is most commonly administered sublingually in tablets of 0.4 or 0.6 mg. Patients with angina should be instructed to take the medication both to relieve angina and also ~5 min before activities that are likely to induce an episode. Nitrates improve exercise tolerance in patients with chronic angina and relieve ischemia in patients with unstable angina as well as patients with vasospastic variant angina (Chap. 285). A diary of angina and nitroglycerin use may be valuable for detecting changes in the frequency, severity, or threshold for discomfort that may signify the development of unstable angina pectoris and/or herald an impending myocardial infarction. Long-Acting Nitrates None of the long-acting nitrates is as effective as sublingual nitroglycerin for the acute relief of angina. These organic nitrate preparations can be swallowed, chewed, or administered as a patch or paste by the transdermal route (Table 284-4). They provide effective plasma levels for up to 24 h, but the therapeutic response is highly variable. Different preparations and/or administration during the daytime should be tried only to prevent discomfort while avoiding side effects such as headache and dizziness. Individual dose

titration is important to prevent side effects. To minimize the effects of nitrate tolerance, the minimum effective dose should be used and a minimum of 8 h each day kept free of the drug to restore any useful response(s).

Beta-Adrenergic Blockers These drugs represent an important component of the pharmacologic treatment of angina pectoris (Table 284-5). They reduce myocardial oxygen demand by inhibiting the increases in heart rate, arterial pressure, and myocardial contractility caused by adrenergic activation. Beta blockade reduces these variables most strikingly during exercise but causes only small reductions at rest. Long-acting beta-blocking drugs or sustained-release formulations offer the advantage of once-daily dosing (Table 284-5). The therapeutic aims include relief of angina and ischemia. These drugs also can reduce mortality and reinfarction rates in patients after myocardial infarction and are moderately effective antihypertensive agents. Use of beta blockers beyond 1 year after myocardial infarction may be reassessed in the absence of LV systolic dysfunction, angina, arrhythmias, or uncontrolled hypertension, as their long-term benefit in such patients is unclear.

CHAPTER 284 Ischemic Heart Disease Relative contraindications include asthma and reversible airway obstruction in patients with chronic lung disease, atrioventricular conduction disturbances, severe bradycardia, Raynaud's phenomenon, and a history of mental depression. Side effects include fatigue, reduced exercise tolerance, nightmares, impotence, cold extremities, intermittent claudication, bradycardia (sometimes severe), impaired atrioventricular conduction, LV failure, bronchial asthma, worsening claudication, and intensification of the hypoglycemia produced by oral hypoglycemic agents and insulin. Reducing the dose or even discontinuation may be necessary if these side effects develop and persist. Since sudden discontinuation can intensify ischemia, the doses should be tapered over 2 weeks. Beta blockers with relative β_1 -receptor specificity such as metoprolol and atenolol may be preferable in patients with mild bronchial obstruction and insulin-requiring diabetes mellitus.

Calcium Channel Blockers Calcium channel blockers (Table 284-6) are coronary vasodilators that produce variable and dose-dependent reductions in myocardial oxygen demand, contractility, and arterial pressure. These combined pharmacologic effects are advantageous and make these agents as effective as beta blockers in the treatment of angina pectoris. They are indicated when beta blockers are contraindicated, poorly tolerated, or ineffective. Because of differences in the dose-response relationship on cardiac electrical activity between the dihydropyridine and nondihydropyridine calcium channel blockers, verapamil and diltiazem may produce symptomatic disturbances in cardiac conduction and bradyarrhythmias. They also exert negative inotropic actions and are more likely to aggravate LV failure, particularly when used in patients with LV dysfunction, especially if the patients are also receiving beta blockers. Although useful effects usually are achieved when calcium channel blockers are combined with beta blockers and nitrates, individual titration of the doses is essential with these combinations. Vasospastic angina responds particularly well to calcium channel blockers (especially members of the dihydropyridine class), supplemented when necessary by nitrates (Chap. 285). Verapamil ordinarily should not be combined with beta blockers because of the combined adverse effects on heart rate and contractility. Diltiazem can be combined with beta blockers in patients with normal ventricular function and no conduction disturbances. Amlodipine and beta blockers have complementary actions on coronary blood supply and myocardial oxygen demands. Whereas the former decreases blood pressure and dilates coronary arteries, the latter slows heart rate and decreases contractility. Amlodipine and the other second-generation dihy

dihydropyridine calcium antagonists (nicardipine, isradipine, long-acting nifedipine, and felodipine) are potent vasodilators and are useful in the simultaneous treatment of angina and hypertension. Short-acting dihydropyridines should be avoided because of the risk of precipitating infarction, particularly in the absence of concomitant beta blocker therapy.

Choice Between Beta Blockers and Calcium Channel Blockers for Initial Therapy Since beta blockers have been shown to improve life expectancy after acute myocardial infarction (Chaps. 285 and 286) and calcium channel blockers have not, the former may also be preferable in patients with angina and a damaged left ventricle. However, calcium channel blockers are indicated in patients with the following: (1) inadequate responsiveness to the combination of beta blockers and nitrates; many of these patients do well with a combination of a beta blocker and a dihydropyridine calcium channel blocker; (2) adverse reactions to beta blockers such as depression, sexual disturbances, and fatigue; (3) angina and a history of asthma or chronic obstructive pulmonary disease; (4) sick-sinus syndrome or significant atrioventricular conduction disturbances; (5) vasospastic angina; or (6) symptomatic peripheral arterial disease.

PART 6 Disorders of the Cardiovascular System Ranolazine, a piperazine derivative, may be useful for patients with chronic angina despite standard medical therapy (Table 284-7). Its antianginal action is believed to occur via inhibition of the late inward sodium current (I_{Na}). The benefits of I_{Na} inhibition include limitation of the Na⁺ overload of ischemic myocytes and prevention of Ca²⁺ overload via the Na⁺-Ca²⁺ exchanger. A dose of 500-1000 mg orally twice daily is usually well tolerated. Ranolazine is contraindicated in patients with hepatic impairment or with conditions or drugs associated with QTc prolongation, and when drugs that inhibit the CYP3A metabolic system (e.g., ketoconazole, diltiazem, verapamil, macrolide antibiotics, HIV protease inhibitors, and large quantities of grapefruit juice) are being used. A comparison of the common side effects, contraindications, and potential drug interactions of many of the frequently presented antianginal agents is shown in Table 284-7.

Antiplatelet Drugs Aspirin is an irreversible inhibitor of platelet cyclooxygenase and thereby interferes with platelet activation. Chronic administration of 75-325 mg orally per day has been shown to reduce coronary events in asymptomatic adult men over age 50, patients with chronic stable angina, and patients who have or have survived unstable angina and myocardial infarction. There is a dose-dependent increase in bleeding when aspirin is used chronically. It is preferable to use an enteric-coated formulation in the range of 75-162 mg/d. Administration of this drug should be considered in all patients with IHD in the absence of gastrointestinal bleeding, allergy, or dyspepsia.

Clopidogrel (300-600 mg TABLE 284-7)

AGENT	COMMON SIDE EFFECTS	CONTRAINDICATIONS	POTENTIAL DRUG INTERACTIONS
Agents That Have a Physiologic Effect	Short-acting and long-acting nitrates	Headache, flushing, hypotension, syncope and postural hypotension, reflex tachycardia, methemoglobinemia	Hypertrophic obstructive cardiomyopathy
Phosphodiesterase type 5 inhibitors (sildenafil and similar agents), betaadrenergic blockers, calcium channel blockers	Beta blockers	Fatigue, depression, bradycardia, heart block, bronchospasm, peripheral vasoconstriction, postural hypotension, impotence, masked signs of hypoglycemia	Low heart rate or heart conduction disorder, cardiogenic shock, asthma, severe peripheral vascular disease, decompensated heart failure, vasospastic angina; use with caution in patients with COPD (cardioselective beta blockers may be used if patient receives adequate treatment with long-acting beta agonists)
Calcium-channel blockers	Heart rate-lowering agents	Bradycardia, heart conduction defect, low ejection fraction, constipation, gingival hyperplasia	Cardiogenic shock, severe aortic stenosis, obstructive cardiomyopathy

Dihydropyridine Headache, ankle swelling fatigue, flushing, reflex tachycardia Low heart rate or heart rhythm disorder, sick-sinus syndrome, congestive heart failure, low blood pressure Agents That Affect Myocardial Metabolism Ranolazine Dizziness, constipation, nausea, QT interval prolongation Liver cirrhosis CYP3A4 substrates (digoxin, simvastatin, cyclosporine), drugs that prolong the corrected QT interval Abbreviations: AV, atrioventricular; COPD, chronic obstructive pulmonary disease; CYP3A4, cytochrome P450 3A4. Source: Data from SE Husted: Lancet 386:691, 2015, and EM Ohman: N Engl J Med 374:1167, 2016.

loading and 75 mg/d) is an oral agent that blocks P2Y₁₂ ADP receptor-mediated platelet aggregation. It provides benefits similar to those of aspirin in patients with stable chronic IHD and may be substituted for aspirin if aspirin causes the side effects listed above. Clopidogrel combined with aspirin reduces death and coronary ischemic events in patients with an acute coronary syndrome (Chap. 285) and also reduces the risk of thrombus formation in patients undergoing implantation of a stent in a coronary artery (Chap. 287). Alternative antiplatelet agents that block the P2Y₁₂ platelet receptor such as prasugrel and ticagrelor have been shown to be more effective than clopidogrel for prevention of ischemic events after placement of a stent for an acute coronary syndrome but are associated with an increased risk of bleeding. Although combined treatment with clopidogrel and aspirin for at least a year is recommended in patients with an acute coronary syndrome treated with implantation of a drug-eluting stent, studies have not shown any benefit from the routine addition of clopidogrel to aspirin in patients with chronic stable IHD. OTHER THERAPIES ACE inhibitors and ARBs are widely used in the treatment of survivors of myocardial infarction, patients with hypertension or chronic IHD including angina pectoris, and those at high risk of vascular diseases such as diabetes. The benefits of ACE inhibitors and ARBs are most evident in IHD patients at increased risk, especially if diabetes mellitus or LV dysfunction is present, and those who have not achieved adequate control of blood pressure and LDL cholesterol on beta blockers and statins. However, the routine administration of ACE inhibitors or ARBs to IHD patients who have normal LV function and have achieved blood pressure and LDL goals on other therapies does not reduce the incidence of events and therefore is not cost-effective. Despite treatment with nitrates, beta blockers, calcium channel blockers, and ranolazine, some patients with IHD continue to experience angina, and additional medical therapy is now available to alleviate their symptoms. Originally introduced for the management of diabetes mellitus, the SGLT-2 inhibitor drugs have emerged as important agents with cardiovascular and renal protective effects. They promote weight loss, lower blood pressure, and reduce plasma volume—all of which are desirable in patients with IHD. In addition, they decrease Heart rate—lowering calcium channel blockers, sinus node or AV conduction depressors CYP3A4 substrates (digoxin, simvastatin, cyclosporine) Agents with cardiodepressant effects (beta blockers, flecainide), CYP3A4 substrates

intraglomerular hypertension and hyperfiltration. Evidence exists that they are helpful in patients with and without diabetes who have a reduced LV ejection fraction. Colchicine exhibits a number of broad cellular effects (interferes with chemotaxis and phagocytosis of inflammatory cells, reduces the expression of adhesion molecules, modifies cytokine production) that result in an anti-inflammatory effect and may favorably affect the progression of atherosclerosis. In placebo-controlled randomized trials after myocardial infarction, low-dose colchicine (0.5 mg daily) prevented future cardiovascular events; however because it has a narrow therapeutic window, has a long half-life dependent upon renal clearance, is metabolized by CYP3A4, and is a substrate for P-glycoprotein (both of which that may result in drug-drug interactions), additional monitoring is

required. In contrast, nonsteroidal anti-inflammatory drug (NSAID) use in patients with IHD may be associated with a small but finite increased risk of myocardial infarction and mortality. For this reason, they generally should be avoided in IHD patients. If they are required for symptom relief, it is advisable to coadminister aspirin and strive to use an NSAID associated with the lowest risk of cardiovascular events, in the lowest dose required, and for the shortest period of time. Nicorandil opens ATP-sensitive potassium channels in myocytes, leading to a reduction of free intracellular calcium ions. It is typically administered orally in a dose of 20 mg twice daily for prevention of angina. Nicorandil is not available for use in the United States but is used in several other countries and is recommended as second-line treatment in the European chronic coronary disease (CCD) guidelines. Similarly, trimetazidine, which improves mitochondrial metabolism through inhibition of myocardial fatty acid uptake and oxidation and consequent stimulation of glucose oxidation, is recommended as a secondline antianginal in CCD and is available in many countries outside the United States. Ivabradine (2.5–7.5 mg orally twice daily) is a specific sinus node inhibiting agent that may be helpful for preventing cardiovascular events in patients with IHD who have a resting heart rate ≥ 70 beats/min (alone or in combination with a beta blocker) and LV systolic dysfunction. However, the data are mixed regarding its clinical benefit, with the most recent U.S. CCD guideline recommending against its use in patients with normal LV function due to an increased risk of death or myocardial infarction). Angina and Heart Failure Transient LV failure with angina can be controlled by the use of nitrates. For patients with established congestive heart failure, the increased LV wall tension raises myocardial oxygen demand. See Chap. 265 for the “pillars” of treatment for heart failure. Treatment of congestive heart failure (Chap. 264) reduces heart size, wall tension, and myocardial oxygen demand, which helps control angina and ischemia. If the symptoms and signs of heart failure are controlled, an effort should be made to use beta blockers not only for angina but because trials in heart failure have shown significant improvement in survival. A trial of the intravenous ultra-short-acting beta blocker esmolol may be useful to establish the safety of beta blockade in selected patients. Nocturnal angina often can be relieved by the treatment of heart failure. The combination of congestive heart failure and angina in patients with IHD usually indicates a poor prognosis and warrants serious consideration of cardiac catheterization and coronary revascularization. CORONARY REVASCULARIZATION Clinical trials have confirmed that with the initial diagnosis of stable IHD, it is first appropriate to initiate a medical regimen as described above. Revascularization should be considered in the presence of unstable phases of the disease, intractable symptoms, high-risk coronary anatomy, diabetes, and impaired LV function. Revascularization should be employed in conjunction with but not replace the continuing

Initiate medical therapy:

1. Decrease demand ischemia
2. Minimize IHD risk factors
3. ASA (clopidogrel if ASA intolerant) CHAPTER 284 Any high-risk features? Low exercise capacity or ischemia at low workload, EF <40%, ACS presentation Ischemic Heart Disease No Yes Are exertional symptoms controlled? Refer for coronary arteriography Anatomy suitable for revascularization? Yes No Yes No Consider unconventional treatments Single-vessel disease LM +/-or multivessel disease PCI Assess: PCI vs CABG Continue medical therapy periodic stress assessment (see Fig. 284-3) FIGURE 284-4 Algorithm for management of a patient with ischemic heart disease. All patients should receive the core

elements of medical therapy as shown at the top of the algorithm. If high-risk features are present, as established by the clinical history, exercise test data, and imaging studies, the patient should be referred for coronary arteriography. Based on the number and location of the diseased vessels and their suitability for revascularization, the patient is treated with a percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery or should be considered for unconventional treatments. See text for further discussion. ACS, acute coronary syndrome; ASA, aspirin; EF, ejection fraction; IHD, ischemic heart disease; LM, left main. need to modify risk factors and assess medical therapy. An algorithm for integrating medical therapy and revascularization options in patients with IHD is shown in Fig. 284-4. ■ ■

■ ■ PERCUTANEOUS CORONARY INTERVENTION

(See also Chap. 287) PCI involving balloon dilatation usually accompanied by coronary stenting is widely used to achieve revascularization of the myocardium in patients with symptomatic IHD and suitable stenoses of epicardial coronary arteries. Whereas patients with stenosis of the left main coronary artery and those with three-vessel IHD (especially with diabetes and/or impaired LV function) who require revascularization are best treated with CABG, PCI is widely employed in patients with symptoms and evidence of ischemia due to stenoses of one or two vessels and even in selected patients with three-vessel disease (and, perhaps, in some patients with left main disease) and may offer many advantages over surgery. Indications and Patient Selection The most common clinical indication for PCI is symptom-limiting angina pectoris, despite medical therapy, accompanied by evidence of ischemia during a stress test. PCI is more effective than medical therapy for the relief of angina. PCI improves outcomes in patients with unstable angina or when used early in the course of myocardial infarction with and without cardiogenic shock. However, in patients with stable exertional angina, clinical trials

have confirmed that PCI does not reduce the occurrence of death or myocardial infarction compared to optimum medical therapy. PCI can be used to treat stenoses in native coronary arteries as well as in bypass grafts in patients who have recurrent angina after CABG.

Risks When coronary stenoses are discrete and symmetric, two and even three vessels can be treated in sequence. However, case selection is essential to avoid a prohibitive risk of complications, which are usually due to dissection or thrombosis with vessel occlusion, uncontrolled ischemia, and ventricular failure (Chap. 287). Oral aspirin, a P2Y₁₂ antagonist, and an antithrombin agent are given to reduce coronary thrombus formation. Left main coronary artery stenosis generally is regarded as a lesion that should be treated with CABG. In selected cases such as patients with prohibitive surgical risks, PCI of an unprotected left main can be considered, but such a procedure should be performed only by a highly skilled operator; importantly, there are regional differences in the use of this approach internationally. PART 6 Disorders of the Cardiovascular System Efficacy Primary success, with relief of angina, is achieved in >95% of cases. In diseased vein grafts, procedural success has been improved by the use of an embolic protection device, when feasible, to prevent ischemia and infarction. The use of current-generation drug-eluting stents that locally deliver antiproliferative drugs have a lower rate of restenosis (<5%) than the initial bare metal stents and are now the standard of care in PCI. Of note, however, the delayed endothelial healing in the region of a drug-eluting stent also extends the period during which the patient is at risk for subacute stent thrombosis. Aspirin should be administered indefinitely and a P2Y₁₂ antagonist daily (dual antiplatelet therapy [DAPT]) ideally for 1 year after

implantation of a drug-eluting stent. Evidence exists of a benefit of continuing DAPT for up to 30 months, albeit at the cost of a higher risk of bleeding. Shorter courses of DAPT may be used in patients who are at high bleeding risk (see Chap. 69) or who have a long-term indication for oral anticoagulation (see Chap. 121). Efforts are underway to develop new antithrombotic regimens to reduce the risk of bleeding. These include (1) shortening the duration of DAPT by eliminating aspirin after 1 or 3 months and continuing a P2Y₁₂ antagonist alone, (2) de-escalating from a potent P2Y₁₂ inhibitor (i.e., prasugrel, ticagrelor) after 1 month to clopidogrel or reduced-dose prasugrel 5 mg daily, and (3) switching from DAPT to dual pathway inhibition with an antiplatelet agent and a low-dose direct oral anti coagulant. While each of these has been compared to standard DAPT regimens, such studies tend to be unpowered for ischemic events, and these alternative strategies have not been compared to one another. When a situation arises in which temporary discontinuation of antiplatelet therapy is necessary, the clinical circumstances should be reviewed with the operator who performed the PCI and a coordinated plan should be established for minimizing the risk of late stent thrombus; central to this plan is the discontinuation of antiplatelet therapy for the shortest acceptable period. The risk of stent thrombosis is dependent on stent size and length, complexity of the lesions, age, diabetes, and technique. However, compliance with DAPT and individual responsiveness to platelet inhibition are very important factors as well. Successful PCI produces effective relief of angina in >95% of cases. The majority of patients with symptomatic IHD who require revascularization can be treated initially by PCI. Successful PCI is less invasive and expensive than CABG and permits savings in the initial cost of care. Successful PCI avoids the risk of stroke associated with CABG surgery and allows earlier return to work and resumption of an active life. However, the early health-related and economic benefits of PCI are reduced over time because of the greater need for follow-up and the increased need for repeat procedures. When directly compared in patients with diabetes or three-vessel or left main CAD, CABG was superior to PCI in preventing major adverse cardiac or cerebrovascular events over a 12-month follow-up. ■ ■CORONARY ARTERY BYPASS GRAFTING Anastomosis of one or both of the internal mammary arteries or a radial artery to the coronary artery distal to the obstructive lesion is the preferred procedure. For additional obstructions that cannot be bypassed by an artery, a section of a vein (usually the saphenous) is

used to form a venous bypass conduit between the aorta and the coronary artery distal to the obstructive lesion. Although some indications for CABG are controversial, certain areas of agreement exist:

1. The operation is relatively safe, with mortality rates <1% in patients without serious comorbid disease and normal LV function and when the procedure is performed by an experienced surgical team.
2. Intraoperative and postoperative mortality rates increase with the severity of ventricular dysfunction, comorbidities, age ≥80 years, and lack of surgical experience. The effectiveness and risk of CABG vary widely depending on case selection and the skill and experience of the surgical team.
3. Occlusion of venous grafts is observed in 10–20% of patients during the first postoperative year and in ~2% per year during 5- to 7-year follow-up and 4% per year thereafter. Long-term patency rates are considerably higher for internal mammary and radial artery implantations than for saphenous vein grafts. In patients with left anterior descending coronary artery obstruction, survival is better when coronary bypass involves the internal

mammary artery rather than a saphenous vein. Graft patency and outcomes are improved by meticulous treatment of risk factors, particularly dyslipidemia.

4. Angina is abolished or greatly reduced in ~90% of patients after complete revascularization. Although this usually is associated with graft patency and restoration of blood flow, the pain may also have been alleviated as a result of infarction of the ischemic segment, denervation due to median sternotomy, or a placebo effect.
5. Survival may be improved by operation in patients with stenosis of the left main coronary artery as well as in patients with three- or two-vessel disease with significant obstruction of the proximal left anterior descending coronary artery. The survival benefit is greater in patients with abnormal LV function (ejection fraction <35). Survival may also be improved in the following patients: (a) patients with obstructive CAD who have survived sudden cardiac death or sustained ventricular tachycardia; (b) patients who have undergone previous CABG and have multiple saphenous vein graft stenoses, especially of a graft supplying the left anterior descending coronary artery; and (c) patients with recurrent stenosis after PCI and high-risk criteria on noninvasive testing.
6. Minimally invasive CABG through a small thoracotomy and/or offpump surgery can reduce morbidity and shorten convalescence in suitable patients but does not appear to reduce significantly the risk of neurocognitive dysfunction postoperatively.
7. Among patients with type 2 diabetes mellitus and multivessel coronary disease, CABG surgery plus optimal medical therapy is superior to optimal medical therapy alone in preventing major cardiovascular events, a benefit mediated largely by a significant reduction in nonfatal myocardial infarction. The benefits of CABG are especially evident in patients with diabetes mellitus treated with an insulin-sensitizing strategy as opposed to an insulin-providing strategy. CABG has also been shown to be superior to PCI (including the use of drug-eluting stents) in preventing death, myocardial infarction, and repeat revascularization in patients with diabetes mellitus and multivessel IHD. Indications for CABG usually are based on the severity of symptoms, coronary anatomy, and ventricular function. The ideal candidate has no other complicating disease and has troublesome or disabling angina that is not adequately controlled by medical therapy or does not tolerate medical therapy. Great symptomatic benefit can be anticipated if a patient wishes to lead a more active life and has severe stenoses of two or three epicardial coronary arteries with objective evidence of myocardial ischemia as a cause of the chest discomfort. Congestive heart failure and/or LV dysfunction, advanced age (≥ 80 years), reoperation, urgent need for surgery, and the presence of diabetes mellitus are all associated with a higher perioperative mortality rate. LV dysfunction can be due to noncontractile or hypocontractile segments that are viable but are chronically ischemic (hibernating myocardium). As a consequence of chronic reduction in myocardial blood flow, these segments downregulate their contractile function.

They can be detected by using radionuclide scans of myocardial perfusion and metabolism, PET, cardiac MRI, or delayed scanning with thallium-201 or by improvement of regional functional impairment provoked by low-dose dobutamine. In such patients, revascularization improves myocardial blood flow, can return function, and can improve survival. The Choice Between PCI and CABG All the clinical characteristics of each individual patient must be used to decide on the method of revascularization (e.g., LV function, diabetes, lesion complexity). A number of randomized clinical trials have compared PCI and CABG in patients with multivessel CAD who were

suitable technically for both procedures. The redevelopment of angina requiring repeat coronary angiography and repeat revascularization is higher with PCI. This is a result of restenosis in the stented segment (a problem largely solved with drug-eluting stents) and the development of new stenoses in unstented portions of the coronary vasculature. It has been argued that PCI with stenting focuses on culprit lesions, whereas a bypass graft to the target vessel also provides a conduit around future culprit lesions proximal to the anastomosis of the graft to the native vessel (Fig. 284-5). By contrast, stroke rates are lower with PCI. Based on available evidence, it is now recommended that patients with lifestyle-limiting angina despite guideline-directed medical management and therapy be considered for coronary revascularization. Patients with single- or two-vessel disease with normal LV function and anatomically suitable lesions ordinarily are advised to undergo PCI (Chap. 287). For patients who are poor candidates for surgery, it is reasonable to choose PCI over CABG to improve symptoms and reduce major adverse cardiac events. **FIGURE 284-5** Difference in the approach to the lesion with percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). PCI is targeted at the “culprit” lesion or lesions, whereas CABG is directed at the epicardial vessel, including the culprit lesion or lesions and future culprits, proximal to the insertion of the vein graft, a difference that may account for the superiority of CABG, at least in the intermediate term, in patients with multivessel disease. (From *The New England Journal of Medicine*, Quantitative Determinants of the Outcome of Asymptomatic Mitral Regurgitation, M Enriquez-Sarano et al. 352, 2235. Copyright © 2005. Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.) In patients with left main disease associated with high-complexity CAD, CABG remains preferred to PCI to improve survival. Similarly, in patients with diabetes and multivessel disease involving the left anterior descending artery, CABG (with a left internal mammary conduit) is preferred over PCI, although in patients with low- or intermediate-complexity CAD, PCI may be considered. Patients with three-vessel disease (or two-vessel disease that includes the proximal left descending coronary artery) and impaired global LV function (LV ejection fraction <50%) or diabetes mellitus and those with left main CAD or other lesions unsuitable for catheter-based procedures should be considered for CABG as the initial method of revascularization. In light of the complexity of the decision-making, it is desirable to have a multidisciplinary team, including a cardiologist and a cardiac surgeon in conjunction with the patient’s primary care physician, provide input along with ascertaining the patient’s preferences before committing to a particular revascularization option. ■ ■ **UNCONVENTIONAL TREATMENTS FOR IHD** On occasion, clinicians will encounter a patient who has persistent, disabling angina despite maximally tolerated medical therapy and for whom revascularization is not an option (e.g., small diffusely diseased vessels not amenable to stent implantation or acceptable targets for bypass grafting). In such situations, unconventional treatments should be considered. Enhanced external counterpulsation utilizes pneumatic cuffs on the lower extremities to provide diastolic augmentation and systolic unloading of blood pressure to decrease cardiac work and oxygen consumption while enhancing coronary blood flow. Clinical trials have shown that regular application improves angina, exercise capacity, and regional myocardial perfusion. Neuromodulation (e.g., spinal cord stimulation, transcutaneous or subcutaneous electrical neural stimulation, sympathectomy) and

PCI CHAPTER 284 Lesion Stent Ischemic Heart Disease CABG Coronary artery Future culprit lesion A Lesion Bypass graft Future culprit lesion B coronary sinus constriction (using a reducer device) have shown promise in small studies. Experimental approaches, such as stem cell therapies and cardiac repair with small noncoding RNA molecules (miRNA), are also under active study. **ASYMPTOMATIC (SILENT) ISCHEMIA** Obstructive CAD, acute myocardial infarction, and transient

myocardial ischemia can occur in the absence of symptoms. During continuous ambulatory ECG monitoring, the majority of ambulatory patients with typical chronic stable angina are found to have objective evidence of myocardial ischemia (ST-segment depression) during episodes of chest discomfort while they are active outside the hospital. In addition, many of these patients also have more frequent episodes of asymptomatic ischemia. Frequent episodes of ischemia (symptomatic and asymptomatic) during daily life appear to be associated with an increased likelihood of adverse coronary events (death and myocardial infarction). In addition, patients with asymptomatic ischemia after a myocardial infarction are at greater risk for a second coronary event. The widespread use of exercise ECG during routine examinations has also identified some of these previously unrecognized patients with asymptomatic CAD. Longitudinal studies have demonstrated an increased incidence of coronary events in asymptomatic patients with positive exercise tests.

TREATMENT Asymptomatic Ischemia The management of patients with asymptomatic ischemia must be individualized. When coronary disease has been confirmed, the aggressive treatment of hypertension and dyslipidemia is essential and will decrease the risk of infarction and death. In addition, the physician should consider the following: (1) the degree of positivity

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