CARDIOLOGY III

PSAP

CHRONIC STABLE ANGINA: MANAGEMENT AND PREVENTION OF FUTURE CARDIOVASCULAR EVENTS

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Learning Objectives

1. Describe the relationship between traditional risk factors, systemic inflammation, and endothelial dysfunction along with their role in the development of atherosclerosis.
2. Distinguish the clinical presentation and pathophysiology of patients with chronic stable angina and those with unstable angina.
3. Develop appropriate pharmacotherapy treatment plans to prevent complications of revascularization.
4. Assess the role of risk factor modification and available nonpharmacological interventions to prevent future cardiovascular events in patients with chronic stable angina.
5. Using patient-specific information, develop a therapeutic plan for a patient with chronic stable angina.
6. Develop a patient-focused education plan for an individual with chronic stable angina.

Introduction

Epidemiology

Cardiovascular disease (CVD) remains the leading cause of death in the United States, accounting for 37.3% of all deaths in 2003. In addition, death from CVD claims more lives each year than the next four leading causes of death combined despite recent advances in preventing and treating specific disease states that compose overall CVD. The economic burden of CVD is substantial. In 2006, it is estimated the total cost of treating CVD will be $403.1 billion.

Of the estimated 71.3 million adult Americans with CVD, 13.2 million have coronary heart disease (CHD). Patients with CHD (also known as coronary artery disease [CAD]) alone account for 1 out of every 5 deaths in the United States, primarily as a result from either myocardial infarction (MI) or sudden cardiac death. The true prevalence of angina pectoris in patients with CHD is difficult to determine, but it is estimated to be 6.5 million. Patients with CHD represent a significant burden on health care resources as well. It is estimated that more than 1 million diagnostic angiograms, more than 1 million percutaneous coronary interventions (PCI), and about 500,000 coronary artery bypass graft (CABG) procedures were performed in 2003. Total health care expenditures for CHD in 2006 are estimated to be $142.5 billion. A significant portion of this total cost is represented by indirect costs ($67.3 million) due to morbidity from CHD and lost productivity. Finally, patients with angina pectoris experience significant reductions in their quality of life due to limitations of activity or, potentially, inability to return to work once the diagnosis of CHD is made.

Definitions

Angina pectoris has been defined as a clinical syndrome that is characterized by pain or discomfort primarily in the chest, but the pain or discomfort may also be described as emanating from the jaw, shoulder, back, or arm. Angina can be classified depending on the circumstances in which it presents. Patients with a stable reproducible pattern of angina that typically occurs with exertion, and is relieved by rest or nitroglycerin, have chronic stable angina. Patients with unstable angina have chest pain that typically occurs at rest, is of prolonged duration, or is increased in severity compared with the pain associated with chronic stable angina.

Angina, whether stable or unstable, is typically the result of CAD, also known as ischemic heart disease (IHD). Atherosclerosis of the epicardial vessels in the heart is now known to be the cause of IHD in a great majority of patients. Rarely, vasospasm of the coronary arteries (Prinzmetal's angina, also known as vasospastic angina) may also be a cause for IHD. In addition to stable and unstable angina, other manifestations of atherosclerosis include MI, heart failure (HF), arrhythmias, stroke, and peripheral vascular disease.

Abbreviations in this Chapter

ACC	American College of Cardiology
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
ACT	Activated clotting time
AHA	American Heart Association
ARB	Angiotensin receptor blocker
ASA	Aspirin
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events
CCB	Calcium channel blocker
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance
CHD	Coronary heart disease
CRP	C-reactive protein
CVD	Cardiovascular disease
CYP	Cytochrome P450
DHP	Dihydropyridine
ECG	Electrocardiogram
EBCT	Electron beam computed tomography
EUROPA	EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease
GP IIb/IIIa	Glycoprotein IIb/IIIa
HF	Heart failure
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HOPE	Heart Outcomes Prevention Evaluation
IHD	Ischemic heart disease
LDL	Low-density lipoprotein
LMWH	Low-molecular-weight heparin
MI	Myocardial infarction
NO	Nitric oxide
PCI	Percutaneous coronary intervention
PEACE	Prevention of Events with Angiotensin-Converting Enzyme Inhibition
PROACTIVE	PROspective pioglitAzone Clinical Trial In MacroVascular Events
UFH	Unfractionated heparin

Pathophysiology

An imbalance between myocardial oxygen supply and demand underlies any episode of myocardial ischemia. In the case of chronic stable angina, this imbalance is typically produced when myocardial oxygen demand is increased in the setting of a fixed oxygen supply. When significant atherosclerotic plaques are present and limit the available blood supply, exertion may raise oxygen demand above available supply in areas of myocardium that are fed by the affected coronary arteries. In addition, the presence of atherosclerosis not only encroaches on the arterial lumen, but also creates vasomotor dysfunction in the affected artery. This vasomotor dysfunction may lead to inappropriate vasoconstriction on top of a flow-limiting atherosclerotic plaque, further limiting oxygen supply to the myocardium.

Understanding the determinants of myocardial oxygen supply and demand is central to understanding the rationale for use and clinical effects of currently available anti-anginal drugs. The main determinants of myocardial oxygen supply include coronary blood flow, oxygen extraction, and oxygen availability within the blood supply itself. The main determinants of myocardial oxygen demand include heart rate, the contractile state of the myocardium, and intra-myocardial wall tension.

In addition to understanding the relationship of myocardial oxygen supply and demand to the development of myocardial ischemia, understanding how atherosclerosis develops and progresses is crucial to the prevention and treatment of not only chronic stable angina, but other manifestations of atherosclerosis such as MI and HF, and ultimately death. Historically, atherosclerosis was thought to be simply the result of excess cholesterol deposition in the arterial wall. Although cholesterol is a central feature of the disease, recent advances in vascular biology have demonstrated that atherosclerosis is primarily a disease of inflammation and proliferation within the vasculature. Leukocytes are recruited and incorporated into the vascular wall in response to stimuli such as oxidized low-density lipoprotein (LDL) and are then transformed into macrophages and, ultimately, foam cells once significant uptake of oxidized LDL has taken place. Activated macrophages secrete many pro-inflammatory cytokines that promote the migration of smooth muscle cells and the deposition of an extra-cellular matrix. The end result of this process, over time, is the development of an elevated atherosclerotic plaque that may encroach on the lumen of the artery.

This generalized state of inflammation and proliferation is the direct result of damage to the vasculature leading to dysfunction of the vascular endothelium. Under normal circumstances, the vascular endothelium promotes a healthy vascular environment through the secretion of a variety of substances that are antithrombotic, anti-inflammatory, and suppress the proliferation of cells and the extra-cellular matrix. Nitric oxide (NO) is the most studied and well-recognized of these compounds. When endothelial dysfunction is present, levels of NO are significantly reduced, facilitating the development of atherosclerosis. In addition, levels of other drugs (e.g., angiotensin II and endothelin) that promote vasoconstriction, inflammation, thrombosis, and proliferation are increased.

Several risk factors, including smoking, diabetes, hypertension, hyperlipidemia, and obesity, that predispose patients to the development of CAD have been identified. Each risk factor has been demonstrated to cause endothelial dysfunction and, hence, promote the development of

atherosclerosis throughout the vasculature. Although the mechanism of how the various risk factors produce endothelial dysfunction is largely unknown, recent work suggests that the common link among them may be that each produces a state of increased oxidative stress within the vasculature. Elevated levels of reactive oxygen intermediates within the vasculature not only result in reduced NO bioavailability, but also facilitate the conversion of NO to peroxynitrite, a compound which is pro-inflammatory. A state of increased oxidative stress has also been demonstrated to occur after the ingestion of a meal composed of what would be considered a typical Western diet (high in saturated fat and simple carbohydrates, low in fruits, vegetables, and whole grains). Consequently, a poor diet not only promotes the development of traditional risk factors such as hyperlipidemia, hypertension, and obesity, but also increases oxidative stress. This may also partly explain the association of a poor diet with CAD. Finally, recent research has demonstrated that adipose tissue is not a passive storage depot for fatty acids, but rather an active metabolic organ that secretes a large number of cytokines. With increasing fat mass, levels of pro-inflammatory cytokines increase within the vasculature. In addition, levels of adiponectin, a substance that has been shown to be protective against the development of vascular disease, decreases with increased fat mass.

Although traditional risk factors for CAD have been recognized and accepted for some time, recently there has been an intense research focus on the identification of novel risk factors for the development of CAD. Historically, the operating consensus was that only about 50% of the events of MI could be predicted using conventional risk factors. Therefore, the purposes for identifying additional risk factors are as follows: 1) to further refine current risk stratification algorithms (such as the Framingham risk calculator) to better identify patients who are at risk for developing CAD; and 2) to develop a more complete understanding of the pathogenesis of atherosclerosis.

A novel risk factor that has received a large amount of attention recently is C-reactive protein (CRP), generally regarded as a marker of systemic inflammation. What is still unclear is whether minor elevations of CRP over time are merely a marker for the presence of vascular disease or a causative factor in the development of atherosclerosis. Although there is still significant controversy over the role of CRP in the pathophysiology of atherosclerosis and the proper role for CRP testing in predicting the occurrence of CAD, current recommendations suggest that obtaining CRP concentrations may be useful to further risk stratify patients who are at intermediate risk for the development of CAD, as determined by the Framingham risk score. Patients at intermediate risk who have elevated CRP levels may warrant aggressive intervention to prevent disease progression, similar to patients with established CAD.

Despite the search for novel risk factors for the development of atherosclerosis, recent large epidemiologic studies demonstrated little is to be gained by looking beyond traditional risk factors in the ability to predict who is at risk for CAD. In a large case-control study of over 29,000 patients in 52 countries around the world, patients who had a first time acute MI were matched to a healthy control at each site. Nine clinical risk factors were found to be strongly associated with the development of CAD as manifested by first time MI (Table 1-1). Taken together, these risk factors accounted for more than 90% of the incidence of MI in the study population. Of importance, the results were consistent among women and men, across different geographic regions in the world, and in different ethnic groups, suggesting strategies to reduce the incidence of CAD need not be tailored for any specific population.

Table 1-1. Risk Factors for First Time MI in the INTER-HEART Study

Risk Factor	Adjusted Odds Ratio (99% CI)
ApoB/Apo A-1 Ratio	3.25 (2.81–3.76)
Current smoker	2.87 (2.58–3.19)
Psychosocial	2.67 (2.21–3.22)
Diabetes	2.37 (2.07–2.71)
Hypertension	1.91 (1.74–2.10)
Abdominal obesity	1.62 (1.45–1.80)
Moderate alcohol intake	0.91 (0.82–1.02)
Exercise	0.86 (0.76–0.97)
Vegetable and fruits daily	0.70 (0.62–0.79)
All combined	129.2 (90.2–185.0)

Apo = apolipoprotein; CI = confidence interval; MI = myocardial infarction.

Regardless of which risk factors should be assessed in predicting risk for CAD, it should be evident that risk factor modification should be a central feature of any treatment plan designed to prevent either the development of CAD or the progression of atherosclerosis in a patient who already has manifested CAD. In addition, knowledge of how risk factors are involved in the development of atherosclerosis is invaluable in understanding how several distinct pharmacological therapies prevent progression of CAD.

Clinical Evaluation

The initial step when evaluating a patient who presents with chest pain is to perform a detailed symptom history and a focused physical examination, along with a directed assessment for the presence of risk factors. Once this information is obtained, a probability estimate for the presence of CAD (low, intermediate, or high) can be developed. Determining the likelihood of CAD being present is a key step in determining not only which diagnostic tests can be used to confirm the presence of CAD, but also the utility (positive predictive value) of a given diagnostic test. Multiple diagnostic testing modalities are available; the selection of which test is most appropriate for a specific patient is predicated on patient-specific information such as ability to exercise, history of previous coronary revascularization, or the presence of clinical findings that may warrant the selection of a specific test. Available testing modalities not only help confirm the presence of CAD, but also provide valuable information regarding long-term prognosis.

In addition to evaluating the nature and quality of chest pain along with the presence of risk factors for CAD, an

attempt should be made to identify comorbid conditions that may precipitate or exacerbate angina such as hyperthyroidism, uncontrolled hypertension, cocaine use, valvular disorders, or hypoxia secondary to pulmonary disorders. The ensuing discussion briefly touches on aspects of the work-up for patients presenting with angina. The reader is referred to the most recent update of the American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines for the Management of Chronic Stable Angina if a more detailed discussion regarding the clinical assessment, estimation of pre-test probability of CAD, classification of angina by symptom severity, or appropriate selection of diagnostic tests is desired.

Clinical Presentation

The description of chest pain is a useful tool in aiding the clinician to determine whether chest pain represents chronic stable angina or acute coronary syndrome (ACS), or is non-cardiac in origin. Chest pain that is characteristic of myocardial ischemia is described as a sensation of pressure or heavy weight located over the sternum. Patients often will also complain of shortness of breath; pain may occasionally be described in the neck, jaw, shoulder, or arm as well. Of importance, pain that is reflective of chronic stable angina is associated with exertion and rapidly resolves with rest or the administration of nitroglycerin. Chest pain that occurs at rest, is prolonged in duration, or is increased in severity is likely reflective of unstable disease and warrants immediate medical attention to prevent complications such as MI, HF, and death. Physical findings in patients with chronic stable angina are nonspecific and may include shortness of breath, tachycardia, diaphoresis, and nausea. Other findings that may be present if the level of ischemia is severe enough include hypotension, pulmonary congestion, or the presence of a third heart sound.

Diagnostic Tests

Noninvasive tests that may be used in the work-up of patients with chronic angina include the electrocardiogram (ECG), chest radiography, electron beam computed tomography (EBCT), and stress testing with exercise or pharmacological measures. In addition, patients often undergo invasive testing with coronary angiography. Each testing modality provides key information relating to either establishing the diagnosis of CAD, estimating long-term prognosis, or determining candidacy for revascularization procedures.

Treatment Options for Chronic Stable Angina

Goals of Therapy

The goals of therapy for chronic stable angina are 2-fold. First, and foremost, from the perspective of the patient, the reduction or elimination of the angina symptoms to improve quality of life should be achieved. Second, and likely more important than the relief of symptoms, the goal is to halt progression of atherosclerosis and prevent complications of the disease, such as MI and death. Both pharmacological and nonpharmacological interventions, in addition to revascularization procedures, are used simultaneously to achieve each of these goals.

Nonpharmacological Therapy

Risk Factor Modification

Before the selection of specific drug therapy to either treat anginal symptoms or prevent complications of CAD, the first step in the development of any treatment plan for a given patient with chronic stable angina should be modification of existing risk factors and implementation of healthy lifestyle habits. Appropriate identification and treatment of risk factors will prevent not only the development of CAD, but also disease progression in patients with existing CAD. Smoking cessation, treatment of lipid abnormalities, and effective control of blood pressure have all reduced the risk of ischemic vascular events or death in patients with CAD. In addition, select drug therapies for each risk factor may be preferred due to their positive effects on the pathophysiology of atherosclerosis. Although several different classes of lipid-modifying drugs exist, 3-hydroxy-3-methylglutaryl coenzyme A inhibitors (HMG-CoA reductase inhibitors or statins) have been demonstrated in multiple trials to significantly reduce the progression of atherosclerosis, as well as reduce the incidence of death and MI. Of importance, HMG-CoA reductase inhibitors exhibit several pleiotropic effects that may ultimately reverse endothelial dysfunction and prevent progression of CAD. In patients who require additional blood pressure control after anti-anginal therapy has been optimized, angiotensin-converting enzyme (ACE) inhibitors may be preferred due to their theoretical potential to reduce the progression of CAD by improving endothelial function.

Although the presence of diabetes has been a significant risk factor for the development and progression of atherosclerosis, historically the majority of clinical trials demonstrated that tight glycemic control did not have a positive effect on the progression of atherosclerosis or reduce the risk of hard end points such as MI. However, recent information from the Diabetes Control and Complications Trial indicates that tight glycemic control with intensive insulin therapy in patients with type 1 diabetes significantly reduces the risk for MI and cardiovascular death. Although these results are significant, type 2 diabetes is more prevalent than type 1. Recently, data from the PROspective pioglitazone Clinical Trial In Macrovascular Events (PROACTIVE) trial demonstrated that aggressive glucose control with the peroxisome proliferator-activated receptor-γ antagonist pioglitazone not only improves glycemic control, but also reduces the incidence of hard cardiovascular end points such as MI and cardiovascular death. Previously, only metformin in patients who are obese demonstrated positive effects on the incidence of CV end points. Although the results of PROACTIVE are promising, they need to be confirmed in subsequent clinical trials along with the delineation of actual mechanisms whereby pioglitazone may reduce the progression of atherosclerosis. Despite these limitations, pioglitazone is emerging as a preferred option to treat diabetes in patients with CAD. It is unclear whether this can be considered a class effect of thiazolidinediones at this time.

Lifestyle Modifications

Appropriate treatment of risk factors not only involves implementation of drug therapy, but also should involve the adoption of lifestyle modifications. These should include ensuring the patient exercises regularly, maintains a healthy weight, and has a regular healthy dietary pattern. Although the positive effects of lifestyle modifications on cardiovascular risk factors are well recognized, the effect of specific lifestyle interventions on reducing hard cardiovascular end points such as MI or death is somewhat underappreciated. One intervention in particular is the adoption of a healthy dietary pattern. Two randomized, controlled trials demonstrated that in patients with documented CAD, adoption of a dietary pattern that emphasizes intake of whole grains, fruit, vegetables, nuts and legumes, moderate dairy intake, moderate amounts of lean protein, and polyunsaturated fats such as olive oil as the main source of fat (the so-called Mediterranean Diet) reduced the relative risk of subsequent MI or cardiac death by 50%–73% compared with a diet similar in composition to the AHA step 1 diet. In one of these studies, the Lyon Diet Heart Study, the improvements in cardiovascular morbidity and mortality occurred without significant changes in the lipid profiles of study subjects. Several additional trials also demonstrated that patients with a history of MI who increased their intake of either fatty fish, or ingested omega-3 fatty acid fish oil supplements, had reductions in cardiovascular death and MI compared with control patients without dietary intervention. Lastly, several epidemiologic studies confirmed the results from randomized, controlled trials showing that adherence to a Mediterranean dietary pattern significantly reduces cardiovascular morbidity and mortality. Evidence from basic science and clinical trials indicate that a Mediterranean diet reduces systemic inflammation as measured by CRP, reduces the incidence of insulin resistance, and improves endothelial function. Although a great deal of attention has been directed to the increased intake of omega-3 polyunsaturated acids (eicosapentaenoic acid and docosahexaenoic acid derived from fish or α-linoleic acid derived from plants) being responsible for the observed benefits in each of these trials, multiple dietary alterations were likely in play. The results should be interpreted as the result of the adoption of a healthy dietary pattern. These considerations, along with a relative lack of information regarding the safety of long-term administration of omega-3 fatty acid supplements, have resulted in the current AHA recommendation that, if patients choose to increase their intake of omega-3 fatty acids, a dietary-approach is preferred to the intake of supplements.

Although it is now accepted that patients with chronic stable angina should make efforts to adhere to an overall healthy dietary plan such as the Mediterranean Diet, the effects of nutritional supplementation with individual drugs present in these healthy dietary patterns have been investigated for a long time. Although early evidence demonstrated there may be a role for vitamin E supplementation in patients with CAD, multiple large, randomized, placebo-controlled studies have now demonstrated that vitamin E supplementation does not have any effect on cardiovascular morbidity and mortality and, therefore, should not be recommended for routine administration in patients with chronic stable angina. Although this recommendation, which is consistent with the current AHA scientific advisory on antioxidant vitamins in cardiovascular disease, was based on demonstrated lack of efficacy, a meta-analysis published in 2005 raised the possibility that high-dose supplementation with vitamin E may also be harmful. In their analysis of available randomized, controlled trials, the authors found a dose-dependent relationship between vitamin E and total mortality. Several studies included in the meta-analysis involved a variety of patients and were not specific to CAD. However, the analysis found an increase in total mortality when the daily dose of vitamin E increased above 150 IU/day.

There was also early enthusiasm regarding the use of folic acid supplementation with or without B vitamins to reduce cardiovascular end points based on their ability to lower homocysteine levels. Elevated levels of homocysteine have been associated with an elevated risk for MI, stroke, and venous thromboembolism. However, based on available data, homocysteine appears to be merely a modifiable marker of disease rather than a causative factor in the development of atherosclerosis. Currently, the majority of randomized, controlled trials indicate that, although supplementation does lower homocysteine levels, folic acid with or without B vitamins does not appear to provide any benefit in terms of reducing cardiovascular events.

In 2000, based on existing evidence at the time, the AHA released a scientific statement recommending the daily consumption of at least 25 g of soy protein, believing soy and its associated phytochemicals could significantly improve lipid profiles in patients with hyperlipidemia. Recently, AHA revised this recommendation based on new information obtained since that time. The statement summarizes the current data evaluating the effects of soy protein on LDL cholesterol, which now appear to be minimal at best even in patients who consume half of their daily protein intake as soy protein. As such, patients should not ingest soy protein supplements for the sole purpose of improving cardiovascular health because benefit has not been proven. Of note, however, many soy products are high in polyunsaturated fats, fiber, and vitamins and minerals, and low in saturated fat. As such, consumption of these products may benefit cardiovascular and overall health.

Pharmacological Therapy

Anti-Ischemic Drugs

Historically, three classes of drugs are used in the treatment of chronic stable angina to prevent the onset of ischemia and improve quality of life. β-Blockers, calcium channel blockers (CCBs), and chronic nitrate therapy have provided relatively equal benefit in terms of preventing anginal attacks when administered in adequate doses. Therefore, the choice of drug in any given patient depends on considerations regarding appropriate use of each drug class and specific patient characteristics, as well as current recommendations found in national guidelines.

In January 2006, the FDA granted labeling approval to ranolazine, representing the first new class of drug to be approved for the treatment of chronic stable angina in the

past 20 years. Due to its unique mechanism of action (described below), along with the lack of significant hemodynamic effects seen with other anti-anginal drugs, the addition of ranolazine is a promising advance in the treatment of patients with CAD and exertional angina.

β-Blockers

β-Blockers reduce myocardial oxygen demand by lowering heart rate, myocardial contractility, and intra-myocardial wall tension. In addition, β-blockers have been effective at relieving silent myocardial ischemia. Neither β-selectivity nor the presence of α_1-blockade appear to affect efficacy of the β-blocker in preventing ischemia and, therefore, the choice of a specific drug for a given patient should depend on cost, number of daily doses, and the presence of other comorbid conditions. The β-blocker dose should be titrated to a goal resting heart rate of 55–60 beats/minute and will, therefore, be patient specific. β-Blockers with intrinsic sympathomimetic activity are not routinely used in patients with stable angina because they are less effective in reducing heart rate. β-Blockers should be avoided in patients with primary vasospastic angina and they may worsen symptoms in patients with reactive airway disease or peripheral arterial disease. The most common adverse effects observed with chronic therapy include bradycardia, hypotension, fatigue, and sexual dysfunction.

Calcium Channel Blockers

Both dihydropyridine (DHP) and non-DHP CCBs produce an increase in myocardial oxygen supply through vasodilation of the coronary arteries. In addition, both classes of CCBs would reduce myocardial oxygen demand to some degree through lowering of intra-myocardial wall tension (by lowering systemic blood pressure). However, non-DHP CCBs would be expected to lower myocardial oxygen demand to a greater degree because of additional reductions in heart rate and contractility. Consequently, patients with compromised left ventricular function or reduced heart rate should receive a DHP if CCB therapy is indicated. Side effects of CCB therapy depend on the specific drug used. Use of non-DHP CCBs may result in bradycardia, hypotension, and atriaventricular block. Patients receiving DHP CCBs may experience reflex tachycardia, peripheral edema, headache, and hypotension.

Short-Acting and Long-Acting Nitrates

Nitrates produce vasodilation through biotransformation and the release of NO. Although vasodilation occurs preferentially on the venous side, arterial dilation can be seen with high doses. Nitrates reduce myocardial oxygen demand by reducing preload, but they also can improve oxygen delivery through dilation of the epicardial coronary arteries. Regardless of which long-acting nitrate formulation is selected for a given patient, appropriate strategies must be implemented to prevent the phenomenon of nitrate tolerance. Nitrate tolerance can develop in as little as 24 hours after continuous exposure to nitrate therapy and can represent either partial or total loss of efficacy. Many theories have been offered regarding the mechanism of nitrate tolerance (activation of neurohormonal systems, plasma volume expansion, and loss of co-factors necessary for biotransformation). Several pharmacological interventions (inhibitors of the renin-angiotensin-aldosterone system, HMG-CoA reductase inhibitors, and L-arginine) have been investigated in an effort to prevent tolerance with mixed results. Recent information indicates that the mechanism of nitrate tolerance can possibly be explained through inactivation of a mitochondrial enzyme necessary for biotransformation of the drug. Chronic administration of nitrates produces a state of oxidative stress leading to dysfunction of mitochondrial aldehyde dehydrogenase, the enzyme responsible for converting nitrates to the active agent NO.

The preferred strategy for prevention of tolerance is a daily nitrate-free interval of 10–14 hours. The drawback of this approach is the lack of anginal protection during the nitrate-free interval. Consequently, chronic nitrate therapy should never be used as monotherapy, but should be considered as add-on therapy for patients who do not have adequate symptomatic control with either a β-blocker or CCB. Common adverse effects of nitrate therapy include hypotension, dizziness, and headache. Concomitant administration (within 24 hours for sildenafil and vardenafil, 48 hours for tadalafil) is contraindicated with phosphodiesterase type 5 inhibitors due to the risk of profound hypotension.

Ranolazine

Ranolazine represents the first new drug available in more than 20 years to treat chronic stable angina in the United States. As such, there will likely be considerable enthusiasm regarding its use. However, available information regarding the drug indicates it has a complex mechanism of action and many safety considerations. Pharmacists will be well-suited to help prescribers use the drug safely and appropriately.

The mechanism of action of ranolazine historically was thought to involve shifting the metabolic substrate in the myocardium from free fatty acids to glucose by inhibiting partial fatty acid oxidation. In doing so, myocardial oxygen demand would be reduced through increased metabolic efficiency. However, it is now known that serum concentrations of ranolazine needed to inhibit partial fatty acid oxidation are 10 times higher than what is produced with the approved dosing strategy, making it unlikely that this is the mechanism for preventing ischemia. Subsequently, it was discovered that ranolazine inhibits the late sodium current, thereby reducing intracellular sodium. When ischemia in the myocardium is present, sodium influx is increased. This indirectly leads to intracellular calcium overload through the sodium/calcium exchanger. Calcium overload leads to increased intra-myocardial wall tension and reduced microvascular perfusion and, ultimately, ischemia. By inhibiting sodium influx, ranolazine effectively prevents ischemia-induced contractile dysfunction and delays the onset of angina. Of importance, ranolazine is distinct from other anti-anginal drugs in that it has no appreciable effect on heart rate and blood pressure. The lack of significant hemodynamic effects will be beneficial for patients who need further anti-anginal therapy, but who have marginal blood pressure or heart rates preventing titration of conventional anti-anginal drugs.

Published clinical trials with ranolazine evaluated primarily the effects of adding the drug to existing anti-anginal therapy with a β-blocker, CCB, long-acting nitrate, or some combination in patients with chronic stable angina. Results from these trials demonstrate that the addition of ranolazine reduced the frequency of anginal attacks and also sublingual nitroglycerin use. Additional results from select clinical trials indicate that the addition of ranolazine increased the time to angina in patients undergoing treadmill exercise. Although the results of available studies indicate that ranolazine is an effective anti-anginal drug when used in combination with traditional drugs, no published literature is available addressing ranolazine as first-line therapy or whether the drug has any effect on long-term morbidity and mortality.

Ranolazine is available as an extended-release tablet that is dosed twice daily. The drug should be initiated at a dosage of 500 mg orally 2 times/day, which can be titrated up to a maximum dosage of 1000 mg 2 times/day. Although not specifically addressed in the package insert, dosage titration above the initial starting dosage of 500 mg 2 times/day is likely unnecessary in patients with renal dysfunction, due to the 50% higher ranolazine plasma concentrations observed in this population.

The drug is extensively metabolized in the liver through both cytochrome P450 (CYP) 3A4 and CYP2D6; therefore, attention should be paid to potential drug interactions. The CYP3A4 enzyme appears to be the major pathway for metabolism and, as such, use of ranolazine is contraindicated in patients receiving potent inhibitors of CYP3A4. Available pharmacokinetic studies demonstrate that diltiazem, verapamil, and ketoconazole significantly elevate ranolazine plasma concentrations. Caution should be used with less potent CYP3A4 inhibitors until more information is available. Potent CYP2D6 inhibitors (such as paroxetine) appear to elevate plasma ranolazine concentrations minimally, and are considered safe as concomitant therapy. Ranolazine has also been demonstrated to be an inhibitor of CYP3A4, CYP2D6, and p-glycoprotein. Studies conducted to date demonstrate that ranolazine inhibits the metabolism of simvastatin, resulting in a 2-fold increase in plasma concentration. In addition, concomitant administration with ranolazine resulted in a 1.5-fold increase in plasma digoxin concentrations.

Another significant concern with ranolazine is QTc prolongation. Clinical studies indicate that patients taking the maximum dosage of 1000 mg 2 times/day had an average increase in QTc of 6 milliseconds. However, in about 5% of patients, the effect was greater than 15 milliseconds. Currently, there are no reported cases of torsades de pointes with ranolazine.

Although ranolazine prolongs the QT interval, it has also decreased repolarization dispersion in the myocardium as well as prevent the occurrence of early-after depolarizations. Both an increase in repolarization dispersion and the presence of early-after depolarizations are needed in conjunction with increased QTc to produce torsades de pointes. Therefore, it is unlikely that there is an elevated risk of proarrhythmia with ranolazine. However, until further safety information becomes available regarding the risk associated with QTc prolongation from ranolazine, the drug should be avoided in patients with pre-existing QTc prolongation or who are receiving other drugs that prolong the QTc interval.

Additional adverse effects noted in clinical trials were an increase in the incidence of constipation, nausea, dizziness, and headache compared with placebo. The increase in these nonspecific adverse effects appears to have been minimal and not clinically significant.

Vasculo-Protective Drugs

Antithrombotic Therapy

Platelets not only play a central role in the development of pathologic thrombus formation during ACS, but also participate in the pathogenesis of atherosclerosis itself. Consequently, antiplatelet therapy has occupied a central place in the treatment of patients with CAD for many years. Aspirin (ASA) therapy has reduced the incidence of MI and sudden cardiac death in patients with chronic stable angina. Aspirin's clinical efficacy in chronic stable angina, coupled with its minimal cost and demonstrated efficacy post-MI, have made it the gold standard for antiplatelet therapy in patients with CAD. Current national guidelines from the ACC/AHA recommend ASA be administered at 75–162 mg/day for preventing MI and death in patients with CAD. Although higher doses have been investigated, they do not increase efficacy, but do increase the risk for adverse effects.

In patients unable to take ASA due to allergy or intolerance, clopidogrel represents a suitable alternative antiplatelet drug to prevent MI and death in patients with CAD. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial demonstrated that clopidogrel significantly reduced the incidence of stroke, MI, or vascular death in patients with atherosclerotic vascular disease (previous MI, stroke or peripheral arterial disease) compared with ASA. In addition, clopidogrel was well tolerated with the major adverse effects noted to be gastrointestinal intolerance and rash. Although the relative risk reduction seen with clopidogrel versus ASA was statistically significant, the absolute difference in the primary outcome between the two strategies was quite small (0.4%; number need to treat = 200). In addition, the majority of benefit for clopidogrel was seen primarily in patients with peripheral arterial disease, with negligible differences seen in patients with CAD. Given the small magnitude of benefit along with significantly higher cost, clopidogrel remains a second-line choice behind ASA in patients with CAD. When used in patients with chronic stable angina, clopidogrel should be administered at 75 mg/day.

Given the different mechanisms of antiplatelet effect, combining ASA with clopidogrel would be expected to provide additional protection from MI and death in patients with CAD as compared with monotherapy. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial assessed the use of long-term, dual antiplatelet therapy in patients with documented CAD or with multiple cardiovascular risk factors. The combination of ASA plus clopidogrel for 28 months did not reduce the risk of death, MI, stroke, or coronary revascularization compared with ASA alone. However, dual therapy did increase the risk of bleeding.

Therefore, at this time, dual antiplatelet therapy in patients with CAD is currently limited to those who have had a recent ACS or recent PCI plus stent placement.

The use of ASA for primary prevention of cardiovascular events in patients at risk of developing CAD has been studied in six randomized, controlled trials. In aggregate, the data from these trials indicate that ASA significantly reduces the future risk of MI and stroke while also increasing the risk of future bleeding events. Therefore, the decision to implement ASA for primary prevention in a given patient will be dependent on the underlying cardiovascular risk, as determined through a risk scoring system such as the Framingham Risk Score. When the future risk of cardiovascular events is high, the benefits of primary prevention will outweigh the risk of future bleeding events. Although different recommendations have been published in recent years from groups such as AHA, American Diabetes Association, and United States Preventative Services Task Force, primary prevention therapy with ASA is generally considered to be indicated when patients have a 10-year risk for cardiovascular disease greater than 10%, as determined by the Framingham Risk Score. Patients with a 10-year risk less than 10% should be thoroughly educated about the expected risks and benefits of ASA therapy.

ACE Inhibitors

Angiotensin-converting enzyme inhibitors are standard drugs in treating patients with diabetes, HF, and MI. Retrospective analyses of some early HF trials evaluating drugs such as enalapril and lisinopril demonstrated that patients randomized to receive ACE inhibitor therapy had a reduced risk of ischemic vascular events as well. The Heart Outcomes Protection Evaluation (HOPE) study demonstrated that ramipril 10 mg/day added to standard therapy for patients with CAD with preserved left ventricular function reduced the risk of death, MI, and stroke. Following publication of HOPE in 2000, the AHA recommended that ACE inhibitors be added as standard therapy for all patients with vascular disease.

Two large, randomized, placebo-controlled trials in patients with documented CAD with preserved left ventricular function that evaluated the use of ACE inhibitors in patients with vascular disease have subsequently been published. In the EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA), perindopril 8 mg/day significantly reduced the incidence of cardiovascular death, MI, or cardiac arrest versus placebo when added to a standard regimen of ASA, lipid-lowering drugs, β-blockers, CCBs, and long-acting nitrates. The results of the EUROPA trial confirmed the benefits observed in the HOPE study, and lent further support to the concept that ACE inhibitors may have beneficial effects on the atherosclerotic disease process. However, some experts speculated that the benefits could be attributed solely to reduction in blood pressure in the patients who received an ACE inhibitor. Others contend that the small, but significant, reductions in blood pressure observed in these studies could not account for the entire magnitude of benefit.

With the positive results seen in HOPE and EUROPA, it was expected that similar results would also be observed in the Prevention of Events with Angiotensin Converting Enzyme Inhibitors (PEACE) trial. However, the addition of trandolapril 4 mg/day to standard therapy in patients with documented CAD and preserved left ventricular function did not have any effect on the incidence of cardiovascular death, MI, or coronary revascularization. These results were surprising and cast some doubt on the role of ACE inhibitors in the treatment of patients with CAD who have preserved left ventricular function.

There are several potential explanations for the discordant results of PEACE from HOPE and EUROPA. The first is that potentially not all ACE inhibitors are the same in their effects in arresting the progression of atherosclerosis. However, this explanation seems unlikely given that positive results have been observed for ramipril, perindopril, and enalapril, indicating the existence of a class effect. A more likely explanation is that the trandolapril dose used in the PEACE trial may not have been sufficient to produce a measurable effect. Other explanations point to differences in the patient populations among trials. Patients in the PEACE trial appeared to be at much lower overall risk as the event rate in the placebo group was substantially lower than the active treatment arm in the HOPE study. It also appears that patients in the PEACE trial were receiving more intensive treatment for risk factors than in HOPE and EUROPA, as evidenced by lower baseline blood pressure and lipid levels, and a higher percentage of patients receiving HMG-CoA reductase inhibitors. Patients in the PEACE trial had a much higher rate of previous revascularization as well. The sum effect of these differences is that it is unlikely that any treatment effect could have been observed for trandolapril due to the low overall event rate in the PEACE study population.

Regardless of whether there is a reasonable explanation for the discordant results of these trials, the PEACE trial does raise a significant issue of whether ACE inhibitors should be added to the drug therapy regimen of patients with CAD who are receiving intensive therapy, including an HMG-CoA reductase inhibitor. Until further information becomes available, it may still be reasonable to routinely add an ACE inhibitor to the drug therapy regimen for patients with CAD, especially if the risk for ischemic vascular events is higher than what was seen in the PEACE trial. Such patients may include those who are post-MI, unable to undergo coronary revascularization, have diabetes, or require further blood pressure control once anti-anginal therapy is optimized.

There have been no randomized controlled trials assessing angiotensin receptor blockers (ARBs) in a CAD population with preserved left ventricular function. However, because there are reasonable data supporting the use of ARBs in patients post-MI who are intolerant to ACE inhibitors, it may be reasonable to use an ARB in patients with CAD as an alternative to an ACE inhibitor.

Revascularization Therapy

Revascularization of the myocardium, either via CABG or PCI, has been a mainstay in treating CAD for some time. Goals of revascularization do not differ from the overall goals in treating patients with chronic stable angina, namely to relieve symptoms, improve quality of life, and prevent

complications of CAD such as MI and death. Historically, a great deal of focus was devoted to comparing CABG, PCI, and medical management with regard to their relative efficacy in relieving symptoms and improving prognosis. In a broad population of patients with CAD, revascularization with either CABG or PCI was found superior to medical management therapy alone in relieving symptoms at 1 year, although there was no difference in overall mortality between treatment strategies. However, CABG therapy was significantly better at providing long-term relief of symptoms, as well as providing a lower need for repeat revascularization therapy, compared with PCI. When subgroups of patients with more severe disease or those who had manifested left ventricular dysfunction were evaluated, differences in long-term mortality were observed among the different treatment strategies. In patients with double-vessel or triple-vessel disease, significant disease of the left main artery, or left ventricular dysfunction, CABG therapy has been demonstrated to provide a reduced 5-year mortality rate compared with PCI or medical therapy alone.

Despite the availability of data regarding the relative effects of PCI, CABG, and medical management on morbidity and mortality, there has been a dramatic increase in the use of PCI in recent years. In fact, the traditional controversy of revascularization therapy, whether it be PCI or CABG, versus medical treatment has reduced in significance with the recognition that effective treatment of patients with CAD incorporates both strategies over the long term. In addition, advances in PCI, CABG, and medical therapy have made comparing the available strategies more difficult as the majority of clinical trials comparing these options were conducted in the 1970s and 1980s. It is somewhat unclear in today's environment of drug-eluting stents, off-pump CABG, and aggressive medical therapy, including HMG-CoA reductase inhibitors, ACE inhibitors, and new anti-anginal drug such as ranolazine, what the relative effects of contemporary PCI, CABG, and medical therapy are in terms of relieving symptoms and improving long-term prognosis.

Despite this uncertainty, CABG remains the preferred strategy for patients with three-vessel disease or multi-vessel disease plus left ventricular dysfunction. In these patients, CABG therapy is considered by most to provide superior relief of symptoms and decreased long-term mortality compared with PCI or medical therapy. In patients with less severe CAD, PCI can be expected to provide similar benefits in mortality compared with CABG, but may not be as effective in reducing symptoms or the need for repeat revascularization procedures. Several recent studies have indicated that aggressive medical treatment, which includes intensive lipid-lowering therapy, may be as effective as PCI in improving prognosis long term, but may be inferior at reducing symptoms of angina. These trials highlight the importance of implementing effective strategies that reduce the progression of CAD, regardless of whether revascularization therapy is used. Relevant issues facing pharmacists today not only include optimizing the medical management of CAD, but also providing effective pharmacotherapy to prevent complications of PCI.

Percutaneous Coronary Intervention

Coronary angioplasty was first introduced in 1977 as an alternative to CABG for coronary revascularization. Since that time, advances in technique, equipment, and experience of operators have allowed the procedure to be expanded to a wide array of patients with CAD. Successful PCI is defined as attainment of angiographic success (a percent diameter stenosis after procedure less than 20%), without incurring any of the major complications of PCI such as death, MI, or emergency CABG. Clinical success can be defined as a successful PCI accompanied by relief of symptoms and adequate recovery in a given patient. Long-term clinical success is dependent on the durability of short-term results. The main complications of PCI that threaten both short-term and long-term success of the procedure include abrupt vessel closure and restenosis.

Restenosis represents a healing response to vessel wall injury as a consequence of balloon inflation during PCI. Typically, the more severe or deep the injury to the vessel wall, the greater the magnitude of the resulting response needed to heal the vessel wall. In the case of PCI, the healing response is composed of vessel remodeling, elastic recoil, and neointimal hyperplasia. Multiple pharmacological and mechanical interventions had been investigated in an attempt to limit the occurrence of restenosis without success until the introduction of bare metal stents. Their introduction as an adjunct to balloon angioplasty resulted in significant reductions in the incidence of restenosis compared with balloon angioplasty alone. Unfortunately, although the incidence was reduced, a significant 20%–30% incidence of restenosis remained at 6 months even after bare metal stent placement. Subsequently, it was realized that stents address negative remodeling and elastic recoil, but have no effect on, and may actually stimulate, neointimal hyperplasia. Basic science work found that inflammation plays a significant role in neointimal hyperplasia, leading to using the stent itself as a platform for delivery of antiproliferative drug therapy. The introduction of drug-eluting stents (using either sirolimus or paclitaxel) has lowered the rate of restenosis from PCI to less than 10%, theoretically removing one of the major disadvantages of PCI compared with CABG for revascularization therapy.

As the procedure for PCI has evolved to include drug-eluting stents, antithrombotic therapy has also evolved to address the acute and chronic risk of thrombotic occlusion. The risk of acute vessel closure due to thrombosis can be prevented through the judicious use of both antiplatelet and antithrombin drugs. Aspirin should be administered to all patients undergoing PCI with or without stent placement, as it has reduced the ischemic complications from the procedure. Patients not taking daily ASA before the procedure should be given 300–325 mg at least 2 hours (preferably 24 hours) before the procedure. Patients taking chronic ASA therapy should be administered a supplemental dose of 75–325 mg before the PCI procedure to ensure adequate antiplatelet response to cover noncompliance. Clopidogrel is also recommended at the time of PCI. Current available evidence supports the use of a 300-mg loading dose at least 6 hours before the intervention to allow for adequate onset of antiplatelet action, as recommended in the current ACC/AHA PCI guidelines. Larger loading doses

have been investigated, with current available studies indicating that a 600-mg loading dose provides a more rapid onset of action at 2 hours. A few select, small trials have also evaluated loading doses of 900–1200 mg. It does not appear that these larger loading doses provide a faster onset of antiplatelet effect compared with 600 mg. Despite the favorable results for the 600-mg loading dose, no large randomized studies have compared the efficacy and safety of different loading doses. The issue of which loading dose to use is often irrelevant for patients with chronic stable angina because PCI is often done electively and a 300 mg loading dose can often be administered at least 6 hours before the procedure.

The administration of a glycoprotein IIb/IIIa (GP IIb/IIIa) receptor antagonist, in addition to ASA and clopidogrel, is also strongly recommended for patients undergoing PCI. Glycoprotein IIb/IIIa receptor antagonists have been shown to reduce the incidence of MI and death in patients undergoing PCI in a variety of settings. In patients with chronic stable angina undergoing elective PCI, the use of any of the available drugs (abciximab, eptifibatide, or tirofiban) is considered reasonable according to the ACC/AHA PCI guidelines. However, many clinicians would argue that the current FDA-approved dosing regimen for tirofiban does not provide adequate platelet inhibition at the time of PCI and would opt to use abciximab or eptifibatide. Regardless of which drug is selected, careful attention should be paid to ensuring that patients receive the appropriate dose and duration of therapy, and that doses are adjusted adequately for renal dysfunction for drugs eliminated primarily through the kidney (tirofiban and eptifibatide) to prevent bleeding complications that can arise with the use of these potent antiplatelet drugs.

Along with antiplatelet therapy, patients should also receive antithrombin therapy with either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) at the time of PCI. When administered without a GP IIb/IIIa antagonist, the dose of UFH should be 70–100 units/kg to produce an adequate level of anticoagulation as measured by the activated clotting time (ACT). When a GP IIb/IIIa antagonist is to be used, the initial dose of UFH should be reduced to 50–70 units/kg because a lower level of anticoagulation (as measured by the ACT) is desired to minimize the risk of bleeding. In either case, supplemental boluses (2000–5000 units) of UFH may be given during the procedure to maintain the ACT above the desired level. Weight-based dosing of UFH is critical for minimizing adverse bleeding complications in the setting of PCI. Enoxaparin represents the LMWH that has been most extensively studied in the setting of PCI and is considered a reasonable alternative to UFH in the setting of unstable angina/non-ST-segment elevation MI. However, due to familiarity, cost, and ability to monitor the level of anticoagulation via the ACT, most patients still receive UFH. In addition, the use of LMWHs for patients undergoing elective PCI has yet to be fully established. In either case, administration of antithrombin therapy with UFH or LMWH is indicated only for the duration of the procedure because post-procedure administration of UFH has increased the risk of bleeding.

In patients with heparin-induced thrombocytopenia, administering a direct thrombin inhibitor (bivalirudin or argatroban) should be used in place of heparin (either UFH or LMWH). Bivalirudin also represents a potential alternative to the routine administration of UFH plus a GP IIb/IIIa receptor antagonist in the setting of low-risk elective PCI. In a trial of low-risk patients undergoing elective PCI, patients randomized to bivalirudin plus provisional GP IIb/IIIa antagonist therapy had a similar rate of the primary end point (death, MI, urgent revascularization, and major bleeding) at 30 days as patients who received UFH plus routine GP IIb/IIIa receptor antagonist therapy. Treatment with bivalirudin was associated with a significantly lower rate of major bleeding, but a slightly higher rate of ischemic events (not statistically significant). This study was not powered to adequately assess mortality at 1 year, and no statistically significant difference between the groups was seen, although the trend was in favor of the bivalirudin treatment arm (1.89% vs 2.46%). These results indicate that a strategy of bivalirudin plus provisional GP IIb/IIIa receptor antagonist therapy, in addition to ASA and clopidogrel, is a reasonable option for the prevention of ischemic complications in patients undergoing elective PCI. Bivalirudin should be administered as a 0.75 mg/kg bolus followed by a 1.75 mg/kg/hour infusion for the duration of the procedure. If clinically needed (such as a patient with active heparin-induced thrombocytopenia), the infusion may be continued after the procedure using 0.2 mg/kg/hour.

With stent implantation in the setting of PCI, the risk of thrombotic closure of the target vessel extends beyond the short term and has become a significant complication in the long-term follow-up of these patients. Studies established that dual antiplatelet therapy with ASA and clopidogrel was the most effective antithrombotic strategy for preventing in-stent thrombosis. The duration of dual antiplatelet therapy is targeted to the duration of time required for the vessel to heal and for the stent surface to be covered with intact endothelium. This duration of healing varies depending on the type of stent and, hence, there are differing durations of dual antiplatelet therapy for each stent type. Patients receiving bare metal stents should receive ASA plus clopidogrel for at least 1 month, after which clopidogrel may be discontinued and ASA maintained for chronic therapy of CAD. As sirolimus and paclitaxel not only inhibit restenosis, but also slow the process of vessel repair, the duration of dual antiplatelet therapy is longer. Patients receiving a sirolimus (CYPHER) stent should receive the combination for at least 3 months, whereas those who receive a paclitaxel (Taxus) stent should be maintained on dual therapy for at least 6 months. Thereafter, clopidogrel may be discontinued and ASA should be maintained. One important caveat with these recommended durations is that current ACC/AHA guidelines also state that dual antiplatelet therapy should ideally be continued for up to 12 months in all patients undergoing PCI, if they are at low risk of bleeding. Therefore, specific recommendations for the duration of dual antiplatelet therapy based on the type of stent represent the minimum requirement, with the understanding that therapy should ideally be continued for up to 12 months in selected patients. In the event that PCI and stent placement was done in the context of ACS, dual

therapy may also be continued for up to 12 months regardless of the stent type used. Aspirin should be dosed at 325 mg/day and clopidogrel at 75 mg/day during the duration of stent prophylaxis. Once the appropriate time frame of dual antiplatelet therapy has been reached, the dose of ASA should be reduced to the lowest effective dose (typically 81 mg) to lower the risk of adverse events.

Therapeutic Approach to the Management of Patients With Chronic Stable Angina

The treatment of patients with chronic stable angina should always begin with appropriate treatment of cardiovascular risk factors and the implementation of lifestyle changes (diet and exercise) that have been demonstrated to prevent progression of disease or improve quality of life. Furthermore, drug therapy for the purposes of risk factor modification should include drugs that have reduced the risk of cardiovascular events in the long term. The HMG-CoA reductase inhibitors have an extensive library of clinical trials demonstrating that they reduce the future risk of MI, stroke, and cardiovascular death and should be the primary lipid-lowering drug used unless contraindicated. Therapy should be titrated to a goal LDL of less than 100 mg/dL; However, a goal of less than 70 mg/dL is reasonable according to recent secondary prevention guidelines from the AHA. In patients requiring drug therapy for the treatment of diabetes, consideration should be given to using metformin or pioglitazone to reach a goal hemoglobin A1c less than 7%, as available clinical trials suggest each may lower the risk of future cardiovascular events. As previously discussed, adoption of a dietary pattern that emphasizes fruits, vegetables, whole grains, lean protein, high fiber, and polyunsaturated fats has resulted in significant reductions in long-term cardiovascular events.

All patients with chronic stable angina should also be on chronic antiplatelet therapy with ASA. In patients with ASA intolerance, or a contraindication to ASA therapy, clopidogrel should be substituted. The use of alternative antiplatelets drugs such as dipyridamole or cilostazol has not been demonstrated to provide benefit in this patient population and is not recommended.

All patients should be provided with a prescription for sublingual nitroglycerin for the treatment of acute anginal attacks, as well as receive education regarding the proper use and storage of the drug. Patients with frequent anginal attacks (several per week to several per day) merit chronic therapy to reduce or eliminate anginal attacks and improve quality of life. As previously discussed, select patients may be appropriate candidates and elect to undergo revascularization (CABG or PCI) to reduce their anginal burden. However, even in patients who have undergone PCI or CABG, many will continue to require chronic anti-anginal therapy to adequately control their disease. The most recent ACC/AHA guidelines for treating chronic stable angina advocate the use of β-blockers as the first-line choice for chronic anti-anginal therapy. This recommendation is not based on any randomized clinical trial evidence that β-blocker therapy reduces cardiovascular morbidity and mortality in patients with chronic angina, but rather on the body of literature that demonstrates the benefit of β-blockade in MI, HF, and hypertension. However, recent data from non-randomized studies indicate that β-blockers may have long-term benefits in reducing hard cardiovascular end points in patients with chronic angina. In addition, the strong recommendation for β-blockers as opposed to CCBs as first-line therapy stems from historical concerns regarding the safety of CCBs, as well as the relative lack of clinical trial data suggesting that CCBs improve long-term prognosis in any CVD state.

Recent clinical trials using long-acting CCBs to treat hypertension and chronic stable angina have put to rest the safety concerns that CCBs may result in increased mortality or risk of cancer. In addition, several hypertension trials have demonstrated that CCB therapy can reduce the long-term incidence of hard cardiovascular end points such as death and MI. Taken together, this new information indicates that either a CCB or β-blocker could be considered relatively equal options as initial anti-anginal therapy for patients with chronic stable angina and that specific patient characteristics should likely drive the choice between the two classes of drugs. Patients with a history of MI or HF should preferentially be treated with a β-blocker due to the clear benefits on morbidity and mortality seen in clinical trials. Patients who are physically active or who have significant reactive airway disease or peripheral arterial disease may benefit from a CCB as their initial anti-anginal choice. However, in the absence of any compelling reason to select a β-blocker or CCB, current guidelines still support the use of a β-blocker as initial therapy.

The argument over the initial choice of anti-anginal drug in many patients is moot because many patients will require combination therapy to attain adequate control of their disease. β-Blockers and CCBs can be an effective combination, so long as appropriate consideration is paid to the potential additive hemodynamic effects that may manifest in an individual patient. Chronic nitrate therapy (patch, isosorbide dinitrate, or isosorbide mononitrate), although not effective as initial monotherapy, is also a reasonable option to combine with either a CCB or β-blocker to provide additional protection from anginal attacks. Similar consideration should also be paid to the potential additive hemodynamic effects when adding a nitrate.

Ranolazine offers an exciting new option in the treatment of chronic stable angina due to its unique mechanism of action, as well as lack of significant hemodynamic effects compared with existing anti-anginal drugs. However, as with any new drug cost will be a significant consideration given that conventional anti-anginal drugs have been available as generic formulations for some time. Relatively high drug cost along with currently available trial data dictate the role of ranolazine as add-on to existing therapy with a β-blocker, CCB, nitrate, or some combination thereof, when additional protection from angina is needed.

In addition, in patients who may not tolerate the hemodynamic effects of adding a β-blocker, CCB, or long-acting nitrate to their drug regimen, ranolazine offers a reasonable alternative to optimize drug therapy for managing chronic stable angina. Appropriate consideration should be given to potential drug-drug interactions, as well as electrophysiologic effects with ranolazine, to optimize safety and efficacy.

Once anti-anginal therapy has been titrated in a patient-specific fashion to an optimal level of symptom control, consideration should be given to implementation of an ACE inhibitor for vascular protection. Patients with diabetes, who are post-MI, who have HF, or who require additional blood pressure control above that provided by the anti-anginal regimen would likely benefit significantly from the institution of an ACE inhibitor. Although the current evidence that ACE inhibitors provide a benefit beyond blood pressure control is controversial, it is reasonable to consider therapy in all patients with CAD based on the HOPE and EUROPA studies. Unless another compelling indication is present for using an ACE inhibitor (e.g., HF and MI), ACE inhibitor therapy should be implemented only after the anti-anginal regimen has been optimized so that titration of β-blockers, CCBs, or long-acting nitrates is not limited by the risk of hypotension.

Patient Education

Key to the effective treatment of any disease state is the complete understanding by the patient of how specific treatments work and how to appropriately use both pharmacological and nonpharmacological therapy. Education of patients with CAD should start with the appropriate role and significant benefits of lifestyle changes and control of risk factors. Emphasis must be placed on encouraging patients to alter lifestyle habits because they will likely be the most effective intervention for preventing disease progression and improving prognosis. Pharmacists should have an active role in educating patients about how to make reasonable, but significant changes in diet, exercise, and other risk factor modification. In addition, pharmacists should serve as a resource in educating the public regarding interventions that will not improve prognosis, such as high-dose vitamin E supplementation.

Pharmacists should also educate their patients on the appropriate use of drugs for control of angina, including the appropriate storage and use of sublingual nitroglycerin, and how to contact emergency medical services in case of an emergency.

Quality Improvement

The most recent ACC/AHA guidelines provided a 10-point plan to help clinicians maximize treatment of patients with chronic stable angina. This 10-point plan includes both treatment and risk factor reduction strategies:

A = Aspirin and anti-anginals, B = β-blocker and blood pressure, C = cholesterol and cigarettes, D = diet and diabetes, E = education and exercise.

Additional quality improvement initiatives are needed to address the increasingly recognized divide between treatment of men and women with CAD. A recent study evaluating how men and women with stable angina are treated demonstrated that women were less likely than men to undergo exercise ECG, be referred for coronary angiography, and receive antiplatelet therapy or an HMG-CoA reductase inhibitor. Pharmacists can play a large role in optimizing therapy for patients with chronic stable angina by advocating for and ensuring the appropriate use of both pharmacological and nonpharmacological treatments for this condition.

Conclusion

Chronic stable angina composes a significant portion of the overall disease burden from CAD. The goals of treatment should include not only relief from symptoms, but also the extension of life through prevention of major complications such as MI, HF, and stroke. Anti-anginal therapy mainly consists of the judicious use of CCBs, β-blockers, and long-acting nitrates. Ranolazine is a promising new option for the treatment of chronic stable angina; however, although close attention is required to ensure safe and appropriate use. Pharmacists have a vital role in ensuring that patients receive appropriate pharmacological and nonpharmacological therapy, as well as educating patients about their disease and treatments.

Annotated Bibliography

1. Parikh P, McDaniel MC, Ashen MD, Miller JI, Sorrentino M, Chan V, et al. Diets and cardiovascular disease: an evidence-based assessment. J Am Coll Cardiol 2005;45:1379–87.

This review paper is an excellent resource that summarizes the current knowledge of various diets on cardiovascular risk factors, as well as hard cardiovascular end points such as death and MI. Although the Mediterranean Diet was the focus for this chapter, this review provides valuable information on the cardiovascular risk and benefits of current dietary fads, such as the Atkins or South Beach Diet. In addition, the authors do an excellent job of synthesizing the positive results from several different dietary interventions and providing the reader with a global dietary pattern that can be used by patients with CAD to reduce morbidity and mortality.

2. Costa MA, Simon DI. Molecular basis of restenosis and drug-eluting stents. Circulation 2005;111:2257–73.

This article is an outstanding review on the pathophysiology of restenosis and current drug-eluting stent technology. In particular, the article does a good job of integrating the molecular basis of restenosis and providing the rationale for the development of current drug eluting-stents used in clinical practice. This review also discusses in detail the role of inflammation in the development of restenosis and provides a nice overview of potential future interventions that are being investigated to prevent the development of restenosis after PCI. This review does not provide an overview of clinical trial information regarding the currently available drug-eluting stents. If further information is desired

on the available clinical trials, the reader is directed to the 2005 ACC/AHA PCI Guidelines.

3. Munzel T, Daiber A, Mulsch A. Explaining the phenomenon of nitrate tolerance. Circ Res 2005;97:618–28.

   This excellent review provides a detailed look at the mechanism of how nitrates produce their pharmacological effect, as well as the most recent information available on how tolerance to nitrates develops. The potential role of neurohormonal systems in the development of tolerance is discussed at length, along with the potential that chronic nitrate therapy is harmful by producing oxidative stress, which also leads to the loss of pharmacological activity. The article then integrates information regarding how certain pharmacological drugs may prevent the development of nitrate tolerance.

4. Williams B. Recent hypertension trials: Implications and controversies. J Am Coll Cardiol 2005;45:813–27.

   Although this paper primarily deals with the treatment of hypertension, it is an excellent and comprehensive contemporary review and addresses some of the relevant issues in the selection of specific drug therapies for chronic stable angina. In particular, it provides an excellent overview of the recent clinical trial evidence supporting the relative equivalency of various antihypertensive drug classes (diuretics, β-blockers, CCBs, ACE inhibitors, and ARBs). The review also provides an in-depth discussion on the controversy of the role of ACE inhibitors in patients with CAD. The author clearly takes the stand that ACE inhibitors provide no added benefit beyond lowering blood pressure. Nevertheless, the controversy is reviewed in detail and provides the reader with the opportunity to formulate his or her own opinion.

5. Bunch TJ, Muhlestein JB, Bair TL, Renlund DG, Lappe DL, Jensen KR, et al. Effect of beta-blocker therapy on mortality rates and future myocardial infarction rates in patients with coronary artery disease but no history of myocardial infarction or congestive heart failure. Am J Cardiol 2005;95:827–31.

   As discussed in the chapter, little clinical trial information exists that supports the ACC/AHA guideline recommendation for β-blockers as the first-line anti-anginal drugs in patients with chronic stable angina and no contraindications to therapy. Although this particular paper is admittedly not scientifically rigorous, it does provide some evidence to support the use of β-blockers as first-line anti-anginal drugs in patients with chronic stable angina. After identifying patients with CAD, but no previous MI or HF, their analysis showed that patients who were receiving β-blocker therapy had a lower incidence of all-cause mortality in 3 years of follow-up. Although this paper could not be used alone to support the statement that a β-blocker should be first-line anti-anginal therapy in patients with chronic stable angina because they improve long-term outcomes, it can be used with other available trials that demonstrate similar findings to support such a statement. Unfortunately, the authors did not analyze β-blockers against other available anti-anginal therapies.

6. Hippisley-Cox J, Coupland C. Effect of combinations of drugs on all cause mortality in patients with ischemic heart disease: a nested case-control analysis. BMJ 2005;330:1059–63.

   This case-control analysis provides direct evidence that β-blocker therapy can improve long-term prognosis in patients with CAD. Along with ASA and HMG-CoA reductase inhibitor therapy, β-blocker therapy significantly reduced the likelihood of all-cause death in patients with CAD (only one-third had previously experienced an MI). Of importance, the benefit of β-blocker therapy was in addition to benefits seen with ASA and HMG-CoA reductase inhibitor therapy. Unfortunately, the authors did not evaluate the effect of other anti-anginal therapies on the incidence of all-cause mortality in this cohort. Although β-blocker therapy was beneficial, the addition of an ACE inhibitor was not beneficial at reducing all-cause death. This finding conflicts with the result of the HOPE and EUROPA trials, but is in line with the results from the PEACE trial and further clouds the issue of whether all patients with CAD should receive ACE inhibitor therapy.

7. Poole-Wilson PA, Lubsen J, Kirwan BA, Van Dalen FJ, Wagener G, Danchin N, et al.; A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system investigators. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. Lancet 2004;364:849–57.

   This trial is the most contemporary investigation of the effects of using a CCB in the treatment of chronic stable angina. Patients on standard therapy (80% β-blocker, 37% chronic nitrates, 60% HMG-CoA reductase inhibitors, and 85% ASA) were randomized to extended-release nifedipine or placebo. Overall, nifedipine did not increase or decrease the incidence of death, MI, or cerebrovascular events over a 5-year period. Nifedipine did lower the incidence of coronary angiography and the need for revascularization, presumably through its anti-anginal effects. Of importance, this trial demonstrated the safety of extended-release nifedipine in this patient population while also demonstrating that CCBs do not reduce hard cardiovascular end points in patients with CAD. These results are consistent with a similar trial evaluating the use of amlodipine in patients with chronic stable angina (PREVENT trial).

8. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al; PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised Controlled Trial. Lancet 2005;366:1279–89.

   There has been a great deal of interest in the peroxisome proliferator-activated receptor-γ agonists and their potential therapeutic benefits that extend beyond glucose control in people with diabetes. Additional work before this publication indicated that pioglitazone may reduce the progression of atherosclerosis as measured by carotid intimal thickness. This paper builds on this work and demonstrates that the addition of pioglitazone reduced the incidence of MI, stroke, and death compared with placebo. Of importance, the study population was receiving what would be considered aggressive medical therapy for CAD. This study did generate some controversy surrounding the issue of not meeting their primary end point, which included not just the hard clinical end points of death, MI, and stroke, but also included revascularization procedures (both cardiac and peripheral). Although the inclusion of revascularization procedures may not have been a good choice, and certainly prevented the primary end point from achieving statistical significance, the reduction in clinical end points cannot be ignored.

Abbreviations

9. Chaitman BR. Ranolazine for the treatment of chronic angina and potential use in other conditions. Circulation 2006;113:2462–72.

This is an excellent contemporary review of the new anti-anginal drug, ranolazine. This review provides a comprehensive assessment of the drug, including its mechanism of action, clinical trial data, and potential safety concerns. The reader will be able to further investigate any aspect of the drug by referring to selected references from this review.

SELF-ASSESSMENT QUESTIONS

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Questions 1–8 pertain to the following case.

R.T. is a 51-year-old woman who presents to the internal medicine clinic for her regular follow-up. Her blood pressure 3 weeks ago was 162/97 mm Hg with a pulse of 68 beats/minute. R.T.'s medical history includes seasonal allergic rhinitis, hypertension, anterior cruciate ligament repair in the left knee 10 years ago, and a cesarean section 7 years ago. She has a 25 pack-year history of smoking and drinks 1–2 glasses of wine with dinner. Current drugs include fluticasone nasal spray (one spray into each nostril daily), ibuprofen 400–600 mg orally as needed for knee pain, and pseudoephedrine 30 mg orally as needed for nasal congestion. Her only complaint is occasional knee pain that limits her ability to exercise and has contributed to weight gain over the past 3 years. Current vital signs are blood pressure of 164/108 mm Hg and heart rate of 66 beats/minute. She is 5'7" and weighs 172 pounds. Her current lipid profile shows a total cholesterol of 244 mg/dL, high-density lipoprotein (HDL) 39 mg/dL, (low-density lipoprotein) LDL 181 mg/dL, and triglycerides 122 mg/dL.

1. Which one of the following is the most appropriate recommendation for R.T. for primary prevention of coronary artery disease (CAD) at this time?
   A. Aspirin (ASA) 325 mg/day by mouth.
   B. Clopidogrel 75 mg/day by mouth.
   C. Aspirin 81 mg/day plus clopidogrel 75 mg/day both by mouth.
   D. Aspirin 81 mg/day by mouth.

2. R.T. is curious about the relationship of risk factors and the potential for developing CAD. She asks for more information from her primary care physician during her visit. Which one of the following statements is the most appropriate response?
   A. Long-standing hypertension can cause endothelial dysfunction, elevating levels of nitric oxide (NO) which facilitate the development of atherosclerosis.
   B. Obtaining a C-reative protein (CRP) level may allow for further refinement of R.T.'s future risk of cardiovascular disease.
   C. The role of excess adipose tissue in the development of CAD is limited to the development of hypertension and dyslipidemia.
   D. The presence of hypertension would be expected to increase the risk of first time myocardial infarction (MI) in R.T. by 4-fold.

3. After discussion with her primary care physician, R.T. is concerned about her overall risk for developing CAD in the future and specifically asks about using vitamin supplements. Which one of the following statements is the most appropriate response?
   A. The administration of vitamin E plus folic acid lowers homocysteine levels and decreases the risk of MI.
   B. Vitamin E, in doses greater than 50 IU/day, may be associated with an increase in total mortality.
   C. Although successful at lowering homocysteine levels, the combination of folic acid and B vitamins has not reduced the risk of MI or death.
   D. Meta-analyses of available randomized, placebo-controlled trials indicate that supplementation with vitamin E can reduce the risk for MI.

R.T. returns 2 years later to her primary care physician with complaints consistent with the development of chronic angina. Coronary angiography reveals the presence of an 80% stenosis in the right coronary artery, along with a 40% stenosis in the left anterior descending artery and 50% stenosis in the circumflex artery. Her left ventricular ejection fraction is estimated to be 60%. R.T. consents to a percutaneous coronary intervention (PCI) of the right coronary artery with possible stent placement.

4. During your consultation with R.T., which one of the following descriptions offered by her would be most consistent with pain secondary to chronic stable angina?
   A. Chest pain occurring at rest or with minimal activity such as washing dishes.
   B. Chest pain that occurs with exertion and lasts several hours.
   C. Chest pain that occurs with exertion and is relieved by nitroglycerin.
   D. Chest pain on exertion that is of increased severity compared with previous anginal pain.

5. Which one of the following is the most appropriate antithrombotic regimen for R.T. for her PCI procedure?
   A. Aspirin 325 mg and clopidogrel 75 mg 2 hours before the procedure; unfractionated heparin (UFH) plus eptifibatide during the procedure.
   B. Aspirin 81 mg and clopidogrel 600 mg 6 hours before the procedure; bivalirudin plus provisional eptifibatide during the procedure.
   C. Aspirin 325 mg and clopidogrel 300 mg 2 hours before the procedure; bivalirudin plus planned eptifibatide during the procedure.
   D. Aspirin 325 mg and clopidogrel 600 mg 2 hours before the procedure; UFH and eptifibatide during the procedure.

6. During PCI, R.T. receives a paclitaxel-eluting stent after balloon inflation of the 80% lesion in her right coronary artery. Which one of the following is the most appropriate choice (minimum duration) for R.T. to prevent in-stent thrombosis chronically?
   A. Aspirin 81 mg/day plus clopidogrel 75 mg/day for 6 months, then ASA 81 mg/day thereafter.
   B. Aspirin 325 mg/day plus clopidogrel 75 mg/day for 3 months, then ASA 81 mg/day thereafter.

C. Aspirin 325 mg/day plus clopidogrel 75 mg/day for 6 months, then ASA 325 mg/day thereafter.
D. Aspirin 325 mg/day plus clopidogrel 75 mg/day for 6 months, then ASA 81 mg/day thereafter.

One year after her PCI, R.T. returns to her primary care physician with a 1-month history of recurrent angina attacks on exertion. She reports experiencing 3–4 attacks/week, typically after having walked 8–10 blocks, all of which are relieved with rest and the administration of 0.4 mg sublingual nitroglycerin. After further evaluation and work-up, the decision is made to medically manage her angina. She reports adhering to a low-fat diet and regular exercise program, which has been curtailed recently with the re-emergence of angina attacks. Vital signs during the current visit include blood pressure of 135/95 mm Hg with heart rate of 60 beats/minute. Her current drugs include fluticasone nasal spray (one spray into each nostril daily), sublingual nitroglycerin 0.4 mg (one tablet sublingually as needed for chest pain), ASA 81 mg/day, and atorvastatin 20 mg/day.

7. Which one of the following represents the best choice for R.T. at this time?
   A. Ranolazine 500 mg orally 2 times/day.
   B. Amlodipine 5 mg/day orally.
   C. Metoprolol 25 mg orally 2 times/day.
   D. Isosorbide mononitrate 60 mg/day orally.

8. Which one of the following statements best describes the expected therapeutic effects of anti-anginal drugs in R.T. during physical exertion?
   A. β-Blocker therapy would be expected to increase oxygen delivery.
   B. Long-acting nitrate therapy would be expected to reduce heart rate and myocardial oxygen demand.
   C. Non-dihydropyridine (DHP) calcium channel blocker (CCB) therapy would be expected to reduce heart rate and myocardial oxygen demand.
   D. Ranolazine therapy would be expected to reduce contractility and myocardial oxygen demand.

9. You have been asked to develop a 2-hour lecture on ischemic heart disease for Doctor of Pharmacy students. Which one of the following statements would be the most appropriate to incorporate into your lecture regarding the development and progression of atherosclerosis?
   A. Decreased oxidative stress results in reduced NO bioavailability and endothelial dysfunction.
   B. A diet high in fruits, vegetables, and polyunsaturated fats results in increased oxidative stress.
   C. Adiponectin promotes the development of endothelial dysfunction by stimulating pro-inflammatory cytokines.
   D. Decreased NO bioavailability is associated with elevated levels of angiotensin II and endothelin.

Questions 10–14 pertain to the following case.

T.B. is a 54-year-old man reporting for his annual physical. He has gained 12 pounds in the past year. His blood pressure is 158/95 mm Hg and heart rate is 71 beats/minute. T.B.'s medical history is significant for type 2 diabetes for 8 years, hypertension for 6 years, depression, hyperlipidemia, and CAD (angina and MI 3 years ago). His drugs include glipizide XL 10 mg/day, ASA 325 mg/day, atenolol 100 mg/day, amlodipine 10 mg/day, simvastatin 10 mg/day, sertraline 150 mg/day, and sublingual nitroglycerin 0.4 mg as needed for chest pain. He is 5'11" and weighs 284 pounds. Physical examination is unremarkable, and significant laboratory results include blood urea nitrogen 12 mg/dL, serum creatinine 1.5 mg/dL, glucose 143 mg/dL, total cholesterol 168 mg/dL, HDL 45 mg/dL, LDL 94 mg/dL, and triglycerides 140 mg/dL.

10. Which one of the following would reduce the progression of atherosclerosis long term in T.B.?
    A. Vitamin E 200 IU/day.
    B. Soy protein 25 g/day.
    C. Mediterranean Diet.
    D. Fish oil 2 g/day.

11. Which one of the following would reduce the risk of death or MI for T.B.?
    A. Pioglitazone 4 mg/day.
    B. Isosorbide mononitrate 60 mg/day.
    C. Losartan 50 mg/day.
    D. Ranolazine 500 mg 2 times/day.

12. During T.B.'s examination, he reports experiencing 2–3 anginal attacks per week on his current drug regimen. The attacks typically happen during exertion and are affecting his ability to exercise regularly. Which one of the following therapies would be the most appropriate to implement for T.B. at this time?
    A. Add ranolazine 500 mg 2 times/day and switch amlodipine to diltiazem CD 180 mg/day.
    B. Add ranolazine 500 mg 2 times/day and increase simvastatin to 20 mg/day.
    C. Add ranolazine 500 mg times/day and add isosorbide mononitrate 60 mg/day.
    D. Add ranolazine 500 mg times/day and add ramipril 5 mg/day.

13. T.B. is unfamiliar with ranolazine, and his physician requests that you as the pharmacist counsel and educate him about the drug. Which one of the following statements should you include in your counseling session?
    A. Ranolazine works to prevent chest pain by decreasing the number of times your heart beats per minute, reducing the amount of oxygen it needs.
    B. If an antidepressant is prescribed for you, tell your doctor or pharmacist because the risk of adverse events with ranolazine is increased.
    C. Watch for muscle aches in the first few weeks after you start taking ranolazine as the adverse effects from simvastatin may be increased.
    D. The most common adverse effects you may experience with ranolazine include drowsiness, joint pain, and constipation.

14. Which one of the following if currently prescribed would prevent the initiation of ranolazine in T.B.?
    A. Concomitant administration of flecainide.
    B. Concomitant administration of digoxin.
    C. Concomitant administration of simvastatin.
    D. Concomitant administration of verapamil.

Questions 15–17 pertain to the following case.

R.S. is a 58-year-old woman in the clinic today for follow-up of her angina pectoris. At her last visit, she was initiated on a nitroglycerin transdermal patch, 0.4 mg/hour every 24 hours, and sublingual nitroglycerin 0.4 mg as needed for chest pain. She states that during the first week her anginal episodes decreased from 4–5/week to 1–2/week. Thereafter, the episodes returned to 4–5/week. All episodes occur with physical exertion and are relieved by rest. She reports being able to walk 4–5 blocks before experiencing chest pain. Medical history is also significant for heart failure (HF) (ejection fraction last estimated at 25%), MI, and hyperlipidemia. Drugs include digoxin 0.125 mg/day, furosemide 40 mg/day, dofetilide 250 mcg 2 times/day, ASA 81 mg/day, atorvastatin 20 mg/day, potassium chloride 20 mEq 2 times/day, nitroglycerin 0.4 mg sublingually as needed, and nitroglycerin patch 0.4 mg/hour. Physical examination is significant for blood pressure 136/82 mm Hg, pulse irregularly irregular with ventricular response of 62 beats/minute, respiratory rate 18 breaths/minute, and positive for a third heart sound.

15. Which one of the following questions would be the most pertinent to ask when assessing R.S.'s recent increase in anginal episodes?
    A. What kind of activity are you doing when you are getting chest pain?
    B. How many sublingual nitroglycerin tablets do you use when you get anginal attacks?
    C. When and how often do you replace your nitroglycerin patch?
    D. Where do you store your nitroglycerin patches?

16. Which one of the following choices would be the most appropriate to implement in R.S. at this time?
    A. Discontinue nitroglycerin patch and initiate amlodipine 2.5 mg/day.
    B. Discontinue nitroglycerin patch and initiate metoprolol 50 mg orally 2 times/day.
    C. Continue nitroglycerin patch and initiate diltiazem CD 120 mg/day.
    D. Continue nitroglycerin patch, but increase dose to 0.6 mg/hour.

17. As you are counseling R.S. on the changes to her drug regimen, she mentions that she recently saw an advertisement of television for a drug called Plavix. After explaining to her that the drug is in the same class as ASA, she asks whether she should be taking it in addition to ASA. In which one of the following scenarios is dual antiplatelet therapy (ASA plus clopidogrel) indicated?
    A. For 1 year after PCI in the setting of non-ST segment elevation acute coronary syndrome (ACS).
    B. For 2 weeks after implantation of a bare metal stent during PCI.
    C. Chronically in patients with documented CAD.
    D. For 3 months after implantation of a paclitaxel-eluting stent.

Questions 18 and 19 pertain to the following case.

M.H. is a 54-year-old man who presents for follow-up with his cardiologist after being discharged from the hospital 3 days ago for the treatment of non-ST segment elevation ACS. He underwent PCI plus stent placement (bare metal stent) of the left anterior descending artery lesion. Medical history includes CAD (post-MI and stent placement 1 year ago), chronic stable angina for 7 years, dyslipidemia for 11 years, type 2 diabetes for 11 years, hypertension for 11 years, obesity, and history of substance abuse (cocaine, alcohol, and marijuana). He admits to a lack of exercise and a sedentary lifestyle. Drugs include ASA 325 mg/day, clopidogrel 75 mg/day, lisinopril 10 mg/day, isosorbide mononitrate 60 mg/day, metoprolol XL 150 mg/day, simvastatin 40 mg/day, nitroglycerin 0.4 mg sublingually as needed for chest pain, metformin 1000 mg 2 times/day, glipizide 20 mg/day in the morning, and omeprazole 40 mg/day. Vital signs include blood pressure 143/93 mm Hg, heart rate 58 beats/minute, respiratory rate 18 breaths/minute, weight 253 pounds, height 5'10", waist circumference 42 inches. Physical examination and laboratory results are normal except for a total cholesterol of 205 mg/dL, HDL 29 mg/dL, LDL 121 mg/dL, triglycerides 275 mg/dL, CRP less than 0.5 mg/dL, hemoglobin A1c 8.1%, and glucose 225 mg/dL.

18. Which one of the following drugs is most likely to reduce cardiovascular outcomes and death in M.H.?
    A. Insulin.
    B. Lisinopril.
    C. Amlodipine.
    D. Glipizide.

19. Which one of the following interventions would be appropriate to implement for M.H. at this time?
    A. Decrease ASA dose from 325 mg/day to 81 mg/day.
    B. Decrease simvastatin from 40 mg to 20 mg/day.
    C. Increase metoprolol from 150 mg to 200 mg/day.
    D. Increase lisinopril from 10 mg to 20 mg/day.

One year later, M.H. returns to his primary care physician with complaints of exertional angina 3–4 times/week. He has recently heard on the news about drug-eluting stents and is looking for information regarding the best treatment approach for him at this time.

Abbreviations

20. Which one of the following is the most appropriate response to M.H.'s inquiry?

    A. Coronary artery bypass graft therapy is superior to PCI in terms of reducing the need for repeat revascularization procedures.
    B. Medical therapy is superior to PCI at providing relief of angina and reduce overall mortality at 1 year.
    C. In a patient with multi-vessel disease and left ventricular dysfunction, PCI reduces long-term mortality compared with coronary artery bypass graft.
    D. In a patient with multi-vessel disease and left ventricular dysfunction, medical therapy and coronary artery bypass graft produce similar 5-year survival rates.