CHAPTER 17

Ischemic Heart Disease

ROBERT L. TALBERT

KEY CONCEPTS

1. Ischemic heart disease (IHD) is primarily caused by coronary atherosclerotic plaque formation that leads to an imbalance between oxygen supply and demand resulting in myocardial ischemia.
2. Chest pain is the cardinal symptom of myocardial ischemia caused by coronary artery disease (CAD).
3. Risk factor identification and modification are important interventions for individual patients with known or suspected IHD and as a population-based policy to reduce the impact of this disease.
4. Major risk factors that can be altered include dyslipidemia (high total and low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, and high triglycerides), smoking, glycemic control in diabetes mellitus, hypertension, and adoption of therapeutic lifestyle changes (exercise, weight reduction and reduced cholesterol and fat in the diet). Reduction in inflammation may also play an important role.
5. Most patients with CAD should be receiving antiplatelet therapy. Chronic stable angina should be managed initially with β-blockers because they provide better symptomatic control, at least as well as nitrates or calcium channel blockers, and decrease the risk of recurrent myocardial infarction and CAD mortality.
6. Nitroglycerin and other nitrate products are useful for prophylaxis of angina when patients are undertaking activities know to provoke angina; however, when angina is occurring on a regular, routine basis, chronic prophylactic therapy should be instituted.
7. Although calcium channel blockers are effective as monotherapy, they are generally used in combination with β-blockers or as monotherapy if patients are intolerant of β-blockers; most patients with moderate to severe angina will require two drugs to control their symptoms. Ranolazine is a second-line drug to be used with β-blockers and certain calcium channel blockers.
8. Pharmacologic management is as effective as revascularization (percutaneous transluminal coronary angioplasty, coronary artery bypass graft, etc.) if one or two vessels are involved and there are no differences in survival, recurrent myocardial infarction, or other measures of effectiveness.
9. Multivessel involvement, especially if the patient has left main coronary artery disease or left main equivalent disease, or two- to three-vessel involvement with significant left ventricular dysfunction is best managed with revascularization.
10. Percutaneous transluminal coronary angioplasty and coronary artery bypass graft produce similar results overall but certain patient subsets (e.g., diabetics) should have coronary artery bypass grafting done.
11. The clinical performance measures for chronic stable CAD recommended by the American College of Cardiology and the American Heart Association include blood pressure measurement, lipid profile, symptom and activity assessment, smoking cessation, antiplatelet therapy, drug therapy for lowering low-density lipoprotein cholesterol, β-blocker therapy for prior myocardial infarction, angiotensin-converting enzyme inhibitor therapy, and screening for diabetes.

Learning objectives, review questions, and other resources can be found at **www.pharmacotherapyonline.com.**

Ischemic heart disease (IHD) caused by atherosclerosis of the epicardial vessels leading to coronary heart disease (CHD) is the main etiology of IHD. This process begins early in life, often not being clinically manifest until the middle-aged years and beyond. IHD may present as an acute coronary syndrome (acute coronary syndrome includes unstable angina, non–ST-segment elevation myocardial infarction or ST-segment elevation myocardial infarction; see Chap. 18), chronic stable exertional angina pectoris, and ischemia without clinical symptoms. Coronary artery vasospasm (variant or Prinzmetal angina) produces similar symptoms but is not caused by atherosclerosis. Other manifestations of atherosclerosis include heart failure, arrhythmias, cerebrovascular disease (stroke), and peripheral vascular disease. The American Heart Association, the American College of Cardiology, and the European Society of Cardiology have published management guidelines for stable and unstable angina.[1–3]

EPIDEMIOLOGY

The American Heart Association (AHA) estimates that 79,400,000 American adults have one or more types of cardiovascular disease (CVD) based on data from 1999 through 2004.[4] Nearly 2,400 Americans die of CVD each day, or an average of 1 death every 33 seconds. In 2004, the death rates from CVD were 448.9 (per 100,000) for black males, 335.7 for white males, 331.6 for black females, and 239.3 for white females.[4] CHD was responsible for 52% of deaths from CVD. Men die earlier from IHD and acute myocardial infarction than women, and aging of both sexes is associated with a higher incidence of these afflictions. The disparity in mortality from IHD between men and women decreases with aging, being about four to five times more common in men from the age of the mid-30s to a preponderance of female deaths in the very elderly.

The syndrome of angina pectoris is reported to occur with an average annual incidence rate (number of new cases per time period/

total number of persons in the population for the same time period) of approximately 1.5% (range: 0.1 to 5/1,000) depending on the patient's age, gender, and risk-factor profile.[5] The presenting manifestation in women is more commonly angina, whereas men more frequently have myocardial infarction as the initial event. Estimates of the incidence and prevalence of angina are not entirely accurate because of waxing and waning of symptoms; angina may disappear in up to 30% of patients with angina that is less severe and of recent onset.

Data from the Framingham study show that the prevalence in a 1970 cohort followed for 10 years was approximately 1.5% for women and 4.3% for men ages 50 to 59 years at inception.[5] The annual rate of new episodes of angina range from 28.3 to 33 per 1,000 population for nonblack men, 22.4 to 39.5 for black men, 14.1 to 22.9 for nonblack women, and 15.3 to 35.9 for black women in the age range of 65 to 84 years or older.[4] AHA estimates that the prevalence of angina was 8.9 million in 2004.[4] Other interesting trends noted included a 21% decline in the incidence of cardiovascular disease in women, but only a 6% decline in men over two cohorts from 1950 and 1970. Cardiovascular mortality was reduced by 59% in women and 53% in men from the same cohorts. The risk of developing ischemic heart disease is not the same worldwide. Countries such as Japan and France are on the low end of the spectrum, whereas Finland, Northern Ireland, Scotland, and South Africa have very high rates of IHD.[6,7]

Angina may be classified according to symptom severity, disability induced, or a specific activity scale (Tables 17–1 and 17–2). The specific activity scale developed by Goldman and coworkers[8] may be preferable because it has been shown to be equal to or better than the New York Heart Association or Canadian Cardiovascular Society functional classifications for reproducibility and provides better agreement with exercise treadmill testing.

TABLE 17-1 Criteria for Determination of the Specific Activity Scale Functional Class

	Any Yes	No
1. Can you walk down a flight of steps without stopping (4.5–5.2 MET)?	Go to 2	Go to 4
2. Can you carry anything up a flight of 8 steps without stopping (5–5.5 MET)? Or can you: a. Have sexual intercourse without stopping (5–5.2 MET) b. Garden, rake, weed (5.6 MET) c. Roller skate, dance foxtrot (5–6 MET) d. Walk at a 4-miles/h rate on level ground (5–6 MET)	Go to 3	Class III
3. Can you carry at least 24 lb up 8 steps (10 MET)? Or can you: a. Carry objects that weigh at least 80 lb (18 MET) b. Do outdoor work, shovel snow, spade soil (7 MET) c. Do recreational activities such as skiing, basketball, touch football, squash, handball (7–10 MET) d. Jog/walk 5 miles/h (9 MET)	Class I	Class II
4. Can you shower without stopping (3.6–4.2 MET)? Or can you: a. Strip and make bed (3.9–5 MET) b. Mop floors (4.2 MET) c. Hang washed clothes (4.4 MET) d. Clean windows (3.7 MET) e. Walk 2.5 miles/h (3–3.5 MET) f. Bowl (3–4.4 MET) g. Play golf, walk and carry clubs (4.5 MET) h. Push a power lawnmower (4 MET)	Class III	Go to 5
5. Can you dress without stopping because of symptoms (2–2.3 MET)?	Class III	Class IV

MET, metabolic equivalents of activity.
From Goldman L, Hashimoto B, Cook F, et al. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: Advantages of a new specific activity scale. Circulation 1981;64:1228, with permission.

TABLE 17-2 Grading of Angina Pectoris by the Canadian Cardiovascular Society Classification System

Class	Description of Stage
Class I	Ordinary physical activity does not cause angina, such as walking, climbing stairs. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.
Class II	Slight limitation or ordinary activity. Angina occurs on walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after wakening. Walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and in normal condition.
Class III	Marked limitations of ordinary physical activity. Angina occurs on walking 1 to 2 blocks on the level and climbing 1 flight of stairs in normal conditions and at a normal pace.
Class IV	Inability to carry on any physical activity without discomfort–anginal symptoms may be present at rest.

From Campeau L. Grading of angina [letter]. Circulation 1976;54:522–523, with permission.

An important determinate of outcome for the angina patient is the number of vessels obstructed. Twelve-year survival from the Coronary Artery Surgery Study (CASS) for patients with zero-, one-, two-, and three-vessel disease was 88%, 74%, 59%, and 40%, respectively.[9] Other factors that increase the risk of death in medically managed patients include the presence of heart failure (or markers such as poor ventricular wall motion and low ejection fraction), smoking, left main or left main equivalent coronary artery disease, diabetes, and prior myocardial infarction. Twelve-year survival for patients with at least one diseased vessel and ejection fractions in the ranges of ≥50%, 35% to 49%, and 0% to 34% is 73%, 54%, and 21%, respectively. Of particular note, patients with left main coronary artery disease (or left main equivalent) are at extremely high risk and constitute a unique group for therapeutic consideration.[10] In the CASS, at 15 years of followup, 37% of the surgery group and 27% of the medical group are surviving; median survival is 13.3 years versus 6.7 years, respectively (P <0.0001). If systolic function was normal, then median survival and percent surviving were not different between the surgery and medical groups (median survival of about 15 years). Patients screened but not randomized to CASS had similar survival rates, suggesting that results from randomized patients may be applicable to more generalized populations as a measure of external reliability.

ETIOLOGY AND PATHOPHYSIOLOGY

The pathophysiology that underlies this disease process is dynamic, evolutionary, and complex. An understanding of the determinants of myocardial oxygen demand (MVO_2), regulation of coronary blood flow, the effects of ischemia on the mechanical and metabolic function of the myocardium, and how ischemia is recognized are important to understanding the rationale for the selection and use of pharmacotherapy for IHD.

1 Ischemia may be defined as lack of oxygen and decreased or no blood flow in the myocardium. In contrast, anoxia, defined as the absence of oxygen to the myocardium, results in continued perfusion with washout of acid by-products of glycolysis, thereby preserving the mechanical and metabolic status of the heart to a greater extent than does ischemia for short periods of time.

DETERMINANTS OF OXYGEN DEMAND

The major determinants of MVO_2 are (a) heart rate, (b) contractility, and (c) intramyocardial wall tension during systole. Overall, intramyocardial wall tension is thought to be the most important among these three factors. As the consequences of IHD are a result

of increased demand in the face of a fixed supply of oxygen in most situations, alterations in MVO_2 are critically important in producing ischemia and for interventions intended to alleviate ischemia. MVO_2 cannot be directly measured in patients; however, an indirect assessment that correlates reasonably well with MVO_2 as determined in experimental animal models is the tension–time index. This is a measure of the area under the curve of the left ventricular (LV) pressure curve. Tension in the ventricle wall is a function of the radius of the LV and intraventricular pressure. These factors are related through the Laplace law, which states that wall stress is related directly to the product of intraventricular pressure and internal radius and inversely to wall thickness multiplied by a factor of two. Increasing systemic blood pressure or ventricular dilation would increase wall tension and oxygen demand whereas ventricular hypertrophy would tend to minimize increasing MVO_2. Clinical application of these principles has led to the use of the double product (DP), which is heart rate (HR) multiplied by systolic blood pressure (SBP) ($DP = HR \times SBP$). Although this is a clinically useful indirect estimate of MVO_2, it does not consider changes in contractility (an independent variable), and because only changes in pressure are considered with the double product, volume loading of the LV and increased MVO_2 related to ventricular dilation are underestimated.

REGULATION OF CORONARY BLOOD FLOW

Although coronary blood flow is influenced by multiple factors, the caliber of the resistance vessels delivering blood to the myocardium and MVO_2 are the prime determinants in the occurrence of ischemia. The anatomy of the vascular bed will affect oxygen supply and, subsequently, myocardial metabolism and mechanical function.

Anatomic Factors

The normal coronary system (Fig. 17–1 illustrates normal anatomy) consists of large epicardial or surface vessels (R1) that normally offer little intrinsic resistance to myocardial flow and intramyocardial arteries and arterioles (R2), which branch into a dense capillary network (about 4,000 capillaries per mm^2) to supply basal blood flow of 60 to 90 mL/min per 100 g of myocardium. R1 and R2 are in series and total resistance is the algebraic sum; however, under normal circumstances, the resistance in R2 is much greater. Myocardial blood flow is inversely related to arteriolar resistance and directly related to the coronary driving pressure. The arterioles dynamically alter their intrinsic tone in response to demands for oxygen and other factors, and as a result, myocardial oxygen delivery and myocardial oxygen demand are tightly coupled in a rapidly responsive system.

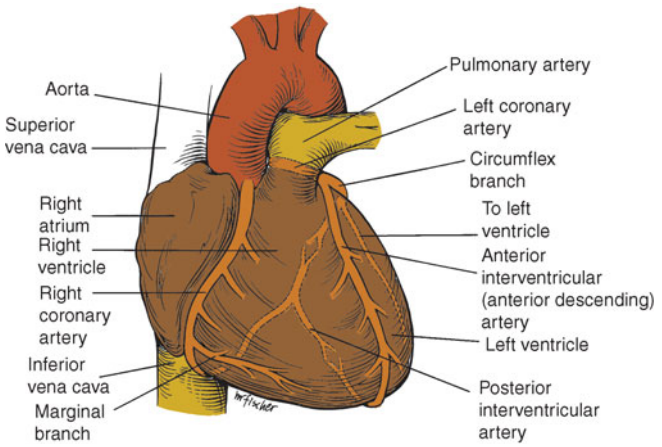

FIGURE 17-1. Coronary anatomy. *(From Tintinalli JE, Kelen GD, Stapczynski JR, eds. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 6th ed. New York: McGraw-Hill, 2004:344.)*

Atherosclerotic lesions encroaching on the luminal cross-sectional area of the larger epicardial vessels (R1) transform the relationships among R1, R2, and blood flow. As resistance increases in R1 owing to occlusion, R2 can vasodilate to maintain coronary blood flow. This response is inadequate with greater degrees of obstruction, and the coronary flow reserve afforded by R2 vasodilation is insufficient to meet oxygen demand (also referred to as autoregulation). The extent of functional obstruction is important in the limitation of coronary blood flow, and the presence of relatively severe stenosis (>70%) may provoke ischemia and symptoms at rest, whereas less-severe stenosis may allow a reserve of coronary blood flow for exertion.[11]

The diameter of the lesion impeding blood flow through a vessel is important, but other factors such as length of the lesion and the influence of pressure drop across an area of stenosis also affect coronary blood flow and function of the collateral circulation. Resistance to flow in a vessel is directly related to length of the obstructing lesion, but resistance is inversely related to the diameter of the vessel to the fourth power. Consequently, diameter is much more important. As blood flows across a stenotic lesion the pressure drops (energy losses) as a result of friction between blood and the lesion and to the abrupt turbulent expansion as blood emerges from the stenosis. This pressure drop is dynamic and directly related to flow giving rise to a resistance that is not fixed, but rather fluctuates, as flow is changed. This relationship can dramatically affect collateral blood flow and its response to exercise, resulting in what has been called "coronary steal." A similar situation may also occur when the epicardial or subepicardial vessels "steal" blood flow from the endocardium in the presence of a stenotic lesion.

Large and small coronary arteries may undergo dynamic changes in coronary vascular resistance and coronary blood flow. Dynamic coronary obstruction can occur in normal vessels and vessels with stenosis in which vasomotion or spasm may be superimposed on a fixed stenosis. Although it is possible that these changes may be "active" in small coronary arteries, it is also possible that the observed changes may reflect collapse owing to poststenotic intraluminal pressure drop or increased intramyocardial compressive forces associated with inadequate ventricular relaxation.

Collateral blood flow exists to a certain extent from birth as native collaterals, but persisting ischemia may promote collateral growth as developed collaterals. These two types of collaterals differ in anatomy and in their ability to regulate coronary blood flow. Collateral development is dependent on the severity of obstruction, the presence of various growth factors (basic fibroblast growth factor [β-FGF] and vascular endothelial growth factor), endogenous vasodilators (e.g., nitrous oxide, prostacyclin), hormones such as estrogen, and, potentially, exercise. Collateral development is highly species dependent and this should be considered when reading experimental literature.

Metabolic Regulation

Coronary blood flow is closely tied to the oxygen needs of the heart. Changes in oxygen balance lead to very rapid changes in coronary blood flow. Although a number of mediators may contribute to these changes, the most important ones are likely to be adenosine, other nucleotides, nitric oxide, prostaglandins, CO_2, and H^+. Adenosine, which is formed from adenosine triphosphate and adenosine monophosphate under conditions of ischemia and stress, is a potent vasodilator that links decreased perfusion to metabolically induced vasodilation or "reactive hyperemia." The synthesis and release of adenosine into coronary sinus venous effluent occurs within seconds after coronary artery occlusion, and approximately 30% of the hyperemic response can be blocked by metabolic blockers of adenosine.[12]

Endothelial Control of Coronary Vascular Tone

The vascular endothelium, a single-cell tissue with an enormous surface area separating the blood from vascular smooth muscle of the artery wall, is capable of a broad range of metabolic functions. The endothelium functions as a protective surface for the artery wall, and as long as it remains intact and functional, it promotes vascular smooth muscle relaxation and inhibits thrombogenesis and atherosclerotic plaque formation; damaged endothelium reacts to numerous stimuli with vasoconstriction, thrombosis, and plaque formation. The vascular endothelium of the coronary arteries synthesizes large molecules such as fibronectin, interleukin-1, tissue plasminogen activator, and various growth factors. Small molecules that are also produced include prostacyclin, platelet-activating factor, endothelin-1, and endothelium-derived relaxing factor (EDRF) that is now characterized as nitric oxide. EDRF is synthesized from l-arginine via nitric oxide synthase and released by shear force on the endothelium, as well as through interaction with many biochemical stimuli such as acetylcholine, histamine, arginine, catecholamines, arachidonic acid, adenosine diphosphate, endothelin-1, bradykinin, serotonin, and thrombin.[12] EDRF or nitric oxide then causes relaxation of the underlying smooth muscle and may be thought of as a paracrine homeopathic defense mechanism against noxious stimuli. Denudation or loss of the vascular endothelium results in loss of EDRF and this protective mechanism. Loss of the endothelial cell layer and function may occur secondary to physical disruption (percutaneous transluminal angioplasty [PTCA]), factors impinging from the vascular side (cyanide from smoke), or disruption of the intimal–medial layers (oxidized low-density lipoprotein). Impaired endothelial function may be related to the development of premature atherosclerosis based on recent family studies.[13]

Factors Extrinsic to the Vascular Bed

Blood flow to the coronary arteries arises from orifices located immediately distal to the aorta valve. Perfusion pressure is equal to the difference between the aortic pressure at an instantaneous point in time minus the intramyocardial pressure. Coronary vascular resistance is influenced by phasic systolic compression of the vascular bed. Consequently, the driving force for perfusion is not constant throughout the cardiac cycle. Opening of the aortic valve may also lead to a Venturi effect, which can slightly decrease perfusion pressure. If perfusion pressure is elevated for a period of time, coronary vascular resistance declines and blood flow increases; however, continued perfusion pressure increases lead, within limits, to a return of coronary blood flow back toward baseline levels through autoregulation.

Alterations in intramyocardial wall tension throughout the cardiac cycle will also impose significant changes in coronary blood flow. Diastole is the period during which coronary artery filling can occur as a result of these pressure differences and little or no coronary blood flow occurs to the left ventricle during systole. The extent of pressure development in the ventricle and heart rate have a major effect on the development of wall tension, time for diastolic coronary artery filling, and myocardial oxygen demand.

Under normal conditions, the average global distribution of blood flow between the epicardial and endocardial layer is about 1:1 at rest and remains approximately even during exercise secondary to autoregulatory changes. Regional disparity of blood flow distribution does exist normally, and these disparities are magnified in the presence of diseased coronary arteries and with increased cardiac work as the vasodilator reserve in the resistance vessels of the subendocardium layers is exhausted. Factors that favor a reduction in subendocardial blood flow include decreased perfusion pressure because of decreased diastolic blood pressure or coronary artery obstruction by atherosclerotic plaques with or without vasomotion, abbreviation of diastole (increased heart rate), and increased intraventricular diastolic pressure (e.g., valvular obstruction to flow).

Extravascular resistance may decrease coronary blood flow, primarily during systole. This effect is much more pronounced in the left ventricle compared with the right ventricle. When the effect of increased contractility is separated from the effect of ventricular pressure, approximately 75% of extravascular resistance is accounted for by passive stretch in equilibrium with ventricular pressure whereas only 25% results from active myocardial contraction.

Factors Intrinsic to the Vascular Bed

Metabolic factors, myogenic responses, neural reflexes, and humoral substances within the vascular bed of the coronary circulation function in an orchestrated fashion to maintain relative consistency in blood flow to the myocardium in the face of imposed changes in perfusion pressures. Autoregulation, mediated primarily through the effects of myogenic responses and metabolic factors, is thought to be responsible for maintaining regional blood flow in a narrow range while systemic pressure varies over a range of approximately 50 to 150 mm Hg.

Myogenic control (also known as the Bayliss effect) of coronary artery tone occurs when the vessel is stretched secondary to an increase in pressure and contracts to return blood flow to normal. It is thought that the myogenic response to stretching in coronary arteries is a modest one and that metabolic factors such as nitric oxide play a much larger role in autoregulation.

There are three well-studied metabolic factors that have the ability to modify coronary artery resistance and blood flow at the local level. Basal coronary blood flow meets oxygen demands of 8 to 10 mL/min per 100 g of myocardium with essentially complete extraction of oxygen from the blood. As cardiac output or mean arterial blood pressure increases, the increased demand for oxygen is met by increasing blood flow because little additional oxygen is available from hemoglobin. Decreased oxygen availability causes vasodilation of vascular smooth muscle and relaxation of precapillary sphincters, which increase tissue oxygen and help maintain blood flow on a regional basis.

At perfusion pressures below 60 mm Hg, as the coronary arteries are maximally dilated and the buffering effect of autoregulation has reached its capacity, further reduction in coronary blood flow will decrease perfusion pressure and tissue oxygenation. It is thought that autoregulation works more efficiently in the epicardial layers than in subendocardial layers, and this may contribute to coronary steal.

Neural components that participate in the regulation of coronary blood flow include the sympathetic nervous system, the parasympathetic nervous system, coronary reflexes, and possibly, central control of coronary blood flow. Within the sympathetic system, stimulation of the stellate ganglion elicits coronary vasodilation, which is associated with tachycardia and enhanced contractility. This indirect coronary vasodilation is secondary to increased MVO_2 related to increased heart rate, contractility, and aortic pressure and occurs following stellate stimulation. The direct effect of the sympathetic system is α_1-mediated vasoconstriction at rest and during exercise. Other receptor types, α_2 and β_1, have little influence on tone, whereas β_2 stimulation produces a modest vasodilatory effect. Although coronary atherosclerosis may decrease blood flow secondary to obstruction, severe coronary atherosclerosis and obstruction may also increase the sensitivity of coronary arteries to the effects of α_1 stimulation and vasoconstriction.

Vagal stimulation within the parasympathetic system produces a small to moderate increase in coronary blood flow, which involves the coronary efferent and afferent parasympathetic components (Bezold-Jarisch reflex). Indirectly, vasoconstriction may result, with vagal stimulation as the result of bradycardia and decreased contractility reducing myocardial oxygen demand.

Coronary reflexes have an undetermined role in the regulation of coronary blood flow. Based on experimental data, coronary reflexes that may be important include the baroreceptor, the chemoreceptor, Bezold-Jarisch reflex, and the pulmonary inhalation reflex.

Factors Limiting Coronary Perfusion

During exercise and pacing, as MVO_2 increases, coronary vascular resistance can be reduced to approximately 25% of basal values, which results in a four- to fivefold increase in coronary blood flow. The cross-sectional area can be reduced by approximately 80% prior to any mechanical or biochemical changes in the myocardium, reflecting a margin of safety for coronary blood flow. The extent of cross-sectional obstruction, the length of the lesion, lesion composition, and the geometry of the obstructing lesion can each affect flow across coronary arteries with atherosclerosis. The Bernoulli theorem states that the pressure drop across a lesion is directly related to the length of the lesion and inversely related to the radius of the lesion to the fourth power; critical stenosis occurs when the obstructing lesion encroaches on the luminal diameter and exceeds 70%. Lesions creating an obstruction of 50% to 70% may reduce blood flow; however, these obstructions are not consistent and vasospasm and thrombosis superimposed on a "noncritical" lesion may lead to clinical events such as myocardial infarction.[14] If the lesion enlarges from 80% to 90%, resistance in that vessel is tripled. Coronary reserve is diminished at approximately 85% obstruction owing to vasoconstriction. Exaggerated responsiveness can be seen when coronary stenosis reaches this critical level and the role of vasoactive substances such as prostaglandins, thromboxanes, and serotonin may play more of a role in the regulation of coronary vascular tone and thrombosis.

Little reserve exists for coronary blood flow and a relatively small reduction of 10% to 20% results in decreased myocardial fiber shortening as the first evidence for abnormal function. The subendocardial layers are affected to a greater extent than the epicardium by ischemia, considering changes in fiber shortening, arteriovenous (AV) difference in oxygen saturation, and lactate production. A reduction of 80% gives rise to akinesis and a 95% reduction of coronary blood flow produces dyskinesis during contraction of the ventricles. Although these abnormalities of contraction are associated with transient impaired function, depletion of high-energy phosphate compounds and ultrastructural changes may last for days, even after transient ischemia; this is referred to as "stunned myocardium." Chronic hypoperfusion may lead to "hibernation," in which ventricular function is impaired over longer time intervals. Hibernating myocardium can be differentiated from necrosis with various techniques (see Chap. 13) and revascularization of hibernating myocardium is useful in improving ventricular function. Regional loss of contractility may impose a burden on the remaining myocardial tissue, resulting in heart failure, increased MVO_2, and rapid depletion of blood flow reserve. Consequently, zones of tissue with marginal blood flow may develop in a lateral or transmural fashion; such development puts this tissue at risk for more severe damage if the ischemic episode persists or becomes more severe. Nonischemic areas of myocardium may compensate for the severely ischemic and border zones of ischemia by developing more tension than usual in an attempt to maintain cardiac output. At the cellular level, ischemia and the attendant acidosis are thought to alter calcium release from storage sites such as the sarcolemma and the sarcoplasmic reticulum, as well as inhibiting the binding of calcium to troponin, thereby impairing the association of actin and myosin. The clinical correlates of these cellular biochemical events leading to the development of left ventricle or right ventricle dysfunction include an S_3, dyspnea, orthopnea, tachycardia, fluctuating blood pressure, transient murmurs, and mitral or tricuspid regurgitation.

Calcium accumulation and overload secondary to ischemia impairs ventricular relaxation as well as contraction. This is apparently a result of impaired calcium uptake after systole from the myofilaments, leading to a less negative decline of the pressure in the ventricle over time. Impaired relaxation is associated with enhanced diastolic stiffness, decreased rate of wall thinning, and slowed pressure decay, producing an upward shift in the ventricular pressure–volume relationship; put more simply, MVO_2 is likely to be increased secondary to increased wall tension. Impairment of both diastolic and systolic function leads to elevation of the filling pressure of the left ventricle.

CLINICAL PRESENTATION AND DIAGNOSIS OF ANGINA

General

- Many episodes of ischemia do not cause symptoms of angina (silent ischemia)
- Patients often have a reproducible pattern of pain or other symptoms which appear after specific amount of exertion
- Increased frequency, severity, duration, or symptoms at rest suggest an unstable angina pattern and the patient should seek help immediately

Symptoms

- 2 Sensation of pressure or burning over the sternum or near it, often but not always radiating to the left jaw, shoulder and arm; also chest tightness, shortness of breath
- Pain usually lasts from 0.5 to 30 minutes, often with a visceral quality (deep location)
- Precipitating factors include exercise, cold environment, walking after a meal, emotional upset, fright, anger, and coitus
- Relief occurs with rest and nitroglycerin

Signs

- Abnormal precordial (over the heart) systolic bulge
- Abnormal heart sounds

Laboratory Tests

- Typically, no laboratory tests are abnormal; however, if the patient has intermediate to high-risk features for unstable angina, electrocardiographic changes and serum troponin, or creatine kinase may become abnormal (Table 17–3)
- Patients are likely to have laboratory test abnormalities for the risk factors for IHD such as elevated total and low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, impaired fasting glucose or elevated glucose, high blood pressure, elevated C-reactive protein, and abnormal renal function. Hemoglobin should be checked to make sure the patient is not anemic.

Other Diagnostic Tests (See Chap. 13)

- A resting electrocardiogram followed by an exercise tolerance test are usually the first tests done in stable patients. A chest radiograph should be done if the patient has heart failure symptoms. Cardiac imaging using radioisotopes to detect ischemic myocardium and measure ventricular function are commonly done when revascularization is being considered. Echocardiography may also be used to assess ventricular wall motion at rest or during stress. Cardiac catheterization and coronary arteriography are used to determine coronary artery anatomy and if the patient would benefit from angioplasty, coronary artery bypass surgery or other revascularization procedures. Coronary artery calcium may be useful in detecting early disease.

TABLE 17-3 Short-Term Risk of Death or Nonfatal Myocardial Infarction in Patients with Unstable Angina

Feature	High Risk (At least 1 of the following features must be present)	Intermediate Risk (No high-risk feature but must have 1 of the following)	Low Risk (No high- or intermediate-risk feature but may have any of the following)
History	Accelerating tempo of ischemic symptoms in preceding 48 h	Prior MI, peripheral or cerebrovascular disease, or CABG, prior aspirin use	
Character of pain	Prolonged ongoing (>20 min), rest pain	Prolonged (>20 min), rest angina, now resolved, with moderate or high likelihood of CAD	New-onset CCS class III or IV angina in the past 2 weeks without prolonged (>20 min) rest pain but with moderate or high likelihood of CAD
Clinical findings	Pulmonary edema, most likely caused by ischemia New or worsening MR murmur S_3 or new/worsening rales Hypotension, bradycardia, tachycardia Age >75 y		
ECG	Angina at rest with transient ST-segment changes >0.05 mV Bundle-branch block, new or presumed new	T-wave inversions >0.2 mV Pathologic Q waves	Normal or unchanged ECG during an episode of chest discomfort
Cardiac markers	Markedly elevated (e.g., TnT or TnI >0.1 ng/mL)	Slightly elevated (e.g., TnT >0.01 but <0.1 ng/mL)	Normal

CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; ECG, electrocardiogram; MI, myocardial infarction; MR, mitral regurgitation; TnI, troponin; TnT, troponin T.

CLINICAL PRESENTATION AND DIAGNOSIS

Important aspects of the clinical history for chest pain for patients with angina include the nature or quality of the pain, precipitating factors, duration, pain radiation, and the response to nitroglycerin or rest. Because there can be considerable variation in the manifestations of angina, it is more accurate to refer to these symptoms as an anginal syndrome. For some patients with significant coronary disease, their presenting symptoms may differ from the classical symptoms, yet the symptoms are a result of ischemic pain, and these are often referred to as anginal equivalents. Obtaining an accurate and detailed family history is useful in placing symptoms in perspective. Significant positive information includes premature coronary heart disease (<55 years of age in men and <65 years of age in women) as manifested as fatal and nonfatal myocardial infarction (MI), stroke, and peripheral vascular disease, as well as other risk factors such as hypertension, smoking, familial lipid disorders, and diabetes mellitus. Typical pain radiation patterns include anterior chest pain (96%), left upper arm pain (83.7%), left lower arm pain (29.3%), and neck pain at some time (22%). Pain from other areas is less common. Ischemia detected by electrocardiogram (ECG) monitoring is more likely to be detected in the morning hours (6 AM to 12 noon) than other periods throughout the day. Patients suffering from variant or Prinzmetal angina secondary to coronary spasm are more likely to experience pain at rest and in the early morning hours. Prinzmetal anginal pain is not usually brought on by exertion or emotional stress, nor is it relieved by rest, and the ECG pattern is that of current injury with ST elevation rather than depression.

It is also important to differentiate the pattern of pain for stable angina from that of unstable angina. Unstable angina may be stratified into categories of risk ranging from high to low (see Table 17–3).[15] Ischemia may also be painless or "silent" in 60% to 100% of patients, depending on the series cited and the patient population.[16] In patients with myocardial ischemia, approximately 70% of the episodes of documented ischemia are painless as determined by ambulatory ECG monitoring, and the ST segment changes associated with these episodes can be ST elevation or depression. The mechanism of silent ischemia is unclear, but studies show that patients not experiencing pain have altered pain perception, with the threshold and tolerance for pain being higher than that of patients who have pain more frequently. Although patients with diabetes tend to have more extensive coronary disease than those without diabetes and may suffer from autonomic neuropathy, asymptomatic ischemia is not more prevalent based on the Asymptomatic Cardiac Ischemia Pilot (ACIP) study.[17] Altered endorphin release is a plausible explanation, but investigations with naloxone to block endorphins do not consistently show altered pain thresholds to various stimuli compared with patients with symptomatic ischemia and patients with asymptomatic ischemia do not necessarily have impaired somatic pain sensitivity.[18] Alternatively, adenosine and substance P release during ischemia and mechanical stretch on coronary arteries may play a role in the perception of pain.

Lastly, it should be recognized that the threshold for pain caused by exertion is fixed in some patients and variable in others and that the amount of exercise or stress necessary to provoke symptoms can change over time. A fixed threshold for the induction of pain or ECG evidence of ischemia means these indicators of ischemia occur at the same, or nearly so, double rate–pressure product (systolic blood pressure × heart rate). This is apparently a consequence of at least two factors. Over long periods of time, atherosclerosis may progress, leading to more severe stenosis, reduced oxygen supply, and less of an increase in demand to precipitate ischemic symptoms. Once stenotic lesions reach a critical level of approximately 80% or greater, vasomotion, vasospasm, and thrombotic occlusion become significant factors impairing blood flow to the myocardium. Consequently, anatomic considerations and vasoactive substances may interact to provide an environment amenable to changing thresholds for the production of angina.

There appears to be little relationship between the historical features of angina and the severity or extent of coronary artery vessel involvement. Therefore, one may speculate that severe symptoms might be associated with multivessel disease, but no predictive markers exist on a routine basis.

Chest pain may resemble pain arising from a variety of noncardiac sources and the differential diagnosis of anginal pain from other etiologies may be quite difficult based on history alone. Table 17–4 outlines other common problems that may present with episodic chest pain. Although much less common, nonatherosclerotic etiologies of coronary artery disease do exist and should be excluded with appropriate tests. The clinical classification of chest pain encompasses typical angina including (a) substernal chest pain with a characteristic quality and duration that is (b) provoked by exertion or emotional stress and (c) relieved by rest or nitroglycerin); atypical angina (meets two of the characteristics for typical angina); and noncardiac chest pain (meets ≤1 of the typical angina characteristics).[2,3]

There are few signs apparent on physical examination to indicate the presence of coronary artery disease and usually only the cardio-

TABLE 17-4 Differential Diagnosis of Episodic Chest Pain Resembling Angina Pectoris

	Duration	Quality	Provocation	Relief	Location	Comment
Effort angina	5–15 min	Visceral (pressure)	During effort or emotion	Rest, NTG	Substernal, radiates	First episode vivid
Rest angina	5–15 min	Visceral (pressure)	Spontaneous (? with exercise)	NTG	Substernal, radiates	Often nocturnal
Mitral prolapse	Min–hours	Superficial (rarely visceral)	Spontaneous (no pattern)	Time	Left anterior	No pattern, variable
Esophageal reflux	10 min–1 h	Visceral	Spontaneous, cold liquids, exercise, lying down	Foods, antacids, H_2 blockers, proton pump inhibitors, NTG	Substernal, radiates	Mimics angina
Peptic ulcer	Hours	Visceral, burning	Lack of food, "acid" foods	Foods, antacids, H_2 blockers, proton pump inhibitors	Epigastric, substernal	
Biliary disease	Hours	Visceral (wax and wane)	Spontaneous, food	Time, analgesia	Epigastric, radiates	Colic
Cervical disk	Variable (gradually subsides)	Superficial	Head and neck, movement and palpation	Time, analgesia	Arm, neck	Not relieved by rest
Hyperventilation	2–3 min	Visceral	Emotion, tachypnea	Stimulus removed	Substernal	Facial paraesthesia
Musculoskeletal	Variable	Superficial	Movement, palpation	Time, analgesia	Multiple	Tenderness
Pulmonary	30 min	Visceral (pressure)	Often spontaneous	Rest, time bronchodilator	Substernal	Dyspneic

NTG, nitroglycerin.

vascular system reveals any useful information. Elevated heart rate or blood pressure can yield an increased double product and may be associated with angina, and it would be important to correct extreme tachycardia or hypertension if present. Other noncardiac physical findings that suggest that significant cardiovascular disease may be associated with angina include abdominal aortic aneurysms or peripheral vascular disease. Table 17–5 lists the cardiac examination findings in coronary artery disease. During an angina attack these findings may appear or become more prominent, making them more valuable if present.

TABLE 17-5 Cardiac Findings in Patients with Coronary Artery Disease

Sign	Clinical Significance	Frequency
Abnormal precordial systolic bulge	Left ventricular wall motion abnormality	Not usually present unless patient has sustained a prior MI (especially anterior wall) or is experiencing angina at time of examination
Decreased intensity of S_1	Decrease in left ventricular contractility	Difficult to evaluate in resting state, but can be commonly demonstrated during angina
Paradoxical splitting of S_2	Left ventricular wall motion abnormality	Very uncommon but occasionally noted during angina
S_3 (ventricular gallop)	Increased left ventricular diastolic pressure, with or without clinical CHF	Not usually present unless patient sustained extensive MI; may occasionally be present during angina
S_4 (atrial gallop)	Reduced ventricular compliance ("stiff heart")	Common; very common in patients who have sustained a prior MI as well as during angina
Apical systolic murmur (in absence of rheumatic mitral regurgitation or Barlow syndrome)	Papillary muscle dysfunction	Not usually present unless patient has sustained prior MI
Diastolic murmur (in absence of aortic regurgitation)	Coronary artery stenosis	Rare

CHF, congestive heart failure; MI, myocardial infarction; S_1, first heart sound; S_2, second heart sound; S_3, third heart sound; S_4, fourth heart sound.
From Cohn PF, ed. Diagnosis and Therapy of Coronary Artery Disease, 2d ed. Boston: Martinus Nijhoff, 1985:101, with permission.

In addition to screening for CVD risk factors (see Table 23–7), other recommended tests include hemoglobin, fasting glucose, fasting lipoprotein panel, resting ECG, and chest radiograph in patients with signs or symptoms of heart failure, valvular heart disease, pericardial disease, or aortic dissection/aneurysm.[2] Hemoglobin is assessed to insure adequate oxygen carrying capacity. Fasting glucose determinations to exclude diabetes and glucose monitoring for concurrent diabetes should be performed routinely. Lipids are assessed total-, low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol and triglycerides (see Chap. 23).[19] Other risk factors that may be important for some patients include C-reactive protein, homocysteine level, evidence of chlamydia infection, and elevations in lipoprotein(a), fibrinogen, and plasminogen activator inhibitor.[20,21] Cardiac enzymes should all be normal in stable angina. Troponin T or I, myoglobin, or creatinine phosphokinase-MB (myocardial band) isoform may be elevated in patients with unstable angina, and interventions such as anticoagulation or antiplatelet therapy reduce cardiac end points when these markers for injury are elevated (see Table 17–3).[22]

Patients presenting with chest pain are stratified into chronic stable angina or having features of intermediate or high-risk unstable angina (Fig. 17–2 and see Table 17–3). These features include rest pain lasting longer than 20 minutes, age older than 65 years, ST- and T-wave changes and pulmonary edema. Patients with acute coronary syndrome (unstable angina, non–ST-segment elevation acute myocardial infarction and ST-segment elevation acute myocardial infarction) are managed differently than chronic stable angina.

DIAGNOSTIC TESTS

See also Chap. 13.

Electrocardiogram

The ECG is normal in about one-half of patients with angina who are not experiencing an acute attack. Typical ST-T–wave changes include depression, T-wave inversion, and ST-segment elevation. Forms of ischemia other than exertional angina may have ECG manifestations that are different; variant angina is associated with ST-segment elevation, whereas silent ischemia may produce elevation or depression. Significant ischemia is associated with ST-segment depression of greater than 2 mm, exertional hypotension, and reduced exercise tolerance.

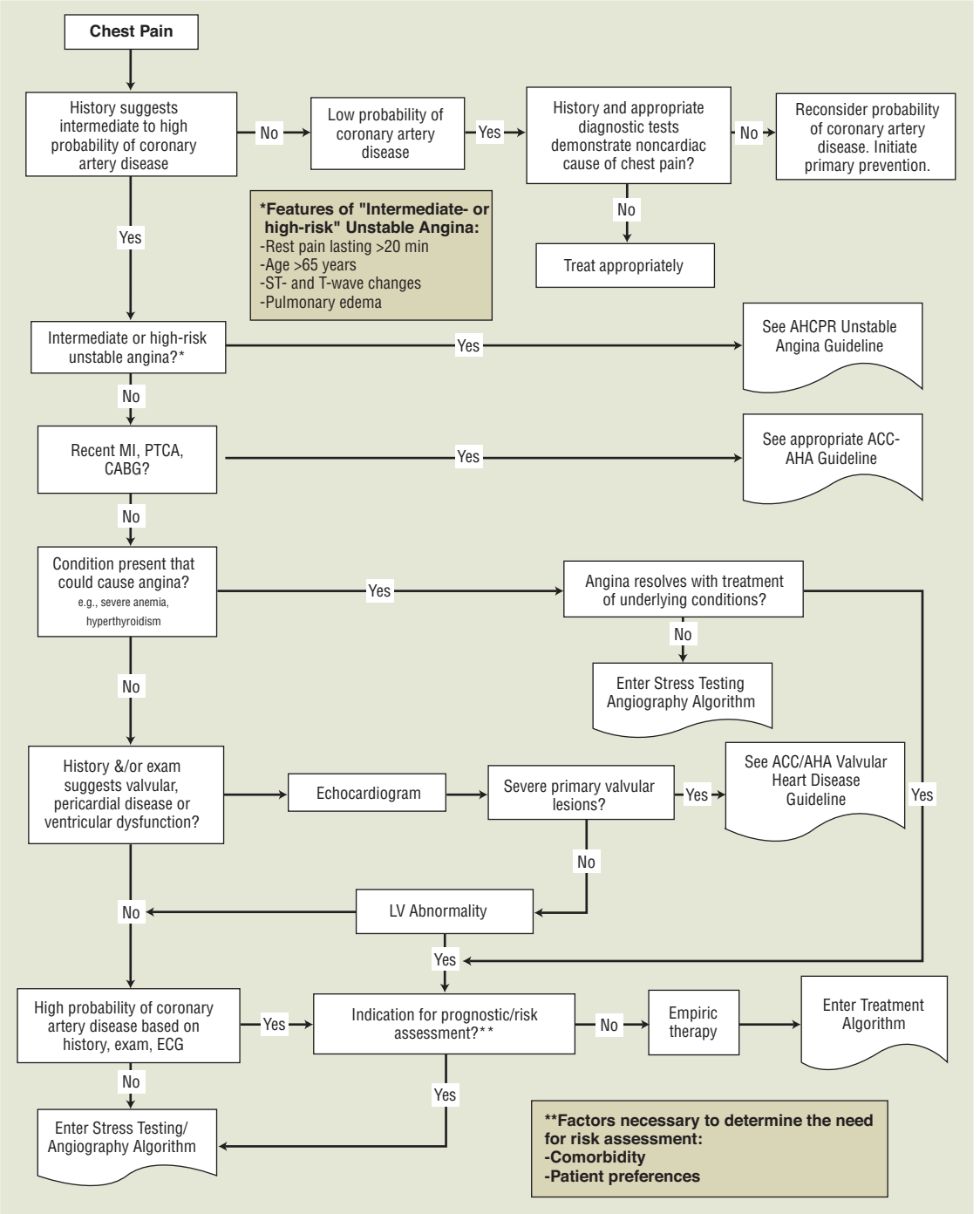

FIGURE 17-2. Clinical assessment. (ACC/AHA, American College of Cardiologists/American Heart Association; AHCPR, Agency for Health Care Policy and Research; CABG, coronary artery bypass graft; ECG, electrocardiogram; LV, left ventricular; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.)

Exercise Tolerance Testing[23]

Exercise tolerance (stress) testing (ETT) is recommended for patients with intermediate pretest probability of coronary artery disease (CAD) based on age, gender, and symptoms, including those with complete right bundle-branch block or <1 mm of rest ST depression (Fig. 17–3). Although ETT is insensitive for predicting coronary artery anatomy, it does correlate well with outcome, such as the likelihood of progressing to angina, the occurrence of acute MI, and cardiovascular death. Ischemic ST depression that occurs during ETT is an independent risk factor for cardiac events and cardiovascular mortality. Thallium (^{201}Tl) myocardial perfusion scintigraphy may be used in conjunction with ETT to detect reversible and irreversible defects in blood flow to the myocardium because it is more sensitive than ETT.

Cardiac Imaging

Radionuclide angiocardiography (performed with technetium-99m, a radioisotope) is used to measure ejection fraction, regional ventricular performance, cardiac output, ventricular volumes, valvular regurgitation, asynchrony or wall motion abnormalities, and intracardiac shunts.[24] Technetium pyrophosphate scans are used routinely for detection and quantification of acute myocardial infarction. Positron emission tomography is useful for quantifying ischemia with metabolically important substrates such as oxygen,

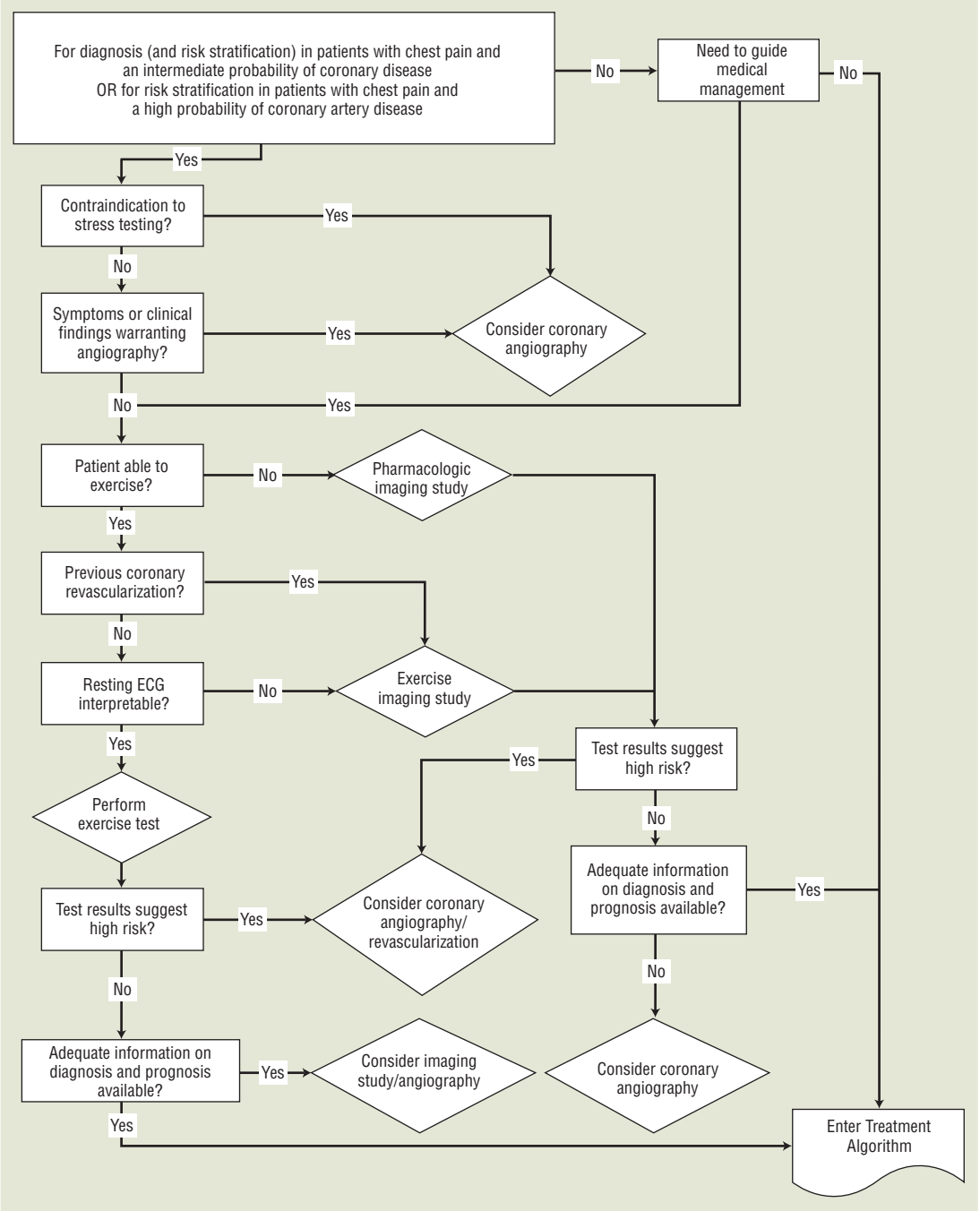

FIGURE 17-3. Stress testing/angiography algorithm. (ECG, electrocardiogram.)

carbon, and nitrogen. Other metabolic probes use radiolabeled fatty acids and glucose to study metabolic processes that may be deranged during ischemia in animals and for investigative purposes in man.

A new method using ultrarapid computerized tomography (spiral CT, ultrafast CT, electron-beam CT) minimizes artifact caused by motion of the heart during contraction and relaxation and provides a semiquantitative assessment of calcium content in coronary arteries.[25] Calcium scores >150 provide a sensitivity of 74% and specificity of 89%; consequently, this method may be cost-effective compared with ETT.

Echocardiography

Echocardiography is useful if patients have history or physical examination suggestive of valvular, pericardial disease or ventricular dysfunction. For patients unable to exercise, pharmacologic stress echocardiography (dobutamine, dipyridamole, or adenosine) or pacing may be done to identify abnormalities during stress.

Cardiac Catheterization and Coronary Arteriography

Cardiac catheterization and angiography in patients with suspected coronary artery disease are used diagnostically to document the presence and severity of disease, as well as for prognostic purposes. High-risk features during ETT suggesting the need for coronary angiography include early and significant (≥2 mm) changes on the ECG during ETT as well as multiple lead involvement, prolonged recovery from ischemia, low workload performance, abnormal blood pressure response (reduction in blood pressure), or ventricular arrhythmias. Multiple defects with thallium scans as well as lung uptake during exercise or postexercise ventricular cavity dilation are also high-risk indications for catheterization. Interventional catheterization is used for thrombolytic therapy in patients with acute myo-

cardial infarction and for the management of patients with significant coronary artery disease to relieve obstruction through PTCA, atherectomy, laser treatment, or stent placement. Catheterization and angiography may be done after coronary artery bypass grafting (CABG) to determine if the graft has closed or if coronary artery disease has progressed. Coronary artery intravascular ultrasound is useful for directly imaging anatomy, calcified and fatty plaques, and thrombosis superimposed on plaque as well as determining patency following revascularization procedures. Intravascular ultrasound guidance of stent implantation may result in more effective stent expansion compared with angiographic guidance alone.[26]

TREATMENT

Ischemic Heart Disease

DESIRED OUTCOME

The short-term goals of therapy for ischemic heart disease are to reduce or prevent the symptoms of angina that limit exercise capability and impair quality of life. Long-term goals of therapy are to prevent CHD events such as myocardial infarction, arrhythmias, and heart failure and to extend the patient's life. Because there is little evidence that revascularization procedures such as angioplasty and coronary artery bypass surgery extend life, the primary focus should be on altering the underlying and ongoing process of atherosclerosis through risk factor modification while providing symptomatic relief through the use of nitrates, β-blockers, calcium channel blockers, and ranolazine for anginal symptoms.

Risk Factor Modification

3 Primary prevention of ischemic heart disease through the identification and modification of risk factors prior to the initial morbid event would be the optimal management approach and should result in a significant impact on the prevalence of IHD. However, early recognition of some risk factors may not be possible in all cases, and in others, the patient may not be willing to undertake intervention until overt evidence of coronary disease is apparent. Secondary intervention continues to be more commonly pursued by both healthcare professionals and patients, and it is important to recognize this type of intervention as effective in reducing subsequent morbidity and mortality. The presence of risk factors in individual patients plays a major role in determining the occurrence and severity of IHD.[19,27] Risk factors are additive in nature and can be classified as alterable or unalterable (see Table 23–7). Unalterable risk factors include gender; age; family history or genetic composition; environmental influences such as climate, air pollution, trace metal composition of drinking water; and to some extent, diabetes mellitus. Improved glycemic control reduces the microvascular complications of diabetes mellitus (see Chap. 77) and reduces coronary end points; however, based on the Diabetes Control and Complications study, the reduction was impressive (40 vs. 23 major events) but not significant because the trial was underpowered to detect these changes.[28] 4 Risk factors that can be altered include smoking, hypertension, hyperlipidemia, obesity, sedentary lifestyle, hyperuricemia, psychosocial factors such as stress and type A behavior patterns, and the use of certain drugs that may be detrimental, including progestins, corticosteroids, and cyclosporine.

Cigarette smoking is common. The Centers for Disease Control and Prevention estimates that 45.1 million people are current smokers (23.9% men; 18.1% women) in this country, and the risk for CHD is increased by about 1.8 in active smokers and by about 1.3 for passive or environmental smoke exposure.[29] From 1997 to 2001 437,902 Americans died from smoking-related illnesses and 34.7% of the deaths were attributable to CVD.[4] Risk because of smoking is related to the number of cigarettes smoked per day and the duration of smoking. Passive smoking in angina pectoris patients decreases exercise time.[6] Pipe and cigar smokers are at increased risk compared with nonsmokers, but their risk is somewhat less than that of cigarette smokers.[30] The direct effects of cigarette smoke that are detrimental to patients with angina include (a) elevated heart rate and blood pressure from nicotine, which increases MVO_2, and impaired myocardial oxygen delivery due to carboxyhemoglobin generation from carbon monoxide inhalation in smoke; (b) the negative inotropic effect of carboxyhemoglobin; (c) increased platelet adhesiveness and promotion of aggregation resulting in thrombotic tendencies because of nicotine and carboxyhemoglobin; (d) lowered threshold for ventricular fibrillation during ischemia as a consequence of carboxyhemoglobin; and (e) impaired endothelial function owing to smoking.[31] Similar changes have been noted for marihuana smoking as well. Smoking also accelerates the risk for myocardial infarction, sudden death, cerebrovascular disease, peripheral vascular disease, and hypertension, and it reduces high-density lipoprotein concentrations. Clearly, primary prevention is needed for this risk factor and much of the education effort to discourage initiation of smoking should be targeted for teenagers. Techniques for cessation of smoking that may be useful include aversive conditioning, group programs, self-help programs, hypnosis, "cold turkey," and the use of nicotine substitutes (lobeline) or other sources of nicotine replacement products for short-term substitution during withdrawal syndrome. The antidepressant sustained-release bupropion is more effective than placebo and best used with smoking cessation counseling. Recently, varenicline, a partial agonist selective for the $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtype also was shown to improve cessation rates.[32,33] Cessation of smoking reduces the incidence of coronary events to approximately 15% to 25% of that associated with continued smoking and these benefits are noted within 2 years of cessation.[34]

Hypertension, whether labile or fixed, borderline or definite, casual or basal, systolic or diastolic, at any age regardless of gender, is the most common and a powerful contributor to atherosclerotic coronary vascular disease.[35] Morbidity and mortality increase progressively with the degree of blood pressure elevation of either systolic or diastolic pressure and pulse pressure, and no discernible critical value exists (see Chap. 15). Numerous trials have documented the reduction in risk associated with blood pressure lowering; however, most of these studies show that mortality and morbidity reduction is a result of fewer strokes and less renal failure and heart failure. The reduction in coronary heart disease end points is significant but not as dramatic. The reasons for this are unclear but perhaps relate to the multifactorial etiology of IHD. Recent guideline changes from the AHA recommend goal blood pressure of <130/80 mm Hg for patients with stable angina, unstable angina, non–ST-segment myocardial infarction, ST-segment myocardial infarction and <120/80 mm Hg in patients with left ventricular dysfunction.[36]

Hypercholesterolemia is a significant cardiovascular risk factor, and risk is directly related to the degree of cholesterol elevation.[19,27] As with hypertension, there is no critical value that defines risk, but rather, risk is incrementally related to the degree of elevation and the presence of other risk factors (see Chap. 23 for a detailed discussion). A fasting lipoprotein panel should be obtained in all patients with known CAD. Chapter 23 discusses the goals for total-, LDL-, and HDL-cholesterol and triglycerides. All patients should undertake therapeutic lifestyle changes. Reductions in LDL-cholesterol for primary prevention and secondary intervention have been shown to reduce total and CAD mortality and stroke as well as the need for interventions such as PTCA and CABG. Supplemental vitamin E or other antioxidants reduce the susceptibility of LDL-cholesterol to oxidation, but clinical trial data fail to show any benefit with supplementation.[37]

The prevalence of overweight and obesity, defined as a body mass index (weight in kilograms divided by height in meters squared) of ≥25 kg/m^2 and ≥30 kg/m,^{2} respectively, are estimated to occur in 66.3% and 32.2% of the U.S. population. Body mass index is associated with an increased mortality ratio compared with individuals of normal body weight, and the objective for patients with IHD is to maintain or reduce to a normal body weight.[4] This may be accomplished through dietary modification, exercise, pharmacologic therapy, or surgical therapy. Frequently associated with obesity is a sedentary lifestyle, and inactivity may contribute to higher blood pressure, elevated blood lipid levels, and insulin resistance associated with glucose intolerance in diabetics (insulin resistance or metabolic syndrome). Exercise to the level of about 300 kcal three times a week is useful in improving maximal oxygen uptake, improving cardiorespiratory efficiency, promoting collateral artery formation, and promoting potential alterations in the risk of ventricular fibrillation, coronary thrombosis, and improved tolerance to stress. Epidemiologic studies have found that mortality is directly related to resting heart rate and a low heart rate difference between resting and maximal exercise heart rate, and inversely related to exercise heart rate. A regular exercise program has been shown to reduce all-cause and cardiac mortality.[38]

Competitiveness, intense striving for achievement, easily provoked hostility, a sense of urgency about doing things quickly and being punctual, impatience, abrupt and rapid speech and gestures, and concentration on self-selected goals to the point of not perceiving and attending to other aspects of the environment are traits that characterize the behavioral pattern known as the type A or coronary prone personality. Although the issue is somewhat controversial, type A individuals may have increased cardiovascular risk with risk ratios ranging from insignificant to three times that of a matched population. Psychological stress and type D personality have been associated with adverse cardiac prognosis, but little is known about their relative effect on the pathogenesis of CHD. "Type D" refers to the tendency to experience negative emotions and to inhibit the expression of these emotions in social interactions. The mechanism by which personality affects the cardiovascular system is not understood, but may reflect the activity of the sympathetic system and enhanced responsiveness of other stress hormones when compared with non-type A personalities.

Alcohol ingestion in small to moderate amounts (<40 g/day of pure ethanol) reduces the risk of coronary heart disease; however, consumption of large amounts (>50 g/day) or binge drinking of alcohol is associated with increased mortality from stroke, cancer, vehicular accidents, and cirrhosis.[39,40] There appears to be a differential effect depending on race with an inverse relationship between ethanol consumption in whites but a direct relationship in Blacks between consumption and CAD risk. The mechanisms for the presumed protective effects of alcohol are not known but the effects may be related to increased high-density lipoprotein levels, impaired platelet function, or associations between the amount of alcohol ingested and personality type. Whatever the relationship, it is well to remember that alcohol drinking is implicated in more than 40% of all fatal automobile accidents and consumption of alcohol predisposes to hepatic cirrhosis, the sixth to seventh most common cause of death in middle age adults in the United States. With this in mind, it seems illogical to suggest alcohol ingestion as a prophylactic measure for coronary disease but rather to advise moderation of alcohol consumption, if it is the preference of the individual.

Thiazide diuretics elevate serum cholesterol and triglyceride levels whereas β-blockers tend to lower HDL and raise LDL slightly; however, a direct association between these drugs and cardiovascular risk is tenuous and based on aggregating results rather than randomized clinical trials. Conjugated equine estrogen alone or in combination with progestin lowers LDL and raises HDL based on the Postmenopausal Estrogen/Progestin Interventions (PEPI) study.[41] Unfortunately, the Heart and Estrogen/Progestin Replacement Study (HERS) trial showed no benefit of hormone replacement therapy for secondary intervention and an increased risk for thromboembolism.[42] In secondary intervention, hormone replacement therapy or estrogen alone in women after hysterectomy, HERS found that hormonal therapy health risks exceeded benefits as well.[43] Unopposed estrogen is the optimal regimen for elevation of HDL, but the high rate of endometrial hyperplasia restricts use to women without a uterus. In women with a uterus, estrogen with cyclic medroxyprogesterone has the most favorable effect on HDL and no excess risk of endometrial hyperplasia. Use of oral contraceptives in women who smoke and are older than age 35 years increases the risk of MI, stroke, and venous thromboembolism by threefold or greater. Alternative forms of contraception and cessation of smoking should be promoted in these patients. The risk for nonsmoking oral contraceptive users younger than age 35 years is very small. The relative risk of breast cancer is increased, but in the absence of risk factors for breast cancer, the relative risk is approximately 1.3 (30% increase). Coffee consumption is also linked to coronary heart disease and caffeine does transiently elevate blood pressure; however, the overall risk, if any, appears to be low and may be related to genetic makeup.[44] Although thiazide diuretics and β-blockers (nonselective without intrinsic sympathomimetic activity) may elevate both cholesterol and triglycerides by some 10% to 20%, and these effects may be detrimental, no objective evidence exists from prospective well-controlled studies to support avoiding these drugs at this time. This controversy is most pertinent in the treatment of mild hypertension and it is discussed in greater detail in Chap. 15.

TREATMENT

Stable Exertional Angina Pectoris

Table 17–6 lists the American College of Cardiology and American Heart Association's evidence-grading recommendations.

The current national guidelines recommend that all patients be given the following unless contraindications exist: (a) aspirin (Class I, Level A); (b) β-blockers with prior MI (Class I, Level A); (c) angiotensin-converting enzyme inhibitor (ACEI) to patients with CAD and

TABLE 17-6 The American College of Cardiology and American Heart Association Evidence Grading System

Recommendation Class	
I	Conditions for which there is evidence or general agreement that a given procedure or treatment is useful and effective
II	Conditions for which there is conflicting evidence or a divergence of opinion about the usefulness/efficacy of a given procedure or treatment is useful and effective
IIa	Weight of evidence/opinion is in favor or usefulness/efficacy
IIb	Usefulness/efficacy is less-well established by evidence/opinion
III	Conditions for which there is evidence or general agreement that a given procedure or treatment is not useful/effective and in some cases may be harmful

Level of Evidence	
A	Data derived from multiple randomized clinical trials with large numbers of patients
B	Data derived from a limited number of randomized trials with small numbers of patients, careful analyses of nonrandomized studies, or observational registries
C	Expert consensus was the primary basis for the recommendation

diabetes or LV systolic dysfunction (Class I, Level A); (d) LDL-lowering therapy with CAD and LDL >130 mg/dL (Class I, Level A) (target LDL <100 mg/dL; <70 mg/dL in patients with CHD and multiple risk factors is reasonable)[27]; (e) sublingual nitroglycerin or immediate relief of angina (Class I, Level B); (f) calcium antagonists or long-acting nitrates for reduction of symptoms when β-blockers are contraindicated (Class I, Level B); (g) calcium antagonists or long-acting nitrates in combination with β-blockers when initial treatment with β-blockers is unsuccessful (Class I, Level C); (h) calcium antagonists or long-acting nitrates are recommended as a substitute for β-blockers if initial treatment with β-blockers leads to unacceptable side effects (Class I, Level A). Clopidogrel may be substituted for when aspirin is absolutely contraindicated (Class IIa, Level B) and long-acting nondihydropyridine calcium antagonists used instead of β-blockers as initial therapy (Class IIa, Level B). ACEIs are recommended in patients with CAD or other vascular disease (Class IIa, Level B). Angiotensin receptor antagonists are not mentioned in these guidelines but substitution for ACEI intolerance is reasonable. Low-intensity anticoagulation with warfarin, in addition to aspirin is recommended, but bleeding would be increased (Class IIb, Level B).[2] Therapies to be avoided include dipyridamole (Class III, Level B) and chelation therapy (Class III, Level B). Ranolazine is not addressed in these guidelines because it was released after their publication. In the European Society of Cardiology guidelines, it has a Class IIb, Level B recommendation.

After assessing and manipulating the alterable risk factors as discussed previously, the next intervention that could be undertaken is the institution of a regular exercise program. Training is possible in many patients with angina and the observed benefits include decreased heart rate and systolic blood pressure, as well as increased ejection fraction and duration of exercise. Although the mechanism of these effects has been debated, improved overall cardiovascular and muscular condition are probably most important. Improved production of nitric oxide and coronary vasomotion may account partially for the beneficial effects of exercise. The intensity of exercise influences training and more vigorous programs provide better overall results.[38] Obviously, an exercise program should be undertaken with caution and in a graded fashion with adequate supervision.

5 Chronic prophylactic therapy for patients with more than one angina episode per day may also be instituted with β-adrenergic blocking agents, and in many instances β-blockers may be preferable because of less-frequent dosing and other properties inherent in β-blockade (e.g., potential cardioprotective effects, antiarrhythmic effects, lack of tolerance, and antihypertensive effects), as well as their antianginal effects and documented protective effects in post-MI patients.[2] Patients who continue to smoke have reduced antianginal efficacy of β-blockers. This may be a result of enhanced hepatic metabolism of drugs that are eliminated through this route or related to the effects of smoking on MVO_2 and oxygenation.[45] The one characteristic that is relevant is the duration of effect on the double product. β-Blockers with longer half-lives (e.g., nadolol) are more likely to affect the double product for a longer period of time and require fewer doses per day. The choice of β-blocker for angina rests on choosing the appropriate dose to achieve the goals outlined for heart rate and double product, and choosing an agent that is well tolerated by individual patients and cost. Selective use may incorporate ancillary properties but these are secondary considerations in overall drug product selection. Patients most likely to respond well to β-blockade are those who have a high resting heart rate and those who have a relatively fixed anginal threshold. In other words, their symptoms appear at the same level of exercise or workload on a consistent basis. Symptoms appearing with variable work loads suggest fluctuations in myocardial oxygen supply, perhaps due to coronary artery vasomotion, and these patients are more likely to respond to calcium channel antagonists.

6 Nitrate therapy should be the first step in managing acute attacks for patients with chronic stable angina if the attacks are infrequent (i.e., a few times per month) or for prophylaxis of symptoms when undertaking activities known to precipitate attacks. In general, if angina occurs no more often than once every few days, then sublingual nitroglycerin tablets or spray or buccal products may be sufficient to allow the patient to maintain an adequate lifestyle. For episodes of "first-effort" angina occurring in a predictable fashion, nitroglycerin may be used in a prophylactic manner with the patient taking 0.3 to 0.4 mg sublingually about 5 minutes prior to the anticipated time of activity. Nitroglycerin spray may be useful when inadequate saliva is produced to rapidly dissolve sublingual nitroglycerin or if a patient has difficulty opening the container. Most patients have a response that lasts about 30 minutes or so, but this is subject to interindividual variability. When angina occurs more frequently than once a day, a chronic prophylactic regimen using β-blockers as the first line of therapy should be considered (Fig. 17–4 illustrates the stable angina algorithm). Chronic prophylactic therapy with long-acting forms of nitroglycerin (oral or transdermal), isosorbide dinitrate, 5-mononitrate, and pentaerythritol trinitrate may be effective; however, the development of tolerance is a major limiting step in their continued effectiveness. Because long-acting nitrates are not as effective as β-blockers and do not have beneficial effects, monotherapy with nitrates should not be first-line therapy unless β-blockers and calcium channel blockers are contraindicated or not tolerated. As described previously, providing a nitrate-free interval of 8 hours per day or longer appears to be the most promising approach to maintaining the efficacy of chronic nitrate therapy. Recent investigations into the mechanisms of nitrate tolerance have shown in normal volunteers that treatment with isosorbide mononitrate for 7 days resulted in tolerance as well as endothelial dysfunction, which is thought to be a consequence of reactive oxygen species generated during bioactivation of high-potency nitrates.[46,47] Oral administration of nitrates is susceptible to a saturable first-pass effect; consequently, larger doses can produce a measurable hemodynamic effect and dose titration should be based on these changes in the double product. There are few well-controlled studies that compare oral or sublingual nitrate efficacy, and the choice among these products should be based on familiarity with the preparation, cost, and patient acceptance.

7 Calcium channel antagonists have the potential advantage of improving coronary blood flow through coronary artery vasodilation as well as decreasing MVO_2 and may be used instead of β-blockers for chronic prophylactic therapy; however, in chronic stable angina, comparative trials of long-acting calcium channel blockers with β-blockers do not show significant differences in response.[48,49] They are as effective as β-blockers and are most useful in patients who have a variable threshold for exertional angina. Calcium antagonists may provide better skeletal muscle oxygenation, resulting in decreased fatigue and better exercise tolerance. Additionally, if contraindications exist to β-blocker therapy, calcium antagonists can be safely used in many patients. The available calcium channel blockers appear to have similar efficacy in the management of chronic stable angina. Differences in their electrophysiology, peripheral and central hemodynamic effects, and adverse-effect profiles are useful in selecting the appropriate agent. Patients with conduction abnormalities and moderate to severe LV dysfunction (ejection fraction <35%) should not be treated with verapamil, whereas amlodipine may be safely used in many of these patients. Diltiazem has significant effects on the AV node and can produce heart block in patients with preexisting conduction disease or when other drugs with effects on conduction, such as digoxin or β-blockers, are used concurrently. Nifedipine may cause excessive heart rate elevation, especially if the patient is not receiving a β-blocker, and this may offset the beneficial effect it has on MVO_2. Gingival hyperplasia has also been reported

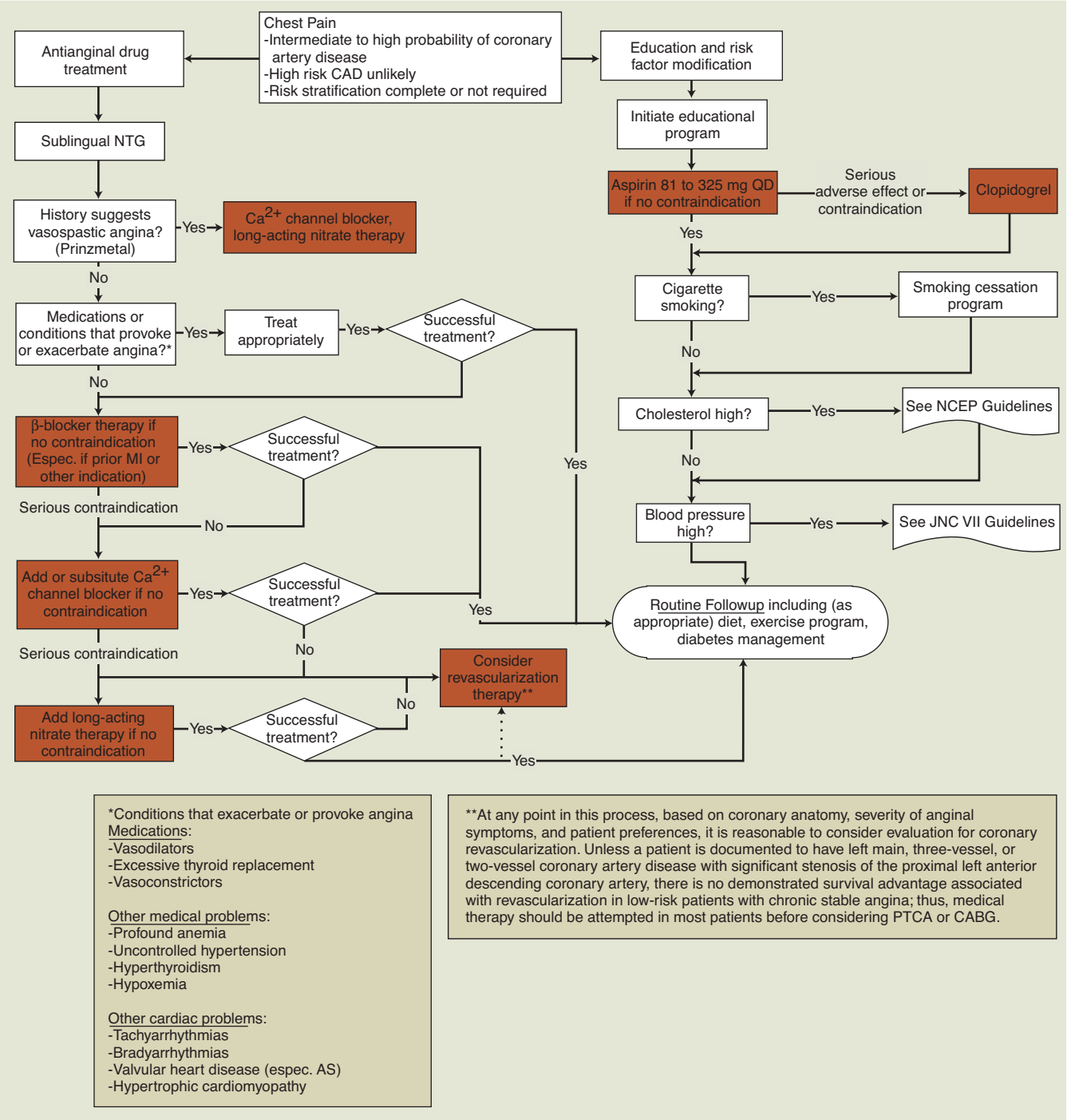

FIGURE 17-4. Treatment algorithm. (AS, aortic stenosis; CABG, coronary artery bypass grafting; CAD, coronary artery disease; JNC VII, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; MI, myocardial infarction; NCEP, National Cholesterol Education Program; NTG, nitroglycerin; PTCA, percutaneous transluminal coronary angioplasty; QD, every day.)

with nifedipine, and some dental authorities say this may be seen in as many as 20% of patients on nifedipine. Case control studies with calcium blockers suggest an increased risk for MI and cancer.[50,51] The relationship to cancer appears to be weak to nonexistent whereas the risk for MI is probably real and related to the type of drug used and relationship to recent MI. Immediate-release formulations of calcium blockers can activate the sympathetic nervous system and in patients with recent MI or significant coronary disease, may induce ischemia. This effect has not been shown for longer-acting products. The hemodynamic effect of calcium antagonists is complementary to β-blockade and, consequently, combination therapy is rational but clinical trial data do not support the notion that combination therapy is always more effective.[48,52]

Although revascularization (see below) would seem to provide better symptomatic relief and improved survival rates, recent randomized trials have shown no advantage of angioplasty or surgery over medical therapy in patients with stable coronary artery disease.[53,54] In the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, the 4.6-year cumulative primary event rates (death from any cause and nonfatal myocardial infarction) were 19.0% in the percutaneous coronary intervention (PCI) group and 18.5% in the medical therapy group (hazard ratio for the PCI group, 1.05; 95% confidence interval [CI], 0.87 to 1.27; $P = 0.62$).[53] The Medicine, Angioplasty, or Surgery Study (MASS II) found medical therapy was associated with an incidence of long-term events and rate of additional revasculariza-

tion similar to those for PCI. CABG was superior to medical therapy in terms of the primary end points, reaching a significant 44% reduction in primary end points at the 5-year followup of patients with stable multivessel coronary artery disease.[54]

■ ❽ NONPHARMACOLOGIC THERAPY

Revascularization

The decision to undertake PCI or CABG for revascularization is based on the extent of coronary disease (number of vessels and location/amount of stenosis) and ventricular function. Table 17–7 outlines the recommended mode of coronary revascularization.[15,55]

The largest randomized trial of PCI versus CABG is the Bypass Angioplasty Revascularization Investigation (BARI) trial conducted in 1,829 patients with two- or three-vessel disease; 64% of these patients had an admitting diagnosis of unstable angina and 19% were diabetic.[56] The 10-year survival was 71.0% for PTCA and 73.5% for CABG (P= 0.18). At 10 years, the PTCA group had substantially higher subsequent revascularization rates than the CABG group (76.8% vs. 20.3%, P<0.001), but angina rates for the two groups were similar. In the subgroup of patients with no treated diabetes, survival rates were nearly identical by randomization (PTCA 77.0% vs. CABG 77.3%, P = 0.59).[57] Insulin-requiring diabetics seem to be at the highest risk and CABG is the revascularization procedure of choice for this population.[58] In a large observational study by Hannan et al., patients with proximal left anterior descending (LAD) lesions and multivessel disease had higher survival rates with CABG than with PTCA.[59] High-risk patients who should be considered for CABG over PCI are those with LV systolic dysfunction, patients with diabetes, and those with two-vessel disease with severe proximal LAD involvement or severe three-vessel or left main disease (see Table 17–7).[15] AWESOME (Angina With Extremely Serious Operative Mortality Evaluation) found that either bypass or percutaneous intervention effectively relieves medically refractory ischemia among high-risk unstable angina patients whose age was greater than 70 years.[60]

PCI has been used successfully in the management of unstable angina.[55,61] PTCA involves the insertion of a guidewire and inflatable balloon into the affected coronary artery and enlarging the lumen of the artery by stretching the vessel wall. This frequently causes atheroma plaque fracture by stretching inelastic components and denudation of the endothelium resulting in loss of nitric oxide and other vasodilators and exposure of plaque contents to the vascular compartment. Consequently, immediate vascular recoil, platelet adhesion and aggregation, mural thrombus formation, and smooth muscle proliferation, and synthesis of extracellular matrix may give rise to acute occlusion and early or late restenosis.[62,63] The presence of coronary artery spasm and intraluminal thrombus, common occurrences in unstable angina, increases the hazard of these complications. The advent of combination therapy with acetylsalicylic acid, unfractionated heparin or low-molecular-weight heparin, and glycoprotein IIb/IIIa receptor antagonists and coronary artery stents has dramatically reduced the occurrence of early reocclusion and late restenosis.[64] Patients best suited for PTCA are those with recent onset of worsening of angina without a long history of symptoms. Angiographic characteristics associated with these clinical findings that allow the greatest probability of success for PTCA are severe, discrete, proximal lesions found in a large epicardial vessel subtending a moderate or large area of viable myocardium and have high-risk features. Patients with focal saphenous vein graft lesions who are poor candidates for reoperation have a class IIa recommendation for PCI. Class IIb indications include patients with one or more lesions to be dilated in vessels subtending a less-than-moderate area of viable myocardium and patients with multivessel disease and proximal LAD lesions, diabetes, or abnormal LV function.[65] Candidates for PTCA must also be suited for CABG because a small percentage of procedures results in emergency CABG. Success of PCI may be defined as angiographic success (Thrombolysis In Myocardial Infarction [TIMI] 3 flow and <20% residual stenosis), procedural success (lack of in-hospital clinical complications), and clinical success (anatomic and procedural success with relief of ischemic pain for at least 6 months). In trials of invasive versus conservative strategies (medical management) using PCI, death or MI is less frequent in some, but not all, trials.[66–69] Numerous studies support the use of glycoprotein IIb/IIIa receptor antagonists in addition to acetylsalicylic acid and unfractionated heparin or low-molecular-weight heparin, and as described previously, abciximab was superior to tirofiban in the only comparative study available.[15,65] The initial success rate for PTCA in unstable angina is ~80% to 90%, but these patients are at risk for more complications than are those with stable angina because of the underlying pathophysiology.

In the event of prolonged chest pain and ischemic ECG changes unrelieved by nitrate therapy or calcium channel antagonists, one may assume total occlusion of a coronary vessel and steps should be taken to restore blood flow with either PCI or CABG.

TABLE 17-7 Recommended Mode of Coronary Revascularization

Extent of Disease	Treatment	Class/Level of Evidence
Left main disease,[a] candidate for CABG	CABG	I/A
	PCI	III/C
Left main disease, not a candidate for CABG	PCI	IIb/C
Three-vessel disease with EF <0.50	CABG	I/A
Multivessel disease including proximal LAD with EF <0.50 or treated diabetes	CABG	I/A
	PCI	IIb/B
Multivessel disease with EF >0.50 and without diabetes	PCI	I/A
One- or two-vessel disease without proximal LAD but with large areas of myocardial ischemia or high-risk criteria on noninvasive testing (see text)	CABG or PCI	I/B
One-vessel disease with proximal LAD	CBAG or PCI	IIa/B
One- or two-vessel disease without proximal LAD with small area of ischemia or no ischemia on noninvasive testing	CABG or PCI	III/C
Insignificant coronary stenosis	CABG or PCI	III/C

CABG, coronary artery bypass grafting; EF, ejection fraction; LAD, left anterior descending coronary artery; PCI, percutaneous coronary intervention.

[a] ≥50% diameter stenosis.

From Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non–ST-segment elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). J Am Coll Cardiol 2000;36:970–1062, with permission.

Coronary Artery Bypass Grafting[70]

Following the introduction of saphenous vein graft replacement for the severely occluded coronary arteries by Favorolo and Garrett in 1967, CABG became an accepted and commonly used approach for the management of IHD. The objectives in performing CABG are twofold: (a) to reduce the number of symptomatic anginal attacks not controlled with medical management or PCI and improve the lifestyle of the patient, and (b) to reduce the mortality associated with coronary artery disease. Surgery is effective in providing pain relief in large numbers of patients, with approximately 70% to 95% being pain-free at 1 year and 46% to 55% being pain-free at 5 years. This compares favorably with medical management, with which only approximately 30% are free of symptoms at 5 years. Mortality at 10 years from the largest published studies is 26.4% with CABG and 30.5% with medical management (P = 0.03) but there are significant differences based on subgroup analysis (e.g., left main disease vs. one-vessel disease without a proximal LAD lesion).[71] The second

objective is met in certain patients and was addressed in three large, well-controlled trials of bypass surgery. These three studies, the Veterans Administration, European Cooperative Surgery Study, and the CASS, are not directly comparable because the inclusion and exclusion criteria for entry into each study were different and patients were followed for different periods of time. They have also been criticized for not being representative of the population that may be candidates for surgery, lacking women or late-middle aged or elderly patients, and for crossover of medically managed patients to the surgical group. A major change in medical practice that influences the interpretation of these older studies is the common procedure of stent placement at the time of angioplasty.[72] There are about 20 different types of stents available and their use is associated with greater luminal diameter after angioplasty, fewer acute reocclusions and less restenosis after stent placement. Consequently, the validity of generalizing the results from these studies to routine practice has been questioned, but these studies are useful for providing a basis for decisions concerning surgery. Current class I recommendations for CABG in asymptomatic or mild angina patient includes significant (>50%) left main coronary artery stenosis, left main equivalent (≥70% stenosis of the proximal LAD and proximal left circumflex artery), and three-vessel disease, especially in patients with a LV ejection fraction <0.50.[71] Class IIa recommendations for CABG are proximal LAD stenosis with one- or two-vessel disease and class IIb recommendations for one- or two-vessel disease not involving the proximal LAD. In stable angina, class I recommendations are the same as for mild angina with the following additions: one- or two-vessel disease without significant proximal LAD stenosis, but with a large area of viable myocardium and high-risk criteria in noninvasive testing; disabling angina despite maximal medical therapy, when surgery can be performed with acceptable risk. Class IIb recommendations in stable angina include proximal LAD stenosis with one-vessel disease and one- or two-vessel disease without significant proximal LAD stenosis but with a moderate area of viable myocardium and ischemia on noninvasive testing. The indications for CABG in unstable angina/non–ST-segment elevation myocardial infarction were described previously. In ST-segment MI, CABG is indicated for ongoing ischemia/infarction not responsive to maximal medical therapy (class IIb).

In patients with poor LV function CABG is indicated for the same indications as in mild angina for class I. Class IIa recommendations include poor LV function with significant viable, noncontracting, revascularizable myocardium without any of the aforementioned anatomic patterns (e.g., left main disease). CABG is useful in patients with life-threatening ventricular arrhythmia in the presence of left main disease, three-vessel disease (class I) and in bypassable one- or two-vessel disease causing life-threatening ventricular arrhythmias and proximal LAD disease with one- or two-vessel disease (class IIa).

CABG may also be used for patients who have failed PTCA if there is ongoing ischemia or threatened occlusion with significant myocardium at risk and in patients with hemodynamic compromise (class I). Class IIa recommendations for failed PTCA include a foreign body in a crucial anatomic position and hemodynamic compromise in patient with impairment of the coagulation system and without a previous sternotomy. CABG may be repeated in patients with a previous CABG if disabling angina exists despite maximal noninvasive therapy (class I) and if a large area of myocardium is threatened and is subtended by bypassable distal vessels (class IIa).

The need for nitrates and β-blockers is clearly reduced by surgery, with only 30% of CABG patients requiring chronic medication, whereas 70% of their medical counterparts received anginal drugs. CASS showed that employment status after surgery was more dependent on the pretreatment status than an effect induced by the treatment arm, and that approximately 70% of patients are employed before and after surgery. Recent followup analyses of these studies suggest that patients who have diabetes or peripheral vascular disease, who are African Americans, or who continue to smoke are at high risk for CAD events, and diabetics, in particular, are more likely to have a better outcome with CABG than PTCA.[56,73,74] The overall benefit noted after CABG is similar in men and women, and elderly patients appear to have outcomes similar to younger patients.

Operative mortality is reported to range from 1% to 3% and is related to the number of vessels involved and preoperative ventricular function. Patients in CASS with one-, two-, or three-vessel disease had operative mortalities of 1.4%, 2.1%, and 2.8%, respectively. The relationship to left ventricular ejection fraction follows a similar trend with ejection fractions of greater than 50%, 20% to 40%, and less than 20% having operative mortality rates of 1.9%, 4.4%, and 6.7%, respectively. Perioperative infarction averages 5% depending on the sensitivity of the method for assessment, and the occurrence of an infarct reduces long-term survival. Neurologic dysfunction is relatively common postoperatively in CABG patients (~6%), but many of the deficits are clinically insignificant and resolve with time. Fatal brain damage occurs in 0.3% to 0.7%, stroke in approximately 5%, and ophthalmologic defects in 25%, but only 3% have clinically apparent field defects. Peripheral nerve lesions (12%) and brachial plexopathy (7%) are also reported to occur. Other complications include constrictive pericarditis (0.2%), cellulitis at the site of vein graft, and mediastinal infections (1% to 4%).

Graft patency influences the success for symptom control, and survival and the mechanism for early graft occlusion is probably different from that associated with late closure. Early occlusion is related to platelet adhesion and aggregation whereas late occlusion may be related to endothelial proliferation and progression of atherosclerosis. Patency of grafts early on after the CABG are reported to range from 88% to 97% in at least one graft and 58% to 81% in all grafts at 1 year. Long-term patency based on the CASS Montreal Heart Institute experience suggests that 60% to 67% of all grafts remain patent at 5 to 11 years. Antiplatelet therapy has been demonstrated to improve early and late patency rates and should probably be used in all patients who do not have any contraindications. Aspirin with or without other antiplatelet agents (clopidogrel) reduces the late development of vein-graft occlusions. Late graft closure is related to elevated lipid levels and the progression of atherosclerosis in the grafted vessels as well as the native circulation. Elevation of very-low-density lipoprotein, LDL, and LDL apolipoprotein B is correlated to disease progression and graft closure. Aggressive lipid lowering can stabilize the progression of CAD and may induce regression in selected coronary artery segments within a patient following CABG. Cessation of smoking is an important preoperative and postoperative objective as well as in the management of other coronary risk factors (e.g., hypertension) and institution of a supervised, daily exercise program is recommended. Internal mammary artery grafts should be used for revascularizing the left anterior descending artery system when possible owing to better graft survival and clinical outcomes.

Valvular heart disease can coexist with coronary heart disease, although this is relatively uncommon with rheumatic valve disease, usually the mitral valve, and more common with aortic stenosis and regurgitation. Angina may occur in 35% to 65% of patients with aortic stenosis or regurgitation, and if severe, may be the cause of angina in the absence of coronary artery disease. Patients being evaluated for possible CABG should also be evaluated for valvular disease to determine if valve replacement needs to be performed along with bypass grafting.

Percutaneous Transluminal Coronary Angioplasty[55]

Since the introduction into clinical cardiology of PTCA by Gruentzig in 1977, this procedure has gained rapid acceptance as a safe and

effective means of managing coronary artery disease. It is estimated that more than 750,000 PCI procedures are done each year in this country and 525,000 of them are PTCA. The proposed mechanisms of reduced stenosis with PTCA include (a) compression and redistribution of the atherosclerotic plaque; (b) embolization of plaque contents; (c) aneurysm formation; and (d) disruption of the plaque and arterial wall with distortion and tearing of the intima and media, which leads to denudation of the endothelium, platelet adhesion and aggregation, thrombus formation, and smooth muscle proliferation. Of these mechanisms, the last one is felt to be the most important, but the others may contribute to opening of the lesions in some situations.

9 The indications for PTCA have been provided by the American College of Cardiology/American Heart Association (ACC/AHA) and now span single or multivessel disease, as well as asymptomatic and symptomatic patients (Table 17–8).[55] In addition to providing recommendations for which type of patients are appropriate for PTCA, the guidelines also provide recommendations for the volume of procedures, the use of intravascular ultrasound, and surgery backup when PTCA is being considered. 10 PTCA generally is not useful if only a small area of viable myocardium is at risk, or when ischemia cannot be demonstrated, borderline (<50%) stenosis or lesions that are difficult to dilate are present, or the patient were at high risk for morbidity or mortality or both (e.g., left main or equivalent disease or three-vessel disease). PTCA alone or when used in conjunction or sequentially with thrombolysis for acute myocardial infarction is discussed in Chap. 18. Stent placement accompanies balloon angioplasty in approximately 80% of cases in the United States. Table 17–8 lists the current recommendations for PCI based on class of angina.

Assessment of outcome with PCI can be based on several angiographic, procedural, and clinical outcomes, as discussed previously. The success of PCI is dependent on the experience of the operator (high volume, better outcome), on complicating factors for the patient (including the number of vessels to be dilated), and on technical advances in the equipment used (e.g., steerable and low-profile catheters). The acute success rate for opening of uncomplicated stenotic lesions ranges from 96% to 99% with the combined balloon/device/pharmacologic approach in experienced hands, and angina is decreased or eliminated in approximately 80% of cases. The success rate totally occluded lesions is somewhat less (~65%). Mortality at 1 year is 1% for single-vessel disease and 2.5% for multivessel involvement, reflecting the good prognosis associated with this degree of coronary artery disease. At 10 years, survival is 95% for single-vessel disease and 81% for multivessel disease.[75] Most patients remain event-free (no death, MI, or CABG) for an extended period. Symptomatic status, as measured by the New York Heart Association classification, is improved in many patients. Restenosis is noted in 32% to 40% after balloon angioplasty at 6 months, and half of these patients will have symptoms associated with restenosis.[75] A few late restenotic events occur, but most restenosis occurs within the first 6 months. Anatomic factors that predict restenosis include lesions >20 mm in length, excessive tortuosity of the proximal segment, extremely angulated segments (>90°), total occlusions >3 months old and and/or bridging collaterals, inability to protect major side branches, and degenerated vein grafts with friable lesions. Clinical factors that predict worse outcome include diabetes, advanced age, female gender, unstable angina, heart failure and multivessel disease. A four-variable scoring system that predicts cardiovascular collapse for failed PTCA includes percentage of myocardium at risk (e.g., >50% viable myocardium at risk and LV ejection fraction <25%), preangioplasty percent diameter stenosis, multivessel CAD, and diffuse disease in the dilated segment or a high myocardial jeopardy score.[65] Strut thickness of the stent influences restenosis as well and thicker struts are associated with angiographic and clinical restenosis.[76]

The overall complication rate ranges from 2% to 21%, depending on the lesion type.[77] Coronary occlusion, dissection, or spasm occurs in 4% to 8% of patients, whereas ST-segment elevation MI occurs in 1.6% to 4.8%.[65] Prolonged angina and ventricular tachycardia or fibrillation occurs in 6.9% and 2.3%, respectively. In-hospital mortality ranges from 0.7% to 2.5% overall, and high-risk events for mortality includes ventricular arrhythmias and myocardial infarction. The frequency of urgent CABG because of complications ranges from 0.4% to 5.8%.[65]

Table 17–9 outlines current AHA/ACC recommendations for antithrombotic therapy in PCI.[55,78] Antiplatelet therapy with acetylsalicylic acid 80 to 325 mg/day given at least 2 hours prior to angioplasty is currently recommended. If patients are sensitive to acetylsalicylic acid, clopidogrel or ticlopidine are acceptable alternatives. Most centers now use clopidogrel because of adverse effects (described in Chap. 18) and prolonged time to onset for ticlopidine. In elective settings, clopidogrel should be started at least 72 hours in advance of the procedure to allow for maximal antiplatelet effects. Alternatively, a loading dose of clopidogrel (300 to 600 mg) or ticlopidine (500 mg) may be given to achieve a more rapid antiplatelet effect.[79] The combination of acetylsalicylic acid plus clopidogrel is currently recommended for patients undergoing angioplasty and stenting, and this combination is safer and superior to antiplatelet therapy plus anticoagulation with warfarin-like drugs.[80] Followup for up to 4 years from the ISAR (Intracoronary Stenting and Antithrombotic Regimen) trial shows that the benefit of combined antiplatelet therapy evident after 30 days is maintained after 4 years.[81] Aspirin is an incomplete inhibitor of platelet aggregation; combination therapy of acetylsalicylic acid plus a glycoprotein (GP) IIb/IIIa receptor antagonist for PCI shows a relative risk reduction of 37.5% for death and nonfatal MI at 30 days, favoring GP IIb/IIIa receptor antagonists over placebo (absolute rates of 5.5% vs. 8.9% based on PCI trials. As discussed in Chap. 18, high-risk patients and those having a stent placed are most likely to benefit from GP IIb/IIIa receptor antagonist use. Patients presenting with elevated cardiac biomarkers are also more likely to receive benefit from GP IIb/IIIa receptor antagonists than patients with normal levels of biomarkers.[82] In the only comparative trial, abciximab was superior to tirofiban.[83]

During PTCA patients are usually heparinized to prevent immediate thrombus formation at the site of arterial injury and on coronary guidewires and catheters; anticoagulation is continued for up to 24 hours. The intensity of anticoagulation is monitored using the activated clotting time and the targeted range for activated clotting time is 250 to 300 seconds (HemoTec device) in the absence of GP IIb/IIIa receptor antagonist use.[65] When GP IIb/IIIa receptor antagonists are not used, unfractionated heparin is given as an IV bolus of 70 to 100 international units/kg to achieve a target activated clotting time of 200 seconds. The loading dose is lowered to 50 to 70 international units/kg when GP IIb/IIIa receptor antagonists are given. Target activated clotting time for eptifibatide and tirofiban is <300 seconds during angioplasty; post-procedure unfractionated heparin infusions are not recommended during GP IIb/IIIa receptor antagonist therapy. Mechanisms that result in restenosis include acute lumen loss owing to "recoil," mural thrombosis formation, and smooth muscle cell proliferation with synthesis of extracellular matrix.[84] Approaches to prevent restenosis may be aimed at altering the underlying mechanisms. Recoil and loss of luminal diameter may be reduced by the use of stent placement; however, this beneficial effect is offset by an increased number of vascular complications. Cracking of the plaque leads to severe damage to the arterial wall, exposure of collagen, and endothelial dysfunction. These factors promote mural thrombi, and the propensity for thrombus formation is related, in part, to the composition of the plaque as well as the depth of injury. Combination therapy with acetylsalicylic acid, heparin and GP IIb/IIIa receptor antagonists is recommended to minimize acute occlusion and numerous clinical

TABLE 17-8 Percutaneous Coronary Intervention Based on Angina Class

Patients with Asymptomatic Ischemia or Canadian Cardiovascular Society (CCS) Class I or II Angina		
Class I Patients who do not have treated diabetes with asymptomatic ischemia or mild angina with 1 or more significant lesions in 1 or 2 coronary arteries suitable for PCI with a high likelihood of success and low risk of morbidity and mortality. The vessels to be dilated must subtend a large area of viable myocardium. *(Level of Evidence: B)*	**Class IIa** 1. PCI is reasonable in patients with asymptomatic ischemia or CCS class I or II angina and with 1 or more significant lesions in 1 or 2 coronary arteries suitable for PCI with a high likelihood of success and a low risk of morbidity and mortality. The vessels to be dilated must subtend a moderate to large area of viable myocardium or be associated with a moderate to severe degree of ischemia on noninvasive testing. *(Level of Evidence: B)*	Phrasing has been changed to reflect current terminology. The recommendation and all of those that follow in Section 5 have been reworded to be consistent with the CCS classification system of angina. This recommendation has been changed to class IIa to reflect the published data and Writing Committee consensus that not all patients in this clinical category must have PCI performed.
Class IIa 1. The same clinical and anatomic requirements as for Class I, except the myocardial area at risk is of moderate size or the patient has treated diabetes. *(Level of Evidence: B)*		This recommendation has been merged with other class IIa recommendations of this section, and the phrasing has been changed to reflect current terminology.
	2. PCI is reasonable for patients with asymptomatic ischemia or CCS class I or II angina, and recurrent stenosis after PCI with a large area of viable myocardium or high-risk criteria on noninvasive testing. *(Level of Evidence: C)*	This is a new recommendation dealing with the management of recurrent stenosis after PCI among patients with asymptomatic ischemia or class I or II angina.
	3. Use of PCI is reasonable in patients with symptomatic ischemia or CCS class I or II angina with significant left main CAD (greater than 50% diameter stenosis) who are candidates for revascularization but are not eligible for CABG. *(Level of Evidence: B)*	This recommendation for PCI among patients who are eligible for CABG who have significant left main disease has been added to reflect the favorable results noted by several trials with PCI.
Class IIb Patients with asymptomatic ischemia or mild angina with greater than or equal to 3 coronary arteries suitable for PCI with a high likelihood of success and a low risk of morbidity and mortality. The vessels to be dilated must subtend at least a moderate area of viable myocardium. In the physician's judgment, there should be evidence of myocardial ischemia by ECG exercise testing, stress nuclear imaging, stress echocardiography or ambulatory ECG monitoring or intracoronary physiologic measurements. *(Level of Evidence: B)*		This recommendation has been eliminated and replaced by the following 2 recommendations. For each, the phrasing has been constructed to reflect current terminology.
	Class IIb 1. The effectiveness of PCI for patients with asymptomatic ischemia or CCS class I or II angina who have 2- or 3-vessel disease with significant proximal LAD CAD who are otherwise eligible for CABG with 1 arterial conduit and who have treated diabetes or abnormal LV function is not well established. *(Level of Evidence: B)*	Phrasing has been changed to reflect current terminology. Among patients who are eligible, CABG with 1 arterial conduit is generally preferred for treatment of multivessel disease with significant proximal LAD obstruction in patients with treated diabetes and/or abnormal OV function.
	2. PCI might be considered for patients with asymptomatic ischemia or CCS class I or II angina with nonproximal LAD CAD that subtends a moderate area of viable myocardium and demonstrates ischemia on noninvasive testing. *(Level of Evidence: C)*	Phrasing has been changed to reflect current terminology. PCI might be considered in this clinical setting.
Class III Patients with asymptomatic ischemia or mild angina who do not meet the criteria as listed under Class I or Class II and who have: a. Only a small area of viable myocardium at risk b. No objective evidence of ischemia c. Lesions that have a low likelihood of successful dilation d. Mild symptoms that are unlikely to be due to myocardial ischemia e. Factors associated with increased risk of morbidity or mortality f. Left main disease g. Insignificant disease less than 50% *(Level of Evidence: C)*	**Class III** PCI is not recommended in patients with asymptomatic ischemia or CCS class I or II angina who do not meet the criteria as listed under the class II recommendations or who have 1 or more of the following: a. Only a small area of viable myocardium at risk *(Level of Evidence: C)* b. No objective evidence of ischemia *(Level of Evidence: C)* c. Lesions that have a low likelihood of successful dilation *(Level of Evidence: C)* d. Mild symptoms that are unlikely to be due to myocardial ischemia *(Level of Evidence: C)* e. Factors associated with increased risk of morbidity or mortality *(Level of Evidence: C)* f. Left main disease and eligibility for CABG *(Level of Evidence: C)* g. Insignificant disease (less than 50% coronary stenosis) *(Level of Evidence: C)*	Phrasing has been changed to reflect current terminology. Recommendation has been reworded to be consistent with CCS classification system for angina. Level of evidence has been added for each subgroup.

(continued)

TABLE 17-8 Percutaneous Coronary Intervention Based on Angina Class (continued)

Patients with CCS Class III Angina		
Class I	**Class IIa**	
Patient with 1 or more significant lesions in 1 or more coronary arteries suitable for PCI with a high likelihood of success and low risk of morbidity or mortality. The vessel(s) to be dilated must subtend a moderate or large area of viable myocardium and high risk. *(Level of Evidence: B)*	1. It is reasonable that PCI be performed in patients with CCS class III angina and single-vessel or multivessel CAD who are undergoing medical therapy and who have 1 or more significant lesions in 1 or more coronary arteries suitable for PCI with a high likelihood of success and low risk of morbidity or mortality. *(Level of Evidence: B)*	Phrasing has been changed to reflect current terminology. Recommendation has been reworded to be consistent with CCS classification system for angina. The recommendation class has been changed to IIa to reflect published data and Writing Committee consensus. Criteria regarding viable and high-risk myocardium have been deleted from this commendation.
Class IIa		
Patients with focal saphenous vein graft lesions or multiple stenoses who are poor candidates for reoperative surgery. *(Level of Evidence: C)*	2. It is reasonable that PCI be performed in patients with CCS class III angina with single-vessel or multivessel CAD who are undergoing medical therapy with focal saphenous vein graft lesions or multiple stenoses who are poor candidates for reoperative surgery. *(Level of Evidence: C)*	Phrasing has been changed to reflect current terminology.
	3. Use of PCI is reasonable in patients with CCS class III angina with significant left main CAD (greater than 50% diameter stenosis) who are candidates for revascularization but are not eligible for CABG. *(Level of Evidence: B)*	This recommendation for PCI among patients with significant left main disease who are not eligible for CABG has been added to reflect the favorable results noted by several trials with PCI.
Class IIb	**Class IIb**	
Patient has 1 or more lesions to be dilated with reduced likelihood of success of the vessel(s) subtend a less than moderate area of viable myocardium. Patients with 2- or 3-vessel disease, with significant proximal LAD CAD and treated diabetes or abnormal LV function. *(Level of Evidence: B)*	1. PCI may be considered in patients with CCS class III angina with single-vessel or multivessel CAD who are undergoing medical therapy and who have 1 or more lesions to be dilated with a reduced likelihood of success. *(Level of Evidence: B)*	Phrasing has been changed to reflect current terminology. The 2001 recommendation has been split into 2 separate recommendations.
	2. PCI may be considered in patients with CCS class III angina and no evidence of ischemia on noninvasive testing or who are undergoing medical therapy and have 2- or 3-vessel CAD with significant proximal LAD CAD and treated diabetes or abnormal LV function. *(Level of Evidence: B)*	Phrasing has been changed to reflect current terminology. The use of noninvasive testing to evaluate for evidence of ischemia has been added.
Class III	**Class III**	
Patient has no evidence of myocardial injury or ischemia on objective testing and has not had a trial of medical therapy, or has a. Only a small area of myocardium at risk b. All lesions or the culprit lesion to be dilated with morphology with a low likelihood of success c. A high risk of procedure-related morbidity or mortality. *(Level of Evidence: C)*	PCI is not recommended for patients with CCS class III angina with single-vessel or multivessel CAD, no evidence of myocardial injury or ischemia on objective testing, and no trial of medical therapy, or who have 1 of the following: a. Only a small area of myocardium at risk *(Level of Evidence: C)* b. All lesions or the culprit lesion to be dilated with morphology that conveys a low likelihood of success *(Level of Evidence: C)* c. A high risk of procedure-related morbidity or mortality *(Level of Evidence: C)* d. Insignificant disease (less than 50% coronary stenosis) *(Level of Evidence: C)* e. Significant left main CAD and candidacy for CABG *(Level of Evidence: C)*	Phrasing has been changed to reflect current terminology. Class II recommendations #2 and #3 from the 2001 guidelines have been merged into this recommendation.
2. Patients with insignificant coronary stenosis (e.g., less than 50% diameter). *(Level of Evidence: C)* 3. Patients with significant left main CAD who are candidates for CABG. *(Level of Evidence: B)*		

CAEBG, coronary artery bypass graft; CAD, coronary artery disease; ECG, electrocardiography; LAD, left anterior descending; LV, left ventricle; OV, outflow volume; PCI, percutaneous coronary intervention.
From Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention–Summary article: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). Circulation 2006;113:156–175.

trials document the efficacy of this combined approach.[55,78] Bivalirudin is a specific and reversible direct thrombin inhibitor that is indicated for use as an anticoagulant in patients with unstable angina undergoing PTCA. Bivalirudin is comparable to heparin in preventing thrombosis and may be associated with less bleeding.[85–87] Chapter 18 has a more complete discussion of antithrombotic therapy.

Alternatives to PTCA include directional coronary atherectomy (DCA), excimer laser, rotational atherectomy (rotablator), and intracoronary stents, or some combination of these interventions.[88] Based on randomized trials, DCA produces greater initial luminal diameter but results in a higher rate of post-procedure complications, such as non–Q-wave MI and death, and is more expensive. Consequently, PTCA is considered to be superior to DCA for most patients. Tissue debulking with DCA is useful for in-stent restenosis, particularly for diabetic patients.[89] The use of abciximab may improve these results.[90] Excimer laser angioplasty followed by balloon angioplasty or rotational atherectomy provides no benefit additional to balloon angioplasty alone.[91]

TABLE 17-9 Pharmacologic Management of Percutaneous Coronary Intervention

Antiplatelet and antithrombotic adjuctive therapies for PCI–oral antiplatelet therapy	
Class I	
1. Patients already taking daily chronic aspirin therapy should take 75 to 325 mg of aspirin before the PCI procedure is performed. *(Level of Evidence: A)*	A daily dose of 75 mg of aspirin has been shown to result in improved cardiovascular outcomes similar to daily doses of 325 mg but with fewer bleeding complications.
2. Patients not already taking daily chronic aspirin therapy should be given 300 to 325 mg of aspirin at least 2 hours and preferably 24 hours before the PCI procedure is performed. *(Level of Evidence: C)*	Higher doses of aspirin are recommended for patients not already taking aspirin therapy immediately before PCI procedures.
3. After the PCI procedure, in patients with neither aspirin resistance, allergy, nor increased risk of bleeding, aspirin 325 mg daily should be given for at least 1 month after bare-metal stent implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation, after which daily chronic aspirin use should be continued indefinitely at a dose of 75 to 162 mg. *(Level of Evidence: B)*	The doses and duration of aspirin therapy recommended herein and derived from those used for US Food and Drug Administration approval of the specific stent types noted in the recommendation. Daily chronic aspirin therapy is based on recommendations in the *ACC/AHA Guidelines for the Management of Patents with ST-Elevation Myocardial Infarction* and evidence indicating that aspiring therapy in dosages as low as 75 mg per day yields outcomes similar to those achieved with 325 mg per day but with fewer side effects.
4. A loading dose of clopidogrel should be administered before PCI is performed. *(Level of Evidence: A)* An oral loading dose of 300 mg, administered at least 6 hours before the procedure, has the best established evidence of efficacy. *(Level of Evidence: B)*	Clopidogrel is an important adjunctive therapy for patients undergoing PCI with stent placement. The best evidence of efficacy exists for 300 mg given at lest 6 hours before PCI is performed.
5. In patients who have undergone PCI, clopidogrel 75 mg daily should be given for at least 1 month after bare-metal stent implantation (unless the patient is at increased risk for bleeding; then it should be given for a minimum of 2 weeks), 3 months after sirolimus stent implantation, and 6 months after paclitaxel stent implantation, and ideally u to 12 months in patients who are not at high risk of bleeding. *(Level of Evidence: B)*	Clopidogrel therapy in the dosage of 75 mg daily should be given after stent placement to all patients. The duration of therapy varies for each stent and is based on data from clinical trails used for U.S. Food and Drug Administration approval of that stent.
Class IIa	
1. If clopidogrel is given at the time of procedure, supplementation with GP IIb/IIIa receptor antagonists can be beneficial to facilitate earlier platelet inhibition than with clopidogrel alone. *(Level of Evidence: B)*	When clopidogrel is given at the time of a PCI procedure, supplementation with glycoprotein IIb/IIIa receptor antagonists can be beneficial, especially among high-risk patients.
2. For patients with an absolute contraindication to aspirin, it is reasonable to give a 300-mg loading dose of clopidogrel, administered at least 6 hours before PCI, and/or GP IIb/IIIa antagonists, administered at the time of PCI. *(Level of Evidence: C)*	A significant number of patients will have resistance to aspirin. The strongest evidence for clopidogrel benefit exists for doses of 300 mg given at least 6 hours before the procedure.
3. When a loading dose of clopidogrel is administered, a regimen of greater than 300 mg is reasonable to achieve higher levels of antiplatelet activity more rapidly, but the efficacy and safety compared with a 300-mg loading dose are less established. *(Level of Evidence: C)*	Many patients receive clopidogrel therapy at the time of PCI in dosages greater than 600 mg. Although more pronounced inhibition of platelet function has been demonstrated for doses of clopidogrel greater than 300 mg, the safety of these higher doses and their benefits on clinical outcome are not fully established.
4. It is reasonable that patients undergoing brachytherapy be given daily clopidogrel 75 mg indefinitely and daily aspirin 75 to 325 mg indefinitely unless there is significant risk for bleeding. *(Level of Evidence: C)*	Subacute or later thrombosis has been observed in patients undergoing brachytherapy, and for this reason long-term antiplatelet therapy is recommended.
Class IIb	
In patients in whom subacute thrombosis may be catastrophic or lethal (unprotected left main, bifurcating left main, or last patent coronary vessel), platelet aggregation studies may be considered and the dose of clopidogrel increased to 150 mg per day if less than 505 inhibition of platelet aggregation is demonstrated. *(Level of Evidence: C)*	Clopidogrel resistance is a significant problem, and owing to its contribution to catastrophic clinical outcomes, the Writing Committee recommends studies be performed with increases in clopidogrel dose being recommended for use in those with higher-risk lesions.
Glycoprotein IIb/IIIa inhibitors	
Class I	
In patients with UA/NSTEMI undergoing PCI without clopidogrel administration, a C IIb/IIIa inhibitor (abciximab, eptifibatide, or tirofiban) should be administered. *(Level of Evidence: A)* It is acceptable to administer the GP IIb/IIIa inhibitor before performance of the diagnostic angiogram ("upstream treatment") or just before PCI ("in-lab treatment").	This recommendation and phrasing are compatible with the *ACC/AHA 2002 Guideline Update for the Management of Patients With Unstable Angina and Non–ST-Segment Myocardial Infarction* and current evidence from randomized clinical trials. The benefits of GP IIb/IIa inhibition are especially efficacious when clopidogrel is not given.
Class IIa	
1. In patients with UA/NSTEMI undergoing PCI with clopidogrel administration, it is reasonable to administer a GP IIb/IIIa inhibitor (abciximab, eptifibatide, or tirofiban). *(Level of Evidence: B)*	
It is acceptable to administer the GP IIb/IIIa inhibitor before performance of the diagnostic angiogram ("upstream treatment") or just before PCI ("in-lab treatment").	
2. In patients with STEMI undergoing PCI, it is reasonable to administer abciximab as early as possible. *(Level of Evidence: B)*	Recommendation has been added for consistency with the *ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction*.
3. In patients undergoing elective PCI with stent placement, it is reasonable to administer a GP IIb/IIIa inhibitor (abciximab, epitifibatide, or tirofiban). *(Level of Evidence: B)*	Phrasing has been changed to reflect current terminology, especially in a high-risk patient.
Class IIb	
In patients with STEMI undergoing PCI, treatment with eptifibatide or tirofiban may be considered. *(Level of Evidence: C)*	Recommendation has been added for consistency with the *ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction*.
Antithrombotic therapy	
Unfractionated heparin, low-molecular-weight heparin, and bivalirudin	
Class I	
1. Unfractionated heparin should be administered to patients undergoing PCI. *(Level of Evidence: C)*	Phrasing has been changed to reflect current terminology.
2. For patients with heparin-induced thrombocytopenia, it is recommended that bivalirudin or argatroban be used to replace heparin. *(Level of Evidence: B)*	Bivalirudin and argatroban are established therapies in place of heparin among patients with heparin-induced thrombocytopenia.

(continued)

TABLE 17-9 Pharmacologic Management of Percutaneous Coronary Intervention (continued)

Class IIa	
1. It is reasonable to use bivalirudin as an alternative to unfractionated heparin and glycoprotein IIb/IIIa antagonists in low-risk patients undergoing elective PCI. *(Level of Evidence: B)*	New recommendation is based on data from a clinical trial (REPLACE-2) indicating bivalirudin is an acceptable alternative to heparin and GP IIb/IIIa antagonists in low-risk patients undergoing PCI.
2. Low-molecular-weight heparin is a reasonable alternative to unfractionated heparin in patients with UA/NSTEMI undergoing PCI. *(Level of Evidence: B)*	Recommendation from the *ACC/AHA 2002 Guideline Update for the Management of Patients with Unstable Angina and Non–ST-Segment Myocardial Infarction* has been approved by this Writing Committee and included in these guidelines for consistency.
Class IIb	
Low-molecular-weight heparin may be considered as an alternative to unfractionated heparin in patients with STEMI undergoing PCI. *(Level of Evidence: B)*	Recommendation from the *ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction* has been approved by this Writing Committee and included in these guidelines for consistency.

GP, glycoprotein; NSTEMI, non–ST-segment elevation myocardial infarction; PCU, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.
From Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention–Summary article: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). Circulation 2006;113:156–175.

When medical therapy, PTCA, and CABG have been compared, low-risk patients with single-vessel coronary artery disease and normal left ventricular function had greater alleviation of symptoms with PTCA than with medical treatment; mortality rates and rates of myocardial infarction were unchanged. In high-risk patients (risk was defined by severity of ischemia, number of diseased vessels, and presence of left ventricular dysfunction), improvement of survival was greater with CABG than with medical therapy. In moderate-risk patients with multivessel coronary artery disease (most had two-vessel disease and normal left ventricular function), PTCA and CABG produced equivalent mortality rates and rates of myocardial infarction.

The development of drug-eluting stents has changed the natural course of stent thrombosis when compared to bare-metal stents that have existed for a longer period of time. Currently there are two types of drug-eluting stents available: (sirolimus (Cypher) and paclitaxel (Taxus). Soon after the introduction of bare-metal stents, it became apparent that early stent thrombosis (≤30 days) was an uncommon but serious complication of therapy.[92–95] Stent thrombosis is an infrequent but severe complication of both bare-metal stents and drug-eluting stents but there is no apparent difference in overall stent thrombosis frequency at 4 years of followup, but the time course appears to be different. Although there is a relative numeric excess of stent thrombosis late after drug-eluting stents implantation, no differences in death or death and infarction have been observed. Target lesion revascularization is needed less often with drug-eluting stents than with bare-metal stents. Implantation of drug-eluting stents outside of approved indications is probably related to the occurrence of late stent thrombosis. Longer-term followup with larger subsets of patients (i.e., lesion number, type and location, and patient comorbidities) is needed to fully understand this issue and the evolution of newer platforms for drug delivery will likely alter the natural history of drug-eluting stent thrombosis. A very important consideration is the use of combination antiplatelet therapy (aspirin + clopidogrel) for at least 1 year following implantation.[96] Patients who are hyporesponsive to clopidogrel may be treated with 150 mg/day rather than 75 mg/day.[94]

PHARMACOLOGIC THERAPY

Historically, approximately 30% of anginal syndrome symptoms have responded regardless of which therapy was instituted. These observations stem from two problems inherent in clinical trials undertaken to assess the efficacy of any therapy for angina: (a) adequate trial design incorporating appropriate controls and washout periods, and (b) assessment of treatment effects using objective measures of efficacy, including improvement in exercise performance, resting and ambulatory ECG improvement in ischemic changes, or other objective tests to address other aspects of myocardial function or metabolism. The use of pain episode frequency and nitroglycerin consumption is subjective, and their use as sole measures of efficacy should be avoided. Objective assessment using ETT has shown that placebo does not provide improvement in patients with exertional angina, substantiating this as a valid means to assess efficacy.

β-Adrenergic–Blocking Agents[97]

Decreased heart rate, decreased contractility, and a slight to moderate decrease in blood pressure with β-adrenergic receptor antagonism reduce MVO_2. The predominant receptor type in the heart is the β_1-receptor, and competitive blockade minimizes the influence of endogenous catecholamines on the chronotropic and inotropic state of the myocardium. These beneficial effects may be countered to some degree with increased ventricular volume and ejection time seen with β-blockade; however, the overall effect of β-blockers in patients with effort-induced angina is a reduction in oxygen demand (Table 17–10). The β-blockers do not improve oxygen supply, and in certain instances, unopposed α-adrenergic stimulation following the use of β-blockers may lead to coronary vasoconstriction. For patients with chronic exertional stable angina, β-blockers improve symptoms approximately 80% of the time and objective measures of efficacy demonstrate improved exercise duration and delay in the time at which ST-segment changes and initial or limiting symptoms occur. β-Blockers do not alter the rate–pressure product (double product) for maximal exercise, therefore substantiating reduced demand rather than improved supply as the major consequence of their actions. Reflex tachycardia from nitrate therapy can be blunted with β-blocker therapy, making this a common and useful combination. Although β-blockade may decrease exercise capacity in healthy individuals or in patients with hypertension, it may allow angina patients previously limited by symptoms to perform more exercise and ultimately improve overall cardiovascular performance through a training effect. Ideal candidates for β-blockers include patients in whom physical

TABLE 17-10 Effect of Drug Therapy on Myocardial Oxygen Demand[a]

			LV Wall Tension	
	Heart Rate	**Myocardial Contractility**	***Systolic Pressure***	***LV Volume***
Nitrates	⇓	0	⇓	⇓⇓
β-Blockers	⇓⇓	⇓	⇓	⇓
Nifedipine	⇓	0 or ⇓	⇓⇓	0 or ⇓
Verapamil	⇓	⇓	⇓	0 or ⇓
Diltiazem	⇓⇓	0 or ⇓	⇓	0 or ⇓

LV, left ventricular.
[a]Calcium channel antagonists and nitrates also may increase myocardial oxygen supply through coronary vasodilation. Diastolic function also may be improved with verapamil, nifedipine, and perhaps, diltiazem. These effects may vary from those indicated in the table depending on individual patient baseline hemodynamics.

activity figures prominently in their anginal attacks, those who have coexistent hypertension, those with a history of supraventricular arrhythmias or post-MI angina, and those who have a component of anxiety associated with angina.[3] β-Blockers may also be safely used in angina and heart failure as described in Chap. 16.

Pertinent pharmacokinetics for the β-blockers include half-life and route elimination, which are reviewed in Chap. 15. Drugs with longer half-lives need to be dosed less frequently than drugs with shorter half-lives; however, disparity exists between half-life and duration of action for several β-blockers (e.g., metoprolol), which may reflect attenuation of the central nervous system-mediated effects on the sympathetic system, as well as the direct effects of this category on heart rate and contractility. Renal and hepatic dysfunction can affect the disposition of β-blockers, but these agents are dosed to effect, either hemodynamic or symptomatic, and route of elimination is not a major consideration in drug selection.

Guidelines for the use of β-blockers in treating angina include the objective of lowering resting heart rate to 50 to 60 beats per minute and limiting maximal exercise heart rate to about 100 beats per minute or less. It has also been suggested that exercise heart rate should be no more than about 20 beats per minute or a 10% increment over resting heart rate with modest exercise. Because β-blockade is competitive and circulating catecholamine concentrations vary depending on the intensity of exercise and other factors, and cholinergic tone may be important in controlling heart rate in some patients, these guidelines are general in nature. These effects are generally dose and plasma concentration related, and for propranolol, plasma concentrations of 30 ng/mL are needed for a 25% reduction of anginal frequency. Initial doses of β-blockers should be at the lower end of the usual dosing range and titrated to response as indicated above.

Although there is little evidence to suggest superiority of any β-blocker, the duration of β-blockade is dependent partially on the half-life of the agent used, and agents with longer half-lives may be dosed less frequently. Of note, propranolol may be dosed twice a day in most patients with angina and the efficacy is similar to that seen with more frequent dosing. The ancillary property of membrane stabilizing activity is irrelevant in the treatment of angina, and intrinsic sympathomimetic activity appears to be detrimental in rest or severe angina because the reduction in heart rate would be minimized, therefore limiting a reduction in MVO_2. Cardioselective β-blockers may be used in some patients to minimize adverse effects such as bronchospasm in asthma, intermittent claudication, and sexual dysfunction. A common misunderstanding is that β-blockers are not well tolerated in peripheral arterial disease but, in fact, their use is associated with a reduction in death and improved quality of life.[98] It should be remembered that cardioselectivity is a relative property and the use of larger doses (e.g., metoprolol 200 mg/day) is associated with the loss of selectivity and with adverse effects. Post-acute-MI patients with angina are particularly good candidates for β-blockade, both because anginal symptoms may be treated and the risk of post-MI reinfarction reduced, and because mortality has been demonstrated with timolol, propranolol, and metoprolol (see Chap. 15). Combined β- (nonselective) and α-blockade with labetalol may be useful in some patients with marginal LV reserve, and fewer deleterious effects on coronary blood flow are seen when compared with other β-blockers.

Extension of pharmacologic effect is the underlying reason for many of the adverse effects seen with β-blockade. Hypotension, decompensated heart failure, bradycardia and heart block, bronchospasm, and altered glucose metabolism are directly related to β-adrenoreceptor antagonism. Patients with preexisting left ventricular systolic decompensated and heart failure and the use of other negative inotropic agents are most prone to developing overt heart failure, and in the absence of these, heart failure is uncommon (less than 5%). Other drugs that depress conduction are additive to β-blockade, and intrinsic conduction system disease predisposes the patient to conduction abnormalities. Altered glucose metabolism is most likely to be seen in insulin-dependent diabetics, and β-blockade obscures the symptoms of hypoglycemia except for sweating. β-Blockers may also aggravate the lipid abnormalities seen in patients with diabetes; however, these changes are dose related, are more common with normal baseline lipids than dyslipidemia, and may be of short-term significance only. One of the more common reasons for discontinuation of β-blocker therapy is related to central nervous system adverse effects of fatigue, malaise, and depression. Cognition changes seen with β-blockers are usually minimal and comparable to other categories of drugs based on studies done in hypertension.[99,100] Abrupt withdrawal of β-blocker therapy in patients with angina has been associated with increased severity and number of pain episodes and myocardial infarction. The mechanism of this effect is unknown but may be related to increased receptor sensitivity or disease progression during therapy, which becomes apparent following discontinuation of β-blockade. In any event, tapering of β-blocker therapy over about 2 days should minimize the risk of withdrawal reactions for those patients in whom therapy is being discontinued.

β-Adrenoreceptor blockade is effective in chronic exertional angina as monotherapy and in combination with nitrates and/or calcium channel antagonists. β-Blockers should be the first-line drug in chronic angina that requires daily maintenance therapy because β-blockers are more effective in reducing episodes of silent ischemia, reducing early morning peak of ischemic activity, and improving mortality after Q-wave MI than nitrates or calcium channel blockers (see Fig. 17–4).[3] If β-blockers are ineffective or not tolerated, then monotherapy with a calcium channel blocker or combination therapy if monotherapy is ineffective may be instituted. Patients with severe angina, rest angina, or variant angina (i.e., a component of coronary artery spasm) may be better treated with calcium channel blockers or long-acting nitrates.

Nitrates[101,102]

Nitroglycerin has a well-documented role in the alleviation of acute anginal attacks when used as rapidly absorbed and readily available preparations by the oral and intravenous routes (Table 17–11; see also Fig. 17–4). Sublingual, buccal, or spray products are the products of choice for this indication. Prevention of symptoms may be accomplished by the prophylactic use of oral or transdermal products; however, recent concern has been expressed over the long-term efficacy of many of these preparations and the development of tolerance.[46,47]

Nitrates have multiple potential mechanisms of action, and for a given patient it is not always clear which of these is most important. In general, the major action appears to be indirectly mediated

TABLE 17-11 Nitrate Products

Product	Onset (min)	Duration	Initial Dose
Nitroglycerin			
IV	1–2	3–5 min	5 mcg/min
Sublingual/lingual	1–3	30–60 min	0.3 mg
Oral	40	3–6 h	2.5–9 mg tid
Ointment	20–60	2–8 h	0.5–1 in
Patch	40–60	>8 h	1 patch
Erythritol tetranitrate	5–30	4–6 h	5–10 mg tid
Pentaerythritol tetranitrate	30	4–8 h	10–20 mg tid
Isosorbide dinitrate			
Sublingual/chewable	2–5	1–2 h	2.5–5 mg tid
Oral	20–40	4–6 h	5–20 mg tid
Isosorbide mononitrate	30–60	6–8 h	20 mg daily, bid[a]

[a]Product dependent.

through a reduction of myocardial oxygen demand secondary to venodilation and arterial–arteriolar dilation, leading to a reduction in wall stress from reduced ventricular volume and pressure (see Table 17–10). Systemic venodilation also promotes increased flow to deep myocardial muscle by reducing the gradient between intraventricular pressure and coronary arteriolar (R2) pressure. Direct actions on the coronary circulation include dilation of large and small intramural coronary arteries, collateral dilation, coronary artery stenosis dilation, abolition of normal tone in narrowed vessels, and relief of spasm; these actions occur even if the endothelium is denuded or dysfunctional. It is likely that depending on the underlying pathophysiology, different mechanisms become operative. For example, in the presence of a 60% to 70% stenosis, venodilation with MVO_2 reduction is most important; however, with higher grade lesions, direct effects on the coronary circulation and vessel tone are the predominant effects. Nitroglycerin and pentaerythritol tetranitrate in low doses are bioactivated by mitochondrial aldehyde dehydrogenase to nitrite or denitrated metabolites, which require further activation by cytochrome oxidase or acidic disproportionation in the inner membrane space, finally yielding nitric oxide. Nitric oxide activates soluble guanylate cyclase to increase intracellular concentrations of cyclic guanosine monophosphate (GMP) resulting in vasorelaxation.[47] In contrast, isosorbide dinitrate (ISDN) and isosorbide mononitrate (ISMN) are bioactivated via P450 enzymes to nitric oxide. At higher concentrations, nitroglycerin and pentaerythritol tetranitrate may also be bioactivated to nitric oxide via P450 enzymes. Increased cyclic GMP induces a sequence of protein phosphorylation associated with reduced intracellular calcium release from the sarcoplasmic reticulum or reduced permeability to extracellular calcium and, consequently, smooth muscle relaxation. Oxidative stress within the mitochondria causes inactivation of mitochondrial aldehyde dehydrogenase, leading to impaired bioactivation of nitroglycerin during prolonged treatment.[103,104] Thomas et al. performed a study in normal volunteers to evaluate the effect of ISMN 120 mg/day given for 7 days on endothelial function. They found that ISMN impaired endothelial function suggesting a role for oxygen free radicals and nitrate induced abnormalities in endothelial-dependent vasomotor responses that were reversed with a vitamin C infusion of 24 mg/min given for 15 minutes.[46] Furthermore, ISDN impairs flow-mediated dilation and carotid intimal-media thickness after 3 months of treatment.[105] These deleterious changes in endothelial function, intima-media thickness and the occurrence of tolerance suggest that the role of nitrates in IHD may be changing.

Pharmacokinetic characteristics common to the organic nitrates used for angina include a large first-pass effect of hepatic metabolism, short to very short half-lives (except for isosorbide mononitrate), large volumes of distribution, high clearance rates, and large interindividual variations in plasma or blood concentrations. Pharmacodynamic–pharmacokinetic relationships for the entire class remain poorly defined, presumably because of methodologic difficulty in characterizing the parent drug and metabolite concentrations at or within vascular smooth muscle and secondary to counterregulatory or adaptive mechanisms from the drug's effects, as well as the occurrence of tolerance. Nitroglycerin is extracted by a variety of tissues and metabolized locally; differential extraction and metabolite generation occur depending on the tissue site. There are also numerous technical problems limiting the generation of reliable pharmacokinetic parameter estimates including the following: assay sensitivity; arterial–venous extraction gradients and therefore extrahepatic metabolism; in vitro degradation; drug adsorption to polyvinyl chloride tubing and syringes; potentially saturable metabolism; accumulation of metabolites (some of which are active) with multiple doses; postural and exercise-induced changes in pharmacokinetics; a variety of variables associated with transdermal delivery including the delivery system (matrix, membrane-limited, ointment), vehicle used, the surface area and thickness of application, the site application, and other skin variables (temperature, moisture content).

Nitroglycerin concentrations are affected by the route of administration, with the highest concentrations usually obtained with intravenous administration, the lowest seen with lower oral doses. Peak concentrations with sublingual nitroglycerin appear within 2 to 4 minutes, with the oral route producing peaks at about 15 to 30 minutes and by the transdermal route at 1 to 2 hours. The half-life of nitroglycerin is 1 to 5 minutes regardless of route; hence the potential advantage of sustained-release and transdermal products. Transdermal nitroglycerin does produce sufficient concentrations for acute hemodynamic effects to occur and these concentrations are maintained for long intervals; however, the hemodynamic and antianginal effects are minimal after 1 week or less with chronic, continuous (24 h/day) therapy.

ISDN is metabolized to isosorbide 2-mono- and 5-mononitrate (ISMN). ISMN is well absorbed and has a half-life of about 5 hours and may be given once or twice daily depending on the product chosen. Multiple, larger doses of ISDN lead to disproportionate increases in the area under the plasma time profile, suggesting that metabolic pathways are being saturated or that metabolite accumulation may influence the disposition of ISDN. Little pharmacokinetic information is available for other nitrate compounds.

Nitrate therapy may be used to terminate an acute anginal attack, to prevent effort or stress-induced attacks, or for long-term prophylaxis, usually in combination with β-blockers or calcium channel blockers. Sublingual nitroglycerin 0.3 to 0.4 mg will relieve pain in approximately 75% of patients within 3 minutes, with another 15% becoming pain free in 5 to 15 minutes. Pain persisting beyond about 20 to 30 minutes following the use of two or three nitroglycerin tablets is suggestive of acute coronary syndrome and the patient should be instructed to seek emergency aid. Patients should be instructed to keep nitroglycerin in the original, tightly closed glass container and to avoid mixing with other medication, because mixing may reduce nitroglycerin adsorption and vaporization. Additional counseling should include the facts that nitroglycerin is not an analgesic but rather it partially corrects the underlying problem and that repeated use is not harmful or addicting. Patients should also be aware that enhanced venous pooling in the sitting or standing positions may improve the effect, as well as the symptoms of postural hypotension, and that inadequate saliva may slow or prevent tablet disintegration and dissolution. An acceptable, albeit expensive, alternative is lingual spray, which may be more convenient and has a shelf-life of 3 years, compared with 6 months or so for some forms of nitroglycerin tablets.

Chewable, oral, and transdermal products are acceptable for the long-term prophylaxis of angina; however, considerable controversy surrounds their use and it appears that the development of tolerance or adaptive mechanisms limits the efficacy of all chronic nitrate therapies regardless of route. Dosing of the longer-acting preparations should be adjusted to provide a hemodynamic response and, as an example, may require doses of oral ISDN ranging from 10 to 60 mg as often as every 3 to 4 hours owing to tolerance or first-pass metabolism, and similar large doses are required for other products. Nitroglycerin ointment has a duration of up to 6 hours, but it is difficult to apply in a cosmetically acceptable fashion over a consistent surface area, and response varies depending on the epidermal thickness, vascularity, and amount of hair. Percutaneous adsorption of nitroglycerin ointment may occur unintentionally if someone other than the patient applies the ointment, and limiting exposure through the use of gloves or some other means is advisable. Peripheral edema may also impair the response to nitroglycerin because venodilation cannot increase capacitance to a maximum and pooling may be reduced. Transdermal patch delivery systems were approved

on the basis of sustained and equivalent plasma concentrations to other forms of therapy. Trials required by the Food and Drug Administration using transdermal patches as a continuous 24-hour delivery system revealed a lack of efficacy for improved exercise tolerance. Subsequently, large, randomized, double-blind, placebo-controlled trials of intermittent (10 to 12 hours on; 12 to 14 hours off) transdermal nitroglycerin therapy in chronic stable angina demonstrated modest but significant improvement in exercise time after 4 weeks for the highest doses at 8 to 12 hours after patch placement.[106] Subjective assessment methods for nitrate effects include reduction in the number of painful episodes and the amount of nitroglycerin consumed. Objective assessment includes the resolution of ECG changes at rest, during exercise, or with ambulatory ECG monitoring. Because nitrates work primarily through a reduction in MVO_2, the double product can be used to optimize the dose of sublingual and oral nitrate products. It is important to realize that reflex tachycardia may offset the beneficial reduction in systolic blood pressure and calculation of the observed changes is necessary. The double product is best assessed in the sitting position and at intervals of 5 to 10 minutes and 30 to 60 minutes following sublingual and oral therapy, respectively. Owing to the placebo effect, unpredictable and variable course of angina, numerous pharmacologic effects of nitroglycerin, diurnal variation in pain patterns, stringent investigative protocols, and interindividual sensitivity to nitroglycerin, assessment with transdermal and sustained-release products is difficult. ETT provides valuable information concerning efficacy and mechanism of action for nitrates but its use is usually reserved for clinical investigation rather than routine patient care. Most ETT studies have shown nitrates to delay the onset of ischemia (ST-segment changes or initial chest discomfort) at submaximal exercise but that the threshold for maximal exercise is unaltered, suggesting a reduction in oxygen demand rather than an improved oxygen supply. More sophisticated studies of myocardial function, such as wall motion abnormalities and myocardial metabolism, could be used to document efficacy; however, these studies are generally only for investigative purposes.

Adverse effects of nitrates are related most commonly to an extension of their pharmacologic effects and include postural hypotension with associated central nervous system symptoms, headaches and flushing secondary to vasodilation, and occasional nausea from smooth muscle relaxation. If hypotension is excessive, coronary and cerebral filling may be compromised, leading to myocardial infarction and stroke. Although reflex tachycardia is most common, bradycardia with nitroglycerin has been reported. Other noncardiovascular adverse effects include rash with all products, but particularly with transdermal nitroglycerin, the production of methemoglobinemia with high doses given for extended periods, and measurable concentrations of ethanol (intoxication has been reported) and propylene glycol (found in the diluent) with intravenous nitroglycerin.

Tolerance with nitrate therapy was first described in 1867 with the initial experience using amyl nitrate for angina and later widely recognized in munitions workers who underwent withdrawal reactions during periods of absence from exposure. Tolerance to nitrates is associated with a reduction in tissue cyclic GMP, which results from decreased production (guanylate cyclase) and increased breakdown via cyclic GMP-phosphodiesterase and increased superoxide levels. One proposed mechanism for the lack of cyclic GMP is lack of conversion of organic nitrates to nitric oxide as described previously.[47,97]

Most of the published information from controlled trials examining nitrate tolerance have been done with either ISDN or transdermal nitroglycerin, and these studies demonstrate the development of tolerance within as little as 24 hours of therapy. Although the onset of tolerance is rapid, the offset may be just as rapid, and one alternative-dosing strategy to circumvent or minimize tolerance is to provide a daily nitrate-free interval of 6 to 8 hours. Studies with a variety of nitrate preparations and dosing schedules demonstrate that this approach is useful and the nitrate-free interval should be a minimum of 8 hours, and perhaps 12 hours for even better effects.[97] Another concern for intermittent transdermal nitrate therapy is the occurrence of rebound ischemia during the nitrate-free interval. Freedman et al.[107] found more silent ischemia during the patch-free interval during a randomized, double-blind, placebo-controlled trial than during the placebo patch phase, although others have not noted this effect. ISDN, for example, should not be used more often than three times per day if tolerance is to be avoided. Interestingly, hemodynamic tolerance does not always coincide with antianginal efficacy, but this is not well studied.

Nitrates may be combined with other drugs for anginal therapy including β-adrenergic-blocking agents and calcium channel antagonists. These combinations are usually instituted for chronic prophylactic therapy based on complementary or offsetting mechanisms of action (see Table 17–10). Combination therapy is generally used in patients with more frequent symptoms or with symptoms that are not responding to β-blockers alone (nitrates plus β-blockers or calcium blockers), in patients intolerant of β-blockers or calcium channel blockers, and in patients having an element of vasospasm leading to decreased supply (nitrates plus calcium blockers).[108] Modulation of calcium entry into vascular smooth muscle and myocardium as well as a variety of other tissues is the principal action of the calcium antagonists. The cellular mechanism of these drugs is incompletely understood and it differs among the available classes of the phenylalkylamines (verapamil-like), dihydropyridines (nifedipine-like), benzothiazepines (diltiazem-like), bepridil, and a recent class referred to as T-channel blockers. Receptor-operated channels stimulated by norepinephrine and other neurotransmitters, and potential-dependent channels activated by membrane depolarization, control the entry of calcium, and, consequently, the cytosolic concentration of calcium responsible for activation of actin–myosin complex leading to contraction of vascular smooth muscle and myocardium. In the myocardium, calcium entry triggers the release of intracellular stores of calcium to increase cytosolic calcium, whereas in smooth muscle, calcium derived from the extracellular fluid may do this directly. Binding proteins within the cell, calmodulin and troponin, after binding with calcium, participate in phosphorylation reactions leading to contraction. Decreased calcium availability, through the actions of calcium antagonists, inhibits these reactions.

Direct actions of the calcium antagonists include vasodilation of systemic arterioles and coronary arteries, leading to a reduction of arterial pressure and coronary vascular resistance, as well as depression of the myocardial contractility and conduction velocity of the sinoatrial and atrioventricular nodes (see Chap. 19). Reflex β-adrenergic stimulation overcomes much of the negative inotropic effect, and depression of contractility becomes clinically apparent only in the presence of LV dysfunction and when other negative inotropic drugs are used concurrently. Verapamil and diltiazem cause less peripheral vasodilation than nifedipine, and, consequently, the risk of myocardial depression is greater with these two agents. Conduction through the AV node is predictably depressed with verapamil and diltiazem, and they must be used cautiously in patients with preexisting conduction abnormalities or in the presence of other drugs with negative chronotropic properties. MVO_2 is reduced with all of the calcium channel antagonists because of reduced wall tension secondary to reduced arterial pressure and, to a minor extent, depressed contractility (see Table 17–10). Heart rate changes are dependent on the drug used and the state of the conduction system. Nifedipine generally increases heart rate or causes no change, whereas either no change or decreased heart rate is seen with verapamil and diltiazem because of the interaction of these direct and indirect effects. In contrast to the β-blockers, calcium channel antagonists have the potential to improve coronary blood flow through areas of fixed coronary

obstruction and by inhibiting coronary artery vasomotion and vasospasm. Beneficial redistribution of blood flow from well-perfused myocardium to ischemic areas and from epicardium to endocardium may also contribute to improvement in ischemic symptoms. Overall, the benefit provided by calcium channel antagonists is related to reduced MVO_2 rather than improved oxygen supply, based on lack of alteration in the rate pressure product at maximal exercise in most studies performed to date. However, as coronary artery disease progresses and vasospasm becomes superimposed on critical stenotic lesions, improved oxygen supply through coronary vasodilation may become more important.

Absorption of the calcium channel antagonists is characterized by excellent absorption and large, variable, first-pass metabolism resulting in oral bioavailability ranging from approximately 20% to 50% or greater for diltiazem, nicardipine, nifedipine, verapamil, felodipine, and isradipine. Amlodipine has a range of bioavailability of approximately 60% to 80%. Saturation of this effect may occur with verapamil and diltiazem, resulting in greater amounts of drug being absorbed with chronic dosing. Nifedipine may have slow or fast absorption patterns, and the ingestion of food delays and impairs its absorption as well as potential enhanced absorption in elderly patients. This variability in absorption produces fluctuation in the hemodynamic response with nifedipine. Sublingual nifedipine is frequently used to provide a more rapid response; however, the rationale for this application is suspect because little nifedipine is absorbed from the buccal mucosa and the swallowed drug is responsible for the observed plasma concentrations. Absorption of verapamil in sustained-release products may be influenced by food, and when used in the fasted state, dose dumping may occur, resulting in high peak concentrations with some products. The approved sustained-release products for nifedipine, verapamil, and diltiazem are approved primarily for the treatment of hypertension (see Chap. 15). The presence of severe liver disease (e.g., alcoholic liver disease with cirrhosis) reduces the first-pass metabolism of verapamil, and this shunting of drug around the liver gives rise to higher plasma concentrations and lower dose requirements in these patients. Interestingly, this effect appears to be stereoselective for the more active isomer of verapamil. Verapamil may also reduce liver blood flow; however, evidence for this reduction is based primarily on animal experiments. Few data are available regarding the influence of liver disease on the kinetics of calcium blockers; however, these drugs undergo extensive hepatic metabolism with little unchanged drug being renally excreted, and liver disease can be expected to alter the pharmacokinetics. Nifedipine has no active metabolites whereas norverapamil possesses 20% or less activity of the parent compound. Desacetyl-diltiazem has not been studied in man, but canine studies suggest its potency ranges from 100% to 40% of the parent compound for various cardiovascular effects; the clinical importance of these observations remains to be determined. With chronic dosing of verapamil and diltiazem, apparent saturation of metabolism occurs, producing higher plasma concentrations of each drug than those seen with single-dose administration. Consequently, the elimination half-life for verapamil is prolonged, and less-frequent dosing intervals may be used in some patients. The elimination half-life for diltiazem is also somewhat prolonged and the half-life of desacetyl-diltiazem is longer than that of the parent drug, but it is not clear if less-frequent dosing may be used. Bepridil also undergoes hepatic elimination and an active metabolite, 4-hydroxyphenyl bepridil, is produced; the parent compound has a long half-life of 30 to 40 hours. Nifedipine does not accumulate with chronic dosing; however, it is eliminated via oxidative pathways that may be polymorphic, and slow and fast metabolizers have been described for nifedipine. Most of the calcium channel blockers are eliminated via cytochrome (CYP) 3A4 and other CYP isoenzymes and many inhibit CYP3A4 activity as well.[109] Renal insufficiency has little or no effect on the pharmacokinetics of these three drugs. Although disease alterations in kinetics have been described, the most important quantitative alteration is the influence of liver disease on bioavailability and elimination that reduce the clearance of verapamil and diltiazem, and dosing in this population should be done with caution. Altered protein binding because of renal disease, decreased protein concentration, or increased α_1-acid glycoprotein has been noted, but the clinical import of these changes is unknown.

Good candidates for calcium channel blockers in angina include patients with contraindications or intolerance of β-blockers, coexisting conduction system disease (except for verapamil and diltiazem), patients with Prinzmetal angina (vasospastic or variable threshold angina), the presence of peripheral vascular disease, severe ventricular dysfunction (amlodipine is probably the calcium channel blocker of choice and others need to be used with caution if the ejection fraction is <40%), and concurrent hypertension.

Ranolazine is a new drug for angina that has a unique mechanism of action which is unlike that of any other drug used to alter the relationship between oxygen supply and demand. Ranolazine reduces calcium overload in the ischemic myocyte through inhibition of the late sodium current (I_{Na}). Myocardial ischemia produces a cascade of complex ionic exchanges that can result in intracellular acidosis, excess cytosolic Ca^{2+}, myocardial cellular dysfunction, and, if sustained, cell injury and death. Activation of the adenosine triphosphate-dependent K^+ current during ischemia results in a strong efflux of K^+ ions from myocytes. Sodium channels are activated on depolarization, leading to a rapid influx of sodium into the cells. The inactivation of I_{Na} has a fast component that lasts a few milliseconds and a slowly inactivating component that can last hundreds of milliseconds.[110] Ranolazine is a relatively selective inhibitor for late I_{Na}. In isolated ventricular myocytes in which the late I_{Na} was pathologically augmented, ranolazine prevented or reversed the induced mechanical dysfunction, as well as ameliorated abnormalities of ventricular repolarization. Ranolazine does not affect heart rate, inotropic state, or hemodynamic state or increase coronary blood flow.

Ranolazine is extensively metabolized via CYP450 3A and potent inhibitors of 3A increase the plasma concentration by a factor of about three. Ketoconazole, diltiazem and verapamil should not be coadministered with ranolazine. Absorption from the gut is quite variable and the apparent half-life is 7 hours. Steady state is reached after 3 days of twice-daily dosing. Ranolazine is indicated for the treatment of chronic angina and because it prolongs the QT interval, it should be reserved for patients who have not achieved an adequate response with other antianginal agents. Contraindications include preexisting QT interval prolongation, hepatic impairment, concurrent QT interval-prolonging drugs, and moderately potent to potent concurrent 3A inhibitors. QT prolongation occurs in a dose-dependent fashion with ranolazine with an average increase of 6 milliseconds but 5% of the population has QT_c prolongation of 15 milliseconds. Baseline and followup ECGs should be obtained to evaluate effects of the QT interval. In controlled trials, the most common adverse reactions are dizziness, headache, constipation and nausea. Ranolazine should be started at 500 mg twice daily and increased to 1,000 mg twice daily as needed based on symptoms.[111]

Based on randomized, placebo-controlled trials, the improvement in exercise time is a modest increase of 15 to about 45 seconds compared with placebo.[112,113] In a large acute coronary syndrome trial, ranolazine reduced recurrent ischemia but did not improve the primary efficacy end point of the composite of cardiovascular death, MI, or recurrent ischemia.[114]

Investigational Agents

Therapeutic angiogenesis aims to deliver an angiogenic growth factor or cytokine to the myocardium to stimulate collateral blood vessel

growth throughout the ischemic tissue. The angiogenic factor may be administered as a recombinant protein or as a transgene within a plasmid or gene-transfer vector. An example of this approach is the intracoronary administration of the adenoviral gene for fibroblast growth factor (Ad5FGF-4) to determine if therapeutic angiogenesis could improve myocardial perfusion compared with placebo.[115] In this study of 52 patients with stable angina and reversible ischemia, Ad5FGF-4 decreased ischemic defect by 21% (P <0.001) as determined by single-photon emission computed tomography imaging.[115] More trials are needed before angiogenesis becomes a standard therapy.[116]

TREATMENT

Coronary Artery Spasm and Variant Angina Pectoris (Prinzmetal Angina)[117]

Prinzmetal, in his original description of variant angina pectoris, noted the waxing and waning course of this syndrome associated with ST-segment elevation and that it most commonly resolves without progression to MI. Patients who develop variant angina are usually younger, have fewer coronary risk factors but more commonly smoke than patients with chronic stable angina. Hyperventilation, exercise, and exposure to cold may precipitate variant angina attacks, or there may be no apparent precipitating cause. The onset of chest discomfort is usually in the early morning hours. The exact cause of variant angina is not well understood, but may be an imbalance between endothelium-produced vasodilator factors (prostacyclin, nitric oxide) and vasoconstrictor factors (e.g., endothelin, angiotensin II) as well as an imbalance of autonomic control characterized by parasympathetic dominance or inflammation may also play a role.[118,119] More recently there have been a number potential common adrenoreceptor polymorphisms that may predispose patients to developing vasospasm.[120,121]

The diagnosis of variant angina is based on ST-segment elevation during transient chest discomfort (usually at rest) that resolves when the chest discomfort diminishes in patients who have normal or nonobstructive coronary lesions. In the absence of ST-segment elevation, provocative test using ergonovine, acetylcholine, or methacholine may be used to precipitate coronary artery spasm, ST-segment elevation and typical symptoms. Nitrates and calcium antagonists should be withdrawn prior to provocative testing. Provocative testing should not be used in patients with high-grade lesions. Hyperventilation may also be used to provoke spasm and patients who positive a hyperventilation test are more likely to have higher frequency of attacks, multivessel disease, and a high degree of AV block or ventricular tachycardia.

Optimization of therapy includes dose titration using sufficiently high doses to obtain clinical efficacy without unacceptable adverse effects in individual patients. All patients should be treated for acute attacks and maintained on prophylactic treatment for 6 to 12 months following the initial episode. The occurrence of serious arrhythmias during attacks is associated with a greater risk of sudden death, and these patients should be treated more aggressively and for prolonged periods. Patients without arrhythmias who become asymptomatic and remain so for several months after treatment has been instituted, withdrawal of therapy may be safe after first ascertaining that disease activity is quiescent. Aggravating factors such as alcohol or cocaine use or cigarette smoking should be eliminated when instituting treatment.

Nitrates have been the mainstay of therapy for the acute attacks of variant angina and coronary artery spasm for many years. Most patients respond rapidly to sublingual nitroglycerin or isosorbide dinitrate; however, intravenous and intracoronary nitroglycerin may be very useful for patients who do not respond to sublingual preparations. In particular, vasospasm provoked by ergonovine may require intracoronary nitroglycerin. Although studies with nitrates generally show them to be efficacious, high does are often required and it is unclear if they reduce mortality. Because calcium antagonists may be more effective, have few serious adverse effects in effective doses, and can be given less frequently than nitrates, some consider them the agents of choice for variant angina.

Nifedipine, verapamil, and diltiazem are all equally effective as single agents for the initial management of variant angina and coronary artery spasm. Dose titration is important to maximize the response with calcium antagonists. Comparative trials are few in number and do not reveal significant differences among these three drugs for variant angina. Patients unresponsive to calcium antagonists alone, may have nitrates added. Combination therapy with nifedipine–diltiazem or nifedipine–verapamil is reported to be useful for patients who are unresponsive to single-drug regimens. Although this is probably rational as at the cellular level the drugs have different receptors, the combination of verapamil–diltiazem should be used cautiously owing to their potential additive effects on contractility and conduction.

β-Adrenergic blockade has little or no role in the management of variant angina according to most authorities.[122] Although not all studies report increased painful episodes of variant angina with the addition of β-blockers, they may induce coronary vasoconstriction and prolong ischemia, as documented by continuous ECG monitoring. Other approaches to therapy attempting to modify sympathetic/parasympathetic tone include α-antagonists, anticholinergics, plexectomy, surgical interruption of the sympathetic innervation of the heart, thromboxane receptor antagonism, prostacyclin, lipoxygenase inhibition, and ticlopidine but these drugs or procedures do not occupy a major place in therapy at the present time.

TREATMENT

Silent Ischemia[16]

The objective in the treatment of silent myocardial ischemia is to reduce the total number of ischemic episodes, both symptomatic and asymptomatic, regardless of the direction of ST-segment shift. The incidence of silent ischemia in the general, asymptomatic population is unknown. Significant day-to-day variability in the number of episodes, the duration of ischemia, and the amount of ST-segment deviation complicates both the understanding of this process and the utility of various therapeutic interventions. Silent ischemia in patients with known CAD is common (~80% of all ischemic episodes) and associated with the extent of disease as well as a high risk for myocardial infarction and sudden death when compared with symptomatic episodes of ischemia. Although the underlying mechanisms for silent ischemia are continuing to be defined, increased physical activity, activation of the sympathetic nervous system, increased cortisol secretion, increased coronary artery tone, and enhanced platelet aggregation as a result of endothelia dysfunction leading to intermittent coronary obstruction may be additive in lowering the threshold for ischemia. Platelet aggregability is increased in the morning hours (7 AM to 11 AM), corresponding to circadian rhythms noted for the peak frequency of ischemia, acute myocardial infarction, and sudden death. Silent ischemia is associated with ST-segment elevation or depression and frequently occurs without antecedent changes in heart rate or blood pressure, suggesting that this form of ischemia is a result of primary reduction in oxygen supply. Silent ischemia is classified into class I, patients who

do not experience angina at any time, and class II, patients who have both asymptomatic and symptomatic ischemia. Patients with silent ischemia have a defective warning system for angina pain that may encourage excessive myocardial demand. Regardless of the exact mechanism, there is increasing concern that painless ischemia carries considerable risk for myocardial perfusion defects, detrimental hemodynamic changes, arrhythmogenesis, and sudden death. Silent ischemia is associated with reduced survival and increased need for PTCA and CABG, as well as increased risk of acute MI.[123] Because it is apparently very common in some settings, major emphasis should be placed on its management. Although a consensus has not been reached for the most appropriate method of detecting and quantifying the magnitude of silent ischemia, ambulatory electrocardiogram monitoring is thought by many to be the most useful tool at the present time.

The initial step in management is to modify the major risk factors for IHD, hypertension, hypercholesterolemia, and smoking, and data from the Multiple Risk Factor Intervention Trial (MRFIT) show these interventions to be useful in patients with silent ischemia. In a subset of the study population who had abnormal baseline exercise ECG responses, the special intervention group had a 57% reduction in coronary heart disease death (22.2/1,000 vs. 51.8/1,000) and a reduction in sudden death resulting from cessation of smoking and lowering of blood pressure and cholesterol when compared with the usual-care group.

ACIP, a randomized trial of medical therapy versus revascularization (PTCA or CABG), at the 2-year followup demonstrated that total mortality was 6.6% in the angina-guided strategy (i.e., therapy based on symptoms), 4.4% in the ischemia-guided strategy (based on ECG changes), and 1.1% in the revascularization strategy (P <0.02). The rate of death or myocardial infarction was 12.1% in the angina-guided strategy, 8.8% in the ischemia-guided strategy, and 4.7% in the revascularization strategy (P <0.04).[124] The rate of death, myocardial infarction, or recurrent cardiac hospitalization was 41.8% in the angina-guided strategy, 38.5% in the ischemia-guided strategy, and 23.1% in the revascularization strategy (P <0.001). Post-MI patients and those with a high level of sympathetic nervous system activity are perhaps the best candidates for β-blocker therapy.

Calcium channel antagonists alone and in combination are effective in reducing symptomatic and asymptomatic ischemia; however, they do not interrupt the diurnal surge in ischemia observed on ambulatory monitoring and, in general, are somewhat less effective than β-blockers for silent ischemia.[125,126] Nifedipine in particular seems to provide less protection and provides wide fluctuations in response, with approximate reductions in the number of episodes ranging from 0% to 93% and in duration from 23% to 65% unless combined with β-blockers. Fewer studies are available with other calcium blockers and comparative trials are uncommon. Earlier studies showed that combination therapy with calcium and β-blockers provides a better response than calcium blockers and nitrates or monotherapy.[127,128]

Swiss Interventional Study on Silent Ischemia Type II (SWISSI II), a randomized, unblinded, controlled trial of PCI in patients with silent ischemia after acute MI, found that PCI, compared with antiischemic drug therapy, reduced the long-term risk of major cardiac events with better preservation of ventricular function than did medical therapy.[129]

PHARMACOECONOMIC CONSIDERATIONS

Pharmacoeconomic studies have been performed primarily in patients with acute coronary syndromes and only with low-molecular-weight heparins, GP IIb/IIIa receptor antagonists, and statins.[130] Most of the studies on low-molecular-weight heparins have been cost-minimization analyses that focused on enoxaparin sodium, because this is the only low-molecular-weight heparin proven to be superior to unfractionated heparin. Several analyses show that, compared with unfractionated heparin plus aspirin, enoxaparin sodium provides cost savings both during hospitalization (30 days) and at 1-year followup. These cost savings are mainly attributable to fewer cardiac interventions, shorter hospital stays, and lower administrative costs. Indeed, the clinical and economic advantages of enoxaparin sodium have led to its recommendation in recent guidelines as the antithrombotic agent of choice for coronary artery disease. Most of the economic analyses of GP IIb/IIIa inhibitors have been cost-effectiveness analyses.[131] Such analyses indicate that the high acquisition costs of these drugs may be at least partially offset by reductions in other costs if a noninvasive approach to risk stratification is used. Furthermore, use of GP IIb/IIIa inhibitors appears to give favorable cost-effectiveness ratios compared with other accepted therapies, such as fibrin-specific thrombolytic therapy, in the cardiovascular field, particularly in high-risk patients and those undergoing percutaneous coronary intervention. However, more comprehensive economic data on the GP IIb/IIIa inhibitors are needed. Bivalirudin combined with provisional glycoprotein IIb/IIIa inhibitors appears to be an acceptable alternative to the standard of care and is superior to unfractionated heparin alone in PCI and is considered to be cost-effective.[132]

Atorvastatin when used in acute coronary syndrome reduces events, which offsets the upfront acquisition costs.[131] The total expected cost was $1,573.83 per patient in the placebo cohort and $1,709.39 per patient in the atorvastatin cohort, resulting in an incremental cost of $135.56 per patient in the atorvastatin group. The cost per event avoided was $3,536.95. A third of the cost of atorvastatin treatment was offset within 16 weeks by the cost savings resulting from the reduction in the number of events in the atorvastatin cohort compared with the placebo cohort. Other analyses of statins have found this class to be cost-effective, especially in patients who are at higher risk of an ischemic event.[133]

Aspirin and clopidogrel have been evaluated for secondary prevention of CHD, and although aspirin is very cost-effective, clopidogrel is only cost-effective for patients who cannot take aspirin.[134]

CLINICAL CONTROVERSIES

Once patients with angina develop symptoms sufficient for pharmacologic therapy on a daily basis, the initial prophylactic therapy recommended is a β-blocker. There is a paucity of comparative, long-term clinical trials of β-blockade versus calcium channel blockers to determine which is superior for survival benefit. β-Blockers are recommended first-line therapy because of their efficacy in post-MI patients and favorable adverse effect profile.

Recent developments in the understanding of bioactivation of organic nitrates have given rise to concern over endothelial dysfunction induced by nitrates when administered long-term. Not all nitrate products are activated via the same mechanisms and this may impact how effective individual drugs are in long-term treatment.

In stable CAD, medical management has been reported to produce outcomes similar to revascularization and these findings may have a significant impact on how healthcare resources are used in the future.

EVALUATION OF THERAPEUTIC OUTCOMES

Improved symptoms of angina, improved cardiac performance and improvement in risk factors may all be used to assess the outcome of treatment of IHD and angina. Symptomatic improvement in

exercise capacity (longer duration) or fewer symptoms at the same level of exercise is subjective evidence that therapy is working. Once patients have been optimized on medical therapy, symptoms should improve over 2 to 4 weeks and remain stable until their disease progresses. There are several instruments (e.g., Seattle angina questionnaire, specific activity scale [see Table 17–1], Canadian classification system [see Table 17–2]) that could be used improve the reproducibility of symptom assessment.[2] If the patient is doing well, then no other assessment may be necessary. Objective assessment is obtained through increase exercise duration on ETT and the absence of ischemic changes on ECG or deleterious hemodynamic changes. Echocardiography and cardiac imaging may also be used, however, due to their expense, they are only used if a patient is not doing well to determine if revascularization or other measures should be undertaken. Coronary angiography may be used to assess the extent of stenosis or re-stenosis after angioplasty or CABG. Table 17–12 outlines the performance measurement set recommended by the ACC/AHA.

TABLE 17-12 American College of Cardiology, American Heart Association, and Physician Consortium for Performance Improvement Chronic Stable Coronary Artery Disease Core Physician Performance Measurement Set[a]

	Clinical Recommendations
Blood pressure measurement	A blood pressure ready is recommended at every visit. Recommended blood pressure management targets are ≤130 mm Hg systolic *(Class I Recommendation, Level A Evidence)* and ≤85 mm Hg diastolic in patient with CAD coexisting condition (e.g., diabetes, heart failure, or renal failure) and <140/90 mm Hg in patient with CAD and no coexisting condition.
Lipid profile	A lipid profile is recommended and should include total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides. *(Class I Recommendation, Level C Evidence)*
Symptom and activity assessment	Regular assessment of patients' anginal symptoms and levels of activity is recommended. (Serves as a basis for treatment modification.)
Smoking cessation	Smoking status should be determined and smoking cessation counseling and interventions are recommended. *(Class I Recommendation, Level B Evidence)*
Antiplatelet therapy *Denominator exclusion* Documentation of medical reason(s)[b] for not prescribing antiplatelet therapy; documentation of patient reason(s)[c] for not prescribing antiplatelet therapy	Routine use of aspirin is recommended in the absence of contraindications. If contraindications exist, other antiplatelet therapies may be substituted. *(Class I Recommendation, Level A Evidence)*
Drug therapy for lowering LCL-cholesterol *Denominator exclusion* Documentation that a statin was not indicated;[e] documentation of medical reason(s)[b] for not prescribing a statin; documentation of patient reason(s)[c] for not prescribing statin	The LCL-C treatment goal is <100 mg/dL. Persons with established coronary heart disease (CHD) who have a baseline LCL-C ≥130 mg/dL should be started on a cholesterol-lowering drug simultaneously with therapeutic lifestyle changes and control of nonlipid risk factors. *(Class I Recommendation, Level A Evidence)*
β-Blocker therapy–prior myocardial infarction (MI) *Denominator inclusion* Prior MI *Denominator exclusion* Documentation that a β-blocker was not indicated; documentation of medical reason(s)[b] for not prescribing a β-blocker; documentation of patient reason(s)[c] for not prescribing a β-blocker	β-Blocker therapy is recommended for all patients with prior MI in the absence of contraindications. *(Class I Recommendation, Level A Evidence)*
ACE inhibitor therapy *Denominator inclusion* Patient with CAD who also has diabetes and/or left ventricular systolic dysfunction (LVSD) (left ventricular ejection fraction [LVEF] <40% or moderately or severely depressed left ventricular systolic function) *Denominator exclusion* Documentation that ACE inhibitor was not indicated (e.g., patients on angiotensin receptor blockers [ARB]); documentation of medical reason(s)[b] for not prescribing ACE inhibitor; documentation of patient reason(s)[c] for not prescribing ACE inhibitor	ACE inhibitor use is recommended in all patients with CAD who also have diabetes and/or LVSD *(Class I Recommendation, Level A Evidence)* ACE inhibitor use is also recommended in patients with CAD or other vascular disease *(Class IIa Recommendation, Level B Evidence)*
Screening for diabetes[f] *Denominator exclusion* Patients with documented diabetes	Screening for diabetes is recommended in patients who are considered high risk (e.g., CAD) *(Class I Recommendation, Level A Evidence)*

ACE, angiotensin-converting enzyme; CAD, coronary artery disease; MI, myocardial infarction.

[a] Refers to all patients diagnosed with CAD

[b] Medical reasons for not prescribing **antiplatelet therapy** (aspirin, clopidogrel, or combination of aspirin and dipyridamole): active bleeding in the previous 6 months with required hospitalization and/or transfusion(s), patient on other antiplatelet therapy, etc.

Medical reasons for not prescribing a **statin**: clinical judgement, documented LCL-C <130 mg/dL, etc.

Medical reasons for not prescribing a **β-blocker**: bradycardia (defined as heart rate <50 beats/min without β-blocker therapy), history of class IV (congestive) heart failure, history of second- or third-degree atrioventricular block without permanent pacemaker, etc.

Medical reasons for not prescribing **ACE inhibitor (ACEI)**: allergy, angioedema caused by ACEI, anuric rental failure caused by ACEI, pregnancy, moderate or severe aortic stenosis, etc.

[c] Patient reasons for not prescribing antiplatelet therapy, statin, β-blocker, or ACEI: economic, social, and/or religious, etc.

[d] Antiplatelet therapy may include aspirin, clopidogrel, or combination of aspirin and dipyridamole.

[e] Not indicated for a stat refers to LCL-C <100 mg/dL.

[f] Test measure.

[g] Screening for diabetes is usually done by fasting blood glucose or 2-hour glucose tolerance testing. Clinical recommendations indicate screening should be considered at 3-year intervals.

ABBREVIATIONS

ACC: American College of Cardiology

ACEI: angiotensin-converting enzyme inhibitor

ACIP: Asymptomatic Cardiac Ischemia Pilot

AHA: American Heart Association

AV: arteriovenous

CABG: coronary artery bypass grafting

CAD: coronary artery disease

CASS: Coronary Artery Surgery Study

CHD: coronary heart disease

CT: computed tomography

CVD: cardiovascular disease

DCA: directional coronary atherectomy

ECG: electrocardiogram

EDRF: endothelium-derived relaxing factor

ETT: exercise tolerance (stress) testing

GMP: guanosine monophosphate

HDL: high-density lipoprotein

HERS: Heart Estrogen/Progestin Replacement Study

IHD: ischemic heart disease

I_{Na}: late sodium current

ISDN: isosorbide dinitrate

ISMN: isosorbide mononitrate

LAD: left anterior descending

LDL: low-density lipoprotein

LV: left ventricle

MI: myocardial infarction

MVO_2: myocardial oxygen demand

PCI: primary coronary intervention

PTCA: percutaneous transluminal angioplasty

R1: resistance 1-large epicardial or surface vessels

R2: resistance 2-intramyocardial arteries and arterioles

REFERENCES

1. Fraker TD Jr, Fihn SD, writing on behalf of the 2002 Chronic Stable Angina Writing Committee. 2007 chronic angina focused update of the ACC/AHA 2002 guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Group to Develop the Focused Update of the 2002 guidelines for the management of patients with chronic stable angina. Circulation 2007;116:2762–2772.
2. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—Summary article: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Chronic Stable Angina). Circulation 2003;107:149–158.
3. Fox K, Garcia MA, Ardissino D, et al. Guidelines on the management of stable angina pectoris: Executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J 2006;27:1341–1381.
4. Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics—2007 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2007;115:69–171.
5. Sytkowski PA, D'Agostino RB, Belanger A, Kannel WB. Sex and time trends in cardiovascular disease incidence and mortality: The Framingham Heart Study, 1950–1989. Am J Epidemiol 1996;143:338–350.
6. Menotti A, Keys A, Blackburn H, et al. Comparison of multivariate predictive power of major risk factors for coronary heart diseases in different countries: Results from eight nations of the Seven Countries Study, 25-year follow-up. J Cardiovasc Risk 1996;3:69–75.
7. Keys A. Mediterranean diet and public health: Personal reflections. Am J Clin Nutr 1995;61:1321S–1323S.
8. Goldman L, Hashimoto B, Cook F, et al. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: Advantages of a new specific activity scale. Circulation 1981;64:1227–1234.
9. Emond M, Mock MB, Davis KB, et al. Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. Circulation 1994;90:2645–2657.
10. Caracciolo EA, Davis KB, Sopko G, et al. Comparison of surgical and medical group survival in patients with left main coronary artery disease. Long-term CASS experience. Circulation 1995;91:2325–2334.
11. Epstein SE CRI, Talbot TL. Hemodynamic principles in the control of coronary blood flow. Am J Cardiol 1985;56:4E–10E.
12. Gielen S, Schuler G, Hambrecht R. Exercise training in coronary artery disease and coronary vasomotion. Circulation 2001;103:E1–E6.
13. Wassmann S, Faul A, Hennen B, Scheller B, Bohm M, Nickenig G. Rapid effect of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibition on coronary endothelial function. Circ Res, 2003;93:e98–e103.
14. Libby P. Coronary artery injury and the biology of atherosclerosis: Inflammation, thrombosis, and stabilization. Am J Cardiol 2000;86:3J–8J.
15. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: Executive summary and recommendations. A report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee on the management of patients with unstable angina). Circulation 2000;102:1193–1209.
16. Cohn PF. A new look at benefits of drug therapy in silent myocardial ischemia. Eur Heart J 2007;28:2053–2054.
17. Caracciolo EA, Chaitman BR, Forman SA, et al. Diabetics with coronary disease have a prevalence of asymptomatic ischemia during exercise treadmill testing and ambulatory ischemia monitoring similar to that of nondiabetic patients. An ACIP database study. ACIP Investigators. Asymptomatic Cardiac Ischemia Pilot Investigators. Circulation 1996;93:2097–2105.
18. Glusman M, Coromilas J, Clark WC, et al. Pain sensitivity in silent myocardial ischemia. Pain 1996;64:477–483.
19. Panel E. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III). JAMA 2001;285:2486–2497.
20. Hoeg JM. Evaluating coronary heart disease risk. Tiles in the mosaic. JAMA 1997;277:1387–1390.
21. Ridker PM, Morrow DA. C-reactive protein, inflammation, and coronary risk. Cardiol Clin, 2003;21:315–325.
22. O'Rourke RA, Hochman JS, Cohen MC, Lucore CL, Popma JJ, Cannon CP. New approaches to diagnosis and management of unstable angina and non-ST-segment elevation myocardial infarction. Arch Intern Med 2001;161:674–682.
23. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: Summary article: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Circulation 2002;106:1883–1892.
24. Klocke FJ, Baird MG, Lorell BH, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). J Am Coll Cardiol 2003;42:1318–1333.
25. Raggi P, Callister TQ, Cooil B, Russo DJ, Lippolis NJ, Patterson RE. Evaluation of chest pain in patients with low to intermediate pretest probability of coronary artery disease by electron beam computed tomography. Am J Cardiol 2000;85:283–288.