

# MANAGEMENT OF CHRONIC STABLE ANGINA



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## Learning Objectives

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1. Assess the clinical and economic impact of chronic stable angina on the United States population.
2. Distinguish between the clinical presentation and pathophysiology of patients with chronic stable angina and those with unstable angina.
3. Analyze the clinical and diagnostic findings to establish a patient's probability of having coronary artery disease (CAD).
4. Design an appropriate pharmacotherapy plan to prevent complications of revascularization.
5. Using patient-specific information, develop a therapeutic plan for a patient with chronic stable angina, including goals of therapy and monitoring.
6. Justify the role of different vitamin supplementations and hormone replacement therapy in the secondary prevention of CAD.
7. Evaluate the appropriate use of sildenafil in a patient with chronic stable angina.
8. Develop a patient focused education plan for an individual with chronic stable angina.

## Introduction

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### Magnitude of the Problem

Cardiovascular disease remains the largest cause of death in the United States, despite recent trends demonstrating a decline in attributable mortality. Coronary artery disease (CAD) is thought to affect more than 1 million patients annually and takes the lives of more than 500,000 patients per year. The economic impact on the national health care system is tremendous. Data from Medicare reveal that the direct costs of hospitalizations for patients with chronic ischemic heart disease are greater than \$15 billion annually. Coronary artery disease is no longer thought to be a disease

impacting only the western world, as populations in China and Japan are facing a similar incidence. This increase in the incidence of CAD will require a shift in resources for the care of patients who these countries have not had to consider in the past.

Among patients with CAD, the total number of patients with chronic stable angina is difficult to determine. Chronic stable angina is the initial manifestation of ischemic heart disease in about one-half of patients. Using these numbers, along with estimates based on patient survival of myocardial infarction (MI), it is predicted that between 6 and 12 million Americans have chronic stable angina. The risk of mortality is greatest for white men, followed by white women, black men, and black women.

Besides the high mortality, morbidity also is considerable in patients with chronic stable angina. Most of these patients eventually will need hospitalization for episodes of unstable angina or acute MI. These patients often have a reduced quality of life because of their inability to conduct activities of daily living without chest pain. There also is a significant amount of lost time from work and lost productivity that can have a large indirect cost to patients and society. Data from the Bypass Angioplasty Revascularization Investigation (BARI) suggest that about 15–20% of patients rate their own health as fair or poor despite revascularization, and 30% of patients are never able to return to work.

### Pathophysiology

Anginal episodes in patients with chronic stable angina typically are precipitated by an increase in myocardial oxygen demand ( $MVO_2$ ) in the setting of a fixed decrease in supply. The major determinants of  $MVO_2$  include heart rate, myocardial contractility, and intramyocardial wall tension. Intramyocardial wall tension is the leading contributor to increased  $MVO_2$  and is directly related to the radius or size of the ventricular cavity and blood pressure, and indirectly related to the ventricular muscle mass. The

## Abbreviations in this Chapter

ABCD	Appropriate Blood Pressure Control in Diabetes	GISSI	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico
ACADEMIC	Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with Chlamidia	HERS	Heart and Estrogen/Progestin Replacement Study
ACC	American College of Cardiology	HF	Heart failure
ACE	Angiotensin-converting enzyme	HOPE	Heart Outcomes Prevention Evaluation
ACIP	Asymptomatic Cardiac Ischemia Pilot	HPS	Heart Protection Study
ACME	Angioplasty Compared to Medicine	HRT	Hormone replacement therapy
ACP-ASIM	American College of Physicians-American Society of Internal Medicine	HTN	Hypertension
ACS	Acute coronary syndrome	IMAGE	International Multicenter Angina Exercise
ADP	Adenosine diphosphate	IU	International units
AHA	American Heart Association	LDL	Low-density lipoprotein
APSYS	Angina Prognosis Study in Stockholm	LV	Left ventricle
ASIST	Atenolol Silent Ischemia Study	METS	Metabolic equivalents
AVERT	Atorvastatin Versus Revascularization Trial	MI	Myocardial infarction
BARI	Bypass Angioplasty Revascularization Investigation	MID-CAB	Minimally invasive direct coronary artery bypass
CABG	Coronary artery bypass graft	MVO <sub>2</sub>	Myocardial oxygen demand
CAD	Coronary artery disease	NTG	Nitroglycerin
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events	PACIFIC	Potential Angina Class Improvement from Intramyocardial Channels
CASS	Coronary Artery Surgery Study	PCI	Percutaneous coronary intervention
CCB	Calcium channel blocker	PDE	Phosphodiesterase
cGMP	Cyclic guanosine monophosphate	PEACE	Prevention of Events with Angiotensin-Converting Enzyme Inhibition
CHAOS	Cambridge Heart Antioxidant Study	PTCA	Percutaneous transluminal coronary angioplasty
CLASSICS	Clopidogrel Aspirin Stent International Cooperative Study	QUIET	Quinapril Ischemic Events Trial
COURAGE	Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation	RITA	Randomized Intervention Treatment of Angina
CREDO	Clopidogrel for the Reduction of Events During Observation	SAPAT	Swedish Angina Pectoris Aspirin Trial
DHP	Dihydropyridine	SVG	Saphenous vein graft
ECG	Electrocardiogram	TIBBS	Total Ischemic Burden Bisoprolol Study
FACET	Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial	TIBET	Total Ischemic Burden European Trial
		TMR	Transmyocardial laser revascularization
		VEGF	Vascular endothelial growth factor
		WIZARD	Weekly Intervention with Zithromax for Atherosclerosis and Related Disorders

rate of increase of MVO<sub>2</sub> can be as important as the total amount of MVO<sub>2</sub>. The rate-pressure product, or double product, is a common noninvasive measure of MVO<sub>2</sub>, which is the product of the heart rate and systolic blood pressure. However, any change in contractility or volume-loading of the left ventricle (LV) is not considered by the double product.

The etiology of the fixed decrease in supply is long-standing, well-developed atherosclerotic plaques. Coronary plaques that contribute to exertional angina symptoms usually obstruct 70% or more of the epicardial coronary vessel lumen. The reduction in supply is a result of obstruction of coronary blood flow by a large plaque compared to a ruptured plaque as in an acute coronary syndrome (ACS). The plaques in patients with chronic stable angina are more stable, have a reduced lipid pool, and

rupture infrequently. Because their geometry typically does not change acutely, they provide a relatively fixed decrease in myocardial oxygen supply. The slow growth of these plaques over time can contribute to development of collateral circulation, especially when 90% or more of the vessel lumen is obstructed.

The plaques provide a resistance to coronary blood flow in the epicardial vessels that typically do not offer any resistance to flow in patients without disease. Increases in MVO<sub>2</sub> are met by vasodilation of endocardial vessels that feed the myocytes. In patients with a fixed coronary lesion in the epicardial vessels, the endocardial vessels must dilate to provide adequate oxygen and blood supply to the myocytes at rest. During periods of increased MVO<sub>2</sub> in these patients, the endocardial vessels are already maximally vasodilated and, therefore, can provide no

additional myocardial oxygen supply. The increased  $MVO_2$  can come from increased physical activity or emotional stress. The increased  $MVO_2$  cannot be satisfied because of the fixed reduction in supply and maximal endocardial vasodilation at rest; therefore, angina is precipitated.

The previously discussed scenario describes the events leading to chest pain in patients with a fixed angina threshold, where the amount of exertion leading to chest pain is fairly consistent for a particular patient. Other patients may have a variable-threshold angina. In these patients, the amount of exertion leading to chest pain may differ from day to day. An example is patients who could walk 6 blocks before experiencing angina yesterday, but today can only walk 3 blocks before becoming symptomatic. These patients also have an obstructing atherosclerotic plaque leading to a fixed decrease in supply, but they also have a reduction in myocardial oxygen supply because of transient vasospasm superimposed at the site of the obstructing plaque. The vasospasm at or distal to the location of atherosclerotic plaque is because of endothelial damage induced by the plaque. Damaged endothelial cells are thought to produce less vasodilator substances (endothelium-derived relaxing factor) while also having an increased response to vasoconstrictors in response to exercise. Patient symptoms differ depending on the extent of the underlying fixed obstruction and the degree of dynamic change in coronary arterial tone. Although the fixed obstruction usually is sufficient to produce symptoms with exertion, episodes of transient vasospasm superimposed on the obstruction significantly reduce myocardial blood flow leading to ischemia. The changing pattern of ischemia in these patients reflects a variable amount of vasospasm under certain conditions. Anginal episodes typically are more common in the morning hours because of the circadian release of vasoconstrictors. Exposure to cold temperature, emotion, and mental stress also lower the angina threshold in patients with variable threshold angina. Variable threshold angina differs from patients with Prinzmetal's angina, whose etiology of chest pain is pure vasospasm, without a coronary flow-obstructing lesion.

## Clinical Evaluation of the Patient

### Clinical Presentation

A patient's description of chest pain is a useful differentiating factor when determining if he or she suffers from stable angina or an ACS. A commonly used method for incorporating the important aspects of the chest pain story is the PQRST mnemonic:

P = precipitating factors and palliative measures

Q = quality of the pain

R = region and radiation

S = severity of the pain

T = timing or temporal pattern

The typical chest pain description of a patient with chronic stable angina includes chest pain that is precipitated by exertion, such as walking, gardening, house cleaning, or sexual activity. On exertion,  $MVO_2$  has exceeded what can be provided by the fixed decrease in supply from the occlusive atherosclerotic plaque. The chest pain typically is relieved by rest or sublingual nitroglycerin (NTG). Use of sublingual NTG allows the  $MVO_2$  to fall to the point where there is no longer a supply/demand mismatch. The quality of anginal chest pain often is described as squeezing, crushing, a heaviness, or tightness in the chest. It also can be more vague and described as numbness or burning in the chest. Chest pain that is described as sharp in origin, that increases with inspiration or expiration, or that is reproducible with palpation usually is not cardiac pain. The region of the pain is substernal and may radiate to the right or left shoulder, right or left arm (left more commonly than right), neck, back, or abdomen. Cardiac chest pain rarely radiates above the mandible or below the umbilicus. The severity of cardiac chest pain can be difficult to quantify because pain is a subjective measure, but the pain usually is considered severe and ranked a 5 or higher on a 10-point scale. Women and the elderly may present with atypical chest pain, and patients with diabetes mellitus may have a decreased sensation of pain because of complications of neuropathy. By definition, the timing or duration of the chest pain in patients with chronic stable angina is less than 20 minutes but usually about 5–10 minutes. The severity of the angina and the impact of the disease on daily activity

**Table 1-1. Canadian Cardiovascular Society Classification System for Grading of Angina Pectoris**

Class	Description of Stage
Class I	Ordinary physical activity such as walking and climbing stairs, does not cause angina. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.
Class II	Slight limitation of ordinary activity. Angina occurs while walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in the cold, in the wind, under emotional stress, or only during a few hours after wakening. Walking more than 2 blocks on the level or climbing more than 1 flight of ordinary stairs at a normal pace and in normal conditions.
Class III	Marked limitations of ordinary physical activity. Angina occurs on walking 1-2 blocks on the level or climbing one 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.

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often are evaluated using the Canadian Cardiovascular Society classification system (Table 1-1). Other classification systems and scales have been developed but are not as widely used as the Canadian Cardiovascular Society.

A patient with typical stable angina will perform some form of exertional activity, develop chest pain, rest and/or take sublingual NTG, and feel better. Relief of chest pain with sublingual NTG use can be a helpful diagnostic tool; however, esophageal pain also responds well to sublingual NTG. Esophageal pain also is relieved by food, antacids, milk, and occasionally warm liquids; ischemic chest pain is not. The major differences between the pain with chronic stable angina and the pain with an ACS are the precipitating factors and the duration of the chest pain. The patient with ACS typically has chest pain at rest that lasts longer than 20 minutes. Patients with ACS are impacted by an abrupt decrease in myocardial oxygen supply from a plaque rupture, whereas increases in  $MVO_2$  precipitate chest pain in patients with chronic stable angina.

“Typical” angina is composed of three components: 1) substernal chest discomfort with a characteristic quality and duration that is 2) provoked by exertion or emotional stress, and 3) relieved by rest or NTG. Patients with “atypical” angina meet two of the three criteria for typical angina. Patients meeting one or none of the typical anginal characteristics are described as having noncardiac chest pain. The differential diagnosis of chest pain commonly includes gastroesophageal reflux, esophageal motility disorders, biliary colic, costosternal syndrome, or musculoskeletal disorders.

After a description of the chest pain has been obtained, a review of the patient’s CAD risk factors should be performed. Nonmodifiable risk factors include the patient’s age, sex, and family history of atherosclerotic disease in first-degree relatives. The existence of the modifiable risk factors of hypertension (HTN), diabetes mellitus, dyslipidemia, and cigarette smoking also should be evaluated. Patients with a history of cerebrovascular or peripheral vascular disease also are at high-risk for CAD. It is likely that patients having atherosclerosis in cerebral or peripheral vascular arteries also have atherosclerosis in their coronary arteries even if it has not yet led to episodes of angina.

### Physical Findings

The physical findings of a patient with chronic stable angina are nonspecific. At the time of an acute episode, patients may present with tachycardia, diaphoresis, shortness of breath, and nausea. Dyspnea at rest may be the presenting symptom in the elderly, patients with diabetes mellitus, or women who do not have typical chest pain. Other physical findings are related to the discovery of risk factors that may have led to angina development. These positive findings may include an increased blood pressure or a fourth heart sound, reflecting long-standing HTN. Other positive findings may include pulmonary rales, displaced point of maximal impulse, or a third heart sound in patients with heart failure (HF). Findings outside of the coronary vasculature such as a carotid bruit or diminished peripheral pulses may increase the likelihood of CAD.

## Diagnostic Tests

### Electrocardiogram

It is recommended that all patients with symptoms suggestive of angina should have a 12-lead electrocardiogram (ECG). In the resting state, the ECG will be normal in 50% or more of patients with chronic stable angina even if patients have severe symptoms. Patients with ECG evidence of LV hypertrophy or ST-T wave changes consistent with ischemia favor the diagnosis of angina. Evidence of prior MI, with the presence of Q-waves on the ECG, is highly suggestive of CAD, but this may or may not indicate the presence of stable angina. Not all Q-waves are diagnostic for MI, such as those found in lead III or QS patterns in leads  $V_1$  and  $V_2$ . Patients with chronic stable angina with ECG evidence of ST-T wave changes, LV hypertrophy, atrial fibrillation, prior MI, or ventricular tachyarrhythmias at rest have a poorer prognosis than patients with a normal ECG when at rest without symptoms. Patients with evidence of a prior MI or LV hypertrophy are at an exceptionally higher risk and are recommended to receive echocardiography to identify any myocardial functional defects.

Of the patients with chronic angina with a normal ECG at rest, about 50% will develop ischemic ST-T wave changes with an ECG taken during an episode of angina. These changes are more likely to be ST-segment depression or T-wave inversion, but could be transient ST-segment elevation. These changes can be precipitated during the exercise ECG conducted during the exercise stress test.

### Exercise Stress Testing

Exercise stress testing is a relatively easy and inexpensive method for detecting CAD in patients without ECG changes at rest. Although exercise testing typically is safe, MI and death have occurred in one of every 2500 tests. Absolute contraindications for exercise stress testing include acute MI within the previous 2 days; high-risk unstable angina; cardiac arrhythmia, causing symptoms or hemodynamic compromise; symptomatic aortic stenosis; uncontrolled symptomatic HF; acute pulmonary embolus or pulmonary infarction; acute myocarditis or pericarditis; and acute aortic dissection. Despite the long list of contraindications, the test can still be performed safely and give useful information for a large number of patients. The test is especially useful for patients thought to have a moderate probability of having CAD. The test is not as useful for patients in which there is a low or high likelihood of disease. When the pretest probability is already high, a positive test confirms only the pretest suspicion, whereas a negative test may not decrease the probability enough to make a clinical difference. When the pretest probability is already low, a negative test confirms only the pretest suspicion, whereas a positive test may not increase the probability enough to make a clinical difference. In either situation (low or high pretest probability) no new information can be gained to justify the test. When the patient has a moderate pretest probability of disease (i.e., 50%), a positive or negative test leads to a separation in the likelihood of disease. Exercise testing has a good correlation to prognosis, but provides only an indirect estimate of location of atherosclerotic disease. Although

exercise testing can be completed on a treadmill or cycle ergometer, treadmill testing is more common in the United States because quadriceps fatigue is common with the cycle ergometer in patients who are not experienced cyclists.

Despite the use of commonly used treadmill protocols (standard Bruce, modified Bruce, and modified Naughton), it is advantageous to customize the protocol to the individual patient to allow him or her to exercise for 6–12 minutes. The test often is divided into stages, with each stage representing a higher workload. A diagnostically useful test is one in which the patient is capable of achieving an adequate workload. The test often is stopped when patients exercise until they reach 85% or more of their maximal predicted heart rate (220 - age). Because there is variability in individual maximal heart rates, this may not be the optimal parameter for stopping the exercise stress test, and patients should be monitored closely for other indications for discontinuing the test. Absolute indications for terminating the exercise stress test include moderate to severe angina; ST-segment elevation; drop in systolic blood pressure of 10 mm Hg or more; sustained ventricular tachycardia; technical difficulties with monitoring the ECG or systolic blood pressure; signs of poor perfusion; increasing ataxia, dizziness, or near-syncope; or patient desire to stop because of fatigued or dyspnea. The sensitivity of the exercise stress test in this last group of patients is greatly diminished.

The most significant finding on the exercise ECG is ST-segment depression or elevation. The standard criteria for confirming a positive test is 1 mm or more of horizontal or downsloping ST-segment depression or elevation for at least 60–80 msec after the end of the QRS complex. In patients with ST-segment depression at baseline (1 mm or less), an additional 1 mm of ST-segment depression with hemodynamic abnormalities is needed for a positive test. During the ETT, several other measurements are evaluated, including the patient's exercise capacity and symptomatic, hemodynamic, and electrocardiographic responses. The patient's exercise capacity should be reported in estimated metabolic equivalents (METs) of exercise and the stage of the protocol the patient achieved should be noted. Ischemia leading to discontinuation of the test is an important finding. The rate-pressure product should be recorded at the time of angina and/or ST-segment changes. The patient's perceived exertional level or fatigue at the time of angina and/or ST-segment changes also should be recorded using either a 10-grade or 15-grade Borg Scale. Although patients with chronic stable angina may have asymptomatic premature ventricular contractions and nonsustained ventricular tachycardia with exercise, these findings have no diagnostic or prognostic significance if they are not accompanied by other findings. If ventricular arrhythmias are accompanied by ST-segment depression or angina they predict a high likelihood of CAD.

Patients already taking anti-ischemic drugs present a special challenge when performing exercise stress testing. The need to discontinue drugs depends on the purpose of the test. If the test is being used to identify safe levels of daily activity and exertion, then the drugs should not be discontinued. The test can then serve as a routine monitoring parameter for efficacy of the agents. If the test

is to detect CAD as the cause of stable angina, then anti-ischemic agents will reduce the sensitivity of the test. Unless the patient has severe angina, long-acting  $\beta$ -blockers usually should be discontinued about 2–3 days before the test if possible. Short-acting  $\beta$ -blockers, chronic nitrates, or calcium channel blockers (CCBs) can be discontinued 1–2 days before the test. Patients can usually use sublingual NTG to control symptoms during this time.

Patients with lower extremity arthralgias, severe peripheral vascular disease, reactive airway disease, HF, general disability, or who are obese often cannot adequately perform the ETT. These populations account for almost 40% of all patients needing an exercise stress test. In these patients, the myocardium can be stressed chemically with adenosine, dipyridamole, or dobutamine. Pharmacological stress testing with adenosine and dipyridamole commonly is used with many myocardial perfusion-imaging techniques, whereas dobutamine is used almost exclusively during echocardiography. Adenosine and dipyridamole provide myocardial stress by inducing coronary vasodilation. The coronary vasodilation also creates heterogeneity of myocardial blood flow, with more vasodilation in normal coronary arteries compared to arteries with atherosclerotic obstruction. Adenosine produces a direct vasodilation by increasing cyclic adenosine diphosphate, whereas dipyridamole inhibits cellular uptake and degradation of endogenous adenosine. Because of use of the same binding site, patients should avoid caffeine or other xanthine compounds for 24 hours before the test. Despite the good safety profile of adenosine and dipyridamole, patients report side effects in more than 50% of cases. Common side effects include angina, headache, nausea, and flushing. Patients with reactive airway disease frequently report severe bronchospasm; therefore, these agents should be avoided in these patients. If side effects occur with use of dipyridamole, aminophylline can be given as a reversal agent because of its competitive binding for the adenosine receptor. Because of adenosine's short half-life, aminophylline reversal often is unnecessary.

Dobutamine induces myocardial stress through its positive inotropic and chronotropic properties. As previously discussed, dobutamine stress testing is commonly used with echocardiography. When the myocardium is stressed with dobutamine, areas of ischemia are detected by echocardiography as regional wall motion abnormalities or with thallium scanning. Dobutamine stress testing is the preferred test in patients who cannot exercise and have reactive airway disease because adenosine and dipyridamole are contraindicated in this patient population. Dobutamine is relatively well tolerated but has been associated with adverse effects of angina, arrhythmias, anxiety, nausea, and tremor.  $\beta$ -Blockers can be used to reverse most adverse effects if they persist.

Meta-analysis has shown exercise stress testing to have a mean sensitivity of 68% and a mean specificity of 77% compared to angiography for the ability to detect CAD. The diagnostic accuracy of pharmacological stress testing is similar to exercise stress testing if both are used with radionuclide imaging. Exercise stress testing is preferred because additional useful clinical and physiological parameters, such as exercise duration, total workload,

maximal heart rate, exercise-induced symptoms, ECG changes, and blood pressure response, can be collected and correlated to prognosis.

Stress testing is less useful in patients with LV hypertrophy, left bundle branch block, Wolff-Parkinson-White syndrome, implanted pacemakers, or in those taking digoxin. In these patients, it is more difficult to detect ischemic ECG changes; therefore, stress imaging testing is more appropriate. Exercise stress testing without imaging also is less sensitive for detecting CAD in women, obese patients, and the elderly (70 years of age or older). The reduced diagnostic accuracy of exercise stress testing in women is because of the low pretest probability of CAD in young and middle-aged women. In addition, women are more likely to have false-positive ST-segment changes on exercise ECG, possibly because of increased catecholamine release during exercise compared to men. Women also are less likely than men to exercise to their maximal aerobic capacity. The reduced diagnostic potential of the exercise stress test in patients who are obese or elderly is because of a reduced exercise capacity from muscle weakness and deconditioning. For the elderly, exercise capacity is reduced 8–10% per decade in sedentary men and women older than 30 years of age. These patients are more likely to hold on to hand rails and exercise for an insufficient length of time, therefore, not reach a necessary level of exercise needed to provide diagnostic or prognostic information. Finally, patients taking digoxin can have abnormal ST-segment responses to exercise. The ST-segment depression occurs during exercise in 25–40% of patients without CAD who take digoxin. The occurrence of false-positive findings increases with age.

### Coronary Angiography

Coronary angiography is the most accurate test for diagnosing and assessing patients with CAD and is commonly considered the “gold standard”. Coronary angiography is an invasive technique that requires arterial access, usually through the femoral artery; however, more recently, brachial artery access has been used. Once arterial access is established, a catheter is advanced to the base of the aortic arch where the left main coronary artery and the right coronary artery commence. The catheter can then gain access to the coronary arteries where radiopaque contrast dye is injected and the epicardial coronary vasculature is visualized (Figure 1-1). The ability to visualize the location and extent of coronary atherosclerotic disease is the major advantage of coronary angiography over other diagnostic procedures. An experienced operator can detect atherosclerotic lesions that occlude the vessel by as little as 20%. Occlusions of 50% or more commonly are detected. Patients with chronic stable angina have single-vessel (25%), double-vessel (25%), or triple-vessel (25%) disease, with 5–10% presenting with left main coronary disease. The finding that about 15% of patients do not have significant atherosclerotic disease also is useful information. These patients may have to be evaluated for the presence of vasospasm, microvascular disease (syndrome X), or noncardiac reasons for their chest pain. During the cardiac catheterization, information on valve function along with LV function and ejection fraction can be obtained.

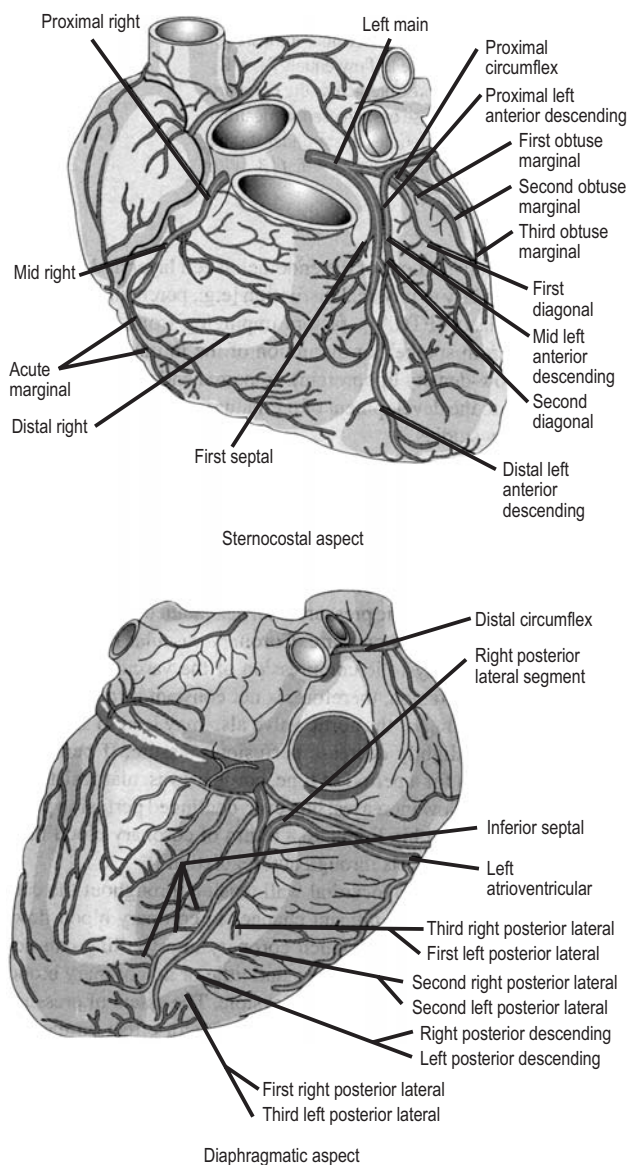


Figure 1-1. Coronary artery anatomy with sternocostal and diaphragmatic views.

Reprinted with permission from McGraw-Hill Education. Talbert RL. Ischemic heart disease. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. *Pharmacotherapy: A Pathophysiologic Approach*, 5<sup>th</sup> ed. New York: McGraw-Hill, 2002:219-50.

Guidelines for the appropriate use of coronary angiography are available from the American College of Cardiology (ACC) and American Heart Association (AHA). Patients initially presenting with Canadian Cardiovascular Society class II or III typical angina usually undergo coronary angiography. Other indications for angiography include patients who have survived sudden cardiac death; patients who are not candidates for noninvasive testing because of disability, illness, or obesity; patients thought to have a nonatherosclerotic etiology of ischemia; patients with an occupational requirement for a definitive diagnosis (i.e., pilots or firefighters); and patients with a high pretest probability of left main or three-vessel disease. Significant

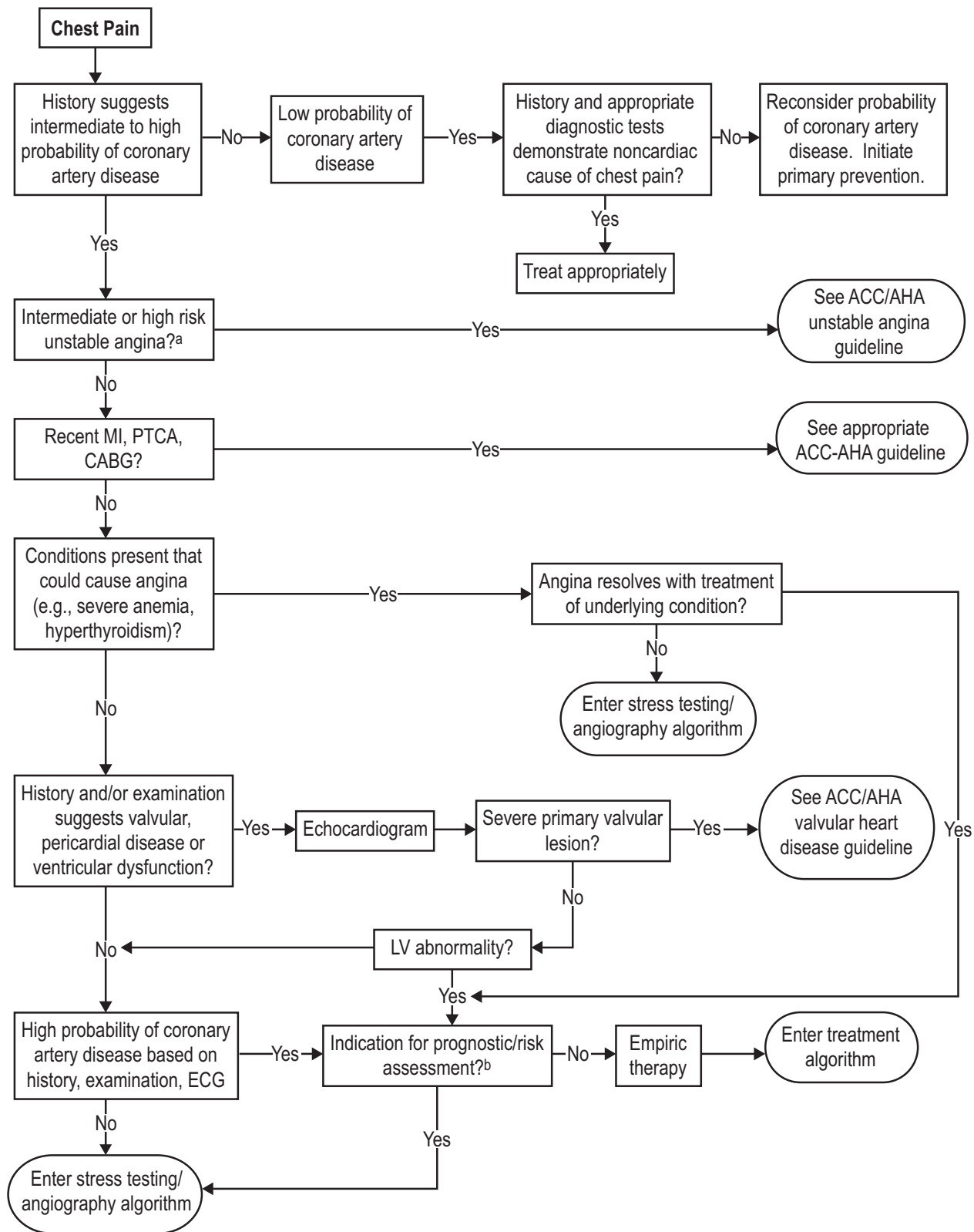


Figure 1-2. Clinical assessment of chest pain.

<sup>a</sup> Features of “intermediate- or high-risk” unstable angina: rest pain lasting > 20 minutes; age > 65 years; ST and T wave changes; pulmonary edema.

<sup>b</sup> Factors necessary to determine the need for risk assessment: comorbidity and patient preferences.

ACC = American College of Cardiology; AHA = 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.

disease is defined as 50% stenosis in the left main coronary artery or 70% or more in another coronary artery.

Coronary angiography also can be used to diagnose and assess patients with coronary vasospasm. Invasive provocation of coronary vasospasm can be conducted using intravenous ergonovine in doses ranging from 0.05 mg to 0.40 mg, with most patients responding to doses less than 0.2 mg. This test is not without risk because ergonovine has led to prolonged coronary vasospasm that can lead to endothelial damage, hypotension, ischemia, and ventricular arrhythmia. Therefore, it is recommended that the ergonovine test be conducted only in patients found to have angiographic evidence of normal or near normal coronary arteries. Ergonovine must be given in gradually increasing doses and intracoronary vasodilators, such as NTG and/or verapamil, need to be available for vasospasm reversal.

Despite the diagnostic and assessment advantages of coronary angiography, there are limitations to the procedure. The invasive procedure can lead to bleeding, infection, or arterial perforation. Using contrast dye can be problematic in patients with preexisting renal disease. Various trials have evaluated preprocedural hydration, *N*-acetylcysteine, and fenoldopam for preventing contrast dye-induced nephropathy. Outcomes from these trials have produced mixed results. Finally, coronary angiography is much more expensive than other noninvasive diagnostic tests; therefore, its use should be reserved for patients who meet the appropriate criteria.

Patients with symptoms of angina but negative coronary angiograms for atherosclerosis and vasospasm often are referred to as having syndrome X. This syndrome should not be confused with metabolic syndrome X that includes patients with diabetes mellitus, HTN, dyslipidemia, and obesity. The etiology of angina in patients with syndrome X is not completely understood, but hypotheses include microvascular disease, abnormal pain perception, or a complication of such psychiatric disorders as anxiety or depression. Patients with suspected microvascular disease are thought to have an exaggerated response to vasoconstrictors in small coronary arteries that are not seen by coronary arteriography. The vasoconstriction may be because of abnormal endothelial function and/or an increased sympathetic drive or responsiveness.

## Probability of Disease Estimates

Even after the patient history and physical examination are completed, it can still often be difficult to determine if the patient is suffering from anginal pain. Diagnostic tests can help with making the final determination, but test selection and timing can be difficult decisions (Figure 1-2). The ability of a particular test to assist in making the diagnosis depends not only on the specificity and sensitivity of the test, but also on the pretest probability of disease based on history and physical findings. A positive test result in a patient with an atypical chest pain story would have a much higher false-positive rate than a patient with a typical chest pain story. Patients with a negative test result and a more typical chest pain story could suffer from a false-negative result. Knowing the pretest probability of disease can assist with interpreting the respective diagnostic test and impact the decision regarding antianginal drugs and revascularization procedures.

Data from angiographic studies performed in the 1960s and 1970s have shown that a description of a patient's chest pain, age, and gender can be powerful predictors of the presence or absence of CAD. Patients who were male, older age, or had a typical description of chest pain were more likely to have significant CAD than patients who were female, younger, or had nonanginal or atypical chest pain. These early observations were confirmed in more recent prospective studies. The chest pain description, age, and gender were still the strongest predictors of CAD. Additional information about the presence of the risk factors of smoking history, diabetes mellitus, and hyperlipidemia increased the ability to predict the presence of CAD in patients. This additional information not only assists with determining the likelihood of CAD, but also shows the importance of risk factor prevention and modification in the younger population. Table 1-2 illustrates how these factors can be used to determine a patient's pretest probability of CAD using the Duke Database. The first number is the pretest probability of CAD based on the patient's chest pain description, age, and gender without a smoking history, diabetes mellitus, or hyperlipidemia. The second number represents the same patient with concomitant smoking, diabetes mellitus, and hyperlipidemia. For example, a 35-year-old man with an atypical chest pain story has a low pretest probability of CAD of 8%. If that same individual

**Table 1-2. Comparing the Likelihood of CAD in Low-risk Symptomatic Patients With High-risk Symptomatic Patients—Duke Database**

Age (Years)	Nonanginal Chest Pain		Atypical Angina		Typical Angina	
	Men	Women	Men	Women	Men	Women
35	3–35%	1–19%	8–59%	2–39%	30–88%	10–78%
45	9–47%	2–22%	21–70%	5–43%	51–92%	20–79%
55	23–59%	4–25%	45–79%	10–47%	80–95%	38–82%
65	49–69%	9–29%	71–86%	20–51%	93–97%	56–84%

Each value represents the percentage of patients with significant CAD. The first number is the percentage for low-risk, mid-decade patients without diabetes, smoking, and hyperlipidemia. The second number in the range is the percentage for high-risk, mid-decade patients with diabetes who smoke and have hyperlipidemia. Both high- and low-risk patients have normal resting ECGs. If ST-T wave changes or Q-waves had been present, the likelihood of CAD would be higher in each entry of the table.

ACC = American College of Cardiology; AHA = American Heart Association; CAD = coronary artery disease; ECG = electrocardiogram. Reprinted with permission from the American College of Cardiology Foundation and American Heart Association. Our ACC/AHA guidelines for the management of chronic stable angina: a report of the ACC/AHA Task Force on Practice Guidelines. JACC 2002. [www.acc.org](http://www.acc.org).



also was a smoker, had diabetes mellitus, and had hyperlipidemia, his pretest probability would increase to 59%. This predictive information assumes a normal resting ECG. Patients with Q-waves or ST-segment deviation would have an even higher likelihood of CAD. The patient's pretest probability and the sensitivity and specificity of the diagnostic test are needed to calculate the positive or negative predictive values of a diagnostic test for a specific patient.

### Risk Stratification

Risk stratification of patients with CAD can be difficult. Coronary artery disease is a chronic disorder that spans several decades of a patient's life. In each patient, the disease can manifest in various clinically defined phases such as asymptomatic disease, stable disease, progressive angina, unstable angina, or acute MI. The rate in which a patient progresses through these phases may depend on the presence of cardiac risk factors such as smoking, HTN, dyslipidemia, and diabetes mellitus. Despite this "moving target", there are four patient characteristics that place a patient at higher risk of serious ischemic events and mortality. The first and strongest predictor of long-term survival in a patient with CAD is the functional status of the LV. Several trials have shown that patients with CAD with LV dysfunction have a significantly higher mortality rate than patients with preserved LV function. The second characteristic is the anatomic extent and severity of atherosclerotic involvement of the coronary circulation is another patient characteristic that correlates with higher patient risk. Trials such as the Coronary Artery Surgery Study (CASS) have shown that patients with disease in the left main coronary artery or disease in multiple major vessels are at higher risk of mortality than patients with less extensive atherosclerotic disease. The third patient characteristic is evidence of recent atherosclerotic plaque rupture. Patients with a recent ACS are at significant short-term risk of recurrent nonfatal MI or death. Finally, the last characteristic that can place a patient into a higher risk group is the patient's general health and non-coronary comorbidities (age, obesity, chronic obstructive pulmonary disease, and malignancy).

Risk stratification in patients with asymptomatic CAD can be especially difficult. In general, the same clinical characteristics presumably are helpful in assessing asymptomatic patients, although there are limited data to this effect. When clinical characteristics suggest a high risk of severe CAD, exercise stress testing and/or coronary angiography may be indicated, but this is not well established. The noninvasive test findings that identify high-risk patients are based on studies in symptomatic patients. These findings are probably also applicable to asymptomatic patients but are associated with a lower level of absolute risk in the absence of symptoms. Because these patients do not have symptoms to be reduced, the principal goal of evaluation and treatment is the improvement of patient outcomes by reducing the rate of death and MI.

## Pharmacological Therapy of Chronic Stable Angina

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### Goals of Therapy

There are two main goals for treating patients with chronic stable angina. The first goal is to prevent an acute MI or death. Clearly any intervention or therapy that has the ability to prevent mortality would carry the highest priority. The second goal is to reduce or eliminate symptoms of angina. If these two goals are achieved, the quantity and quality of life for patients with chronic stable angina is enhanced. Pharmacological therapy directed toward risk factor reduction has provided a mortality reduction, whereas anti-ischemic therapy has not resulted in improved mortality.

### Practice Guidelines

Practice guidelines for managing patients with chronic stable angina were published in June 1999. As with other guidelines in the area of cardiology, this set of guidelines was created and endorsed in a joint venture by the ACC and the AHA. The task force also invited the American College of Physicians-American Society of Internal Medicine to participate in the process because many patients with chronic stable angina are encountered in the practice of internal medicine. The full publication of this guideline is published in the *J Am Coll Cardiol*, whereas the executive summary is published in *Circulation*. This was the first time an official guideline was created to manage patients with chronic stable angina. An update to the guidelines was published in January 2003. The full-text guideline with the updated material in either strike-out (deleted text) and highlighted (new text) version or a "clean" version is available on the Internet ([www.acc.org](http://www.acc.org) or [www.americanheart.org](http://www.americanheart.org)). The executive summary is published in the *J Am Coll Cardiol* in January 2003.

As with other ACC/AHA practice guidelines, recommendations are evidence-based with the weight of the evidence supporting the recommendations ranked as A, B, or C. The highest rank of A is obtained if the data are derived from multiple randomized, clinical trials with large numbers of patients. An intermediate rank of B comes from data that are derived from a limited number of randomized trials with small numbers of patients. Data from a careful analysis of nonrandomized studies or observational registries also are given the rank of B. Finally, the lowest rank of C is given when expert consensus is the primary basis for the recommendation.

The traditional ACC/AHA classifications of I, II, or III for recommendations also are used in the practice guideline. Class I recommendations are those in which there is evidence or general agreement that a given procedure or treatment is useful and effective. A class II recommendation is given when there is conflicting evidence or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. Class II recommendations are further divided into class IIa and class IIb. A class IIa recommendation is one in which the weight of evidence/opinion is in favor of usefulness/efficacy. A class IIb recommendation is one in

which the usefulness/efficacy is less well established by evidence/opinion. Finally, a class III recommendation is given when there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful and should be avoided.

These guidelines are intended for use in adult patients with chronic stable angina. Practitioners managing patients with chest pain at rest or patients suffering from an ACS should refer to the specific ACC/AHA guidelines for managing unstable angina/non-ST-segment elevation MI and/or for managing acute MI. The ACC/AHA also has published specific guidelines for percutaneous coronary intervention (PCI) in 2001 and guidelines for coronary artery bypass graft (CABG) surgery in 1999 ([www.acc.org](http://www.acc.org) or [www.americanheart.org](http://www.americanheart.org)). The revascularization guidelines include a wealth of information on using revascularization to manage chronic angina. The class of recommendation from the ACC/AHA guidelines for certain therapeutic options are cited throughout this chapter.

### Nitrates

Organic nitrates were found to have antianginal properties more than 100 years ago when William Murrell first reported in 1879 the ability of a 1% NTG solution administered orally to relieve and prevent angina attacks. Organic nitrates typically are regarded as prodrugs that require biotransformation into the active compounds. This process leads to denitration of the nitrate and the release of nitric oxide, also known as endothelium-derived relaxing factor. The endothelium-derived relaxing factor works on the vascular endothelium to increase concentrations of cyclic guanosine monophosphate (cGMP), leading to a reduction in cytoplasmic calcium and vasodilation. Most of this vasodilation occurs on the venous side of the vascular system, leading to a reduction in preload, although higher doses of nitrates also produce significant arterial dilation. Because of their vasodilatory effects, nitrate therapy can produce reflex tachycardia that can antagonize the antianginal benefit. Nitrates also provide vasodilation of stenotic vessels as well as the intracoronary collateral circulation. Because of the exponential reduction in flow with increasing stenosis, even small increases in vasodilation in these narrowed vessels can produce a significant increase in myocardial oxygen supply to ischemic portions of the myocardium. Nitrate-induced coronary vasodilation occurs predominately in epicardial vessels, with minimal effect on the coronary microcirculation. This explains why nitrates do not induce coronary steal similar to such agents as dipyridamole or nitroprusside. Possible explanations for this lack of microcirculatory vasodilation include autoregulatory influences from the adjacent myocardium that counteract the vasodilatory effects of NTG, an absence of guanylate cyclase in these vessels, or an inability of the nitrate to undergo denitration in these vessels. Nitrates also relieve coronary vasospasm and, therefore, are effective for patients with variant or Prinzmetal's angina. Nitrates have an antiaggregating effect on platelets, but the clinical relevance of this effect has not been documented.

Several different formulations of nitrates are available for acute and chronic use. Therapy with sublingual NTG is

effective for terminating acute episodes of chronic stable angina and should be part of the drug regimen for all patients with CAD. Sublingual NTG also can be used for prophylaxis of acute episodes of angina. When patients want to involve themselves in a particular activity which they know leads to angina after a certain amount of exertion, they can take a sublingual NTG about 2–5 minutes before the activity. This prophylactic dose can provide up to 30 minutes of protection and allows patients to take part in activities that they may otherwise be unable to because of anginal episodes. Because of its longer half-life, sublingual isosorbide dinitrate could provide protection for up to 1 hour. In a select number of patients, this can prevent the need for long-term antianginal therapy.

Common side effects of nitrate therapy include headache, flushing, nausea, postural hypotension, and syncope. The hypotension usually is not severe but in patients with volume depletion who stand, the hypotension can be accompanied by a paradoxical bradycardia. Headache usually resolves after about 2 weeks of continued therapy. However, this resolution does not necessarily represent tolerance or loss of antianginal effectiveness of the nitrate. Acetaminophen is effective in managing nitrate-induced headaches during the initial weeks of therapy. Patients using transdermal NTG may experience skin erythema and inflammation. Initiating therapy with smaller doses and/or rotating the application site can manage adverse effects of transdermal NTG.

### Nitrate Tolerance

Using chronic nitrate therapy for chronic stable angina has been limited because of the phenomenon of nitrate tolerance. Several trials have shown that continuous nitrate therapy for more than 24 hours leads to a reduction or loss of the hemodynamic and antianginal effects of nitrates. In a trial of 562 patients receiving 24 hours of transdermal NTG, almost all of the patients lost anginal control that could not be overcome with higher doses.

Nitrate tolerance is not necessarily an “all or none” phenomenon. Some patients may experience a reduction in the efficacy, whereas others may experience a total loss of efficacy. It is known that despite continued use of nitrates and a loss of antianginal effect, plasma volume remains expanded and some hemodynamic effects are maintained. Because the impact of continuous nitrate use varies from patient to patient and is unpredictable, the appropriate clinical strategy is to prescribe nitrates with a nitrate-free interval.

The mechanism of nitrate tolerance remains unknown. Much debate has led to differing hypotheses (Table 1-3), and several pharmacological approaches to manage or prevent nitrate tolerance. Acetylcysteine has been investigated as a potential strategy for preventing nitrate tolerance because it supplies sulfhydryl groups needed for using organic nitrates. This approach has not proven to be useful. Angiotensin-converting enzyme (ACE) inhibitors also have been investigated with mixed results. Agents such as captopril can supply sulfhydryl groups, but ACE inhibitors may prevent nitrate tolerance through other mechanisms. The inhibition of angiotensin II production can reduce superoxide anion production, leading to reduced

**Table 1-3. Hypotheses of Nitrate Tolerance and Proposed Mechanisms**

**Decreased Tissue cGMP (necessary for vasodilation)**

- Decreased production via guanylate cyclase
- Increased degradation via cGMP phosphodiesterases
- Depletion of intracellular sulfhydryl cofactors, leads to a decrease in the conversion of organic nitrates to nitric oxide, decreasing cGMP levels (more pronounced in venous vessels compared to arterial vessels)

**Baroreceptor Reflex**

- Increased angiotensin II production, resulting in vasoconstriction, and loss of nitrate response

**Neurohormonal (mediated by sympathoadrenal axis and renin-angiotensin-aldosterone system)**

- Increased renin serum activity, increased aldosterone secretion
- Vasopressin and catecholamine release
- Increased vascular production of endothelin

**Volume Expansion (reducing ability of nitrate to reduce ventricular filling pressures)**

- Fall in hematocrit as a result of hemodilution
- Migration of fluid from the perivascular to the intravascular space

**Superoxide Anion Production**

- Free radical produced by endothelium that inactivates nitric oxide

**Decreased Vascular Uptake**

- Cellular uptake of nitrate decreased

cGMP =cyclic guanosine monophosphate.

nitrate degradation. Angiotensin-converting enzyme inhibitors also cause a reduction in protein kinase C and endothelin leading to a reduction in vasoconstriction. Diuretics also have been investigated with and without ACE inhibitors for managing nitrate tolerance. This approach is based on the hypothesis that fluid retention and plasma volume expansion are related to the development of nitrate tolerance. Unfortunately, none of these approaches is effective in maintaining the antianginal effects of continuous nitrate therapy despite their ability to maintain the hemodynamic effects of nitrates.

Despite multiple hypotheses for the mechanism of nitrate tolerance, the preferred management of nitrate tolerance for patients with CAD remains a 10–14-hour nitrate-free interval daily. This approach maintains antianginal efficacy with using chronic nitrates. The rationale for this approach is based on the observation that although nitrate tolerance develops rapidly, it also is rapidly reversed. Unfortunately, this approach does not provide the patient anti-ischemic coverage during the nitrate-free interval and places the patient at risk for anginal episodes. Usually the nitrate-free interval is provided during the nighttime hours when the patient is sleeping, and should have a reduced MVO<sub>2</sub>. Several trials have used a nitrate-free interval and have demonstrated an increase in exercise time, and a reduction in exercise-induced ischemic events and in the need for sublingual NTG. Despite these benefits, a nitrate-free interval would not provide protection to the 20–30% of patients with chronic stable angina who also experience occasional nocturnal episodes of angina. The greatest concern with using chronic nitrates as the only antianginal therapy relates to the circadian timing of MI and other ischemic episodes. It is well documented that anginal episodes and MI commonly occur in the morning hours,

either right before or after awakening. Patients using chronic nitrate therapy typically would not have taken or applied their nitrate therapy for the day during this critical time period. Nitrates should not be routinely used as monotherapy for chronic stable angina because of the lack of coverage during the nitrate-free interval, lack of protection against circadian rhythm ischemic events, and potential for reflex tachycardia from vasodilatory properties. Trials have shown that patients taking intermittent transdermal NTG typically did not have rebound ischemia during the nitrate-free interval when concomitant  $\beta$ -blockers or diltiazem also were being administered.

**$\beta$ -Blockers**

$\beta$ -Blockers commonly are used to manage patients with chronic stable angina and are effective in reducing both symptomatic and silent episodes of myocardial ischemia. By reducing heart rate, myocardial contractility, and intramyocardial wall tension (through blood pressure reduction),  $\beta$ -blockers impact all of the major contributing factors of MVO<sub>2</sub>. Heart rate reduction also may improve myocardial oxygen delivery by prolonging diastole and increasing the time for myocardial perfusion.  $\beta$ -Selectivity does not impact the efficacy of  $\beta$ -blockers in chronic stable angina treatment and all agents appear equally effective.  $\beta_1$ -Selective agents are preferred for patients with chronic obstructive pulmonary disease, peripheral vascular disease, diabetes mellitus, dyslipidemias, and sexual dysfunction.  $\beta$ -Blockers with combined  $\alpha_1$ - and  $\beta$ -blockade also are effective for managing patients with angina.  $\beta$ -Blockers with intrinsic sympathomimetic activity cause a slight to moderate activation of the  $\beta$ -receptor, in addition to preventing the binding of natural catecholamines. Because

of this unique pharmacological property,  $\beta$ -blockers provide little or no reduction in resting heart rates. There is a reduction in exercise heart rate when catecholamine concentrations are increased. Although these agents may be useful for patients with peripheral vascular disease and hyperlipidemia, they are not preferred in patients with chronic stable angina or who are post-MI. In general, selection of a  $\beta$ -blocker in patients with chronic stable angina usually depends on the presence of comorbid disease states, preferred dosing frequency, and cost.

$\beta$ -Blocking agents should not be used in patients who have vasospasm as the primary etiology of their anginal episodes (Prinzmetal's angina).  $\beta$ -Blockers actually worsened and prolonged episodes of ischemia in these patients. The proposed mechanism is that if patients have significant blockade of  $\beta$ -receptors,  $\alpha$ -receptors are left unopposed and vulnerable for activation by an increased proportion of circulating catecholamines. Because patients with variable threshold angina still have increases in  $MVO_2$  as the cause of angina,  $\beta$ -blockers do play a role in managing these patients. Because of the concomitant vasospasm that can occur in these patients,  $\beta$ -blockers are considered add-on therapy to CCBs and/or nitrates.

Common side effects of  $\beta$ -blockers usually are because of an extension of their pharmacological activity. Patients receiving  $\beta$ -blockers may experience bradycardia, hypotension, heart block, impaired glucose metabolism, and altered serum lipids. Central nervous system adverse effects, such as fatigue, depression, insomnia, and overall malaise, are somewhat less severe, but they account for a significant number of  $\beta$ -blocker discontinuations. Impotence has been reported in about 1% of patients receiving  $\beta$ -blockers, and inability to maintain an adequate erection has been reported in up to 25% of patients in some series. Patients with a history of airway disease may suffer from bronchospasm; patients with a history of peripheral vascular disease may suffer from intermittent claudication; and patients with LV dysfunction may suffer from fluid overload. Patients without these preexisting disease states usually do not suffer from these adverse effects, and even patients at risk for adverse effects receive significant benefit from using  $\beta$ -blockers.  $\beta$ -Blockers are absolutely contraindicated in patients with existing bradycardia, hypotension, second- or third-degree atrioventricular block, a history of reactive airway disease (asthma or severe chronic obstructive pulmonary disease), severe peripheral vascular disease, LV dysfunction with unstable fluid status, and patients with difficult to control diabetes mellitus who have frequent episodes of hypoglycemia. The highest risk patients who are post-MI should all receive  $\beta$ -blockers unless there is an absolute contraindication. A patient with chronic stable angina who has never had an ACS, especially acute MI, with moderate chronic obstructive pulmonary disease could be treated adequately with an appropriate CCB or a  $\beta$ -blocker.

### Calcium Channel Blockers

Calcium channel blockers also are effective in reducing anginal episodes in patients with chronic stable angina. Like  $\beta$ -blockers, non-dihydropyridine (DHP) CCBs reduce

all of the components of  $MVO_2$ . Non-DHP CCBs should be avoided in patients with concomitant systolic HF because of the agents' negative inotropic effects; however, non-DHP CCBs can provide benefit to patients in atrial fibrillation with rapid ventricular response to because of the drugs' negative dromotropic effects. All DHP CCBs provide blood pressure reduction and, therefore, a reduction in intramyocardial wall tension. However, there is variation among the DHP CCBs in their impact on contractility and development of reflex tachycardia. Agents such as nifedipine produce more impairment of LV function than newer agents, such as amlodipine and felodipine. Because of their propensity to cause reflex tachycardia, short-acting DHP CCBs should not be used to treat chronic stable angina, chronic hypertension, hypertensive crisis, or an ACS.

Both DHP and non-DHP CCBs provide some increase in myocardial blood flow. This increase in flow is because of the ability of the CCBs to decrease the cellular uptake of calcium and dilate epicardial coronary arteries. In patients with variant (Prinzmetal's) angina, CCBs completely abolish vasospastic angina recurrence in about 70% of patients and reduce episodes in another 20% of patients.

Common side effects of CCBs vary among agents. Patients taking non-DHP CCBs may experience bradycardia, hypotension, atrioventricular block, and symptoms of LV depression. Non-DHP CCBs should not be used in patients who have contraindications or cannot tolerate  $\beta$ -blockers associated with these same effects. Verapamil also caused significant constipation in up 8% of patients. Patients taking DHP CCBs may experience reflex tachycardia, hypotension, headache, and peripheral edema.

Calcium channel blockers undergo hepatic oxidative biotransformation through the cytochrome P450 isoenzyme 3A4 and other isoenzymes. Verapamil and diltiazem inhibit clearance of other substrates that use the 3A4 isoenzyme, such as carbamazepine, cyclosporin, lovastatin, simvastatin, and benzodiazepines. The DHP CCBs typically do not have this same impact on these drugs. Verapamil, and to a lesser extent diltiazem, also inhibits P-glycoprotein-mediated drug transport. This interaction is partially responsible for increases in serum concentrations of agents such as digoxin and cyclosporine. Verapamil also decreases the clearance of digoxin, requiring close monitoring if these agents are used together. Agents that induce the P450 3A4 isoenzyme can reduce the effectiveness of all CCBs. Pharmacodynamic interactions also need to be monitored in patients taking CCBs. Patients receiving verapamil or diltiazem concomitantly with other agents that reduce heart rate and atrioventricular nodal conduction (e.g.,  $\beta$ -blockers, digoxin, and amiodarone) should be monitored for the development of bradycardia or heart block. Patients with LV dysfunction should not receive verapamil or diltiazem, especially if patients are treated with  $\beta$ -blockers.

### Safety Concerns with CCB Use

Controversy exists over the potential of CCBs to increase ischemic events and mortality. In 1995, a case-controlled study of patients with HTN demonstrated a 60% higher rate of MI in patients receiving CCBs compared to patients receiving thiazide diuretics. That same year, a

meta-analysis of CAD trials reported a significant association between high doses of nifedipine and increased mortality. In both of these analyses, short-acting nifedipine was the predominant CCB. Other case-controlled studies evaluating longer-acting CCBs have not produced similar outcomes.

Two studies have raised questions about using DHP CCBs in patients with diabetes mellitus. Both of these trials were investigating the role of DHP CCBs compared to an ACE inhibitor for treating HTN. The Appropriate Blood Pressure Control in Diabetes (ABCD) trial compared nisoldipine to enalapril and the Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial (FACET) compared amlodipine to fosinopril. Both trials showed significantly higher rates of serious cardiovascular events in the DHP CCB groups. Roughly 30% of the patients in the ABCD trial had preexisting CAD, whereas CAD was an exclusion criteria in FACET. It is unknown if these results are because of a harmful effect of DHP CCBs, a beneficial effect of ACE inhibitors, or both. Despite the fact that these trials were conducted in the setting of HTN, it is prudent to avoid DHP CCBs as monotherapy in patients with diabetes mellitus and chronic stable angina.

The possibility of a relationship between CCB use and cancer development has been raised based on the results of a small number of retrospective, observational analyses. It has been proposed that CCB use may interfere with apoptosis, leading to an increased potential for abnormal cell proliferation and tumor growth. Analysis of basic and clinical literature indicates that cellular  $Ca^{2+}$  modulation is complex and apoptosis can be linked to both increases and decreases in intracellular  $Ca^{2+}$ . Supra-pharmacological doses of CCBs are required to have any impact on programmed cell death. The conclusion of this well-done analysis is that there is no support for a causal relationship between therapeutic doses of CCBs and an increased incidence of cancer development.

## Revascularization

Surgical revascularization plays an important and growing role in treating chronic stable angina. Revascularization options usually consist of CABG surgery or PCI with or without stent placement. Other options are available or under development, but are less established. The goal with revascularization is to prolong life and eliminate or reduce symptoms. Whereas most of the pharmacological approaches reduce  $MVO_2$ , revascularization increases myocardial oxygen supply in vessels with critical stenosis. This increase in myocardial oxygen supply is accomplished by opening the vessel through PCI with or without stent placement, or using alternative transplanted vessels to bypass a critical stenosis in the setting of CABG surgery. Although both of these therapies provide significant improvement in the care of

patients with chronic stable angina, and have advantages in certain groups of patients over a pharmacological approach, both revascularization treatments have limitations.

### Coronary Artery Bypass Graft Surgery Versus Medical Management

Much has been learned about the use and impact of CABG surgery throughout the past 30 years. Almost 600,000 CABG surgeries are performed annually. The majority of the data investigating the impact of CABG surgery on relieving angina symptoms and improving survival compared to initial medical therapy comes from three large multicenter, randomized trials initiated between 1972 and 1975. The Veterans Affairs Cooperative Study, the European Coronary Surgery Study, and CASS were powered to evaluate mortality benefit from CABG surgery compared to medical treatment. These trials have reported both short- and long-term outcomes and have provided the cardiology community with valuable data on the role of CABG surgery for treating chronic stable angina.

There are several limitations to applying these data to current practice. As previously discussed, these trials were conducted 2–3 decades ago. Since that time, cardiovascular surgeons have gained significant experience in performing CABG surgery while newer techniques, such as off-pump and minimally invasive surgeries, have been used. In addition, use of arterial grafts was limited to one trial in which only 14% of the patients received one vessel. These trials also are limited by the narrow spectrum of patients selected for enrollment. These trials primarily enrolled patients 65 years of age or younger (more than 90%), few women (less than 5%), and low- to moderate- risk patients who were clinically stable. Finally, the medical treatment in the comparative arm was clearly suboptimal by today's standard. Aspirin was not widely used, lipid-lowering therapy and ACE inhibitors were not yet considered standard of care, and  $\beta$ -blockers were used in only about one-half of the patients.

Despite these issues, these trials, along with a meta-analysis, have provided us with valuable information about the role of an initial strategy of CABG surgery compared to medical management. Use of CABG surgery provides a mortality benefit over medical management at 5 years (10.2% vs. 15.8%;  $p=0.0001$ ), 7 years (15.8% vs. 21.7%;  $p<0.001$ ), and at 10 years (26.4% vs. 30.5%;  $p=0.03$ ). In the 18-year follow-up to the Veterans Affairs Cooperative Study, there was no longer a survival benefit.

Despite the survival benefit seen in the entire patient cohort, there were several subgroups of patients for which the survival benefit was even more profound. These patients included those at high risk of death without surgery. Patients with significant (more than 50% stenosis) left main CAD have a median survival of 13.3 years with CABG surgery versus 6.6 years for those with medical treatment. Patients with left main equivalent disease (70% or more stenosis in both the proximal left anterior descending and

Mason RP. Calcium channel blockers, apoptosis and cancer: is there a biologic relationship? *J Am Coll Cardiol* 1999;34:1857–66.

Yusuf S, Zucker D, Peduzzi P, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomized trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 1994;344:563–70.

proximal circumflex arteries) experience a similar survival advantage to CABG surgery. Patients with three-vessel disease with reduced LV function, or two- or three-vessel disease with more than 75% stenosis in the proximal left anterior descending also have pronounced benefit from CABG surgery compared to medical therapy. Women and older patients have a higher risk of short-term mortality, but have a similar long-term prognosis compared to the general population.

Coronary artery bypass graft surgery significantly reduces postprocedural MI, but not overall MI, which is mainly because of an increase in periprocedural MI during CABG surgery. During CABG surgery, patients can have significant increases in creatine kinase-myocardial band. Patients with increases in creatine kinase-myocardial band greater than 5 times normal have an increased mortality rate, whereas the implications of enzymatic MI with less than that amount are questionable. Coronary artery bypass graft surgery also significantly reduces ischemic chest pain episodes, with 70–95% of patients being free of chest pain at 1 year and about 66% at 5 years compared to 38% for patients treated medically at 5 years. The difference in pain-free survival was no longer significant at 10 years.

There are three major contributors to the gradual loss of survival benefit and symptom relief in patients undergoing CABG surgery over time, especially after 10 years. First, it is inevitable in studies with long-term follow-up that survival curves of various treatment groups will eventually merge. This result has to do with the reduced life expectancy of patients with ischemic heart disease, regardless of the treatment. The second is the high number of treatment crossovers from medical therapy to CABG surgery. In a meta-analysis of these trials, 25% of the patients randomized to medical therapy had undergone CABG surgery after 5 years. This number increased to 33% by 7 years and to 41% by 10 years. Therefore, as patients in both groups progress and have advanced disease, the highest-risk patients randomized to medical treatment receive the benefits of CABG surgery late in the follow-up period.

Finally, the increased event rate in patients randomized to CABG surgery in the late follow-up period is related to the progressive atherosclerotic disease in native vessels as well as graft disease over time. Atherosclerotic obstruction of a native coronary vessel, leading to ischemic complications, usually takes 5 or more decades to accumulate, but the life span of a saphenous vein graft (SVG) is significantly shorter. Studies have shown occlusion rates of SVGs to be 20–25% at 5 years and almost 40% at 10 years, with one-half of all the remaining patent vessels showing atherosclerotic changes. This is because of the inability of SVG endothelium to withstand the increased blood pressures seen on the arterial side compared to venous pressures. The endothelial damage and incorporation of low-density lipoprotein (LDL) cholesterol accelerates the atherosclerotic process significantly. Using arterial grafts has provided promise in reducing occlusion of the CABGs. The most commonly used arterial graft is the internal mammary artery, which has shown graft patency to be greater than 90% at 10 years. Because of similar endothelial and smooth muscle cell function, arterial grafts are better

designed to accommodate arterial blood pressure compared to SVGs. Limitations to the use of arterial grafts include vasospasm and long surgical times for harvest. Because of the increased time needed, arterial grafts are not ideal in the setting of emergency CABG surgery. There also may be an increase in wound infections in patients with diabetes or who are obese who receive bilateral internal mammary artery grafts.

Despite the advancements in technique and patient care, CABG surgery still has some significant complications. One of the most feared and most common (about 6%) complications is postoperative neurological impairment, which may be attributed to hypoxia, emboli, hemorrhage, or a metabolic abnormality during or shortly after the surgery. Neurological complications are divided into type 1 and type 2 deficits. A type 1 deficit is associated with major, focal neurological deficits, stupor, or coma. In a type 2 deficit a reduction in intellectual function and memory is present. The incidence of neurologic deficits is equal between the two types; mortality may be as high as 21% and 10%, respectively. Many deficits are not clinically significant and resolve with time. Patients of advanced age and/or with a history of HTN are at an increased risk of a neurological complication after CABG surgery.

Other noncardiac complications of CABG surgery include renal dysfunction and mediastinitis. Postoperative serum creatinine levels more than 2.0 mg/dl or an increase in baseline creatinine level of more than 0.7 mg/dl occurs in as many as 8% of patients undergoing CABG surgery. Although most patients recover without problems, the mortality rate in these patients is 19%, and increases to almost 65% in the 1.5% of patients undergoing CABG surgery who require dialysis. Patients with advanced age, a history of HF, prior CABG surgery, diabetes mellitus type 1, and preexisting renal impairment are at an increased risk of developing postoperative renal dysfunction. Patients with preoperative renal dysfunction (serum creatinine more than 2.5 mg/dl) are at an exceptionally high risk of needing postoperative hemodialysis (40–50%). Despite the infrequent occurrence of mediastinitis (1–4%), the mortality rate can be as high as 25%. Patients with obesity, reoperation, use of both internal mammary arteries, longer surgeries with increased complexity, and diabetes mellitus are at an increased risk of developing postsurgical mediastinitis.

Pharmacotherapy after CABG surgery needs to include aspirin and lipid-lowering therapy (class I recommendations). Aspirin in doses between 100 mg/day and 325 mg 3 times/day is effective in reducing vein graft closure during the first year after the surgery. It is recommended that the first dose of aspirin be given within the first 24 hours of surgery. The efficacy of aspirin is lost if initiation is delayed more than 48 hours postoperatively. Aspirin usually is continued indefinitely because of its benefit in primary and secondary prevention of acute MI. If patients are truly allergic to aspirin, ticlopidine provides a relative reduction of 39% ( $p < 0.01$ ) in graft occlusion at 1 year compared to placebo. Clopidogrel is an attractive alternative to ticlopidine. Evidence in other areas such as intracoronary stenting have demonstrated equal efficacy with less neutropenia and

**Table 1-4. ACC/AHA Indications for CABG Surgery in Patients with Stable Angina**

**Class I**

1. Significant left main coronary artery stenosis.
2. Left main equivalent: significant ( $\geq 70\%$ ) stenosis of proximal LAD and proximal left circumflex artery.
3. Three-vessel disease. (Survival benefit is greater in patients with abnormal LV function; for example, patients with an EF  $< 0.50$ .)
4. Two-vessel disease with significant proximal LAD stenosis and either EF  $< 0.50$  or demonstrable ischemia on noninvasive testing.
5. One- or two-vessel coronary artery disease without significant proximal LAD stenosis but with a large area of viable myocardium and high-risk criteria on noninvasive testing.
6. Disabling angina despite maximal medical therapy when surgery can be performed with acceptable risk. If angina is not typical, objective evidence of ischemia should be obtained.

**Class IIa**

1. Proximal LAD stenosis with one-vessel disease. (Becomes class I if extensive ischemia documented by noninvasive study and/or LVEF  $< 0.50$ .)
2. One- or two-vessel coronary artery disease without significant proximal LAD stenosis, but with a moderate area of viable myocardium and high-risk criteria on noninvasive testing.

**Class III**

1. One- or two-vessel disease not involving significant proximal LAD stenosis in patients who have mild symptoms which are unlikely because of myocardial ischemia or who have not received an adequate trial of medical therapy and A) have only a small area of viable myocardium or B) have no demonstrable ischemia on noninvasive testing.
2. Borderline coronary stenosis (50–60% diameter in locations other than the left main coronary artery) and no demonstrable ischemia on noninvasive testing.
3. Insignificant ( $< 50\%$  diameter) coronary stenosis.

ACC = American College of Cardiology; AHA = American Heart Association; CABG = coronary artery bypass graft; EF = ejection fraction; LAD = left anterior descending; LV = left ventricle; LVEF = left ventricular ejection fraction.

thrombocytopenia. Because of the accelerated atherosclerotic process in patients with vein grafts, lipid-lowering therapy should be used aggressively to a target LDL cholesterol of less than 100 mg/dl. The Cholesterol Lowering Atherosclerotic Study and the Post Coronary Artery Bypass Graft Trial have both shown angiographic evidence of significant reductions in vein graft atherosclerosis. The need for long-term antianginal therapy is significantly reduced with the use of CABG surgery. Only 30% of patients undergoing CABG surgery required chronic nitrate or  $\beta$ -blocker therapy compared with more than 70% of patients treated medically. It is reasonable to include a  $\beta$ -blocker and/or CCB for treating preexisting HTN after surgery. Patients need to continue to have access to sublingual NTG after surgery. Smoking cessation (class 1 recommendation) and cardiac rehabilitation also are critical to successful postoperative outcomes.

**Coronary Artery Bypass Graft Surgery Versus PCI**

The first percutaneous transluminal coronary angioplasty (PTCA) was performed by Andreas Gruentzig in 1977. Since that time, the use and techniques of the procedure have advanced several-fold. There currently are more than 750,000 PCI procedures performed annually, with most of them consisting of PTCA, with or without stent placement. Advantages of PTCA include a low level of procedure-related morbidity and mortality, a short hospital stay, early return to work and activity, and the ability to perform multiple procedures if needed. Disadvantages of

PTCA include a risk of abrupt vessel closure and a high incidence of restenosis at 6 months. Successful procedures depend highly on operator experience. Current expectations of PTCA, especially with stent use, are a procedure success rate more than 90%, a mortality rate of less than 1%, a rate of Q-wave MI of less than 1.5%, and a need for emergency CABG surgery of 1–2%.

Several randomized, clinical trials have compared revascularization strategies. Because CABG surgery was used for almost a decade before PTCA, patients who already had gained benefit from CABG surgery compared to medical treatment were not included in these trials. The small size and short duration of these trials also limited the ability to detect any modest mortality difference that may or may not have been present. Recruitment of patients in these trials was extremely difficult because patients with three-vessel disease seemed to be referred to CABG surgery, and patients with two-vessel disease seemed to be referred to PTCA before enrollment. Less than 10% of patients enrolled in these trials had an ejection fraction less than 50%. These trials enrolled patients with stable and unstable CAD, but the results did not appear to vary between the two types of patients.

The largest comparison trial was BARI, which randomized 1792 patients to either PTCA or CABG surgery to evaluate the primary end point of mortality at 5 years. Most patients had normal LV function and had one- or two-vessel disease with a low use of stents. Survival at 5.4 years and freedom from MI was not different between the groups. There was a higher incidence of in-hospital MI

Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. Bypass Angioplasty Revascularization Investigation (BARI) Investigators. *N Engl J Med* 1996;335(4):217–25.

**Table 1-5. ACC/AHA Indications for CABG Surgery in Patients with Asymptomatic or Mild Angina**

**Class I**

1. Significant left main coronary artery stenosis.
2. Left main equivalent: significant ( $\geq 70\%$ ) stenosis of proximal LAD and proximal left circumflex artery.
3. Three-vessel disease. (Survival benefit is greater in patients with abnormal LV function; for example, patients with an EF  $< 0.50$ .)

**Class IIa**

1. Proximal LAD stenosis with one- or two-vessel disease. (Becomes class I if extensive ischemia documented by noninvasive study and/or LVEF  $< 0.50\%$ .)

**Class IIb**

1. One- or two-vessel disease not involving the proximal LAD. (If larger area of viable myocardium and high-risk criteria on noninvasive testing, becomes class I.)

ACC = American College of Cardiology; AHA = American Heart Association; CABG = coronary artery bypass graft; EF = ejection fraction; LAD = left anterior descending; LV = left ventricle; LVEF = left ventricular ejection fraction.

in patients receiving CABG surgery, but there was a significant increase in rehospitalization and need for repeat revascularization over the follow-up period for those randomized to PTCA. Despite the initial increase in cost of CABG surgery, the cost of the two revascularization approaches became almost neutral, because of the high need for repeat procedures in patients undergoing PTCA. Despite the longer follow-up and larger number of patients compared to other trials, BARI is still limited because of the narrow scope of patients enrolled and the high crossover rate of patients undergoing PTCA who received CABG surgery (31%).

New approaches to CABG surgery have been developed to minimize the morbidity related to the operation. One of these approaches is the off-pump bypass coronary surgery that is performed on a beating heart. This type of surgery currently accounts for about 20% of all CABG surgeries performed in the United States. Patients undergoing off-pump bypass experience the same relief from angina, vessel patency, and mortality benefit (evaluated out to 1 year) as traditional CABG surgery. Patients using off-pump bypass with sternotomy can undergo multivessel bypass, but data on patients with left main disease and impaired LV function are limited. By reducing the need for cardiopulmonary bypass and preventing the need for clamping of the aorta, there is a significant reduction in adverse neurologic events, length of hospitalization, and cost. The cardiac motion is reduced by many pharmacological and mechanical devices. These include slowing the heart rate with  $\beta$ -blockers and non-DHP CCBs, creating a temporary cardiac arrest with adenosine, or vagal stimulation.

Using Minimally Invasive Direct Coronary Artery Bypass Graft (MIDCAB) is conducted without median sternotomy and without using cardiopulmonary bypass. In addition to the benefits of avoiding cardiopulmonary bypass, the prevention of sternotomy reduces the incidence of wound infections as well as patient recovery time. Because of the small incision and technical difficulty of the

surgery, it is limited to patients with single vessel disease of either the left anterior descending or right coronary artery. Both of these newer types of procedures are limited by the needed learning curve of the surgeon and lack of long-term follow-up for patency and mortality compared to standard CABG surgery.

As previously discussed, the ACC/AHA published guidelines for using CABG surgery. The full text of these guidelines provides the recommendations for the use of CABG surgery and a thorough review of the literature supporting the recommendations. The ACC/AHA recommendations for CABG surgery for symptomatic patients with stable angina are listed in Table 1-4. Recommendations for asymptomatic patients or those with mild angina are listed in Table 1-5. These recommendations are based on the groups of patients who have had the most benefit in the clinical trials discussed.

**PCI Versus Medical Therapy**

The first comparison of PTCA to medical therapy was the Angioplasty Compared to Medicine (ACME) study. This relatively small trial randomized 212 patients with 70–99% stenosis in a single vessel and exercise-induced angina to either PTCA or medical therapy. At 6 months, there were significantly more patients free of angina in the PTCA group compared to the medical therapy group (64% vs. 46%;  $p < 0.01$ ), and these patients also had significantly better exercise testing performance. Despite this symptomatic improvement, there were increased costs and complications associated with PTCA.

The Randomized Intervention Treatment of Angina-2 (RITA-2) trial was a much larger and longer study, randomizing 1018 patients to PTCA or medical therapy with 2.7 years of follow-up. Sixty percent of patients in RITA-2 had single-vessel disease. Similar to the ACME trial, there was a significant improvement in angina relief and exercise performance in patients undergoing PTCA compared to medical therapy. The improvement in angina

Parisi AF, Folland ED, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. *N Engl J Med* 1992;326:10–6.

The RITA-2 Participants. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. RITA-2 Trial Participants. *Lancet* 1997;350:461–8.



symptoms was much greater at 3 months than at 2 years, but still significantly better with PTCA. There also was significantly more death and MI in patients receiving PTCA compared to medical therapy (6.3% vs. 3.3%;  $p=0.02$ ). However, this increase in ischemic events was mainly because of an increase in periprocedural enzymatic MI. The results suggest that the improvement in angina symptoms needs to be balanced against the risk of procedure-related complications. Several patients in both groups went on to receive subsequent revascularization procedures for worsening angina (20% of patients undergoing PTCA vs. 25% of patients undergoing medical therapy). About 50% of patients in each group received ACE inhibitors, and 65% received lipid-lowering therapy, although the aggressiveness of this therapy is unknown.

Because many patients with chronic stable angina also have silent ischemic events, the effectiveness of medical therapy or revascularization was evaluated in the Asymptomatic Cardiac Ischemia Pilot (ACIP) study. This trial randomized 558 patients with clinically stable disease (free of angina or symptoms well controlled with medical therapy), with angiographic evidence of CAD suitable for revascularization, and one or more episodes of asymptomatic ischemia documented during 48-hour ambulatory ECG monitoring, to one of three arms: angina-guided medical treatment, ambulatory ECG-guided medical treatment, or revascularization (PTCA or CABG surgery). Medical treatment consisted of atenolol  $\pm$  extended-release nifedipine or diltiazem  $\pm$  isosorbide dinitrate. The mortality rate at 2 years was 6.6%, 4.4%, and 1.1% ( $p<0.02$ ) for the three groups, respectively. Revascularization also showed significant reductions in the rate of death and MI along with death, MI, and need for recurrent cardiac rehospitalization.

Although PTCA has shown a mix of benefits in clinical studies compared to medical therapy, the aggressiveness of medical therapy, especially lipid-lowering therapy, was not optimal in these early trials. The Atorvastatin Versus Revascularization Treatment (AVERT) trial randomized 341 patients with asymptomatic or mild to moderate stable angina and a LDL cholesterol of at least 115 mg/dl to medical treatment with atorvastatin 80 mg/day or angioplasty with usual medical care. Most patients had normal LV function and were at low risk of death without revascularization. At the 18-month follow-up, 13% of patients receiving high-dose atorvastatin experienced the primary end point of an ischemic event compared to 21% for patients undergoing angioplasty. Despite a  $p$  value of 0.048, the difference did not achieve statistical significance. Based on the adjustment from the interim analysis, a  $p$  value of 0.045 would have been needed to show statistical significance. Seventy-one percent of patients in the angioplasty group received lipid-lowering therapy and achieved a mean LDL cholesterol of 119 mg/dl compared to

a mean LDL cholesterol of 77 mg/dl achieved with the more aggressive medical treatment group.

Although AVERT suggests that the aggressive lipid-lowering medical therapy may be as good as PTCA, knowledge about the impact of aggressive medical therapy versus PTCA with equally aggressive medical therapy still is unknown. The ongoing Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial is evaluating aggressive medical therapy compared to aggressive medical therapy plus PTCA. Aggressive medical therapy is targeted against angina and lipids, as well as HTN, diabetes mellitus, and maximizing ACE inhibitor use. The COURAGE trial will enroll 3260 patients with a mean follow-up of 4.5 years evaluating the primary end point of death and nonfatal MI. Results should be available by late 2006.

### Complications of PCI

Three main complications are associated with the use of PCIA: coronary dissection, abrupt vessel closure, and restenosis. Coronary dissection occurs rarely and often needs to be treated with CABG. Abrupt vessel closure and restenosis occur more commonly. These complications present as recurrent angina, MI, or rarely death, and often lead to repeat revascularization with either repeat PTCA or CABG surgery. The dilation of the balloon during angioplasty whereas opening the coronary artery and reducing stenosis also may disrupt the endothelial layer of the atherosclerotic plaque. This disruption can then lead to activation and aggregation of platelets at the site of the procedure and abrupt vessel closure. Previously, abrupt vessel closure occurred in 5–10% of patients, but now occurs relatively rarely (2–5%) with the use of stents and more potent antiplatelet therapy with glycoprotein IIb/IIIa inhibitors. The glycoprotein IIb/IIIa inhibitor eptifibatid significantly reduced death and MI in patients undergoing elective PCI with stenting in the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrelin Therapy trial. Abciximab also has significantly reduced death and MI with PCI without stenting in the Evaluation in PTCA to Improve Long-term Outcomes with ReoPro Glycoprotein IIb-IIIa Blockade trial and with stenting in the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting trial. The abciximab trial that used stenting also showed a significant reduction in mortality alone. Both abciximab trials included both patients undergoing elective procedures and those with unstable angina. Reduced dose heparin (60–70 units/kg) and aspirin were given with glycoprotein IIb/IIIa inhibition in all of these trials. Both PCI with stenting trials used either ticlopidine or clopidogrel for 4–6 weeks after the procedure. The benefit of glycoprotein IIb/IIIa inhibitor therapy with an adenosine diphosphate (ADP) antagonist in patients with chronic stable angina compared to patients with an ACS has not been completely answered. Patients undergoing PCI with stenting for treating stable angina

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Davies RF, Goldberg AD, Forman S, et al. Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. *Circulation* 1997;95:2037–43.

Pitt B, Walters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. *N Engl J Med* 1999;341:70–6.

would not be expected to have the same extent of platelet activity compared to the patient with ACS, and may not realize the same magnitude of benefit from this combination antiplatelet therapy. Despite the potential for less benefit in patients with chronic stable angina, the risk of bleeding would remain the same. This discussion of the risk-benefit ratio also is pertinent to the discussion on in-stent thrombosis found below.

The most common and costly complication of PTCA is restenosis. Restenosis is a late complication that usually takes 1–6 months after the procedure to become apparent. After the procedure, there can be elastic recoil of the vessel wall and endothelial damage. The endothelium takes several weeks to repair after PTCA. During this time, the process of restenosis is initiated by substances, such as thrombin, platelet-derived growth factor, and basic fibroblast growth factor, which lead to smooth muscle cell proliferation. Although several pharmacological methods for reducing restenosis have been investigated, none has been clinically successful. The incidence of restenosis has been reduced significantly from 30–40% to 15–20% by the increased use of intracoronary stents. The development of drug-eluting stents has produced impressive results in reducing the rate of restenosis to 0–9%. With the sirolimus stent gaining Food and Drug Administration approval for preventing restenosis, and the paclitaxel stent pending approval for preventing restenosis, their use will have to be closely monitored because of their high cost. Although their exact cost has yet to be determined, the drug-eluting stents are expected to cost about \$1000–1500 more than a traditional “bare” stent.

Although the increased use of stents has significantly reduced the incidence of restenosis, it has created its own complication of stent occlusion. On expansion of the stent into the atherosclerotic plaque, longitudinal fissures are created in the vessel wall, leading to damaged endothelium and exposure of subendothelial proteins. Proteins, such as collagen and von Willebrand factor, will adhere platelets to the area of injury at the site of stent deployment. The platelets become activated leading to expression of glycoprotein IIb/IIIa receptors, and eventually aggregate through fibrinogen to form a platelet plug and occlusion of the stent. Early clinical trials produced a rate of acute and subacute stent thrombosis of almost 20%. Early attempts to prevent this high rate of stent thrombosis included antiplatelet and anticoagulant regimens, which included aspirin with dipyridamole, dextran, intravenous heparin, and an oral anticoagulant (usually warfarin). These approaches reduced acute and subacute stent thrombosis to 3–5%, but there was a higher rate of bleeding and vascular access site complications.

Because stent thrombosis was determined to be primarily platelet-mediated, a more aggressive antiplatelet strategy was investigated. Several trials demonstrated a significant

reduction in stent thrombosis with the use of dual antiplatelet therapy with ticlopidine for 2–6 weeks and aspirin compared to aspirin alone or aspirin plus warfarin. This reduction in cardiac events with ticlopidine and aspirin was accompanied by a significant reduction in bleeding complications compared to warfarin and aspirin. Based on these results, ticlopidine plus aspirin became the standard of care for patients receiving PTCA with a stent. Most patients receive dual therapy for 30 days with more than 95% of all stent thrombosis events occurring within the first 2 weeks of stent placement. Ticlopidine use is limited by a significant adverse effect profile, including nausea, vomiting, rash, neutropenia, and thrombotic thrombocytopenic purpura.

Clopidogrel also provides antiplatelet activation activity through platelet ADP-receptor blockade similar to ticlopidine, but with a reduced adverse effect profile. The Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS) randomized 1020 patients to either a 300-mg loading dose of clopidogrel followed by 75 mg/day, clopidogrel 75 mg/day without a loading dose, or ticlopidine 250 mg 2 times/day. All patients received treatment for 28 days along with aspirin 325 mg/day. Fifty-six percent of patients received their stent to treat stable angina. The primary end point of the study was the overall incidence of adverse effects, which occurred significantly more frequently in patients receiving ticlopidine. Specific adverse events that were more common with ticlopidine compared to clopidogrel included skin disorders (2.6% vs. 0.7%), gastrointestinal disorders (2.6% vs. 1.3%), and allergic adverse events (1.2% vs. 0%). The incidence of cardiac events was not different between the groups at the end of the 42-day follow-up period.

The efficacy of a clopidogrel loading dose and the appropriate therapy duration in patients undergoing elective PTCA with stent placement was evaluated in the Clopidogrel for the Reduction of Events During Observation (CREDO) trial. This trial randomized patients to a 300-mg loading dose of clopidogrel or placebo given 3–24 hours before the procedure. After the initial dose, all patients received clopidogrel 75 mg/day along with aspirin 325 mg/day for 28 days. Thirty-three percent of patients received their stent for treating stable angina. At 28 days, the primary composite end point of death, MI, or need for urgent target vessel revascularization was not different between the groups. Patients receiving their loading dose at least 6 hours before the procedure had a reduction in the primary end point favoring the loading dose group compared to the group not receiving any loading dose, but this difference did not reach statistical significance ( $p=0.051$ ). This finding warrants further study in an adequately powered trial to evaluate patients receiving a loading dose 6 hours before procedure. At 28 days, clopidogrel was continued at 75 mg/day with aspirin for 1 year in patients who had received the loading dose of

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Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH. Double-blind study of the safety of clopidogrel with and without loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the clopidogrel aspirin stent international cooperative study (CLASSICS). *Circulation* 2000;102:624–9.

Moller SJ, Edvardsson N, Jahmatz B, Rosen A, Sorensen S, Omblus R. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. *Lancet* 1992;340:1421–5.

clopidogrel, whereas the other patients received placebo and aspirin for 1 year. There was a significant reduction in the primary long-term outcome of death, MI, or stroke with long-term use compared to only 28 days of clopidogrel (8.5% vs. 11.5%;  $p=0.02$ ). Although there were two variables that may have contributed to this outcome (loading dose and longer therapy duration), the results of the CREDO trial support the use of continued dual antiplatelet therapy beyond the traditional 30 days out to 1 year. The use of preprocedural dosing usually is feasible in most patients undergoing elective PTCA. The ACC/AHA currently recommend that clopidogrel be held for 5 days before CABG surgery. Despite the potential benefits of early loading doses of clopidogrel seen in this trial, it may not be practical based on the proven risk of bleeding if patients need to go on to CABG surgery. Therefore, loading doses typically should be avoided until this risk is ruled out. Because the need for CABG surgery often cannot be predicted before catheterization, many invasive cardiologists wait and rule out the need for CABG surgery and give the loading dose of clopidogrel immediately before balloon inflation whereas the patient is already in the cardiac catheterization laboratory.

### **Transmyocardial Laser Revascularization**

Even with the advanced technology and techniques involved in current revascularization strategies, there is still a group of patients who are not candidates for PTCA or CABG surgery. These may be patients who are not good surgical candidates, have complicated lesions in vessels not accessible by percutaneous techniques, or patients with frequent restenosis. For these patients, transmyocardial laser revascularization (TMR) may be an alternative.

Transmyocardial revascularization uses a laser that produces channels in the myocardium, providing a network of functional connections for oxygenated blood to flow between the left ventricular cavity and ischemic myocardium. During the procedure, 10–50 of these channels are created, which is similar to the natural myocardial blood supply in the reptilian heart. Despite the subsequent observations in humans that these channels occlude within hours to days after the procedure, clinical trials have shown successful reductions in severity of angina symptoms out to a year after the procedure. Explanations for this reduction in symptom severity include stimulation of angiogenesis, an anesthetic effect caused by the destruction of sympathetic nerve fibers by the laser, or a possible placebo effect.

Trials with transmyocardial laser revascularization typically have enrolled patients with Canadian Cardiovascular Society class III or IV angina who are ineligible for other forms of revascularization. Despite the limited objective data supporting this procedure, it received Food and Drug Administration approved indication to treat class III or IV angina in 1998. The update to the guidelines for managing chronic stable angina gives TMR a class IIa recommendation for patients refractory to medical therapy unable to undergo PTCA or CABG surgery. Because the procedure requires thoracotomy to gain access to the epicardial surface, there are significant complications and cost. With the use of modern endoscopic devices, a new

catheter-based technique called percutaneous myocardial revascularization has been developed. Percutaneous myocardial revascularization does not require open-heart surgery and can be performed in the cardiac catheterization laboratory with standard femoral artery access. The percutaneous myocardial revascularization catheter is advanced to the left ventricular cavity where it can create channels from the endocardial surface. The Potential Angina Class Improvement from Intramyocardial Channels (PACIFIC) trial that randomized 221 patients with an incomplete response to medical therapy and reversible ischemia of Canadian Cardiovascular Society class II or IV to percutaneous myocardial revascularization or medical therapy. After 12 months of follow-up, patients receiving percutaneous myocardial revascularization showed improvement in reducing angina severity and increasing exercise tolerance. The Blinded Evaluation of Laser Percutaneous Myocardial Revascularization Intervention Electively for Angina Pectoris trial has evaluated the effectiveness of percutaneous myocardial revascularization and showed that benefits were not because of a placebo effect. The trial randomized 40 patients with Canadian Cardiovascular Society class III or IV angina to percutaneous myocardial revascularization plus medical therapy or a sham procedure plus medical therapy. More than twice as many patients receiving percutaneous myocardial revascularization had a reduction in angina severity compared to the placebo procedure ( $p=0.03$ ). The role of TMR and percutaneous myocardial revascularization for managing chronic stable angina will need to be determined in future studies.

## **Therapeutic Approach to Managing Chronic Stable Angina**

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### **Lifestyle Modifications**

Despite the fact that a patient with chronic stable angina has already developed CAD, risk factor reduction and management are important to prevent progression of atherosclerotic disease. Management of modifiable risk factors needs to be implemented along with the patient's antianginal therapy (Figure 1-3). When managing patients with chronic stable angina, clinicians should encourage them to eat an appropriate diet and exercise regularly. A balanced diet low in sodium and fat (AHA step II diet) with moderate exercise for 20 minutes/day, most days of the week, has led to significant weight reduction and improved cardiovascular health. Despite the pharmacological agents selected, diet and exercise remain cornerstones of a management plan for these patients. Managing HTN, dyslipidemia, diabetes mellitus, and smoking cessation are covered in other chapters in this book. Whenever possible, blood pressure-lowering agents that also serve to reduce anginal episodes ( $\beta$ -blockers and CCBs) should be used. Lifestyle modifications are discussed in more detail in the

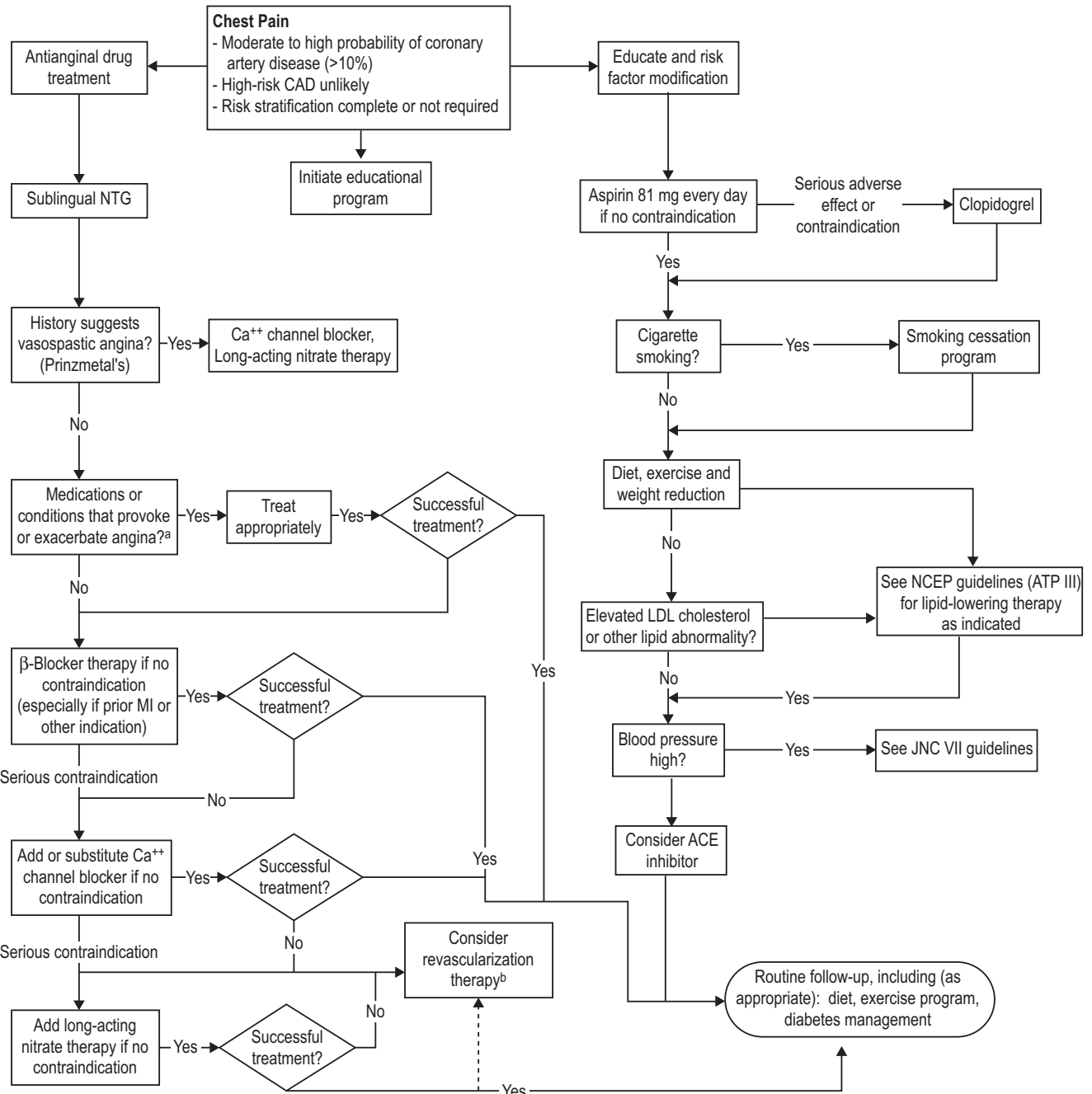


Figure 1-3. ACC/AHA/ACP-ASIM guideline for management of chronic stable angina — treatment.

<sup>a</sup> Vasodilators, excessive thyroid replacement, vasoconstrictors, profound anemia, uncontrolled hypertension, hyperthyroidism, hypoxemia, tachyarrhythmias, bradyarrhythmias, valvular heart disease (especially aortic stenosis), and hypertrophic cardiomyopathy.

<sup>b</sup> On the basis of coronary anatomy, severity of anginal symptoms, and patient preferences, it is reasonable to consider evaluation for coronary revascularization. Unless a patient has documented left main, three-vessel, or two-vessel coronary artery disease with significant stenosis of the proximal left anterior descending coronary artery, there is no demonstrated survival advantage associated with revascularization in low-risk patients with chronic stable angina. Thus, medical therapy should be attempted in most patients before considering percutaneous transluminal coronary angioplasty or coronary artery bypass graft.

ACC = American College of Cardiology; AHA = American Heart Association, ACP-ASIM = American College of Physicians – American Society of Internal Medicine; CAD = coronary artery disease; JNC = Joint National Committee; MI = myocardial infarction; NCEP = National Cholesterol Education Program; NTG = nitroglycerin.

Prevention of Cardiovascular Disease and Secondary Prevention of Stroke and Myocardial Infarction chapters.

### Acute Nitrates

All patients with chronic stable angina should have access to sublingual NTG tablets or spray. Patient access to sublingual NTG is an ACC/AHA class I recommendation. Regardless if patients are being managed with medical treatment, revascularization, or a combination of approaches, patients need treatment for acute attacks of angina. About 75% of all exertional angina episodes are relieved with the first sublingual NTG dose, with another 10–15% of patients achieving relief with the next two doses. Clearly the major contributing factor to successful use of sublingual NTG is appropriate patient education from the pharmacist. If patients do not receive appropriate patient counseling on the use of this agent, the opportunities for successful use are greatly reduced.

### Antithrombotic Therapy

#### Aspirin

Aspirin provides an antithrombotic effect by its irreversible nonselective inhibition of cyclooxygenase and synthesis of thromboxane  $A_2$ . The reduction in thromboxane  $A_2$  production leads to reduced platelet activation and exposure of glycoprotein IIb/IIIa receptors and, therefore, less platelet aggregation for the life of the platelet. Aspirin also provides benefits through some nonplatelet-mediated effects. Low-dose aspirin (325 mg/day or less) has not significantly impaired endothelial secretion of prostacyclin, which provides vasodilation. Even though there may be some inhibition of prostacyclin with the use of aspirin, the effects on the endothelium are not irreversible like those on the platelet. After the daily dose of aspirin has been removed from the body, prostacyclin secretion and its vasodilation effects are restored. Aspirin also may attenuate the synthesis of cytokines, such as interleukin-2, interleukin-6, and interferon in leukocytes. Aspirin also may prevent leukocyte rolling and macrophage-induced endothelial activation.

Clinical evidence describing the effectiveness of aspirin in patients with chronic stable angina first came from a subgroup analysis of the Physicians Health Study. The original trial was a double-blind evaluation of the efficacy of low-dose aspirin (325 mg every other day) compared to placebo in the primary prevention of MI, stroke, or cardiovascular death. Of the 22,071 patients enrolled in the trial, 333 had a history of chronic stable angina. After the 5-year follow-up period, the patients with chronic stable angina had an 87% significant reduction in risk for first MI. Similar to the overall trial results, this benefit came with a significant increase in stroke, although none of the strokes was fatal. There was no difference in total or cardiovascular mortality, but there were too few patients with chronic stable angina to provide a meaningful analysis of these end points.

These beneficial effects of aspirin were confirmed in the much more robust Swedish Angina Pectoris Aspirin Trial (SAPAT). The SAPAT randomized 2035 patients with anginal control who were receiving sotalol (mean dose 160 mg/day) to aspirin 75 mg/day or matching placebo. At the end of the 50-month follow-up, patients receiving aspirin had a 34% relative reduction in first MI or sudden death. There was no difference noted in major bleeding or stroke between the groups. Based on these results, aspirin use in patients without contraindications is an ACC/AHA class I recommendation for patients with chronic stable angina.

#### Adenosine Diphosphate Inhibitors

Ticlopidine and clopidogrel provide antiplatelet effects by inhibiting ADP-induced platelet activation and, therefore, platelet aggregation. Ticlopidine has been evaluated in patients after an ACS compared to placebo and was found to reduce ischemic events to a similar magnitude as aspirin in other trials. No trials using ticlopidine in patients with chronic stable angina have been published. Ticlopidine is no longer widely used because of the increased incidence of neutropenia (requiring a blood count every 2 weeks for the first 3 months of therapy), reports of thrombotic thrombocytopenic purpura, and increased cost compared to clopidogrel. Clopidogrel also has been reported to cause thrombotic thrombocytopenic purpura, but the incidence reported is one case per 250,000 patients treated compared to one case per 40,000 patients treated with ticlopidine.

Clopidogrel also has been evaluated in patients with known atherosclerotic disease. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial randomized 19,185 patients with either a recent history of ischemic stroke, recent MI, or symptomatic atherosclerotic peripheral vascular disease to clopidogrel 75 mg/day or aspirin 325 mg/day. After a mean follow-up of 1.9 years, there was significantly less ischemic stroke, MI, or vascular death in patients receiving clopidogrel compared to those receiving aspirin (5.32% vs. 5.83%;  $p=0.043$ ). Despite the statistical benefit of clopidogrel, 200 patients would need to be treated to prevent one ischemic event. Because 1 month of clopidogrel costs about \$100 compared to the nominal cost of aspirin, clopidogrel would not be a cost-effective substitution for aspirin. If patients have a true aspirin allergy or intolerance, clopidogrel is an effective alternative (class IIa recommendation). Only 22% of the patients in the CAPRIE trial had documented stable angina, and no specific subgroup analysis is available for patients. Studies evaluating the use of aspirin with clopidogrel have been mainly conducted in the post-ACS setting and not in patients with chronic stable angina.

#### Other Agents

Antiplatelet therapy with dipyridamole currently is not recommended because of its potential to enhance exercise-induced myocardial ischemia in patients with

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Moller SJ, Edvardsson N, Jahmatz B, Rosen A, Sorensen S, Omblus R. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. *Lancet* 1992;340:1421–5.

chronic stable angina. Low-intensity warfarin therapy (international normalized ratio = 1.5) reduces the risk of coronary death and MI in patients with risk factors for atherosclerosis, but without symptoms of angina. Warfarin has been evaluated in other patients with CAD, but to date, these trials have mainly been in patients who are post-MI and not in the setting of chronic stable angina.

### **β-Blockers**

Several early trials have demonstrated the ability of β-blockers to significantly reduce angina symptoms, increase exercise tolerance, and increase time to ST-segment depression on exercise testing in patients with chronic stable angina. Trials comparing β-blockers to other antianginal drugs, mainly CCBs, show at least a similar ability to reduce angina symptoms and improve exercise tolerance. Few trials show an advantage of β-blockers in the symptomatic treatment of chronic stable angina. These trials used sustained-release nifedipine as the comparator CCB. The Total Ischemic Burden Bisoprolol Study (TIBBS) randomized 330 patients with exercise-induced stable angina and two or more transient ischemic episodes during 48-hour ambulatory monitoring to bisoprolol 10 mg/day or sustained-release nifedipine 20 mg 2 times/day. At 4 weeks, the doses were doubled. Both groups showed a significant reduction in the number and duration of transient ischemic episodes, with bisoprolol being significantly more effective than sustained-release nifedipine at both doses investigated. A similar result was seen in the International Multicenter Angina Exercise (IMAGE) study. The IMAGE study randomized 280 patients to extended-release metoprolol 200 mg/day or sustained-release nifedipine 20 mg 2 times/day for 6 weeks. Both groups showed significant improvement in exercise time, with extended-release metoprolol providing more improvement than sustained-release nifedipine.

β-Blockers provide significant reductions in mortality and other cardiovascular end points in patients with recent MI. Similar benefits with the use of β-blockers have been demonstrated in patients with systolic HF and HTN. Despite many trials showing symptomatic improvement with β-blockers, there are few randomized trials that have investigated β-blockers for clinical outcomes in patients with chronic stable angina in the absence of prior MI. Three hundred and six patients with asymptomatic or mild angina (Canadian Cardiovascular Society class I or II angina) were randomized to receive atenolol 100 mg/day or placebo in the Atenolol Silent Ischemia Study (ASIST). The results of the primary outcome of ASIST showed a statistically

significantly better rate of event-free survival at 1 year in patients taking atenolol (89% vs. 75%;  $p=0.0066$ ).

Only two trials have been large enough with long enough follow-up to evaluate clinical outcomes between β-blockers and CCBs. The Total Ischemic Burden European Trial (TIBET) randomized 682 patients to atenolol, sustained-release nifedipine, or the combination. Patients needed to have symptomatic chronic angina but without immediate need for revascularization. The occurrence of the composite end points of cardiac death, nonfatal MI, and unstable angina were similar between the β-blocker and CCB groups at the mean 2-year follow-up. There was a trend toward fewer events in the combination group, which provided an additional 30% relative reduction in events compared to the individual agents. The Angina Prognosis Study in Stockholm (APSYS) trial was a similar study that randomized 809 patients to either sustained-release metoprolol or sustained-release verapamil. After the mean follow-up of 3.4 years, there was no significant difference in the occurrence of cardiovascular events (30.8% vs. 29.3%) or mortality (5.4% vs. 6.2%) between metoprolol and verapamil.

β-Blockers currently have a class I recommendation and typically are recommended over CCBs and nitrates by the ACC/AHA for initial treatment of patients with chronic stable angina. This recommendation is based on the mortality benefit seen in patients who have had a recent MI, systolic HF, or HTN. Because of the overlap of these conditions with chronic stable angina, β-blockers are useful agents. On the basis of their potentially beneficial effects on morbidity and mortality, these agents should be strongly considered an initial therapy for all patients (without contraindications) with chronic stable angina.

Patients taking β-blockers typically should have their dose adjusted to provide a resting heart rate of 55–60 beats/minute. Patients with more severe angina may require a resting heart rate closer to 50 beats/minute, assuming there is no development of symptomatic bradycardia or heart block. Also, not all patients with chronic stable angina can tolerate a heart rate less than 60 beats/minute. Some patients, especially the elderly, may become symptomatic (e.g., lightheaded, dizzy, and syncopal) before the heart rate reaches 60 beats/minute or less. Patients should have their dose adjusted to reach the goal heart rate or the lowest tolerated heart rate. Slower titration of β-blockers in the elderly may allow for a lower heart rate to be tolerated over time. Because most episodes of angina are induced by exertion in the patient with chronic stable angina, reduction or suppression of an increased heart

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Von Arnim T. Medical treatment to reduce total ischemic burden: total ischemic burden bisoprolol study (TIBBS), a multicenter trial comparing bisoprolol and nifedipine. *J Am Coll Cardiol* 1995;25:231–8.

Savonitto S, Ardissino D, Egstrup K, et al. Combination therapy with metoprolol and nifedipine versus monotherapy in patients with stable angina pectoris. Results of the International Multicenter Angina Exercise (IMAGE) Study. *J Am Coll Cardiol* 1996;27:311–6.

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Dargie HJ, Ford I, Fox KM. Total Ischemic Burden European Trial (TIBET). Effects of ischemia and treatment with atenolol, nifedipine SR and their combination on outcome in patients with chronic stable angina. *Eur Heart J* 1996;17:104–12.

Rehnqvist N, Hjemdahl P, Billing E, et al. Effects of metoprolol versus verapamil in patients with stable angina pectoris. The Angina Prognosis Study in Stockholm (APSYS). *Eur Heart J* 1996;17:76–81.

rate during exercise is another important goal of  $\beta$ -blocker therapy. Patients should not be able to achieve a heart rate during exercise greater than 75% of the heart rate known to induce angina. This “angina-inducing heart rate” is determined by exercise stress testing. Other defined goals also suggest that  $\beta$ -blocker therapy should be titrated to prevent an increase in exercise heart rate of 20 beats/minute or an increase of 10% over the patient’s resting heart rate.

### Calcium Channel Blockers

Despite the fact that  $\beta$ -blockers and CCBs have not shown significant differences in comparative trials evaluating clinical outcomes, initial therapy with a long-acting non-DHP CCB instead of a  $\beta$ -blocker carries a class IIa recommendation. As previously discussed, this is because of the mortality benefits seen in certain patient populations and a select number of trials (TIBBS and IMAGE) showing more impressive angina relief with  $\beta$ -blocker therapy (vs. sustained-release nifedipine). There is no recommendation for initiating a non-DHP CCB over a  $\beta$ -blocker as initial therapy in  $\beta$ -blocker eligible patients. The current ACC/AHA class I recommendations for CCBs include patients who have contraindications, unsuccessful therapy, or unacceptable side effects with  $\beta$ -blocker therapy. Because most patients with chronic stable angina have heart rates above the goal of 50–60 beats/minute, non-DHP CCBs are a logical selection and the ACC/AHA recommended agents. In patients with preexisting sinus bradycardia, atrioventricular conduction disturbances, or sick sinus syndrome, a long-acting DHP CCB is an appropriate selection. Patients with LV dysfunction unable to tolerate  $\beta$ -blocker therapy can be safely treated with amlodipine and possibly felodipine. Long-acting CCBs typically are recommended over chronic nitrates for maintenance therapy because of their sustained 24-hour effects. Short-acting DHP CCBs should not be used in any patients with chronic stable angina.

Patients with variable threshold angina should receive CCBs unless there are contraindications or complications of therapy. Patients with variable-threshold angina experience better relief of angina symptoms with the use of CCBs compared to  $\beta$ -blocker therapy. Patients without exertion-induced angina and pure vasospasm-induced angina (Prinzmetal’s angina) should receive CCBs as initial therapy and should not receive  $\beta$ -blockers.

Several trials have shown benefits in reducing angina symptoms and increasing exercise tolerance when CCBs are added to  $\beta$ -blockers. Long-acting DHP CCBs usually are the agents selected for addition to  $\beta$ -blockers. The Centralized European Studies in Angina Research Investigators randomized 97 patients with angina resistant to atenolol to either amlodipine or diltiazem. Both groups showed improvement, but patients receiving atenolol and diltiazem had more side effects, especially related to bradycardia and syncope. The combination of a  $\beta$ -blocker and non-DHP CCB must be used with caution because of the combined reduction in heart rate and atrioventricular nodal conduction. Patients receiving this combination should be monitored closely for the development of bradycardia and heart block.

Patients with chronic stable angina with HTN despite  $\beta$ -blocker therapy are good candidates for DHP CCBs. These agents will not only assist with angina relief, but also provide better 24-hour blood pressure reduction than would chronic nitrates. Many trials that have added DHP CCBs to  $\beta$ -blockers have shown that the benefits are not always additive. The lack of efficacy of monotherapy with a  $\beta$ -blocker can often be attributed to the inability to use sufficient doses to achieve appropriate heart rate reduction and symptom relief because of the presence of side effects. For optimal combination therapy, it should first be determined if the initial therapy has provided any improvement in control of angina symptom. Combination therapy may appear to be an improvement only because the initial monotherapy provided no benefit (IMAGE trial and others). If it is determined that initial monotherapy with a  $\beta$ -blocker has not reduced the number and duration of ischemic episodes and not improved exercise tolerance, a CCB should be substituted and not added. If initial monotherapy provided some benefit, but not at the level of symptom reduction and increased activity perceived by the patient and provider to be adequate, combination therapy provides additional angina relief, improves exercise tolerance, and reduces the number and duration of ischemic episodes with ambulatory ECG monitoring.

### Chronic Nitrates

Chronic nitrate therapy has not reduced cardiovascular events, such as death or MI. Because of the potential for reflex tachycardia, lack of protection from angina during nitrate-free intervals, and lack of effect on the circadian rhythm of ischemic events, chronic nitrates are reserved for add-on therapy for patients already receiving a heart rate-controlling agent, such as a  $\beta$ -blocker, verapamil, or diltiazem. Although the results of trials using chronic nitrates for reducing the severity and number of angina episodes have not shown consistent benefit, the overall results show an improvement in exercise tolerance, increased time to onset of angina, and time to ST-segment depression during exercise tolerance testing. Chronic nitrates are a reasonable addition if monotherapy is insufficient in controlling angina. Chronic nitrates may be added directly to  $\beta$ -blocker or CCB therapy or may be part of a regimen including all three. In patients with a vasospastic component to their angina, nitrates are effective and are used after or in addition to CCBs.

### Lipid-lowering Therapy

Several trials have shown the connection of increased total cholesterol, especially LDL cholesterol, to increased ischemic cardiovascular events, including mortality. By reducing elevated cholesterol levels, a patient’s risk of cardiovascular events can be significantly reduced. Clinical trials that have lasted at least 5 years have shown that for every 1% reduction in total cholesterol, cardiovascular events can be reduced by 3%. Trials such as the West of Scotland Coronary Prevention Study and the Air Force/Texas Coronary Atherosclerosis Prevention Study have shown that patients with elevated LDL cholesterol, but without documented CAD, can have significant reductions in cardiovascular events of more than 30% with the use of

pravastatin or lovastatin. Other trials, such as the Scandinavian Simvastatin Survival Study, the Cholesterol and Recurrent Events trial, and the Long-term Intervention with Pravastatin in Ischemic Disease trial, have shown that patients already diagnosed with CAD have significant reductions in cardiovascular events with the use of simvastatin or pravastatin. Most recently, the Heart Protection Study demonstrated a significant reduction in total and cardiovascular mortality in more than 20,000 patients with CAD, other occlusive arterial disease, or diabetes mellitus who were randomized to simvastatin or placebo. These results confirm the benefit of LDL cholesterol lowering in patients with CAD and demonstrate benefit in patients with atherosclerosis in other locations.

These trials provide extensive evidence for treating patients with chronic stable angina with statin drug therapy to reduce the risk of cardiovascular events. The use of gemfibrozil also significantly reduces the incidence of nonfatal MI and cardiovascular death in patients with low high-density lipoprotein cholesterol (40 mg/dl or less) and a modestly elevated LDL cholesterol (140 mg/dl or less). Current recommendations for patients with documented CAD are to lower the LDL cholesterol to less than 100 mg/dl. Patients with a LDL cholesterol greater than 130 mg/dl should begin with lipid-lowering therapy (class I recommendation). If patients' LDL cholesterol is between 100 mg/dl and 129 mg/dl, beginning with lipid-lowering therapy is a class IIa recommendation.

### Angiotensin-converting Enzyme Inhibitors

Angiotensin-converting enzyme inhibitors provide significant mortality benefit in patients with systolic HF or recent MI with reduced ejection fraction. They also reduce the progression of nephropathy in patients with or without HTN. The pharmacology of ACE inhibitors would predict their value in patients with chronic stable angina. With the inhibition of the production of angiotensin II and inhibition of bradykinin breakdown, ACE inhibitors produce vasodilatation without reflex tachycardia and, therefore, a reduction in the rate-pressure product and  $MVO_2$ . Reduction in sympathetic tone also should be beneficial. Other pharmacological activity of ACE inhibitors that would aid in coronary plaque stabilization are a restoration or improvement in endothelial function, inhibition of vascular smooth muscle cell growth, decreased macrophage migration, and possibly some antioxidant activities. They also may possess some antithrombotic properties through inhibition of platelet aggregation and augmentation of the endogenous fibrinolytic system. However, despite a reduction in silent ischemia on ambulatory ECG monitoring in a small number of trials, ACE inhibitors have not improved symptomatic ischemia.

The role of ACE inhibitors in patients at high-risk for cardiovascular events was evaluated in the Heart Outcomes Prevention Evaluation (HOPE) trial. The HOPE trial investigators randomized patients to placebo or ramipril and/or vitamin E. Patients selected for this trial were those who were thought to have some degree of underlying atherosclerotic disease. Patients with atherosclerotic disease included patients with a history of CAD, stroke, peripheral vascular disease, or diabetes mellitus with at least

one additional risk factor. About 80% of the patients had a history of CAD and about 55% had a history of stable angina. The primary composite end point of the trial was the incidence of cardiovascular death, MI, or stroke.

After the 5-year follow-up period, patients taking ramipril had a significant reduction in the primary end point, along with significant reduction in each component of the composite primary end point. These impressive benefits were seen despite the minimal reduction in blood pressure (3/2 mm Hg) observed with the use of ramipril 10 mg/day over the 5-year period. Benefits were consistent across all groups of patients enrolled, regardless of the location of atherosclerotic disease.

The results of the HOPE trial strongly suggest that patients with atherosclerotic disease should receive an ACE inhibitor as long as they have no contraindications. Patients with chronic stable angina made up a significant portion of the trial participants, and the results were similar to all others enrolled. The question of whether other ACE inhibitors provide the same benefit is an area of debate. The role of increased tissue ACE inhibition with ramipril may or may not be clinically important. The outcomes may be more patient-specific than agent-specific because patients with the ACE DD genotype have more tissue ACE and are at higher risk for cardiovascular events than individuals with other genotypes. More information about other agents is being investigated in upcoming trials, such as the Quinapril Ischemic Event Trial (QUIET) and the Prevention of Events with Angiotensin-converting Enzyme Inhibition (PEACE) trial. These trials will be evaluating quinapril and trandolapril in patients at high-risk for cardiovascular events. The 2002 update of the guidelines for managing chronic stable angina does not distinguish among ACE inhibitors. The class I recommendation is that an ACE inhibitor be given to all patients with CAD who also have diabetes mellitus and/or LV systolic dysfunction. The use of an ACE inhibitor in all patients with CAD is a class IIa recommendation.

### Nutritional Supplementation

Dietary supplements to prevent and treat disease have grown into a \$5–10 billion a year market, despite the lack of clinical evidence to support the use of many of these agents. The following sections discuss data for some of the more widely studied supplements in patients with CAD.

#### Vitamin E

The atherosclerotic process is accelerated in patients with increased amounts of oxidized LDL cholesterol. Oxidation of LDL cholesterol occurs as a result of interaction with free radicals. Free radicals are formed during normal metabolism and inflammatory processes, and are highly reactive oxygen species because of the presence of one or more unpaired electrons. When free radicals interact with LDL cholesterol, there is an electron transfer leaving the LDL cholesterol oxidized. Vitamin E consists of a group of eight molecules with the active portion being  $\alpha$ -tocopherol. Vitamin E works as an antioxidant by being a substrate for free radicals and preventing LDL cholesterol from becoming oxidized. Because of the antioxidant properties of vitamin E and some other possible antiplatelet effects, it



was hypothesized that vitamin E is beneficial in patients with CAD.

Several early observational studies suggested an inverse relationship between vitamin E ingestion and cardiovascular outcomes, such as MI or cardiovascular death. Despite the benefits with vitamin E proposed by these observational studies, more prospective, randomized data were needed to validate or refute these findings. The Cambridge Heart Antioxidant Study (CHAOS) randomized 2002 patients to either 400 international units (IU) (n=489) or 800 IU (n=546) of vitamin E daily or placebo (n=967). Patients in this trial had to have angiographic evidence of coronary atherosclerosis. After the average follow-up of 17 months, there was a significant reduction in the primary end point of nonfatal MI and cardiovascular death with the use of vitamin E (4% vs. 7%; p=0.005). Most of this benefit was because of the 77% relative reduction in nonfatal MI, whereas all-cause mortality was not different between the groups.

Since the publication of CHAOS, there have been other large well-conducted randomized trials that have not shown a similar benefit. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI-Prevenzione) investigators randomized 11,324 patients with recent MI (3 months or less) to vitamin E 300 mg/day and n-3 polyunsaturated fatty acids 1 g/day in a 2 × 2 factorial design. At the end of the 3.5-year follow-up, patients receiving vitamin E had no reduction in the primary composite end point of death, nonfatal MI, and stroke. Of interest, the patients receiving n-3 polyunsaturated fatty acids saw significant reduction in the primary end point, especially mortality.

As previously discussed, the HOPE trial randomized more than 9000 patients with atherosclerotic disease to ramipril and vitamin E 400 IU/day in a 2 × 2 factorial design. Unlike the patients using ramipril, patients receiving vitamin E experienced no reduction in the primary composite end point of cardiovascular death, nonfatal MI, or stroke. None of the individual components of the composite end point or any of the secondary end points was reduced.

Finally, the Heart Protection Study randomized 20,536 patients to antioxidant vitamins and/or cholesterol-lowering therapy in a 2 × 2 factorial design. Eligible patients were considered to be at high-risk of a coronary event within the next 5 years and included those with current CAD, other occlusive arterial disease, diabetes mellitus, or treated HTN. Almost two-thirds of the patients enrolled had a history of CAD. The antioxidant regimen included vitamin E 600 mg/day, vitamin C 250 mg/day, and beta-carotene 20 mg/day. At the end of the mean 5-year follow-up there was no reduction in the primary end point of major coronary events. There also was no benefit seen in

any of the individual end points or in any of the secondary end point analyses.

Despite earlier positive data, vitamin E supplementation for patients with CAD is no longer supported. The current ACC/AHA recommendations for managing chronic stable angina give vitamin E supplementation a class III recommendation. General recommendations are to maintain a healthy diet that provides a daily allowance of 15 mg of  $\alpha$ -tocopherol. Twice as much synthetic  $\alpha$ -tocopherol is needed because it is the racemic mixture. Green leafy vegetables are a good source of natural vitamin E. Nuts and seed oils also contain vitamin E, but patients should be aware of the high fat content of these sources of vitamin E.

### Folic Acid

Several retrospective epidemiologic studies have shown a connection between elevated homocysteine concentrations and increased ischemic coronary events. More recent prospective, observational studies have reported mixed results. A recent meta-analysis of 30 prospective and retrospective studies showed that a 25% lower homocysteine concentration was associated with an 11% lower risk of ischemic heart disease and a 19% lower risk of stroke. These reductions were significant, but not as large as previously reported in many of the initial retrospective analyses.

The use of folic acid supplementation has been evaluated as a means to lower homocysteine concentrations. Folic acid takes part in the complicated metabolism of homocysteine. Vitamins B<sub>12</sub> and B<sub>6</sub> also play a role in homocysteine metabolism by functioning as cofactors in certain enzymatic reactions. Normal homocysteine concentrations are considered to be between 5 and 15  $\mu$ mol/L. Moderate, intermediate, and severe hyperhomocysteinemia refer to concentrations between 16 and 30, between 31 and 100, and greater than 100  $\mu$ mol/L, respectively. Many trials have shown folic acid, with and without B vitamins, to reduce homocysteine concentrations. A variety of different doses have been evaluated. Despite the fact that hyperhomocysteinemia is associated with an increased risk of cardiovascular events, lower homocysteine concentrations correlate with a reduction in cardiovascular events, and folic acid with or without B vitamins lowers homocysteine concentrations, it is still unknown if folic acid reduces the incidence of cardiovascular events.

The only completed trial that may support this hypothesis randomized 553 patients undergoing elective PCI to a combination of folic acid 1 mg, vitamin B<sub>12</sub> 400 mcg, and vitamin B<sub>6</sub> 10 mg/day or placebo for 6 months. At the end of the 1-year follow-up there was a significant reduction in major cardiac events in the patients randomized to

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GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 1999;354:447–55.

Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:23–33.

Schnyder G, Roffi M, Flammer Y, et al. Effects of homocysteine-lowering therapy with folic acid, vitamin B<sub>12</sub>, and vitamin B<sub>6</sub> on clinical outcome after percutaneous coronary intervention. *JAMA* 2002;288:973–9.

homocysteine-lowering therapy. The majority of the benefit came from a reduction in restenosis in the target vessel, with no significant reduction in the incidence of death and nonfatal MI. About 50% of the patients in this trial received stents.

Further evaluation of the role of folic acid in medical management of CAD is under way. Clinical trials, such as the Norwegian Vitamin Interventional Trial, Prevention with a Combined Inhibitor and Folate in Coronary Heart Disease, and the Study of Effectiveness of Additional Reduction in Cholesterol and Homocysteine trial, will assist in defining the role of supplemental folic acid, the dose of folic acid, the need for additional B vitamins in patients with CAD and give insight to their role for managing chronic stable angina.

### Hormone Replacement Therapy

Despite the positive effect seen on a patient's lipid profile and several observational studies showing a reduction in cardiovascular events, more recent randomized trials have contradicted these results. The Heart and Estrogen/progestin Replacement Study (HERS) was the first published randomized trial of hormone replacement therapy (HRT) in women with known CAD. At the end of the 4-year follow-up period, there was no benefit seen with regard to cardiovascular mortality or events, and there was even a suggestion of possible harm in the first 1–2 years of the trial. This was despite the 11% reduction in LDL cholesterol and a 10% increase in HDL cholesterol in patients receiving HRT. There also were more thromboembolic events and gallbladder disease reported in the patients receiving HRT. The Women's Health Initiative evaluated HRT (estrogen plus progestin) for primary prevention of CAD in more than 16,000 postmenopausal women. The trial was designed for a mean follow-up of 8.5 years but was stopped after a mean 5.2 years of follow-up. The conclusion of this trial was that the overall health risks of thromboembolic events and breast cancer outweighed any possible benefits. No benefit was seen with regard to cardiovascular events. Based on the results of these trials, the updated ACC/AHA guidelines for managing chronic stable angina give a class III recommendation to HRT use to reduce cardiovascular risk.

### Use of Sildenafil

Erectile dysfunction is a common problem in the United States and has been estimated to impact as many as 10–30 million men. It is commonly defined as the inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance, and it is common in men with the diagnosis of CAD. Sildenafil has provided a significant contribution to erectile dysfunction treatment. Cardiovascular side effects, mainly significant hypotension and even death, have been reported with the concurrent use of sildenafil and organic nitrates. Unfortunately, this drug interaction was not discovered during the Phase II/III clinical trials in more than 3700 patients. These early trials of sildenafil did not exclude patients with CAD, but did not include patients taking long-acting nitrates.

The mechanism of the drug interaction revolves around the similar pharmacological activities of the agents. Penile smooth muscle relaxation needed for erection is mediated by nitric oxide. The arterial dilating actions of nitric oxide

and its relaxing effects on the smooth muscle of the corpus cavernosum in the penis are mediated by the production of cGMP. Therefore, increases in cGMP increase the potential for penile erection. Degradation of cGMP occurs through phosphodiesterase (PDE). In the corpus cavernosum, the specific enzyme is the type 5 PDE isoenzyme. Sildenafil specifically inhibits phosphodiesterase enzyme 5, leading to increased cGMP concentrations, vascular dilation, smooth muscle relaxation, and penile erection. Sildenafil can produce a temporary modest reduction in systolic (8–10 mm Hg) and diastolic (5–6 mm Hg) blood pressures at its peak, which occurs about 1 hour after dosing and returns to baseline 4 hours after dosing. It also is 3000 times more active against PDE5 than PDE4, which is involved in cardiac muscle and, therefore, not associated with the adverse cardiac effects of other PDE inhibitors, such as milrinone, vesnarinone, and enoximone.

Patients with chronic stable angina usually can safely participate in sexual activity. During sexual intercourse, the heart rate and blood pressure increase in the same way as in any form of exercise. Clinical studies have revealed that sexual intercourse between two partners who are known to each other produces heart rates of 120–130 beats/minute, systolic blood pressure of 150–180 mm Hg, and requires about 3.5–5 MET. Therefore, if patients can achieve 5–6 MET of exertion on an exercise stress test, they are at low risk of developing an adverse cardiac event during sexual activity. In patients not taking nitrates, this risk would not be different if the sexual activity was sildenafil-induced or not. Patients who cannot achieve this level of exertion on exercise testing are encouraged to take part in a supervised exercise program and maximize non-nitrate-based antianginal therapy.

As previously discussed, organic nitrates also increase cGMP concentrations. The increased production of cGMP provided by organic nitrates with the impaired metabolism of cGMP by sildenafil significantly amplifies the vasodilating effects of nitrates, leading to severe systemic hypotension and possibly death. For this reason, patients should be warned about the contraindication of taking sildenafil within 24 hours of taking organic nitrates. Even the use of sublingual NTG within the preceding 24 hours should be considered a contraindication to sildenafil use because such recent use of sublingual NTG suggests that it may be needed again after sildenafil-enhanced sexual activity. Patients who may experience angina during or after sildenafil-enhanced sexual activity should not take sublingual NTG. Minimal evidence suggests that immediate-release  $\beta$ -blockers may reduce ischemia in these patients, but it should not supersede contacting emergency medical services. Patients suffering from an episode of unstable angina or acute MI should be treated using standard ACC/AHA guidelines, excluding nitrate therapy. Treatment of hypotension because of concomitant use of sildenafil and sublingual NTG can include any of the following: placing patient in Trendelenburg position, aggressive fluid resuscitation, vasopressors with  $\alpha$ -adrenergic agonist or  $\alpha$ - and  $\beta$ -adrenergic agonist activity, and/or intra-aortic balloon counterpulsation if needed.

Sildenafil is mainly metabolized by the cytochrome P450 3A4 hepatic enzyme system and to a lesser extent by

**Table 1-6. Use of Sildenafil in Patients with Cardiovascular Disease**

- Contraindicated when used within 24 hours of organic nitrates
- Use of sublingual nitroglycerin within 24 hours of sildenafil should be weighed against the risk of hypotension and should only be done in a controlled medical environment
- Patients at risk for hypotension with the use of sildenafil include the following:
  - Patients with active coronary ischemia who are not currently taking nitrates
  - Patients with heart failure who also have borderline low blood pressure and/or low volume status
  - Patients taking a multidrug antihypertensive regimen
  - Patients taking medication which may inhibit the metabolism of sildenafil via the cytochrome P450 3A4 isoenzyme

2C9 isoenzymes. A patient with hepatic impairment or who is receiving agents that inhibit metabolism through the 3A4 isoenzyme system is expected to increase sildenafil plasma concentrations and increase the likelihood of serious adverse effects. Clinicians treating patients with cardiovascular disease should review the recommendations listed in Table 1-6.

## Areas of Investigation

### Antimicrobial Therapy

Infectious etiologies of atherosclerosis have continued to gain attention in the medical literature. *Helicobacter pylori*, *Chlamydia pneumoniae*, and cytomegalovirus have each been implicated as possible causes of CAD. Infection of the arterial wall is thought to stimulate smooth-muscle proliferation and local inflammation. These processes promote the production of atherosclerotic plaques, which can eventually rupture and create thrombosis. Although the existing evidence linking any infection to CAD is scant, the association between *C. pneumoniae* and coronary risk is the strongest.

*Chlamydia pneumoniae*, a gram-negative, intracellular bacteria, has been associated with atherosclerosis in pathological and epidemiological studies. Studies have shown higher anti-*C. pneumoniae* antibody titers in patients with CAD compared to controls, the presence of the organism or its various components in roughly 50% of all atherosclerotic lesions, initiation or progression of atherosclerosis by the organism, and possible reduction of recurrent coronary events with antibiotic therapy. Mechanisms of developing CAD from *C. pneumoniae* infection have been postulated and include dissemination of *C. pneumoniae* from infected leukocytes to the coronary arteries, enhancement of LDL ingestion and foam cell formation by infected macrophages, increased expression of leukocyte adhesion molecules, and stimulating release of inflammatory mediators.

The utility of antibiotics for preventing and reducing risk associated with CAD has been investigated, but studies to date have produced conflicting results and have had flaws in the trial design. A larger case-control analysis of more than 26,000 patients evaluated the use of antichlamydial

antibiotics (tetracyclines, quinolones, and macrolides) and prognosis after acute MI. Exposure to these agents 3 months after the event was associated with a small survival benefit at the 2-year follow-up, but exposure in the 6 months before acute MI did not change survival.

Of the agents with activity against *C. pneumoniae*, the macrolides have been the most extensively investigated in patients with CAD. The Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with Chlamydia (ACADEMIC) study randomized 302 patients who were *C. pneumoniae* seropositive to either placebo or azithromycin 500 mg/day for 3 days then 500 mg once weekly for 3 months. At the end of the 2-year follow-up, treatment with azithromycin was not associated with a reduction in cardiovascular events. Azithromycin also failed to show benefit in the Weekly Intervention with Zithromax for Atherosclerosis and Related Disorders (WIZARD) trial, where more than 7000 patients with elevated *C. pneumoniae* titers who were post-MI received either placebo or azithromycin 600 mg 4 times/day for 3 days, then 600 mg once weekly for 11 weeks. After a 2-year follow-up, there was no difference between the groups for the composite end point of all-cause mortality, recurrent MI, revascularization, or angina.

The Clarithromycin in Acute Coronary Syndrome Patients in Finland included 148 patients with non-Q-wave MI or unstable angina, and randomized patients to either clarithromycin 500 mg/day or placebo for 3 months. The average follow-up period was 1.5 years. Those treated with clarithromycin experienced a significant reduction in cardiovascular events (death, MI, ischemic stroke, or critical peripheral ischemia). However, only a trend toward reduction in the composite of death, MI, or unstable angina was observed.

Investigation of antibiotic treatment for *C. pneumoniae* is ongoing, including evaluations of azithromycin and gatifloxacin in this setting. Further study is needed to resolve uncertainties regarding the relationship between any chronic infection and CAD. The current ACC/AHA guidelines for managing chronic stable angina give a class III recommendation for the use of antibiotics to treat CAD.

### Angiogenesis

Therapeutic angiogenesis is an emerging field of research for treating CAD. Initial investigations with therapeutic

Cheitlin MD, Hutter AM Jr, Brindis RG, et al. ACC/AHA expert consensus document. Use of sildenafil (Viagra) in patients with cardiovascular disease. J Am Coll Cardiol 1999;33:273-82.

angiogenesis in humans showed benefit in patients with critical limb ischemia, and these findings stimulated investigation in patients with ischemic heart disease. Angiogenesis differs from arteriogenesis. Arteriogenesis describes the enlargement of preexisting collateral connections, whereas angiogenesis involves the proliferation, migration, and extension of primitive vasculature and differentiated endothelial cells. Hypoxia is the stimulus for expression of the vascular endothelial growth factor (VEGF) gene and production of VEGF glycoproteins by the endothelium. After binding between VEGFs and VEGF receptors on the endothelial surface occurs, angiogenesis begins.

Therapeutic angiogenesis may be accomplished with supplementation of parenteral recombinant proteins or through gene therapy. Parenteral administration of recombinant proteins theoretically does not appear ideal based on pharmacokinetics and myocardial delivery or protein uptake. The use of recombinant proteins for angiogenesis was evaluated in the Vascular Endothelial Growth Factor in Ischemia for Vascular Angiogenesis and the Fibroblast Growth Factor-2 Initiating Revascularization Support Trial studies. Both investigations failed to find a significant difference in angina severity or exercise time at 60 and 90 days, respectively. These findings support the hypothesis of suboptimal recombinant protein delivery to the sites of myocardial ischemia.

Promotion of angiogenesis through gene transfer presently appears to be the optimal intervention. Delivery of VEGF plasmid deoxyribonucleic acid to patent arterial sites has shown promise in critical limb ischemia. A majority of the studies of therapeutic angiogenesis in CAD have included patients who were not candidates for revascularization and had angina refractory to conventional medical therapy. These investigations also were designed to evaluate only safety or dosing ranges, included small numbers of patients, and failed to include control groups. Measurement of therapeutic angiogenesis efficacy varies among trials, and the best way to measure efficacy remains controversial.

Experience with gene transfer is limited to small dose-escalating studies with the VEGF<sub>165</sub> and VEGF-2 genes administered through naked deoxyribonucleic acid intramyocardially. An increase in exercise time and a decrease in symptoms were observed with this method of therapeutic angiogenesis. The safety of using adenovirus to carry genes was demonstrated in the Angiogenic GENE Therapy (AGENT) study, where treadmill times were not significantly increased over placebo at 4- and 12-week follow-up in this investigation. In summary, much research is still needed to clarify the role, efficacy, and safety of therapeutic angiogenesis in CAD.

## **Patient Education**

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### **Understanding of the Disease**

As with many disease states, patient education is critical for maximizing benefits of pharmacological therapy as well as promoting lifestyle changes in patients with chronic stable angina. The pharmacist should be expected to play a

key role in patient education and reinforcement of management strategies. It is important to recognize the impact that a new diagnosis of CAD or stable angina may have on a patient. Patients may have immediate concerns about their ability to work, exercise, take part in sexual activity, maintain a quality of life, and the overall life expectancy. These concerns may contribute to the development of depression and/or anxiety in these patients. Pharmacists and other health care professionals should convey empathy and compassion for these patients as they assist them in dealing with their disease and their concerns.

One of the first keys to accomplishing treatment goals is to ensure that patients understand their disease state. A discussion about normal heart function and the pathophysiologic mechanisms of chronic stable angina should be explained in terms the patient can comprehend. Many patients may already have some understanding of the disease, but misconceptions and misinformation can be intertwined with fact. Patients also may vary in the amount of detail they want to know. Inclusion of the role of modifiable risk factors in the pathophysiology of CAD can assist in the understanding for the need for lifestyle change and drug compliance. Patients also may want to know about potential complications, such as ACS, HF, arrhythmias, and the increased risk of mortality.

### **Medical Therapy and Lifestyle Modifications**

An appropriately developed patient education plan must involve the pharmacist in the counseling of the patient on his or her medical treatment. Patients must first understand the importance of the therapy that is prescribed for them and should be made aware of the fact that poor compliance with cardiac drugs is associated with increased mortality, increased morbidity, and excess hospitalizations. There also should be a discussion about the way in which treatment may evolve and appropriate goals of therapy. Finally, monitoring, encouragement, and reinforcement are needed to document progress, identify barriers, or identify adverse effects.

Active, continued patient involvement in the management plan is essential. This involvement will lead to a patient who is not only better informed and more satisfied with his or her care but also able to achieve a better quality of life. It is important to identify barriers to patient education and accessing care such as the patient's level of sophistication and prior education, language barriers, and social support. Smoking cessation is the single most important thing patients with CAD can do to improve their overall health. Several studies have shown reductions in cardiovascular events in patients who have successfully quit smoking. The failure of smoking cessation without a well-developed support group and reinforcement is well documented. Involving the family in educational efforts often is advisable and necessary, especially with lifestyle modifications.

Patients should be advised of the goals of therapy such as heart rate and blood pressure reduction. Patients can keep a log of these vital signs when they are at rest and when they exercise. They also should keep track of the number of angina episodes per week and the amount of exertion leading to these episodes. A patient log of sublingual NTG

use is helpful in documenting possible progressive disease or efficacy of therapy. Pharmacists also can keep track of refill records. Adverse effects of therapies should be discussed and other treatment options should be offered if these occur. Information for patients is available in books, pamphlets, and other printed material; audiotapes and videotapes; and computer software. The AHA maintains a Web site (<http://www.americanheart.org>) that presents detailed and practical dietary recommendations, information about physical activity, and a thorough discussion of heart attacks and cardiopulmonary resuscitation.

Patients also need to be aware of the follow-up that is expected. During the first year of therapy, evaluations every 4–6 months are recommended. After the first year of therapy, annual evaluations are recommended if the patient is stable and reliable enough to call or make an appointment when anginal symptoms become worse or other symptoms occur. During each visit, the pharmacist should assess the answers to the following questions regarding the patient's stable angina management:

1. Has the patient decreased his or her level of physical activity since the last visit?
2. Have the patient's anginal symptoms increased in frequency and become more severe since the last visit?
3. How well is the patient tolerating therapy?
4. How successful has the patient been in modifying risk factors and improving knowledge about ischemic heart disease?
5. Has the patient developed any new comorbid illnesses, or has the severity or treatment of known comorbid illnesses worsened the patient's angina?

### Physical Activity

It is difficult to separate the effects of exercise training from the multiple secondary effects that it may have on confounding variables, such as weight reduction, blood pressure control, lipid control, and the patient's sense of well-being. These direct effects are confounders in interpreting the impact of exercise training on exercise tolerance, patient symptoms, and subsequent cardiac events. Despite the increase in  $MVO_2$ , increased physical activity promotes better overall health for patients with chronic stable angina. The major limitation of the published data on exercise training is that it is based almost exclusively on men, whereas observational studies have suggested that women benefit at least as much as men.

Physicians and patients are sometimes concerned about the safety of exercise training in patients with underlying CAD. In treating patients after an MI, a survey of 142 rehabilitation programs reported an event rate of nonfatal MI of one per 294,000 patient-hours. It is unlikely that patients with chronic stable angina are at a higher risk for developing complications. Notwithstanding this excellent safety profile, exercise training should be medically supervised until safe levels of activity can be established.

Patients are given an exercise prescription based on their clinical status (e.g., stable angina, post-MI, and post-CAGB surgery). The exercise prescription includes the frequency of exercise per day and per week; total duration of each exercise session, including warm-up and cool-down time;

and the intensity at which the exercise should take place. The intensity is determined by the heart rate that produces angina symptoms, ST-segment changes, or arrhythmia found on stress testing. The designated target heart rate should be 60–80% of this maximum heart rate, starting at about 60% and progressing to 80% over 4–6 weeks. Heart rate can be measured manually or with the use of a cardiometer, which is fairly accurate for mild to moderate intensity exercise. If a stress test has not yet been performed, a target heart rate of 20 beats/minute above the patient's resting heart rate can be used until the test can be completed. The frequency and duration of exercise typically should be 30–60 minutes/day 4–6 times/week. Appropriate methods of achieving the desired level of aerobic activity could include brisk walking, jogging, cycling, or water aerobics. Resistance exercises, such as light weight lifting, also can be used but less frequently (2–3 times weekly). Patients should be reevaluated 6–12 weeks after their initial exercise prescription. Exercise stress testing should be repeated at least yearly.

Patients can be intimidated by the need for exercise because of misconceptions on the intensity and duration needed to provide benefit and can require significant education. The following information needs to be explained to patients before beginning an exercise program: exercise only when feeling well, do not exercise vigorously soon after eating, adjust exercise to weather, slow down for hills, wear proper clothing and shoes, understand personal limitations, select appropriate exercises, be alert for symptoms of angina, watch for signs of overexercising, and start slow and progress gradually. With appropriate education and reinforcement, patients will be more likely to remain compliant with the program and realize its benefits.

As previously discussed, most patients can be reassured that they can continue with their normal activities, including sexual relations. Sexual activity is similar to moderate-intensity exercise, and rarely achieves heart rates greater than 120 beats/minute. Stable patients recently suffering from an ACS (unstable angina or MI) can be told to resume normal sexual activity with a usual partner. Patients with Canadian Cardiovascular Society class II or less angina can safely take part in sexual activity.

### Contacting the Medical System

Finally, patients and their families need to be clearly instructed on how and when to seek medical attention. The median time from symptom onset to seeking medical care is 2–3 hours, with about 40% of patients waiting more than 4 hours before seeking medical assistance. The reasons for this delay are multifactorial but include the patient's lack of awareness and education about the consequences of chest pain, time of day of symptom onset, perceptions about the severity of symptoms, older age, and female gender. Patients need to be advised on the signs and symptoms of an acute coronary event. Patients need to have a plan for prompt aspirin and sublingual NTG use if available, understand how to access emergency medical services, and know the location of the nearest hospital that offers 24-hour emergency cardiovascular care. Contacting and using emergency medical services (911) can significantly reduce transport time as it reduces time to admission by more than

2 hours compared to patients who transport themselves. Cardiopulmonary resuscitation training for family members also is advisable.

## Quality Improvement

The ACC/AHA guidelines for managing patients with chronic stable angina describe a 10-point plan for maximizing the goals of therapy. These goals are first to improve survival and implement therapeutic plans, which reduce mortality, and second to reduce frequency and severity of anginal symptoms and improve quality of life for patients with chronic stable angina. This 10-point plan describes both angina treatment and risk factor reduction.

The 10-point plan uses the mnemonic ABCDE to assist clinicians in remembering the components of the plan:

- A = Aspirin and antianginals
- B =  $\beta$ -Blocker and blood pressure
- C = Cholesterol and cigarettes
- D = Diet and diabetes
- E = Education and exercise

Pharmacists and other clinicians caring for patients with chronic stable angina should use these 10 points as goals for these patients with a reassessment of the status of obtaining these goals with each visit. The review of these points will serve as reinforcement for both the caregiver and the patient. Patients able to obtain and maintain these 10 points will give themselves the best opportunity to improve their chance for survival and minimize the frequency and severity of angina episodes.

## Conclusion

Patients with chronic stable angina make up a significant portion of patients with CAD. The goals of therapy in these patients consist of reducing angina symptoms and prolonging life. Current medical therapy with the use of  $\beta$ -blockers, CCBs, and nitrates improves anginal symptoms, but not reduce mortality. Proper patient evaluation and screening will aid in appropriate antianginal drug selection for each individual. Patients periodically must be evaluated for revascularization with either PCI or CABG surgery. When used in appropriate situations, revascularization can improve angina control and prolong life compared to medical therapy. Whether a medical and/or revascularization approach is used, patients require aggressive risk factor reduction against smoking, HTN, and hyperlipidemia. The pharmacist must play a key role in not only recommending and monitoring the prescribed therapy, but also in patient education.

## Annotated Bibliography

1. Gibbons RJ, Abrams JA, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—a 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). *J Am Coll Cardiol* 2003;41:159–68.

These practice guidelines are an update of the 1999 American College of Cardiology (ACC)/American Heart Association (AHA)/American College of Physicians—American Society of Internal Medicine guidelines on the management of patients with chronic stable angina. These guidelines provide an extensive review of the literature in patients with chronic stable angina. The guideline begins with an impressive accounting of the magnitude of the problem and creates estimates of the numbers of patients impacted with chronic stable angina. An important discussion about risk stratification, disease probability, and appropriate use of diagnostic tests serves as a good review of concepts of sensitivity, specificity, and positive and negative predictive values. Recommendations are given on the use of different medical therapies along with the use of revascularization approaches. Emphasis on the need for patient education and involvement in the therapeutic plan has several implications for pharmacists. These guidelines provide additional information on the assessment and management of the asymptomatic patient, role of angiotensin-converting enzyme (ACE) inhibitors, importance of non-low-density lipoprotein (LDL) cholesterol, as well as treatment approaches in patients with refractory disease. There is an extensive reference list (1052) if a further review of the primary literature used to construct these guidelines is desired. Clinical pharmacists need to have this guideline in their files, even if they do not practice specifically in cardiology. The 2002 executive summary of the update to these guidelines is available in the *J Am Coll Cardiol* 2003;41:159–68.

2. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA guidelines for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1991 Guidelines for Coronary Artery Bypass Graft Surgery). *J Am Coll Cardiol* 1999;34:1262–346.

These practice guidelines provide an extensive review of the literature and clearly explain the role of coronary artery bypass graft (CABG) surgery for treating patients with coronary artery disease (CAD). An accounting of the history of CABG surgery and advancements are discussed along with a review of the cardiac and noncardiac complications of CABG surgery. There is an in-depth discussion surrounding the clinical trials that have evaluated the use of CABG surgery in comparison to medical therapy and percutaneous coronary intervention (PCI). These discussions not only cover clinical efficacy and safety, but also provide a detailed analysis of the strengths and limitations of the data. Detailed and specific evidence-based recommendations are given for performing CABG surgery for patients with asymptomatic or mild angina and in patients with chronic angina. There is an extensive reference list (753) if a further review of the primary literature used to construct these guidelines is desired.

3. Heidenreich PA, McDonald KM, Hastie T, et al. Meta-analysis of trials comparing beta-blockers, calcium antagonist, and nitrates for stable angina. *JAMA* 1999;281:1927–36.

This meta-analysis serves as an excellent review of the approaches to antianginal medical control. The investigators

collected trials from 1966 to 1977 that used  $\beta$ -blockers, calcium antagonists, and long-acting nitrates in patients with chronic stable angina. Because no significant trials evaluating these agents in this patient population have been reported since that time, this still serves as a complete analysis of the data. The ACC/AHA guidelines used the results of this meta-analysis as part of the evidence-based medicine approach for recommending pharmacotherapy for angina control.

No difference was found in the incidence of cardiac death and myocardial infarction (MI) between  $\beta$ -blockers and calcium antagonists (odds ratio = 0.97; 95% confidence interval = 0.67–1.38;  $p=0.79$ ). As the authors discuss, there is a surprising lack of clinical trials that have evaluated these important end points with these agents in this patient population. There was a significant reduction in the number of ischemic episodes per week (odds ratio = 0.31; 95% confidence interval = 0.00–0.62;  $p=0.05$ ) with the use of  $\beta$ -blockers compared to calcium antagonists. The authors also report significantly less discontinuation of therapy with the use of  $\beta$ -blockers compared to calcium antagonist (odds ratio = 0.72; 95% confidence interval = 0.60–0.86;  $p<0.001$ ). Both findings may be because of trials comparing  $\beta$ -blockers to nifedipine (odds ratio = 0.60; 95% confidence interval = 0.47–0.77). The authors report that there were too few trials comparing long-acting nitrates to either  $\beta$ -blockers or calcium antagonists to make firm conclusions. Although there were more angina episodes per week compared to calcium antagonists ( $p=0.10$ ), and more sublingual nitroglycerin (NTG) use compared to  $\beta$ -blockers ( $p=0.08$ ), these differences did not achieve statistical significance.

4. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342:145–53.

The Heart Outcomes Prevention Evaluation trial investigators randomized 9297 patients to placebo or ramipril and/or vitamin E. Patients included in the Heart Outcomes Prevention Evaluation trial had a prior diagnosis of either CAD, stroke, peripheral vascular disease, or diabetes mellitus with at least one additional risk factor. About 80% of the patients had a history of CAD and about 55% had a history of stable angina. Less than 50% of patients had hypertension (HTN) at enrollment. Patients with systolic HF were excluded from enrollment because of benefits already documented in that patient population. The primary composite end point of the trial was the incidence of cardiovascular death, MI, or stroke at the end of the 5-year follow-up period.

Patients receiving ramipril, most titrated up to 10 mg, had a significant reduction in the primary end point (14% vs. 17.8%;  $p<0.001$ ) compared to placebo along with significant reduction in each of the components of the composite primary end point. There also was a significant reduction in all-cause mortality (10.4% vs. 12.2%;  $p=0.005$ ), need for revascularization, cardiac arrest, development of HF, and complications of diabetes mellitus. There was no benefit seen in the need for hospitalization for unstable angina. Benefits were consistent across all groups of patients enrolled, regardless of the location of atherosclerotic disease.

The Heart Outcomes Prevention Evaluation trial is considered a landmark trial that changed the role of ACE inhibitors in managing patients with atherosclerotic disease. The results show that the benefits were because of another mechanism beside blood pressure reduction, because of the

fact that less than 50% of the patients were hypertensive at baseline, and the blood pressure reduction during the trial was quite minimal. Patients with chronic stable angina were well represented in the Heart Outcomes Prevention Evaluation trial, and the results have led to a change in the 2002 ACC/AHA guidelines.

5. Steinhubl SR, Berger PB, Mann JT III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;288:2411–20.

The Clopidogrel for the Reduction of Events During Observation trial randomized 2116 patients undergoing elective percutaneous transluminal coronary angioplasty (PTCA) with stent placement to either a 300-mg loading dose of clopidogrel given 3–24 hours before the procedure or placebo. After the initial dose, all patients received clopidogrel 75 mg/day along with aspirin 325 mg/day for 28 days. Thirty-three percent of patients received their stent to treat stable angina. The 28-day primary composite end point of death, MI, or need for urgent target vessel revascularization was not different between the groups. Patients receiving their loading dose at least 6 hours before the procedure had a reduction in the primary end point favoring the loading dose group compared to patients not receiving any loading dose, but this difference did not reach statistical significance ( $p=0.051$ ). This finding warrants further study in an adequately powered trial to evaluate patients receiving a loading dose 6 hours before procedure.

After 28 days, clopidogrel was continued at 75 mg/day with aspirin for 1 year in patients who had received the loading dose of clopidogrel, whereas the other patients received placebo and aspirin for 1 year. The 1-year primary long-term outcome of death, MI, or stroke was significantly reduced with long-term use compared to only 28 days of clopidogrel (8.5% vs. 11.5%;  $p=0.02$ ). Patient safety was similar in all groups.

Despite the fact that patients did not have to receive a stent in this trial, more than 90% of them did. Therefore, this trial solidified the role of clopidogrel in patients receiving elective PTCA with stenting. The use of dual antiplatelet therapy after PTCA, without stenting, in patients with chronic stable angina is still unknown. Although there were two variables that may have contributed to the positive outcome (loading dose and longer therapy duration), the results of the Clopidogrel for the Reduction of Events During Observation trial support the use of continued dual antiplatelet therapy beyond the traditional 30 days out to 1 year.





# SELF-ASSESSMENT QUESTIONS

## Questions 1 and 2 pertain to the following case.

H.R. is a 56-year-old woman with a history of chronic stable angina, hypertension (HTN), and osteoarthritis. She had a myocardial infarction (MI) 2 years ago that was treated successfully with fibrinolysis. During this follow-up visit, she states that her chest pain episodes are under control and occur infrequently. H.R. has been able to resume all of her normal daily activities. She currently is compliant with her diet and exercises 3–4 times/week. H.R.'s current drugs include aspirin 81 mg/day, metoprolol 50 mg 2 times/day, amlodipine 10 mg/day, acetaminophen 1000 mg up to 4 times/day, and sublingual nitroglycerin (NTG). Today, her blood pressure is 134/84 mm Hg and her heart rate is 56 beats/minute.

- Which one of the following is an appropriate recommendation to improve H.R.'s survival?
  - H.R.'s heart rate, blood pressure, and chest pain are under control; therefore, no changes are needed at this time.
  - Increase metoprolol to 100 mg 2 times/day.
  - Initiate ramipril 10 mg/day.
  - Increase aspirin to 325 mg/day.
- Your recommendation in question 1 is implemented. H.R. says that she has been hearing a lot about the use of vitamins for patients with chronic angina. She asks for your professional opinion on the use of these supplements. Which one of the following statement represents the correct information to pass on to H.R.?
  - Vitamin E was safe and effective in several large clinical trials.
  - Folic acid reduces mortality in patients with ischemic heart disease.
  - Vitamin E is effective, but only when given with other vitamins such as B<sub>6</sub> and B<sub>12</sub>.
  - Folic acid reduces homocysteine levels and high homocysteine levels are a risk factor of cardiovascular events.
- Which one of the following best represents the societal impact of ischemic heart disease?
  - Cardiovascular mortality has declined throughout the past several years and is now second to cancer mortality.
  - Black women are in the highest risk group for death from ischemic heart disease.
  - Chronic stable angina is the initial manifestation of ischemic heart disease in about 25% of patients.
  - Direct cost of hospitalization is more than \$15 billion.
- M.P. is a 55-year-old man who presents with a history of a heavy squeezing pain in his upper abdomen. He does not report any radiation but ranks the pain as a 6 or 7 out of 10. He does not remember or report anything leading up to this pain, but it went away when he took one of his wife's sublingual NTG tablets. The total episode lasted about 5 minutes. M.P. has a history of diabetes, HTN, and benign prostatic hyperplasia. He currently smokes one pack of cigarettes/day and takes glipizide 5 mg 2 times/day and terazosin 10 mg/day. Which one of the following is M.P.'s likelihood of having coronary artery disease (CAD)?
  - 45%.
  - 59%.
  - 79%.
  - 95%.
- M.R. is a 48-year-old man who has suffered from chronic angina for about 2 years. He currently takes aspirin 81 mg/day, metoprolol XL 50 mg/day, and sublingual NTG. His resting heart rate is

- 64 beats/minute and his blood pressure is 140/88 mm Hg. M.R. underwent a follow-up exercise stress test 2 months ago. M.R. completed stage 2 of the Bruce protocol and achieved a work level of 5 metabolic equivalents (METs), before the test was stopped because of angina and severe fatigue after 7 minutes. At the time the test was stopped his heart rate was 140 beats/minute and blood pressure was 160/98 mm Hg. After these results, M.R. has finally agreed to begin an exercise program. Which one of the following is accurate patient education for M.R. as he begins his exercise program?
- M.R. should exercise to a target heart rate of 110 beats/minute.
  - M.R. should plan to exercise 2–3 times/week.
  - M.R. should not take part in weight-lifting exercises for at least 6 months.
  - M.R. will need to have his exercise prescription reevaluated in 2 months.
6. Your physician partner says that he has had several patients asking for sildenafil. He asks you to review some patients to see if sildenafil is safe. For which one of the following patients would sildenafil be contraindicated?
- A 45-year-old man with a history of four vessel coronary artery bypass graft (CABG) surgery 2 years ago and congestive heart failure (HF). He currently takes ramipril 10 mg/day, aspirin 325 mg/day, digoxin 0.25 mg/day, and furosemide 40 mg/day. He has not needed to use sublingual NTG because of his CABG surgery. His most recent blood pressure was 130/78 mm Hg and his heart rate was 72 beats/minute.
  - A 52-year-old man with a history of chronic stable angina, no history of acute MI, but received percutaneous transluminal coronary angioplasty (PTCA) and stent to the right coronary artery and first diagonal to the left anterior descending 3 months ago. He currently takes atenolol 100 mg/day, aspirin 325 mg/day, and pravastatin 40 mg at bedtime. Has not needed to use sublingual NTG since his recent revascularization procedure. His most recent blood pressure was 128/80 mm Hg and heart rate was 55 beats/minute.
  - A 72-year-old man with a history of class III HF and CAD. He currently is treated with losartan 100 mg/day, metoprolol XL 150 mg/day, furosemide 40 mg 2 times/day, digoxin 0.125 mg/day, and aspirin 81 mg/day. His most recent blood pressure was 102/68 mm Hg and heart rate was 68 beats/minute.
  - A 59-year-old man with a history of stable angina for 3 years. He takes pravastatin 20 mg at bedtime, clopidogrel 75 mg/day, and atenolol 50 mg/day. He uses sublingual NTG about once a month for strenuous activity. Two weeks ago, he was able to achieve 6 METs on his exercise stress test. His most recent blood pressure was 148/96 mm Hg and heart rate was 88 beats/minute.
7. Which one of the following best represents a patient with chronic stable angina?
- Chest pain occurring at rest not relieved by sublingual NTG.
  - Exercise-induced chest pain relieved by rest.
  - Chest pain which has increased in severity within the past month.
  - Exercise-induced chest pain not relieved by sublingual NTG.
8. P.W. is a 62-year-old woman with a history of CAD, HTN, diabetes, and dyslipidemia. Today, she underwent PTCA with stenting and abciximab to her circumflex artery. Her current drugs include aspirin 81 mg/day, atenolol 50 mg/day, atorvastatin 20 mg/day, and insulin. Her blood pressure today is 138/84 mm Hg and her heart rate is 70 beats/minute. Which one of the following changes should occur in P.W.'s therapy?
- Add warfarin 5 mg/day to obtain an international normalized ratio of  $2.5 \pm 0.5$ .
  - Give a 300-mg dose of clopidogrel, followed by 75 mg/day for 4 weeks.
  - Initiate intravenous heparin with a 5000 unit bolus and a 1000 units/hour infusion to maintain an activated partial thromboplastin time between 50 and 70 seconds for 2–5 days.
  - Give 300-mg dose of clopidogrel, followed by 75 mg/day for 4 weeks and increase the dose of aspirin to 325 mg/day.
- Questions 9 and 10 pertain to the following case.**
- J.B. is a 62-year-old man with a several year history of chronic angina. About 6 months ago J.B. underwent exercise stress testing and was able to achieve stage 3 of the Bruce protocol. The test was stopped because of 1 mm of ST-segment depression and angina after 10 minutes. At the time of these ischemic changes, his heart rate was 120 beats/minute and blood pressure was 170/106 mm Hg. J.B. then underwent coronary angiography, which revealed a 75% lesion in his mid-circumflex coronary artery. Because of technical difficulty, the lesion was not amenable to angioplasty. He recently has begun to experience increased angina with exertion that is relieved by rest or a sublingual NTG tablet. He has a strong family history of CAD and also has hyperlipidemia and type 2 diabetes mellitus. His current resting heart rate is 54 beats/minute, exercise heart rate is 70 beats/minute, and blood pressure is 124/74 mm Hg. His current medical regimen includes aspirin 325 mg/day, atenolol 50 mg/day, metformin 500 mg 2 times/day, glipizide XL 10 mg/day, and atorvastatin 20 mg/day.
9. Which one of the following is the best choice to reduce J.B.'s angina symptoms?
- Increase atenolol to 100 mg/day.
  - Add amlodipine 2.5 mg/day.
  - Add a NTG patch 0.4 mg/hour on in the morning and off in the evening.
  - Add lisinopril 5 mg/day.

10. Which one of the following would reduce J.B.'s risk of having an adverse ischemic cardiac event?
- Increase atorvastatin to 80 mg/day.
  - Add vitamin E 800 international units (IU)/day.
  - Add clopidogrel 75 mg/day.
  - Add folic acid 1 mg/day.

**Questions 11 and 12 pertain to the following case.**

T.P. is a 55-year-old woman who has been complaining of chest pain with exertion during the past 2–3 weeks. When describing the pain she states that it is in the middle of her chest and radiates to her left shoulder. The pain is alleviated after about 5–10 minutes of rest. The amount of exertion to induce the angina is variable and unpredictable. She also has type 2 diabetes mellitus, HTN, and is a smoker. Her current heart rate is 74 beats/minute and blood pressure is 138/86 mm Hg. Her current drugs include lisinopril 10 mg/day, chlorthalidone 12.5 mg/day, and glipizide XL 10 mg/day.

11. Which one of the following is the best initial approach for T.P.?
- Add metoprolol 50 mg 2 times/day.
  - Add extended-release isosorbide mononitrate 30 mg/day.
  - Increase lisinopril to 20 mg/day.
  - Add extended-release diltiazem 180 mg/day.
12. Eventually T.P. undergoes revascularization with PTCA. The cardiologist wants your recommendation on any changes that are needed to T.P.'s regimen before she goes home. Which one of the following is the best?
- Discontinue chlorthalidone and initiate amlodipine 5 mg/day.
  - Add folic acid 1 mg, vitamin B<sub>12</sub> 400 mcg, and vitamin B<sub>6</sub> 10 mg for 6 months.
  - Change lisinopril to ramipril.
  - Add 0.625 mg/day of conjugated estrogen.

**Questions 13 and 14 pertain to the following case.**

G.P. is a 62-year-old woman with a history of chronic angina for about 3 years. She also has hyperlipidemia and gout. Initially, her angina episodes were controlled on gradually increasing medical therapy. Her current medical regimen for angina of atenolol 100 mg/day, NTG patch 0.4 mg/hour on in the morning and off in the evening, aspirin 325 mg/day, and as-needed sublingual NTG is now not enough to control her angina symptoms. On coronary angiography, she has more than 75% blockage in her proximal left anterior descending, circumflex artery, and second diagonal artery. Based on the angiography results, the decision was made to undergo CABG surgery.

13. Which one of the following is the probability of G.P. being able to return to work?
- 30%.
  - 50%.
  - 70%.
  - 90%.

14. After G.P.'s hospitalization, she is free of angina symptoms. The appropriate discharge regimen should include which one of the following?
- Aspirin.
  - Aspirin and sublingual NTG.
  - Aspirin, sublingual NTG, and atenolol.
  - Aspirin, sublingual NTG, atenolol, and NTG patch.

**Questions 15 and 16 pertain to the following case.**

F.D. is a 55-year-old woman who has complaints of substernal chest pain that radiates to her left arm. The pain comes when she walks 5–6 blocks. When she stops to rest, the pain goes away in about 3–4 minutes. She has a history of HTN and a family history of early MI. The decision is made to have F.D. undergo exercise stress testing.

15. Given a mean sensitivity of 68% and a mean specificity of 77%, which one of the following is the positive predictive value of the exercise stress test for F.D.?
- 40%.
  - 65%.
  - 80%.
  - 95%.
16. After 10 minutes on the treadmill, F.D. has 1 mm ST-segment depression and angina after completing stage 3 of the Bruce protocol. The decision is made to undergo coronary angiography. Based on F.D.'s chest pain history and exercise stress test results, which one of the following levels of coronary stenosis is most likely to be causing her symptoms?
- 25%.
  - 45%.
  - 75%.
  - 95%.
17. S.S. is a 56-year-old woman who comes to the clinic for follow-up after an acute anterior ST-segment elevation MI 2 weeks ago. She has never been diagnosed with CAD and has no significant surgical or medical history besides hyperlipidemia for which she takes simvastatin 20 mg/day. Before admission, she had a heart rate of about 70 beats/minute, a blood pressure of 124/80 mm Hg, and a homocysteine level of 50 mmol/L. She recently quit smoking and has been doing well with few cravings. At discharge from the hospital, her new drug regimen contained propranolol extended-release 60 mg 2 times/day, aspirin 81 mg/day, captopril 12.5 mg 3 times/day, conjugated estrogen 0.625 mg/day, medroxyprogesterone 2.5 mg/day, folic acid 1 mg/day, sublingual NTG, along with her home simvastatin prescription. Her current heart rate is 58 beats/minute with a blood pressure of 116/74 mm Hg. She has not had any chest pain episodes since her hospitalization. Which one of the following should be done for S.S. to optimize her therapy?
- Discontinue conjugated estrogen and medroxyprogesterone.

- B. Discontinue folic acid.
- C. Discontinue captopril.
- D. Discontinue medroxyprogesterone.

**Questions 18–20 pertain to the following case.**

T.V. is a 48-year-old man with a past medical history that includes chronic angina, HTN, type 2 diabetes mellitus, erectile dysfunction, and gout. He underwent PTCA with stent placement to his right coronary artery 2 years ago. He has been active and compliant with his exercise prescription. He was able to achieve 9 metabolic equivalents on his exercise stress test 6 months ago before having to stop because of fatigue. His current drugs include aspirin 81 mg/day, diltiazem extended-release 240 mg/day, hydrochlorothiazide 25 mg/day, glyburide 5 mg 2 times/day, sildenafil 50 mg as needed, and sublingual NTG as needed. He has come to the pharmacy with a prescription for erythromycin 500 mg 3 times/day for 10 days for a recent upper respiratory infection.

18. As T.V.'s pharmacist, which one of the following is the best recommendation?
  - A. Complete the full 10 days of therapy even if you feel better before then.
  - B. Call the physician and ask to change the prescription to clarithromycin 500 mg 2 times/day.
  - C. Avoid sexual activity while taking his antibiotic therapy.
  - D. Call the physician and ask to change the prescription to amoxicillin 500 mg 3 times/day.
19. In regard to sexual activity, T.V. should be advised to do which one of the following?
  - A. Limit to once a week.
  - B. Avoid sexual activity.
  - C. Maintain normal sexual activity.
  - D. Take one sublingual NTG 5 minutes before sexual activity.
20. Two months later, T.V. suffers an episode of chest pain during sildenafil-enhanced sexual activity that does not go away after a few minutes of rest. Which one of the following is the best course of action for T.V.?
  - A. Call 911.
  - B. Immediately take one sublingual NTG tablet, but no more.
  - C. Immediately take one extra diltiazem capsule.
  - D. Immediately take sublingual NTG tablets every 5 minutes, taking his blood pressure between doses.

**Questions 21 and 22 pertain to the following case.**

W.A. is a 58-year-old woman with chronic stable angina. Her other medical history includes hyperlipidemia, smoking, and type 2 diabetes mellitus. She watches her two young grandchildren a couple of days a week. She has found that the children keep her busy and active. She is disappointed in the fact that she has to stop and rest during these play sessions. She has attempted to take prophylactic sublingual NTG, but it wears off in 20–30 minutes. She then

has to take one more sublingual NTG tablet to gain complete relief of her symptoms. Her current drug regimen consists of atenolol 50 mg/day, ramipril 10 mg/day, aspirin 162 mg/day, metformin 500 mg 3 times/day, and atorvastatin 40 mg/day. Her current low-density lipoprotein (LDL) cholesterol is 102 mg/dl, blood sugar is 105 mg/dl and HbA1C is 7.2. Her current heart rate is 56 beats/minute and blood pressure is 108/70 mm Hg, which is about the same as at her last visit.

21. Which one of the following is an appropriate recommendation for W.A. with her current dilemma?
    - A. Increase atenolol to 100 mg/day.
    - B. Add nifedipine extended-release 30 mg/day.
    - C. Substitute prophylactic sublingual isosorbide dinitrate 5 mg.
    - D. Add verapamil extended-release 120 mg/day.
- Six months later, W.A. undergoes PTCA with stent placement to her proximal left anterior descending artery and mid-circumflex artery.
22. Before or during the procedure, W.A. should receive which one of the following to prevent complications associated with PTCA and stent placement?
    - A. Aspirin and clopidogrel.
    - B. Aspirin, clopidogrel, and heparin.
    - C. Aspirin, clopidogrel, heparin, and abciximab.
    - D. Aspirin, clopidogrel, heparin, abciximab, and folic acid 1 mg/day.

**Questions 23 and 24 pertain to the following case.**

C.S. is a 51-year-old woman who has a past medical history that includes HTN, hyperlipidemia, smoking, and a family history of early death from MI. Her only drugs at this time are chlorthalidone 25 mg/day and simvastatin 20 mg/day. Throughout the past 2 weeks, she reports two episodes of chest pain that radiated up to her neck when she walks about 4–5 blocks. Her current heart rate is 74 beats/minute and blood pressure is 144/92 mm Hg. Her current LDL cholesterol is 155 mg/dl, HDL cholesterol is 38 mg/dl, and triglyceride level is 280 mg/dl. During coronary angiography, she was found to have a 60% stenosis in her mid left anterior descending coronary artery that is not amenable to PTCA because of severe technical difficulty in accessing the area of stenosis.

23. Which one of the following is the best initial antianginal therapy?
  - A. Propranolol.
  - B. Verapamil.
  - C. Nitroglycerin patch on in the morning and off in the evening.
  - D. Amlodipine.
24. Which one of the following additional interventions is best for C.S.'s overall health?
  - A. Add folic acid 1 mg/day.
  - B. Add gemfibrozil 600 mg/day.

- C. Increase simvastatin to 40 mg/day.
- D. Smoking cessation.

25. J.H. is a 62-year-old man currently complaining of decreased exercise tolerance. J.H. suffered from an acute MI for which he received PTCA with stent placement 2 years ago. He also has diabetes mellitus, severe chronic obstructive pulmonary disease, and hyperlipidemia for which he receives verapamil extended-release 240 mg 2 times/day, isosorbide mononitrate 30 mg/day, pravastatin 20 mg/day, aspirin 325 mg/day, NPH insulin 30 units in the morning and 15 units in the evening, and ipratropium and albuterol inhalers. Coronary angiography shows diffuse disease in four vessels, but because of the severity of his chronic obstructive pulmonary disease it is determined that he is not to be a good candidate for CABG surgery and his disease is too extensive for PTCA. Ejection fraction determined during catheterization is 30%, and his fasting LDL cholesterol is 105 mg/dl. His blood pressure today is 114/68 mm Hg. Which one of the following is the best management strategy for J.H.?
- A. Discontinue verapamil.
  - B. Increase isosorbide mononitrate to 60 mg/day.
  - C. Discontinue isosorbide mononitrate and add carvedilol.
  - D. Discontinue verapamil and add carvedilol.

