Chapter 33: Stable Ischemic Heart Disease

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 11, Ischemic Heart Disease.

KEY CONCEPTS

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1. Stable ischemic heart disease (SIHD) is caused by an obstructive atherosclerotic plaque in one or more epicardial coronary arteries. Increases in myocardial oxygen demand in the setting of a fixed decrease in myocardial oxygen supply result in myocardial ischemia. Some patients with SIHD may have a component of vasospasm that requires a slightly different pharmacologic approach.
2. Chest pain (angina) from exertion is the cardinal symptom of myocardial ischemia in patients with SIHD.
3. Assessment of successful treatment of angina includes reducing the number of episodes, enabling patients to participate in activities that provide a high-level quality of life, and decreasing mortality by using guideline-directed medical therapy (GDMT).
4. Management of modifiable atherosclerotic risk factors is key to improving the quantity of life in patients with SIHD.
5. Aspirin, angiotensin-converting enzyme inhibitors, and statins play an important role in preventing adverse cardiovascular events in patients with SIHD.
6. β-Blockers are typically regarded as first-line therapy in the management and control of episodes of angina in patients with SIHD.
7. Calcium channel blockers, long-acting nitrates, and ranolazine are often used as additional therapies for angina. Calcium channel blockers and nitrates are first-line therapies in vasospastic disease.
8. All patients with SHID should receive sublingual nitroglycerin for acute treatment and should receive education regarding its proper use.
9. Revascularization procedures may provide a survival advantage over GDMT in SIHD patients with more extensive atherosclerotic disease but have not demonstrated a clear advantage over GDMT in those with less extensive disease. Antithrombotic therapy is necessary after revascularization for a variable duration of time.

BEYOND THE BOOK

BEYOND THE BOX

To better understand the normal physiology of the heart and the pathophysiology of coronary artery disease (CAD), please watch the following videos. These videos are useful to enhance learner's understanding regarding the COLLECT and ASSESS steps in the Patient Care Process.

1. Pathophysiology of CAD—What is Coronary Artery Disease? Khan Academy: https://tinyurl.com/y3cjyb8v (Duration: 13:38 minutes)
2. Myocardial oxygen supply—University of British Columbia, UBC Anesthesiology: https://tinyurl.com/yxjouoh3 (Duration: 4:59 minutes)
3. Myocardial oxygen demand—University of British Columbia, UBC Anesthesiology: https://tinyurl.com/y5488brm (Duration: 4:37 minutes)

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of ischemic heart disease and is typically the result of atherosclerotic plaques in the epicardial vessels. The process of atherosclerosis begins early in life, with fatty steaks developing in many people in their teenage years or early twenties. These plaques grow over decades and start to become pathologic in a person's fifth decade of life and beyond. In addition to CAD, atherosclerosis also manifests in other vascular beds leading to cerebrovascular disease (Stroke, Chapter 39) and peripheral arterial disease (Chapter e35). Ischemic heart disease may present as an acute coronary syndrome (ACS) (Chapter 34), which includes unstable angina, non-ST-segment myocardial infarction (MI), or ST-segment elevation MI. While the pathophysiology is similar, stable ischemic heart disease (SIHD) is not an acute event but rather manifests as either chronic stable exertional angina or ischemia without clinical symptoms (silent ischemia). Less common causes of SIHD include microvascular angina, which is due to atherosclerosis in endocardial instead of epicardial vessels. Microvascular angina is more common in women and those with metabolic syndrome. Coronary vasospasm represents a form of angina that results from an increase in coronary vascular tone that can occur in either normal or diseased vessels. Prinzmetal's angina is a form of vasospastic angina that does not involve atherosclerotic plaque. Inappropriate, insufficient, or untreated SIHD can lead not only to MI and cardiac death, but also to the development of heart failure (HF), arrhythmias, and valvular disease. The American College of Cardiology (ACC) and American Heart Association (AHA) have published guidelines for the diagnosis and management of SIHD.[1]

EPIDEMIOLOGY

According to AHA statistics, in 2018, an estimated 126.9 million (49%) adult Americans had at least one form of cardiovascular disease (CVD), which includes CAD, HF, stroke, and hypertension (HTN).[2] Among patients with CVD, approximately 20.1 million adult Americans had CAD, corresponding to an estimated prevalence of 7.2%. The prevalence of CAD increases with age and is higher in men. Among patients with CAD, the total number of patients with SIHD is difficult to determine. Statistics from the AHA estimate that approximately 11 million Americans have angina pectoris while the prevalence of MI among adult Americans is approximately 8.8 million, together approximating the prevalence of CAD.[2] Stable angina is the initial manifestation of ischemic heart disease in approximately one-half of all patients who eventually have an MI.

The mortality and costs associated with CAD are enormous. In 2018, CVD was the number one cause of death in the United States with CAD being the most common cause of CVD death, accounting for almost 400,000 deaths—42% of all CVD-related mortality.[2] Adjusting for age, death rates per 100,000 are highest among black patients compared to those of white and Hispanic ancestry and among men compared to women within each racial demographic. The estimated direct and indirect cost of CAD was $220 billion in 2016-2017, with direct healthcare spending of $89 billion.[2]

The prognosis of patients with SIHD is related to the extent of atherosclerotic disease, the presence of left ventricular (LV) dysfunction, and the presence of other comorbidities. The severity of angina symptoms may also be useful in determining the prognosis.[3] In a study of veterans with CAD, the risk of death increased with the degree of self-reported physical limitation due to angina.[4] It is thought that the degree of physical limitation reflects the extent of underlying atherosclerotic disease. In addition to mortality, SIHD leads to significant morbidity. Most patients will eventually need to be hospitalized for ACS. Patients often have a reduced quality of life due to their inability to perform activities of daily living without chest pain.[5,6] Time lost from work and lost productivity have a large indirect cost to patients and society. Approximately 15% to 20% of patients rate their health as fair or poor despite revascularization, and 30% of patients are never able to return to work.[7]

ETIOLOGY AND PATHOPHYSIOLOGY

Angina pectoris is most often the result of an imbalance between myocardial oxygen supply and myocardial oxygen demand (MVO_2). The process of maintaining adequate coronary blood flow to meet the metabolic demands of the myocytes is complex. Multiple factors influence the supply/demand equation.

The pathophysiology of SIHD is driven by an increase in MVO_2 in the setting of a fixed decrease in myocardial oxygen supply.[8] The etiology of the fixed decrease in supply is long-standing, well-developed atherosclerotic plaque. These plaques grow over several decades. The extent and rate of growth are related to risk factors such as smoking, dyslipidemia, HTN, diabetes mellitus (DM), and genetics. The process and development of atherosclerosis are detailed in Chapter 32 (Dyslipidemia). Unlike ACS, the episodes of angina in patients with SIHD are not caused by ruptured atherosclerotic plaque, which leads to thrombus formation and a rapid reduction in coronary blood flow.[9,10] Rather, the atherosclerotic plaques are stable, have a reduced lipid core, and a firm calcified covering. Since the vessel lumen size does not acutely change, the atherosclerotic plaque produces a relatively fixed decrease in myocardial oxygen supply.

Determinants of Myocardial Oxygen Demand

The major determinants of MVO_2 include heart rate (HR), myocardial contractility, and intramyocardial wall tension. A twofold increase in any of these determinants requires an approximate 50% increase of coronary flow to maintain the myocardial oxygen supply. Intramyocardial wall tension is the leading contributor to increased MVO_2 and is directly related to the radius or size of the ventricular cavity and blood pressure (BP), and indirectly related to the ventricular muscle mass. The larger the size of the ventricular cavity, the more energy or myocardial work is needed for myocardial contraction (systole). During early systole, myocardial work peaks when the pressure in the LV overcomes the pressure outside the aortic valve. The aortic valve is then pushed open and blood is ejected into the systemic circulation. The higher the blood pressure outside the aortic valve, the more MVO_2 needed. Increased ventricular muscle mass should make myocardial work easier and reduce MVO_2. For example, some athletes have increased ventricular muscle mass and their heart works more efficiently. Unfortunately, left ventricular hypertrophy results in dysfunctional myocytes that do not improve MVO_2. Left ventricular hypertrophy can worsen the supply/demand balance because the blood vessel development (supply) is less than the native myocardium.

The rate-pressure product, or double product, is a common non-invasive measure of MVO_2. To determine the rate-pressure product, multiply the HR and systolic BP. However, changes in contractility or volume loading of the LV are not accounted for in this calculation. An increase in MVO_2 requirements commonly stems from the release of norepinephrine by adrenergic nerve endings in the myocardium and vascular bed as part of the physiologic response to exertion, emotion, or mental stress. The rate of increase of MVO_2, which correlates to the speed at which a physical task is carried out, can be as important as the total amount of MVO_2. A rapid increase in physical exertion is particularly likely to precipitate angina. Tasks involving motion of the hands over the head can also provoke chest pain. Mental and emotional stress may precipitate angina, presumably by increasing adrenergic tone and reducing vagal activity. Sexual activity may precipitate angina due to the combination of physical exertion and emotional stimulation. Similarly, anger can produce constriction of coronary arteries. Other precipitates of angina include physical exertion after a heavy meal and excessive metabolic demands imposed by chills, fever, exposure to cold, thyrotoxicosis, hypoglycemia, and other causes of tachycardia.

Determinants of Myocardial Oxygen Supply

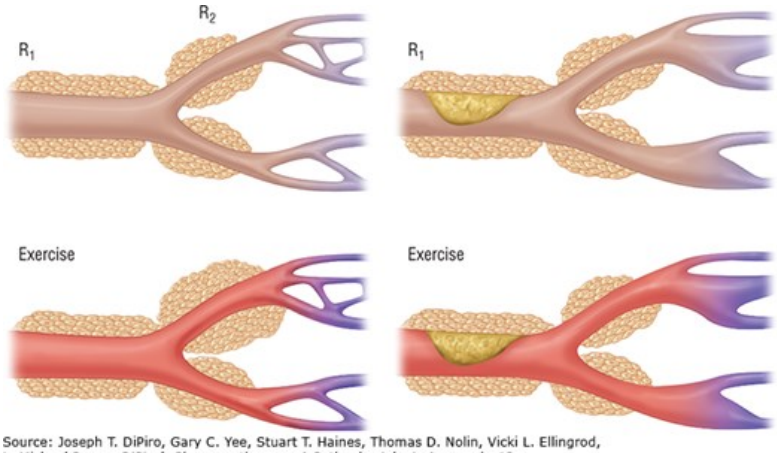
Coronary Blood Flow

Meeting the metabolic demands of the myocardium is centered on the ability to maintain adequate coronary blood flow and coronary arterial pressure. The coronary vasculature is made up of larger epicardial vessels, also referred to as R_1 or conductance vessels, and smaller endocardial vessels called R_2 or resistance vessels (Fig. 33-1).[11] Resistance to coronary blood flow is the sum of the resistance in the R_1 and R_2 vessels. The larger epicardial vessels typically offer little resistance to blood flow and can accommodate large increases in coronary blood flow without producing a

significant change in pressure. These vessels primarily serve a conduit function. In healthy coronary arteries, resistance to flow is controlled by smaller endocardial (R_2) vessels. These vessels will contract and dilate to maintain blood flow based on the metabolic demands of the myocardium. When a person is at rest or not engaged in physical activity, MVO_2 is low and endocardial vessels constrict. The need for blood flow is low. When there is physical exertion or emotional stress, MVO_2 increases and the endocardial vessels dilate to increase myocardial oxygen supply in proportion to the increase in MVO_2 (Fig. 33-1). The process of constricting and dilating the resistance vessels based on MVO_2 is called autoregulation.[8,11] In response to increased MVO_2, several vasodilatory substances (eg, nitric oxide, prostacyclin, and bradykinin) are secreted and this can increase coronary blood flow four- to fivefold over normal resting conditions.[8] The increase in coronary flow above resting conditions is the coronary flow reserve.

FIGURE 33-1

The coronary circulation with large epicardial conductance vessels (R_1) and intramyocardial resistance arterioles (R_2). Resistance to flow equals $R_1 + R_2$. R_2 resistance is normally much greater than R_1; hence, flow is equal to the driving pressure across the coronary bed divided by the resistance in R_2. Dilation in R_2 normally occurs in response to exercise or increased myocardial oxygen demand. When an atherosclerotic lesion narrows the conductance vessel, the arterioles dilate under resting conditions to prevent ischemia. However, during the period of exertion, the vasodilator reserve is limited. *(Reproduced from Epstein SE, O'Cannon R, Talbot TL. Hemodynamic principles in the control of coronary blood flow. Am J Cardiol. 1985;56:4E-10E.)*



Coronary atherosclerotic plaques typically develop in the larger epicardial vessels. As plaques grow and cause luminal narrowing, resistance to blood flow in epicardial vessels transforms from minimal to considerable. This continues to a point where the resistance from the epicardial vessels becomes dominant. Through autoregulation, the increase in resistance from the R_1 or conductance vessels is offset by vasodilation in the R_2 or resistance vessels to maintain flow.[11]

The luminal diameter occupied by the atherosclerotic plaque determines the drop in pressure and blood flow distal to the stenosis. The most important determinant of resistance for any given level of flow is the minimum stenosis cross-sectional area.[8] Because resistance is inversely proportional to the square of the cross-sectional area, small dynamic changes in the luminal area caused by atherosclerotic plaque size, thrombus creation, or vasospasm can lead to large changes in the stenosis pressure-flow relationship and reduce maximal perfusion during vasodilation.[8]

Coronary plaques that occupy less than 50% to 70% of the vessel luminal diameter are often referred to as "non-obstructive". They rarely produce ischemia or angina.[11] These smaller plaques do not produce symptoms, and therefore, the patient and clinician typically have no idea they exist. Small plaques have a rich lipid core and thin fibrous cap, they are more prone to rupture and provoke acute thrombus formation, making them potentially lethal (see Chapter 34 "Acute Coronary Syndrome").[9,10]

Once the epicardial vessel is narrowed by 70% or more of the luminal diameter, the endocardial vessels must fully dilate in order to maintain normal coronary flow. These larger plaques are considered "obstructive."[8,11] At this point, much of the coronary flow reserve has been used to preserve

resting coronary blood flow and minimal physical exertion exhausts any remaining capacity. Further increases in exercise intensity are no longer accompanied by decreases in endocardial (R_2) resistance. Blood flow cannot increase to accommodate the demand and autoregulation has reached its ceiling. The resulting flow deficit causes myocardial ischemia and, frequently, angina. The amount of exertion a patient can endure is largely based on the extent of vessel stenosis and the remaining coronary flow reserve. The endocardial flow reserve is exhausted when the epicardial stenosis severity exceeds 90%. Narrowing of the luminal diameter by 90% or more is called a critical stenosis.

Heart Rate and Systole

Increasing HR not only increases MVO_2 but also reduces myocardial oxygen supply. While most tissues and organs are perfused during systole, the heart is the only organ that is perfused during diastole, the phase of myocardial relaxation. There are two physiologic explanations.[8] First, the pressure created in the ventricles during systole creates an increase in pressure in the coronary circulation well above the pressure for coronary perfusion (50-60 mm Hg). Only during diastole do the pressures drop sufficiently to allow coronary flow. Second, the physical compression force of the myocardium that occurs during systole squeezes the coronary vessels closed, preventing blood flow. During a typical cardiac cycle with a normal resting HR, the myocardium spends twice as much time in diastole compared to systole. When the HR increases, time spent in diastole is reduced while time in systole remains relatively unchanged. During times of exertion and increased HR, the ratio of time spent in diastole to systole is reduced from 2:1 to as little as 1:1. This reduces the time for myocardial perfusion, and thus, myocardial oxygen supply is significantly diminished.[8]

Oxygen Extraction and Oxygen Carrying Capacity

Two additional determinants of myocardial oxygen supply are myocardial oxygen extraction and oxygen-carrying capacity. The oxygen-carrying capacity of the coronary arteries is relatively fixed under normal circumstances and not capable of changing in response to increased MVO_2. Therefore, during exertion, the ability to increase oxygen delivery to myocytes is limited mainly through increasing oxygen extraction from the arterial blood. However, this compensatory mechanism provides little additional oxygen as myocardial arterial oxygen extraction is already approximately 75% under normal circumstances.[12]

Arterial oxygen content is related to hemoglobin concentration and oxygen saturation. Consequently, patients with anemia (low hemoglobin) or hypoxia (low oxygen saturation) have lower than normal oxygen-carrying capacity. Anemia is thought to impact total oxygen-carrying capacity to a greater degree than hypoxia until the oxygen saturation falls below 50% (0.50). This explains why patients with SIHD often require transfusions when hemoglobin concentrations fall below 9 to 10 g/dL (90-100 g/L; 5.59-6.21 mmol/L), whereas patients without SIHD can tolerate hemoglobin concentrations as low as 6 g/dL (60 g/L; 3.72 mmol/L). Most patients have arterial oxygen saturation between 95% and 100% (0.95 and 1.0) so oxygen therapy would not improve oxygen delivery. Therefore, there is little opportunity to improve myocardial oxygen supply by improving myocardial oxygen extraction or oxygen-carrying capacity, leaving increased myocardial blood flow as the principal mechanism for increasing myocardial oxygen supply.

Coronary Collateral Circulation

In the setting of SIHD, preexisting collateral vessels develop in a process termed arteriogenesis. When coronary stenosis exceeds 70%, endocardial vessel pressure falls due to maximized autoregulation. This extent of stenosis also contributes to the severity and duration of the episodes of exertion-induced ischemia. The ischemic episodes stimulate nitric oxide synthase and lead to the production of vascular endothelial growth factor and basic fibroblast growth factor. The combination of altered coronary pressure, growth factors, and endogenous vasodilators (eg, nitrous oxide and prostacyclin) change native collateral vessels in existing epicardial anastomoses into mature vessels.[13] While most functional collateral flow develops from the process of arteriogenesis, collateral perfusion can also occur from the development of new collateral vessels in a process called angiogenesis. The process of angiogenesis is also driven by physical forces and growth factors but produces smaller, capillary-like vessels. These vessels can provide collateral flow in the border between ischemic and nonischemic regions of the myocardium.[13] Capillary angiogenesis may also occur within the ischemic region and can reduce the intercapillary distance for oxygen delivery.

Other Factors

While atherosclerotic coronary stenosis is the leading etiology in the development of SIHD and angina, there are additional pathophysiologic

mechanisms that also contribute to disease onset and progression. These mechanisms include endothelial dysfunction, microvascular dysfunction, vasospasm, platelet activation, and coagulation, as well as inflammation.[13] A reduction in nitric oxide-mediated vasodilation leads to endothelial dysfunction. This can be due to impaired nitric oxide synthesis or availability. Reduced vasodilator response may lead to ischemia at lower levels of exertion. There can also be impairments that reduce microvascular response to endogenous vasodilators or exaggerate the response to vasoconstrictors.[13]

Patients with an ACS event have ruptured atherosclerotic plaque with platelet accumulation and coagulation response producing an acute reduction in myocardial oxygen supply.[9,10] While this is not the pathophysiology of ischemia in patients with SIHD, there can be smaller plaques (30%-50% stenosis) that rupture and produce a limited platelet and coagulation response that does not produce an acute compromise in myocardial oxygen supply. Instead, the thrombotic process is arrested and the thrombus undergoes re-endothelialization.[9] This greatly accelerates plaque accumulation. Finally, inflammation plays a role in the pathophysiology of SIHD. Macrophages and T lymphocytes produce and secrete cytokines, chemokines, and growth factors that activate endothelial cells, increase vasoreactivity, and proliferation of vascular smooth muscle cells.[13,14] C-reactive protein, a marker of inflammation, has been shown to be elevated in patients with SIHD and correlates to adverse CV events. Statin therapy in patients with elevated C-reactive protein and normal cholesterol levels reduces the risk of CV events.[15] While an obstructive atherosclerotic plaque contributes to ischemia and angina in patients with SIHD, the pathophysiology involves multiple mechanisms that can be used as therapeutic targets.

Coronary Vasospasm and Prinzmetal's Angina

Most patients with SIHD have an obstructive coronary stenosis and exertion-induced ischemia. Since the size of the obstructive lesion does not change acutely, the amount of exertion needed to induce ischemia and angina is often predictable in an individual patient. For example, the patient knows that working in the garden for 20 minutes or walking five blocks at a certain pace will produce chest pain. Patients with this pattern of angina have a fixed angina threshold. The threshold of angina varies in some patients. In these patients, the amount of exertion needed to provoke chest pain differs from day-to-day. An example would be the patient who could walk six blocks before experiencing angina yesterday, but today they can only walk one block before becoming symptomatic. These patients have an obstructing atherosclerotic plaque leading to a fixed decrease in myocardial oxygen supply, but also have transient vasospasm superimposed at the site of the obstructing plaque.[11,13] The vasospasm at or distal to the location of atherosclerotic plaque is typically induced by endothelial damage. Damaged endothelial cells produce less than normal amounts of vasodilator substances such as endothelium-derived relaxing factor (EDRF) and often have an exaggerated response to vasoconstrictors during exercise.[13] Symptoms will differ based on the extent of the underlying fixed obstruction and the degree of dynamic change in coronary arterial tone. The changing pattern of ischemia in these patients reflects varying amounts of vasospasm. Angina episodes are typically more common in the morning hours due to the circadian release of vasoconstrictors. Exposure to cold temperature, emotion, and mental stress may also lower the angina threshold in patients with variable threshold angina.

Some patients have variant angina, also known as Prinzmetal's angina. Patients with variant angina usually do not have flow-obstructing atherosclerotic plaques in their coronary arteries, but instead, have vasospasm in epicardial vessels.[8,13] The vasospasm is due to the reduced production of vasodilators and an exaggerated response to endogenous vasoconstrictors. Patients with Prinzmetal's angina also have a different clinical presentation when compared to patients with SIHD due to an obstructive coronary plaque. Patients with Prinzmetal's angina are typically younger, may experience chest pain at rest, often in the early morning, and have transient ST-segment elevation on the electrocardiogram (ECG).

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Stable Ischemic Heart Disease (SIHD)

General

- The patient is not typically in acute distress; however, careful assessment to identify features consistent with ACS is important.

Symptoms

- The classic symptom of ACS is abrupt-onset substernal chest pain or discomfort often described as a squeezing, heaviness, or tightness (Table 33-1). Symptoms may radiate to the arms, shoulders, back, abdomen, or jaw. Nausea, vomiting, diaphoresis, or shortness of breath may also be present.
- The PQRST pneumonic (Table 33-2) is useful for structuring the patient interview to assess the history of chest pain.
- Evaluation of symptoms should include an evaluation of the limitations in daily activities due to angina (eg, CCS classification, see Table 33-3).

Signs

- BP may be elevated in patients with SIHD
- No physical findings are specific for SIHD. Nonspecific findings include S4 or paradoxical splitting of S2 on auscultation.
- Patients with SIHD may present with signs of HF, including jugular venous distention, pulmonary edema, and an S3 on auscultation.

Laboratory Tests

- Cardiac troponin (cTn, either cTnI or cTnT) are not typically elevated in patients with SIHD.
- Fasting lipid panel should be evaluated to assess for the presence of dyslipidemia.
- C-reactive protein may be obtained but is more valuable as a screening tool to detect CAD rather than guide treatment decisions.

Other Diagnostic Tests

- A 12-lead ECG should be obtained in a patient with symptoms of SIHD. However, it is often normal in patients with SIHD.
- Exercise stress testing is a noninvasive test to detect CAD in patients presenting with symptoms of SIHD.
- Coronary angiography is often performed in patients with a high likelihood of SIHD (eg, “positive” exercise stress test) to detect the presence and extent of CAD.
- Other diagnostic tests may be used in select patients to detect CAD or assess for progression of disease and include myocardial perfusion imaging, cardiac magnetic resonance, “ultra-fast computed tomography (CT),” and CT angiography.

2 A thorough patient history is key to the clinical assessment of a patient with SIHD. Exertional chest pain is the classic presenting symptom of patients with SIHD. The differential diagnosis of “chest pain” is broad (Table 33-1). Therefore, it is important to determine if symptoms are due to cardiac or noncardiac pathology. The patient’s description of chest pain can be helpful in determining if the pain is more likely SIHD or ACS. The PQRST pneumonic is commonly used when conducting the patient interview to gather important aspects of the chest pain story (Table 33-2).

TABLE 33-1

Differential Diagnosis of Episodic Chest Pain Resembling Angina Pectoris

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

TABLE 33-2

PQRST Approach to Assessment of a Patient's Chest Pain

Factor	Presentation in Stable Ischemic Heart Disease	Questions to Ask
Precipitating factors	Typically brought on by some level of exercise or exertion	What were you doing when the pain started? What brought on this chest pain?
Palliative measures	Relieved by rest with or without sublingual nitroglycerin in 5-10 minutes	Is there anything that helps the pain go away? If you rest, does the pain get better? Does your sublingual nitroglycerin help?
Quality of the pain	Described as a continuous squeezing, heaviness, or tightness	How would you describe the pain? Does the pain change when you breathe in and out?
Region	Substernal	Where is the pain located? Can you point to where the pain seems to originate?
Radiation	Left or right arm, back, down into the abdomen, up into the neck	Does the pain seem to radiate or go to other locations?
Severity	While pain is subjective, those who have pain report a 5 or higher on a 10-point scale	On a scale from 1 to 10, with 1 being no pain, and 10 being the worst pain you have ever had, how would you rate this pain?
Temporal pattern (timing)	Pain lasts less than 20 minutes and is usually relieved in 5-10 minutes	How long did the pain last? How long before the pain went away? After you started to rest, how long before the pain went away?

The chest pain in a patient with SIHD is often precipitated by exertion, such as walking, gardening, sexual activity, or activities of daily living such as showering, cleaning the house, or doing laundry. In this setting, the exertion produces an increase in MVO_2 that exceeds what can be provided by the fixed decrease in myocardial oxygen supply from the obstructive atherosclerotic plaque. Typically, rest or the use of sublingual (SL) nitroglycerin relieves the symptoms. As the patient rests for a few minutes, the HR and BP come down, re-establishing a balance between myocardial oxygen supply and demand, relieving their chest pain. The use of SL nitroglycerin provides acute relief by increasing myocardial oxygen supply through vasodilation of epicardial vessels and a reduction in preload.

Cardiac chest pain is often described as squeezing, crushing, heaviness, or tightness in the chest. It can also be described as numbness or burning in the chest. Chest pain that is described as sharp, increases with inspiration or expiration, or is reproducible with palpation is less likely to be cardiac in origin. The pain is often substernal and may radiate to the right or left shoulder, right or left arm (left more commonly than right), neck, back, or abdomen. Cardiac chest pain rarely radiates above the mandible (jaw) or below the umbilicus (belly button). The severity of cardiac chest pain can be difficult to quantify since pain is subjective, but most patients will state the pain is severe and rate it five or higher on a 10-point scale. The duration of chest pain in patients with SIHD is less than 20 minutes, usually only 5 to 10 minutes. Other symptoms that may be present during times of ischemia include diaphoresis, nausea, vomiting, and dyspnea.

1 It is helpful to connect the pathophysiology with the clinical presentation. In SIHD, ischemia is produced by an increase in MVO_2 in the setting of a fixed decrease in supply. The exertion exhausts autoregulation and coronary flow reserve. The patient experiences chest pain. When the patient rests for 5 to 10 minutes or uses an SL nitroglycerin, the MVO_2 decreases to a point in which myocardial supply and demand are back in balance—the pain and other symptoms go away. The major differences between the pain with SIHD compared to ACS would be the precipitating factors and the duration of the chest pain. The patient with an ACS typically has angina at rest that lasts longer than 20 minutes. The pathophysiology in a patient with an ACS is an abrupt decrease in myocardial oxygen supply precipitated by a plaque rupture.

The severity of chest pain and the impact of SIHD on daily activities are often evaluated using the Canadian Cardiovascular Society (CCS) classification system (Table 33-3).[16] The CSS system evaluates the level of activity needed to produce angina. All the current severity scores are limited by the subjective nature of a patient's pain as well as the reliability and reproducibility of patient observations.

TABLE 33-3

Grading of Angina Pectoris by the Canadian Cardiovascular Society Classification System

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

Reproduced from Campeau L. Grading of angina pectoris. *Circulation* 1976;54:522-523.

Not all patients have a typical chest pain presentation.[1] "Typical" angina is comprised of three components: (1) substernal chest discomfort with a characteristic quality and duration, which is (2) provoked by exertion or emotional stress, and (3) relieved by rest or nitroglycerin. Patients with "atypical" angina meet two of the three criteria. Patients meeting one or none of the typical angina characteristics likely have non-cardiac causes of chest pain. Patient groups more likely to present with atypical angina include women and older patients. Patients with DM may also have decreased sensation of pain due to neuropathy.[13] Features of atypical angina or angina equivalents include symptoms such as midepigastric discomfort, effort intolerance, dyspnea, and excessive fatigue. One study found that 65% of women with ischemia present with atypical symptoms.[17]

After a description of the chest pain has been obtained, a review of the patient's CAD risk factors should be performed. Non-modifiable risk factors include the patient's age, sex, and a family history of premature atherosclerotic cardiovascular disease (ASCVD) in first-degree relatives (onset in a male before the age of 55 years or a female before the age of 65 years). Modifiable risk factors including HTN, DM, dyslipidemia, and cigarette smoking should also be explored. In addition to considering traditional risk factors, markers of inflammation, such as high sensitive C-reactive protein, may also be obtained. The evidence regarding the utility of C-reactive protein in the setting of primary prevention is growing but its value in guiding therapy in the setting of established CAD (secondary prevention) is less certain. Due to the systemic nature of atherosclerotic cardiovascular disease (ASCVD), patients with a history of cerebrovascular or peripheral arterial disease are also at high risk for CAD. It is likely that patients who have atherosclerosis in cerebral or peripheral arteries also have atherosclerosis in their coronary arteries even if it has not yet led to episodes of angina.

The physical examination of a patient with SIHD usually produces nonspecific findings. At the time of an angina episode, patients may have tachycardia, diaphoresis, and shortness of breath. Patients may also have symptoms of nausea, vomiting, and lightheadedness. Other physical findings may relate to cardiovascular risk factors including an increased BP or a fourth heart sound reflecting long-standing HTN. Other findings may include pulmonary crackles, a displaced point of maximal impulse, or a third heart sound in patients with HF with reduced ejection fraction (HFrEF).

Diagnostic and Prognostic Testing

Several noninvasive and invasive testing can be done to assist in the diagnosis and evaluation of patients with SIHD. A detailed discussion of these tests and when they should be used can be found in the ACC/AHA SIHD guidelines.[1] More information on how each test is performed is available in Chapter

e29, “Evaluation of Cardiovascular Function.”

The results of cardiac testing can provide prognostic information, may help guide pharmacotherapy, and identify patients who need revascularization. All patients with angina symptoms should receive a 12-lead electrocardiogram (ECG). In the resting state, the ECG will be normal in ≥50% of patients with SIHD. In SIHD patients with a normal ECG at rest, about 50% will develop ischemic ST-T wave changes during an episode of angina. These changes can be observed on the ECG conducted during an exercise stress test. Exercise stress testing is a relatively easy and inexpensive method for detecting CAD. Since many patients cannot physically endure an exercise stress test, the myocardium can also be stressed pharmacologically with adenosine, regadenoson, dipyridamole, or dobutamine. Stress testing can provide important diagnostic and prognostic information, especially when conducted with a nuclear imaging study to evaluate myocardial perfusion.

Coronary angiography is the most accurate test for the diagnosis and assessment of patients with CAD and is considered the “gold standard.” Unfortunately, coronary angiography is an invasive technique that requires arterial access. Coronary angiography in patients with SIHD routinely reveals that approximately 25% of patients have a single-vessel disease, 25% have double-vessel disease, and 25% have triple-vessel disease, with 5% to 10% presenting with left main coronary disease and another 15% with no detectable critical vessel obstruction.

Coronary angiography is also useful in determining the fractional flow reserve (FFR) in patients with obstructive coronary stenosis. FFR is an indirect index determined by measuring the driving pressure of microcirculatory flow distal to the area of stenosis relative to the coronary driving pressure available in the absence of stenosis.[18] The FFR is attractive for clinical use in that it can immediately assess the physiologic significance of intermediate stenosis to help guide decisions regarding coronary intervention. Moreover, the FFR is unaffected by alterations in resting flow. Data suggest that patients with an FFR of less than or equal to 0.80 may have a better outcome with a revascularization procedure compared to medical therapy, but more studies are needed to determine the best use of this index.[18,19]

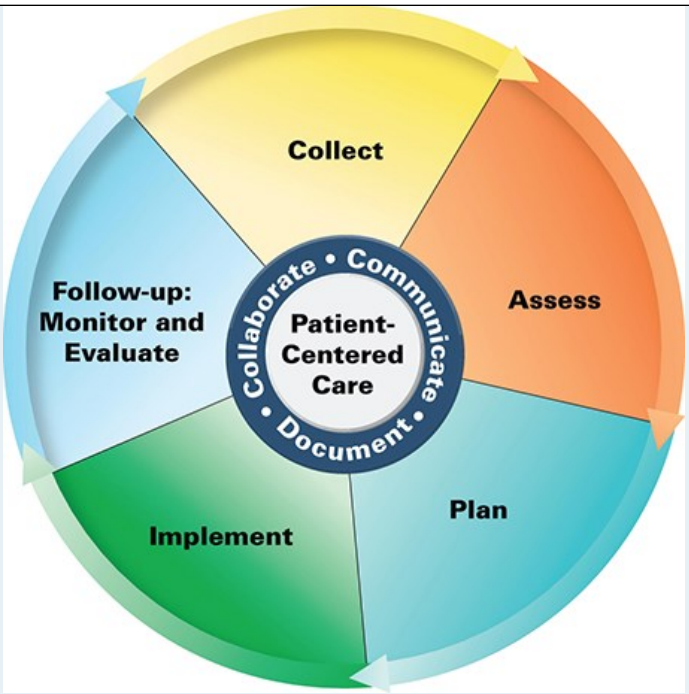
Additional noninvasive diagnostic tests may be used to establish the diagnosis of CAD or follow the progression of disease in patients with SIHD. Myocardial perfusion imaging (eg, nuclear imaging studies) involves the administration of an intravenous radioactive tracer before and after a stressor (exercise or pharmacologic). The uptake of the radioactive tracer is proportional to coronary blood flow in normal myocytes and the resulting images can detect perfusion defects. Cardiac magnetic resonance combined with physiologic or pharmacologic stressors can also detect the presence of perfusion defects as well as wall motion abnormalities. Coronary artery calcium scoring using computed tomography (CT), often called “ultra-fast CT” or electron beam CT, multislice or multidetector CT, and CT angiography can also be used to detect the presence of CAD.

Biomarkers

Cardiac troponin concentrations are released with myocyte death (infarction) and hence are not typically elevated in patients with SIHD. A study of patients undergoing percutaneous coronary intervention (PCI) for the treatment of SIHD found that 6% of patients had an elevated troponin before PCI and these patients were more likely to have an MI or die in-hospital when compared to patients without an elevated troponin (13.4% vs 5.6%).[20] The differences in these outcomes were significant even after 1 year.[20] The study was conducted at multiple sites and, given the lack of a single reference range, no specific troponin value designating increased risk could be determined. The reasons why troponin predicted these outcomes is not completely understood but may be due to increased cardiac cell membrane permeability with repeated ischemia.

PATIENT CARE PROCESS

Patient Care Process for Stable Ischemic Heart Disease (SIHD)



Collect

- Patient characteristics (eg, age, sex, pregnant)
- Description of chest discomfort and/or related symptoms (eg, precipitating factors, palliative measures, quality, location, radiation, and severity)
- Patient medical (personal and family) and social histories (eg, tobacco/ethanol use), dietary habits (eg, intake of foods high in sodium, cholesterol, and/or saturated fat), and physical activity (eg, frequency and duration of moderate-intensity aerobic activity)
- Current medications including over-the-counter (OTC) medications (eg, aspirin-containing medications), herbals/dietary supplements
- History of allergy or intolerance to previous medications
- Objective data
- Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation
    - Labs: serum creatinine (SCr), potassium (K^+), hemoglobin (Hgb), platelets, liver function tests (LFTs), lipid profile, blood glucose, A1c
    - Diagnostic testing results

Assess

- Description of chest discomfort to determine differential diagnosis and classification of angina symptoms
- Presence of provoking factors (eg, exertion, mental/emotional stress, tachyarrhythmia, high adrenergic state including the use of stimulant medications, and exposure to cold)
- Presence/control of risk factors for SIHD (eg, hypertension, dyslipidemia, diabetes, smoking, and obesity)
- Presence/control of SIHD-related complications (eg, myocardial infarction [MI], heart failure [HF], and stroke)
- Adverse drug reactions from current/previous medications used to treat/prevent angina symptoms or major adverse cardiac events (MACE)

- Previous/recent revascularization procedures (eg, percutaneous coronary intervention [PCI] with/without stenting, and coronary artery bypass graft [CABG] surgery)
- Contraindications to medications to treat/prevent angina symptoms and/or prevent MACE
- Barriers that may impair adherence to the care plan

Plan*

- Initiate/modify drug therapy to treat and prevent angina symptoms, prevent MACE, and address risk factors for SIHD including specific drug(s), dose, route, frequency, and duration (see Fig. 33-2, Tables 32-6 and 32-7)
- Monitoring parameters: efficacy (eg, signs and symptoms of angina and SIHD-related complications) and adverse drug reactions; frequency and timing of follow-up
- Patient education: the purpose of treatment, lifestyle modifications, planned procedures, and drug-specific information (eg, indication, dose, route, frequency, adverse drug reactions; see Table 33-8)
- Self-monitoring for worsening angina symptoms, signs and symptoms of SIHD-related complications, adverse drug reactions, when to seek emergency medical attention
- Address barriers to adherence to medications and lifestyle modification
- Referrals to other providers (eg, primary care provider, endocrinologist, dietician, and smoking cessation)

Implement*

- Provide patient education regarding all elements of the treatment plan as described above
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, every 1-2 months until goals achieved, then every 6-12 months)

Follow-up: Monitor and Evaluate

- Frequency and severity of chest discomfort, sublingual nitroglycerin use, exercise tolerance, presence/control of SIHD risk factors, and presence/control of SIHD-related complications
- Presence of adverse drug reactions and drug-drug interactions
- Patient adherence to treatment plan using multiple sources of information

** Collaborate with the patient, caregivers, and other healthcare professionals.*

TREATMENT

Treatment recommendations from the ACC/AHA guidelines use a Class of Recommendation (COR) system, which estimates the size of the treatment effect, balancing efficacy, and safety. Each recommendation is also based on a Level of Evidence (LOE), which describes the quality, quantity, and consistency of supporting data. Table 33-4 describes the ACC/AHA recommendations and the levels of evidence.[1]

TABLE 33-4

The American College of Cardiology and American Heart Association Evidence Grading System

Recommendation Class	Level of Evidence
I. Conditions for which there is evidence or general agreement that a given procedure or treatment is useful and effective II. Conditions for which there is conflicting evidence or a divergence of opinion that the usefulness/efficacy of a given procedure or treatment is useful and effective a. The weight of evidence/opinion is in favor or usefulness/efficacy b. Usefulness/efficacy is less well established by evidence/opinion III. Conditions for which there is evidence or general agreement that a given procedure or treatment is not useful/effective and in some cases may be harmful	A. Data derived from multiple randomized clinical trials with large numbers of patients B. Data derived from a limited number of randomized trials with small numbers of patients, careful analyses of nonrandomized studies, or observational registries C. Expert consensus was the primary basis for the recommendation

Data from Reference 1.

The treatment of patients with SIHD typically involves two complementary strategies.[1] See Fig. 33-2. The first strategy is directed toward slowing the progression of atherosclerosis and preventing complications such as MI, HF, stroke, and death (either sudden cardiac death or progression of underlying CVD). This strategy focuses on risk-factor modification and providing vasculoprotection therapies (see Table 33-5). While vasculoprotective therapies have demonstrated the ability to reduce mortality, and therefore, the quantity of life, they have minimal impact on improving symptoms and the functional limitations caused by angina, or the quality of life. The second strategy is focused on reducing the number of ischemic episodes as well as increasing the amount of exertion or exercise a patient can accomplish before chest pain occurs (see Table 33-6). Antianginal therapies used to prevent or decrease ischemic episodes rarely have demonstrated a survival benefit but improve quality of life through symptom reduction. Each of the antianginal therapies is relatively equivalent in its ability to reduce ischemic episodes.[21]

FIGURE 33-2

Treatment algorithm for stable ischemic heart disease (guideline-directed medical therapy). The Hgb A1c goal of ≤7% (0.07) is equivalent to 53 mmol/mol. (ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; DHP, dihydropyridine; DM, diabetes mellitus; HTN, hypertension; LA, long-acting; LVEF, left ventricular ejection fraction.)

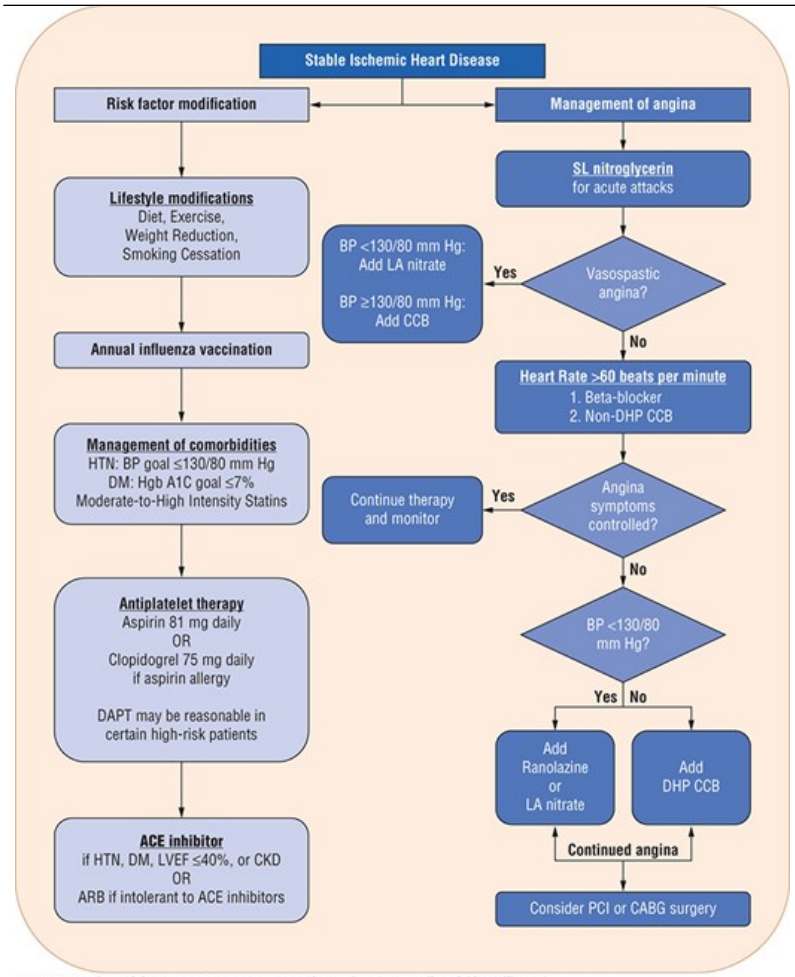


TABLE 33-5

Risk Factor Modification: American College of Cardiology/American Heart Association/American Diabetes Association Recommendations

Lipid Management
Class I
1. Lifestyle modifications, including daily physical activity and weight management, are strongly recommended for all patients with SIHD. 2. Dietary therapy for all patients should include reduced intake of saturated fats (to <7% of total calories), *trans*-fatty acids (to <1% of total calories), and cholesterol (to <200 mg/day). 3. In addition to therapeutic lifestyle changes, a high-intensity statin should be prescribed with a goal of achieving a ≥50% decrease in LDL-C, in the absence of contraindications or documented adverse drug reactions. 4. In patients with contraindications or intolerant to high-intensity statin therapy, moderate-intensity statins should be used, if tolerated, with a goal of achieving a 30%-49% decrease in LDL-C.
Class IIa
1. In patients older than 75 years, moderate- or high-intensity statin therapy should be used after considering the potential benefits (risk reduction) and risks (adverse drug reactions, drug-drug interactions, patient frailty). 2. For patients with an LDL-C >70 mg/dL (1.81 mmol/L) on maximally tolerated statin therapy and at very high risk for CV events, the addition of ezetimibe

is reasonable.
3. For patients with an LDL-C >70 mg/dL (1.81 mmol/L) or a non-HDL-C level ≥100 mg/dL (≥2.59 mmol/L) on maximally tolerated LDL-C lowering therapy (statin plus ezetimibe) and at very high risk for CV events, the addition of a PCSK-9 inhibitor is reasonable depending on benefit, risk, cost, and patient preference.

Blood Pressure Management

Class I

1. All patients should be counseled about the need for lifestyle modification: weight control; increased physical activity; alcohol moderation; sodium reduction; and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products.
2. In patients with SIHD with BP 130/80 mm Hg or higher, antihypertensive drug therapy should be instituted in addition to or after a trial of lifestyle modifications.
3. The specific medications used for the treatment of HTN in SIHD patients should be based on compelling indications (eg, prior MI, angina, and HFrEF) and may include β-blockers, ACE inhibitors, or ARBs with the addition of other drugs, such as thiazide diuretics, dihydropyridine calcium channel blockers, or aldosterone antagonists, if needed to achieve a goal of BP less than 130/80 mm Hg.
4. For patients with angina and persistent uncontrolled HTN, it is recommended to add dihydropyridine CCBs to β-blockers.

Class IIa

1. For patients who have had an ACS, it is reasonable to continue β-blockers long-term if needed for treatment of HTN.

Diabetes Management

Class I*

1. Among patients with type 2 DM who have established ASCVD or indicators of high-risk, established kidney disease, or HF, a sodium-glucose cotransporter 2 (SGLT2) inhibitor or glucagon-like peptide 1 (GLP-1) receptor agonist with demonstrated CVD benefit is recommended as part of the glucose-lowering regimen independent of A1c, metformin use, and in consideration of patient-specific factors.

Class IIa

1. For selected individual patients, such as those with a short duration of diabetes mellitus and a long life expectancy, a goal A1c of 7% (0.07; 53 mmol/mol) or less is reasonable.
2. A goal A1c <8% (0.08; 64 mmol/mol) is reasonable for certain patients according to age, history of hypoglycemia, the presence of microvascular or macrovascular complications, or presence of coexisting medical conditions.

Class IIb

1. Initiation of pharmacotherapy interventions to achieve target A1c might be reasonable.

Influenza Vaccination

Class I

1. Annual influenza vaccinations are recommended for patients with SIHD.

Physical Activity
Class I
1. For all patients, the clinician should encourage 30-60 minutes of moderate-intensity aerobic activity, such as brisk walking, at least 5 days and preferably 7 days per week, supplemented by an increase in daily lifestyle activities (eg, walking breaks at work, gardening, and household work) to improve cardiorespiratory fitness and move patients out of the least-fit, least-active, high-risk cohort (bottom 20%). 2. For all patients, risk assessment with a physical activity history and/or an exercise test is recommended to guide prognosis and prescription. 3. Medically supervised programs (cardiac rehabilitation) and physician-directed, home-based programs are recommended for at-risk patients at first diagnosis.
Class IIa
1. It is reasonable for the clinician to recommend complementary resistance training at least 2 days per week.
Weight Management
Class I
1. BMI and/or waist circumference should be assessed at every visit, and the clinician should consistently encourage weight maintenance or reduction through an appropriate balance of lifestyle, physical activity, structured exercise, caloric intake, and formal behavioral programs when indicated to maintain or achieve a BMI between 18.5 and 24.9 kg/m^2 and a waist circumference less than 102 cm (40 in.) in men and less than 88 cm (35 in.) in women (less for certain racial groups). 2. The initial goal of weight loss therapy should be to reduce body weight by approximately 5%-10% from baseline. With success, further weight loss can be attempted if indicated.
Smoking Cessation Counseling
Class I
1. Smoking cessation and avoidance of exposure to environmental tobacco smoke at work and home should be encouraged for all patients with SIHD. Follow-up, referral to special programs, and pharmacotherapy are recommended along with a systematic strategy for smoking cessation (Ask, Advise, Assess, Assist, Arrange, Avoid).
Management of Psychological Factors
Class IIa
1. It is reasonable to consider screening SIHD patients for depression and to refer or treat when indicated.
Class IIb
1. Treatment of depression has not been shown to improve cardiovascular disease outcomes but might be reasonable for its other clinical benefits.
Alcohol Consumption
Class IIb

1. In patients with SIHD who use alcohol, it might be reasonable for nonpregnant women to have one drink (4 ounces [~120 mL] of wine, 12 ounces [355 mL] of beer, or 1 ounce [30 mL] of spirits) a day and for men to have one or two drinks per day unless alcohol is contraindicated (such as in patients with a history of alcohol abuse or dependence or with liver disease).
Avoiding Exposure to Air Pollution
Class IIa
1. It is reasonable for patients with SIHD to avoid exposure to increased air pollution to reduce the risk of cardiovascular events.

*American Diabetes Association Standards of Medical Care in Diabetes recommendation is A: clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered.[24] This recommendation was considered equivalent to a Class I recommendation by the American College of Cardiology/American Heart Association.

Data from References 1 and 22-24.

TABLE 33-6

American College of Cardiology/American Heart Association Class of Recommendations for Pharmacotherapy to Relieve Symptoms

Class I
1. β-Blockers should be prescribed as initial therapy for the relief of symptoms in patients with SIHD (LOE B). 2. Calcium channel blockers or long-acting nitrates should be prescribed for the relief of symptoms when β-blockers are contraindicated or cause unacceptable adverse drug reactions in patients with SIHD (LOE B). 3. Calcium channel blockers or long-acting nitrates, in combination with β-blockers, should be prescribed for the relief of symptoms when initial treatment with β-blockers is unsuccessful in patients with SIHD (LOE B). 4. Sublingual nitroglycerin or nitroglycerin spray is recommended for the immediate relief of angina in patients with SIHD (LOE B).
Class IIa
1. Treatment with a long-acting non-dihydropyridine calcium channel blocker (verapamil or diltiazem) instead of a β-blocker as initial therapy for relief of symptoms is reasonable in patients with SIHD (LOE B). 2. Ranolazine can be useful when prescribed as a substitute for β-blockers for the relief of symptoms in patients with SIHD if initial treatment with β-blockers leads to unacceptable adverse drug reactions or is ineffective or if initial treatment with β-blockers is contraindicated (LOE B). 3. Ranolazine in combination with β-blockers can be useful when prescribed for relief of symptoms when initial treatment with β-blockers is not successful in patients with SIHD (LOE A).

Data from Reference 1.

Desired Outcomes

In addition to reducing the risk of CV events and mortality, the ACC/AHA SIHD guidelines state that a goal of therapy should be the complete, or nearly complete, elimination of chest pain and return to normal activities with a functional capacity of CCS class I angina.[1]

Pharmacologic Therapy

Providing guideline-directed medical therapy (GDMT), also referred to as optimal medical therapy, reduces the risk of mortality in patients with SIHD.[1] In the absence of proximal CAD, multivessel CAD, or acute ischemia, GDMT reduces the rate of death and MI similar to revascularization therapy for most patients with SIHD. Most of the evidence-based GDMT target risk-factor modification (Table 33-5), but also include aspirin and angiotensin-converting enzyme (ACE) inhibition.

Antithrombotic Therapy

5 Aspirin produces an antiplatelet effect by irreversibly blocking cyclooxygenase-1 (COX-1) activity (~95%) for the life of the platelet, thereby inhibiting thromboxane A_2 production. The reduction in thromboxane A_2 leads to reduced platelet activation and aggregation. Aspirin doses as small as 30 mg daily effectively inhibit COX-1. Aspirin doses above 75 to 100 mg provide little additional antiplatelet activity.[25] Aspirin may also provide benefits through some non-platelet-mediated effects. Higher doses of aspirin (≥325 mg daily) significantly impair endothelial secretion of prostacyclin, which is a natural vasodilator. Low-dose aspirin does not have this deleterious effect. Although aspirin may inhibit prostacyclin secretion, the effects on the endothelium are reversible, unlike its effect on platelets.[26] After unbound aspirin has been removed from the circulation (half-life is about 30 minutes), prostacyclin secretion and its vasodilation effects are restored. Aspirin may also attenuate the synthesis of cytokines such as interleukin-2, interleukin-6, and interferon in leukocytes as well as prevent leukocyte rolling and macrophage-induced endothelial activation.[26] The extent to which these pharmacologic properties contribute to the clinical benefits of aspirin is unknown.

Evidence supporting the effectiveness of aspirin in patients with SIHD first came from a subgroup analysis of the Physicians Health Study.[27] Patients with SIHD who took aspirin (325 mg every other day) had an 87% reduction in first MI compared to placebo. This benefit came with a significant increase in hemorrhagic stroke, although none of the strokes were fatal. These beneficial effects were confirmed in the more robust Swedish Angina Pectoris Aspirin Trial.[28] Patients with controlled angina on sotalol treated with 75 mg of aspirin daily had a 34% reduction in first MI or sudden death compared to placebo. There was no difference in major bleeding or stroke between the groups.

Some patients are nonresponsive to the antiplatelet effects of aspirin, and therefore, do not receive a clinical benefit. In patients with CAD, the risk of recurrent CV events was more than threefold higher in patients with aspirin non-responsiveness.[29] The rate of aspirin non-responsiveness was estimated to be 24% in one meta-analysis, but the range reported in the included studies was wide (0%-57%).[30] In studies that used light transmission aggregotomy induced with arachidonic acid (the gold standard test) or measured serum thromboxane B_2, the rate of aspirin non-responsiveness was only 6%.[30] These results are similar to the findings of the Aspirin-Induced Platelet Effects (ASPECT) trial, in which aspirin non-responsiveness defined by COX-1-nonspecific methods was 27%, compared to only 6% when COX-1-specific methods were used.[31] The ASPECT investigators also reported no difference in aspirin non-responsiveness between patients receiving 81, 162, or 325 mg daily.[31] A lack of dose-response is consistent with the findings of the Antithrombotic Trialists' Collaboration meta-analysis which demonstrated a similar reduction in vascular events regardless if patients were receiving low dose (75-150 mg daily), moderate dose (160-325 mg daily), or high dose (500-1,500 mg daily) aspirin.[25]

Aspirin non-responsiveness may occur because of changes to the COX-1 enzyme, such as changes to the enzyme structure, or temporary blockade of the active site on the enzyme. Of particular concern is the potential for nonsteroidal anti-inflammatory drug (NSAID) therapy to block the COX-1 enzyme. Naproxen and ibuprofen have been shown to interfere with aspirin's antiplatelet effect when coadministered by competing for the site of action.[26] The timing of coadministration appears to be an important factor. The effect of aspirin on platelet aggregation is impaired when ibuprofen is given 2 hours before aspirin, but when aspirin is given first, antiplatelet activity is retained.

While aspirin non-responsiveness does exist, the incidence is probably not as high as once believed. Although patients with aspirin non-responsiveness are more likely to have ischemic events, routinely testing patients is not recommended. Given that increasing the dose of aspirin does not impact responsiveness or improve clinical outcomes, the only effective strategy would be to change to or add an alternative antiplatelet agent.

For patients unable to take aspirin due to allergy or intolerance, clopidogrel represents a suitable alternative antiplatelet agent to prevent MI and death in patients with CAD.[1] While clopidogrel significantly reduced the incidence of stroke, MI, or vascular death in patients with ASCVD compared to aspirin in the The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events trial, the absolute difference between the two strategies was small (0.5%; number needed to treat = 200).[26] Given the small magnitude of benefit and potential for non-responsiveness to clopidogrel, it remains a second-line choice in patients with CAD. When used in patients with SIHD, clopidogrel should be given 75 mg daily.

Dual antiplatelet therapy (DAPT) with aspirin plus a $P2Y_{12}$ inhibitor, such as clopidogrel, has a clear benefit in patients after a PCI with coronary stent placement and following treatment for ACS. The combination of aspirin plus clopidogrel for 28 months did not reduce the risk of death, MI, stroke, or coronary revascularization when compared to aspirin alone but increased the risk of moderate bleeding.[32] However, in those patients with established vascular disease at study entry receiving aspirin plus clopidogrel, there was a significant reduction in the risk of death, MI, and stroke compared to aspirin alone (7.3% vs 8.8%).[32] In patients with a history of MI at least 1 year prior, the combination of ticagrelor 60 mg twice daily plus aspirin reduced the risk of cardiac events compared to aspirin alone but more than doubled the risk of major bleeding complications.[32] This dose of ticagrelor plus aspirin was evaluated in patients with both SIHD and type 2 DM. Although a significant reduction in CV death, MI, and stroke was observed with a similar increase in major bleeding in the overall study population, the benefit was greatest in patients with a previous PCI and may be considered in this setting.[32]

Patient responsiveness to clopidogrel is highly variable and the antiplatelet activity follows a bell-shaped curve.[33] Several tests have been used to evaluate clopidogrel's antiplatelet activity and there are different definitions of non-responsiveness. Thus, estimates of non-responsiveness to clopidogrel range from 5% to 44%.[34,35] Several trials have correlated clopidogrel non-responsiveness with poor clinical outcomes.

It is unclear what to do if a patient is found to have a lack of appropriate response to clopidogrel. The most common cause of non-responsiveness is poor adherence. Even a small number of missed doses will result in an inadequate response to clopidogrel. Data from a large registry provides evidence that poor adherence is associated with increased ischemic events, as well as important insight into patient predictors of poor adherence.[36] Lack of response may also be due to polymorphisms in cytochrome P450 2C19, which is responsible for the conversion of clopidogrel into its active compound.[37] There may also be drug interactions with the cytochrome P450 2C19, such as proton pump inhibitors, that may alter clopidogrel's effectiveness. A more detailed discussion on the clinical impact of these polymorphisms and drug interactions can be found in Chapter 34 (Acute Coronary Syndrome).

Rivaroxaban, a direct factor Xa anticoagulant, has demonstrated benefit in patients with CAD when added to aspirin therapy. In a large, randomized trial, rivaroxaban 2.5 mg twice daily added to low-dose aspirin provided a 24% relative reduction in CV death, MI, and stroke compared to low-dose aspirin alone.[38] Although there was also a significant increase in major bleeding with patients receiving rivaroxaban, 75% of the major bleeding events would not have been considered a major bleed by standard bleeding definitions. Patients with polyvascular disease, heart failure, diabetes mellitus, or at least moderate renal insufficiency seemed to obtain the most benefit from the addition of rivaroxaban to aspirin therapy.[39]

Recommendations from the ACC/AHA for the use of antiplatelet agents in the management of SIHD include a Class I recommendation for the use of aspirin 75 to 162 mg daily.[1] Aspirin should be continued indefinitely in the absence of contraindications (LOE A). Clopidogrel is considered an appropriate alternative when aspirin is contraindicated (LOE B). The guidelines state that treatment with aspirin (75-162 mg daily) and clopidogrel 75 mg daily might be reasonable in certain high-risk patients with SIHD (Class IIb, LOE B recommendation). Data supporting the combination of rivaroxaban and aspirin in patients with SIHD were not available when the ACC/AHA guidelines were published. However, this combination is recommended by the American Diabetes Association.[24]

ACE Inhibitors

6 In the setting of ASCVD, ACE inhibitors stabilize coronary plaque, provide restoration or improvement in endothelial function, inhibit vascular smooth muscle cell growth, decrease macrophage migration, and possibly prevent oxidative stress. They may also possess some antithrombotic properties by inhibiting platelet aggregation and augmenting the endogenous fibrinolytic system. However, ACE inhibitors have not been shown to improve symptomatic ischemia or chest pain episodes.[40]

The role of ACE inhibitors in patients at high risk for CV events was evaluated in the HOPE (Heart Outcomes Prevention Evaluation) trial.[41] Patients with normal LV function and either ASCVD (history of CAD [~80% of patients, including 55% with SIHD], stroke, peripheral arterial disease) or its equivalent (eg, DM with at least one additional risk factor) treated with ramipril 10 mg daily were significantly less likely to experience one of the primary endpoints (CV death, MI, or stroke) compared to placebo. These impressive benefits were seen despite a minimal reduction in BP with the use of ramipril. Benefits were consistent across all groups of patients enrolled, regardless of the location of ASCVD.

Subsequent trials have produced conflicting results. One trial using perindopril 8 mg daily significantly reduced the incidence of CV death, MI, or cardiac arrest compared to placebo in patients with SIHD.[42] In contrast, the addition of trandolapril 4 mg daily to standard therapy in patients with documented CAD did not significantly reduce the incidence of CV death, MI, or coronary revascularization in another trial.[43] A meta-analysis of seven trials with 33,960 patients demonstrated a significant 14% reduction in mortality in patients with CAD treated with an ACE inhibitor.[44] Based on the well-established benefits, it is appropriate to use ACE inhibitors in patients with SIHD who have HTN, DM, HFrEF, or following an MI.[1]

Trials have evaluated the role of angiotensin receptor blockers (ARB) to determine if they provide a similar benefit as ACE inhibitors in the setting of CAD. A trial in patients with preexisting CVD or DM with end-organ damage treated with either the ACE inhibitor ramipril 10 mg daily or the ARB telmisartan 80 mg daily appeared to have a similar benefit.[45] However, there was no added benefit from combining the two agents. There were significantly more episodes of hypotension, syncope, and renal dysfunction in patients treated with combination therapy. In a second trial, telmisartan failed to demonstrate a CV benefit over placebo in patients who were intolerant to ACE inhibitors.[46] Based on these conflicting data, an ARB may be considered if the patient cannot tolerate ACE inhibitor therapy, and combination therapy should be avoided.

Recommendations from the ACC/AHA include a Class I recommendation to use ACE inhibitors in all patients with SIHD who also have HTN, DM, HFrEF, or chronic kidney disease, unless contraindicated (LOE A).[1] ARBs are recommended for the same patient populations if they are intolerant to ACE inhibitors (LOE A). It is a Class IIa recommendation to use ACE inhibitors in patients with both SIHD and other vascular diseases (LOE B), and ARBs in these patients if intolerant to ACE inhibitors (LOE B).

Lipid Management

Multiple studies have demonstrated a continuous increase in coronary events with increasing low-density lipoprotein cholesterol (LDL-C) in men and women with and without SIHD. Statin therapy significantly lowers LDL-C and reduces CV event rates. The Cholesterol Treatment Trialist Collaborators found a 10% reduction in all-cause mortality and a 20% reduction in cardiac mortality for every 40 mg/dL (1.03 mmol/L) reduction in LDL-C.[47] Statin therapy also reduces the risk of MI, stroke, and the need for coronary revascularization. Higher dose and high potency statin regimens are more effective than lower dose, low-potency regimens.[47]

Current guidelines recommend that all patients with known ASCVD, such as SIHD, should receive high-intensity statin therapy to achieve a 50% or more reduction in LDL-C.[23] Patients over the age of 75 years and those who cannot tolerate high-intensity statin therapy should receive moderate-intensity statin therapy to achieve a 30% to 49% reduction in LDL-C. In patients with clinical ASCVD who do not achieve a 50% reduction in LDL-C or who have an LDL ≥70 mg/dL (1.81 mmol/L) on maximally tolerated high-intensity statin therapy, the additional non-statin therapies such as ezetimibe, PCSK9-inhibitors, or bile-acid sequestrates may be considered.[23] In patients with clinical ASCVD with DM, a recent ASCVD event, CKD, or poorly controlled risk factors, targeting an LDL-C less than 70 mg/dL (1.81 mmol/L) or non–HDL-C less than 100 mg/dL (2.59 mmol/L) may be considered.[23]

High-intensity statin options include atorvastatin 40 or 80 mg daily or rosuvastatin 20 or 40 mg daily. Atorvastatin 80 mg is the preferred dose. The 40 mg dose of atorvastatin was only used in one trial in patients who could not tolerate the 80 mg dose.[48] Also, rosuvastatin 20 mg daily is the preferred regimen based on the trial evidence, with the 40 mg daily dose being recommended because it is also an approved dose.[23] Moderate-intensity statin regimens include once-daily atorvastatin 10 to 20 mg, rosuvastatin 5 to 10 mg, simvastatin 20 to 40 mg, pravastatin 40 to 80 mg, lovastatin 40 to 80 mg, pitavastatin 1 to 4 mg, fluvastatin extended-release 80 mg, or twice daily fluvastatin 40 mg.[23]

Regular physical activity, dietary changes, and weight management should also be implemented (Table 33-8). Dietary approaches to lowering LDL-C include replacing saturated and *trans* fatty acids with dietary carbohydrates or unsaturated fatty acids and reducing dietary cholesterol. A diet low in saturated fat and cholesterol typically lowers LDL-C by 10% to 15%. The addition of plant stanols/sterols (2 g/d) can lower LDL-C by 5% to 15%. Viscous fiber (>10 g/d) reduces LDL-C by 3% to 5%. A 10 lb (4.5 kg) weight loss reduces LDL-C by 5% to 8%. Regular physical exercise improves cardiac fitness and facilitates weight loss but does not reliably lower LDL-C.

Blood Pressure Management

A number of observational trials have demonstrated a continuous relationship between BP and the risk of CV events. The risk of vascular death increases linearly over the BP range of 115/75 mm Hg to 185/115 mm Hg. The risk doubles for every 20 mm Hg increase in systolic BP or 10 mm Hg

increase in diastolic BP.[22] Clinical trials have evaluated when to initiate therapy and attempted to define the target BP goal for patients with HTN. However, the specific BP target for patients with and without SIHD has been debated. Clinical trials and meta-analyses support the current guidelines which recommend initiating pharmacotherapy in patients with SIHD with a BP of 130/80 mm Hg or higher and treating to a BP goal of less than 130/80 mm Hg.[22,49,50]

Optimal BP should be achieved using lifestyle modifications as well as pharmacotherapy (Table 33-5). This includes a diet rich in fruits, vegetables, and low-fat dairy products, regular physical exercise, a reduction in dietary sodium, and limited alcohol consumption. Lifestyle modifications can also contribute to weight loss. A 10 kg weight loss can reduce systolic BP by 5 to 20 mm Hg.

Drugs used to treat HTN in patients with SIHD commonly include agents that can be used to treat the symptoms of the disease. β-Blockers are often used to control angina symptoms and they also lower BP. Patients may also be on ACE inhibitors to reduce CV risk. Therefore, most patients with SIHD will receive these two classes of agents for the treatment of HTN. If additional therapy is needed, dihydropyridine (DHP) calcium channel blockers (CCBs) are often added because they treat both HTN and reduce angina symptoms. If the patient's angina symptoms are well controlled, thiazide diuretics may be considered as add-on therapy for HTN. They are considered a first-line treatment in most populations and do not appear to be detrimental when used by patients with SIHD.[22]

Smoking Cessation

The relationship between tobacco use and increased risk of CVD is well documented.[51] Cigarette smoking promotes and accelerates ASCVD through a number of mechanisms including increased platelet adhesion, elevated fibrinogen concentrations, endothelial dysfunction, altered serum lipids, and vasoconstriction.[52] Smoking is perhaps the most important cause of preventable CVD and death.[51] Compared to those who never smoked, smokers lose approximately 10 years of life expectancy and early cessation is associated with an approximately 90% reduction in mortality and improved quality of life.[53] Therefore, abstinence and smoking cessation are key components of lifestyle modifications for patients with SIHD.

Advice from a clinician recommending and discussing the importance of smoking cessation significantly increases the likelihood that a patient will quit. Clinicians should approach smoking cessation by using the 6 A's framework[1]:

1. Ask each patient about tobacco use at every visit
2. Advise each smoker to quit
3. Assess each smoker's willingness to make a quit attempt
4. Assist each smoker in making a quit attempt by offering medication and referral for counseling
5. Arrange for follow-up
6. Avoid exposure to environmental tobacco smoke

Several pharmacologic agents are available over the counter or with a prescription and are all more effective than placebo.[54] Nicotine replacement therapy is available in a number of dosage forms without a prescription to fit the patient's lifestyle including patches, tablets, gum, lozenges, and nasal spray. Sustained-release bupropion and the partial agonist of the $\alpha_4\beta_2$ nicotinic receptor, varenicline, are also first-line medications to treat tobacco dependence in adults. In one study, no evidence of serious CVD or CV adverse events occurred in patients receiving smoking cessation medications, demonstrating all three pharmacotherapies are safe from a cardiovascular standpoint.[55] Nonpharmacologic methods for smoking cessation are just as important as pharmacotherapy. Self-help programs, telephone counseling, behavioral therapy, and exercise all can be used to help patients quit smoking.

Diabetes Management

DM is a strong risk factor for the development of CVD. Patients with type 1 DM have a 10-fold increased risk of having a CV event and patients with type 2 DM have a two- to sixfold risk of CV death compared to those without DM.

Like HTN, the glycemic target for patients with DM, including those with SIHD, is the subject of considerable debate. Studies have found that achieving an A1c of less than 7% (0.07; 53 mmol/mol) reduces microvascular complications from DM such as retinopathy, nephropathy, and neuropathy.[56] While subgroup analyses of larger trials have suggested lower rates of ischemic events in patients randomized to intensive glycemic control (A1c less than 7% [0.07; 53 mmol/mol]), macrovascular events were not significantly reduced in trials comparing intensive to more lenient glycemic control in high-risk patients with DM, including those with preexisting CVD.[56] In these trials, patients in the intensive glycemic control groups had higher rates of adverse events including severe hypoglycemia, CVD death, and overall mortality.[56] In patients with SIHD, current AHA/ACC recommendations target an A1c of less than 7% (0.07; 53 mmol/mol) for patients with DM of short duration and a long life expectancy (Class IIa, LOE B) but a more lenient goal (A1c <8% [0.08; 64 mmol/mol]) for frail or high-risk patients (Class IIa, LOE C; Table 33-5).[1]

Metformin is the drug of first choice for the treatment of type 2 DM, including patients with SIHD. While sulfonylureas provide a similar reduction in A1c, their potential to induce hypoglycemia and weight gain make metformin a more attractive option. Although debate remains regarding the effect of metformin and sulfonylureas on CV events, a recent meta-analysis did not find a significant association between the use of either therapy and CV outcomes.[56] Some newer therapies for the treatment of type 2 DM significantly reduce the risk of CV events, including all-cause mortality.[57] In a recent meta-analysis, the risk of death was reduced by 20% (hazard ratio [HR] 0.80, 95% credible interval [CrI] 0.71-0.89) in patients treated with sodium-glucose-cotransporter 2 (SGLT-2) inhibitors and by 12% (HR 0.88, 95% CrI 0.81-0.94) in patients treated with glucagon-like peptide 1 (GLP-1) agonists compared to patients treated with standard therapies in the control groups.[58] Cardiovascular mortality was also lower in patients treated with either SGLT-2 inhibitors or GLP-1 agonists compared to control subjects.[58] The risk of adverse event rates leading to discontinuation was higher with GLP-1 agonists compared to SGLT-2 inhibitors and dipeptidyl peptidase 4 inhibitors.[58] Consequently, updated guidelines for the treatment of DM now recommend using agents that have been shown to reduce CV events (eg, empagliflozin, canagliflozin, and liraglutide) as part of the glucose-lowering regimen, regardless of the patient's current glycemic control and should be added to metformin therapy in patients with DM type 2 and ASCVD.[24]

Influenza Vaccination

Patients with cardiac disease who develop seasonal influenza are at high risk for complications and more likely to die. In patients with CAD, influenza vaccination has been associated with lower rates of ischemic events, although the benefit may be greatest in those with a recent ACS prior to vaccination.[59,60] Current guidelines recommend that all patients with SIHD should receive an annual influenza vaccination to prevent morbidity and mortality.[1]

Pharmacotherapy to Reduce Symptoms

β-Blockers

9 β-Adrenergic blocking agents are commonly used in the management of patients with SIHD and reduce both symptomatic and silent episodes of myocardial ischemia. β-Adrenergic blocking agents competitively inhibit the effects of circulating catecholamines on β-adrenoceptors. The predominant adrenergic receptor type in the heart is the β_1-receptor, and competitive blockade minimizes the influence of endogenous catecholamines on the chronotropic and inotropic state of the myocardium. β-Blockers also produce a reduction in BP through competitive inhibition of β_1-receptors in the kidney, leading to a reduction in renin release. By reducing HR, myocardial contractility, and intramyocardial wall tension through BP reduction, β-blockers impact all major contributing factors to MVO_2.[61] Reductions in HR may also improve myocardial oxygen delivery by prolonging diastole filling time and increasing myocardial perfusion.

β_1-Selectivity does not improve the efficacy of β-blockers for the treatment of SIHD and all agents appear equally effective. β_1-Selective agents would be preferred in patients with chronic obstructive pulmonary disease, peripheral arterial disease, DM, dyslipidemias, and sexual dysfunction, where blocking β_2-adrenergic receptors may be problematic. It should be noted that even β_1-selective agents lose their selectivity at higher doses. β-Blockers with combined α_1 and β-blockade are also effective in the management of angina. β-Blockers with intrinsic sympathomimetic activity cause a slight-to-moderate activation of the β-receptor, in addition to competing with endogenous catecholamines. Due to this unique pharmacologic property, they do not affect resting HR but do modestly lower HR when catecholamine concentrations are increased during exercise. While agents with intrinsic sympathomimetic activity may be useful for patients with peripheral arterial disease and dyslipidemia, they are not preferred in patients with CAD. The

selection of a β-blocker in patients with SIHD should be guided by the presence of comorbid diseases, preferred dosing frequency, and cost.

Most adverse drug reactions experienced with the use of β-blockers are an extension of their pharmacologic activity. Patients receiving β-blockers may experience bradycardia, hypotension, heart block, impaired glucose metabolism, and altered serum lipids. β-Blockers may alter the lipid profile by increasing triglycerides and decreasing HDL-C. They have no impact on LDL-C. Changes in the lipid profile are greater with non-selective β-blockers and are usually transient. Central nervous system adverse drug reactions such as fatigue, depression, insomnia, and general malaise are usually mild but among the most common reasons for treatment discontinuation. Impotence has been reported in approximately 1% of men receiving β-blockers. Patients with a history of airway disease may suffer from bronchospasm and patients with HFrEF may become fluid overloaded. Patients without these preexisting disease states usually do not suffer from these adverse drug reactions and it is important to note that even patients at risk for adverse drug reactions receive significant benefit from the use of β-blockers. β-Blockers are absolutely contraindicated in patients with preexisting bradycardia, second or third-degree atrioventricular block, a history of uncontrolled reactive airway disease (asthma), severe peripheral arterial disease (critical limb ischemia), hypotension, HFrEF with unstable fluid status, and patients with DM who have frequent episodes of hypoglycemia. All patients should receive a β-blocker following an MI unless there is an absolute contraindication. A patient with SIHD who has never had an ACS, especially acute MI, and who has concurrent chronic obstructive pulmonary disease (COPD) may be treated with a cardioselective β-blocker if there are compelling reasons to use a β-blocker over another antianginal medication. However, in patients with moderate to severe COPD, β-blockers may increase the risk COPD-related hospitalizations.[62]

If β-blocker therapy needs to be discontinued, doses need to be tapered over 2 to 3 weeks to prevent abrupt withdrawal. During β-blocker therapy, β-receptors become up-regulated in the myocardium. After an abrupt withdrawal of β-blocker therapy, these new receptors, along with all of the blocked receptors, are now stimulated by endogenous catecholamines. This can produce a significant increase in MVO_2, induce ischemia, and even MI. If for some reason β-blockers cannot be tapered, patients should be instructed to avoid exertion as much as possible and manage angina episodes with SL nitroglycerin. Using a non-DHP CCB would be the preferred second-line choice if β-blockers are contraindicated or must be discontinued.

Calcium Channel Blockers

7 CCBs effectively reduce the frequency and duration of angina episodes in patients with SIHD. All CCBs reduce MVO_2, as well as provide some increase in supply by inducing coronary vasodilation and preventing vasospasm. CCBs modulate calcium entry into the myocardium and vascular smooth muscle, as well as other tissues. This leads to a reduction in the cytosolic concentration of calcium responsible for activation of the actin-myosin complex leading to the contraction of vascular smooth muscle and myocardium.

CCBs should be considered as two separate classes of drugs. While all CCBs inhibit the influx of calcium ions, the location of the inhibition differs based on the chemical structure of the agents. The DHP CCBs, such as nifedipine, amlodipine, isradipine, and felodipine, primarily block calcium receptors in vascular smooth muscle cells, such as arterioles, with minimal effect on the myocardium. In contrast, the phenylalkylamine (verapamil) and benzothiazepine (diltiazem) agents, commonly referred to as non-DHP CCBs, block calcium ion entry mostly in the myocardium, with minimal effect on vascular smooth muscle. Verapamil has the greatest impact on myocardial calcium channels with diltiazem having an intermediate effect.

All CCBs reduce MVO_2 by reducing wall tension by lowering arterial blood pressure, and to a minor extent, depressing cardiac contractility. Like β-blockers, non-DHP CCBs also reduce HR and contractility through blockade of myocardial calcium channels. The DHP CCBs slightly reduce cardiac contractility and produce either a neutral or increase in HR due to potential reflex tachycardia from direct arterial dilation. The effect on contractility and reflex tachycardia is not uniform across the class of DHP CCBs. Agents such as nifedipine produce more impairment of LV function than amlodipine and felodipine. Due to their potential to cause reflex tachycardia, short-acting DHP CCBs should be avoided when treating SIHD, chronic HTN, hypertensive crisis, or during an ACS event. Reflex tachycardia from longer-acting DHP CCBs can be prevented with concurrent β-blocker therapy.

Common adverse drug reactions of CCBs vary between the two classes. Patients taking non-DHP CCBs may experience bradycardia, hypotension, atrioventricular block, and symptoms of LV depression. Non-DHP CCBs should not be used in patients who have contraindications or cannot tolerate the rate-slowing effects of β-blockers due to their similar pharmacodynamic effects. Non-DHP CCBs should be avoided in patients with concomitant HFrEF due to their negative inotropic effects but can provide benefit to patients in atrial fibrillation with a rapid ventricular response due to their negative dromotropic effects. Verapamil has also been reported to cause constipation in up to 8% of patients. Patients taking DHP CCBs may experience reflex tachycardia, hypotension, headache, gingival hyperplasia, and peripheral edema. While most DHP CCBs are contraindicated in patients with HFrEF, amlodipine, and felodipine are considered safe options in patients with HFrEF and concomitant SIHD or HTN.

CCBs undergo hepatic oxidative biotransformation via the cytochrome P450 isoenzyme 3A4 and other isoenzymes. Verapamil and diltiazem inhibit the clearance of other substrates for the 3A4 isoenzyme such as carbamazepine, cyclosporine, lovastatin, simvastatin, and benzodiazepines. The DHP CCBs do not produce a clinically meaningful interaction with these medications. Verapamil, and to a lesser extent diltiazem, also inhibit P-glycoprotein mediated drug transport. This interaction is partially responsible for increases in serum concentrations of agents such as digoxin and cyclosporine. Because verapamil decreases digoxin clearance, digoxin levels must be closely monitored if these agents are used together. Agents that induce the P450 3A4 isoenzyme can reduce the effectiveness of all CCBs. Potential pharmacodynamic interactions also need to be monitored in patients taking CCBs. Patients receiving verapamil or diltiazem concurrently with other agents that reduce HR and atrioventricular nodal conduction (β-blockers, digoxin, and amiodarone) should be monitored for the development of bradycardia or heart block.

Nitrates

7 Organic nitrates were found to have antianginal properties over 100 years ago when Murrell first reported in 1879, the ability of a 1% nitroglycerin solution administered orally to relieve and prevent angina attacks. Organic nitrates are prodrugs that require biotransformation into the active compounds. This process leads to denitration of the nitrate and the release of nitric oxide, also known as EDRF. Nitric oxide increases concentrations of cyclic guanosine monophosphate in the vascular endothelium leading to a reduction in cytoplasmic calcium and subsequent vasodilation. Vasodilation occurs predominantly in the venous vasculature thereby reducing preload, myocardial wall tension, and MVO_2. As doses are increased, arterial vasodilation also occurs. Arterial vasodilation can produce reflex tachycardia that can negate some of the antianginal benefits. Patients on adequate doses of β-blockers will not have reflex tachycardia, making this an effective combination for controlling a patient's acute and chronic angina symptoms.

Nitrates also vasodilate stenotic vessels as well as the intracoronary collaterals. Given that blood flow is exponentially related to the degree of stenosis, small increases in vasodilation in these narrowed vessels can produce significant increases in myocardial oxygen supply to ischemic areas of the myocardium. Nitrate-induced coronary vasodilation occurs predominately in epicardial vessels, with minimal effect on coronary microcirculation. This explains why nitrates do not cause coronary steal similar to other vasodilators like dipyridamole or sodium nitroprusside. In coronary steal, there is vasodilation in coronary vessels without atherosclerotic disease but coronary vessels with disease are not dilated. Therefore, more blood flow is shifted, or "stolen," to non-diseased vessels away from atherosclerotic vessels that have reduced blood flow. Nitrates may also have anti-aggregant effects on platelets, but the clinical impact is negligible.

Common adverse drug reactions from nitrate therapy include headache, flushing, nausea, postural hypotension, and syncope. While the hypotension is usually not severe, patients who are volume-depleted may experience paradoxical bradycardia if they attempt to rapidly stand. The headache will usually resolve after about 2 weeks when nitrates are used for chronic therapy. It is important to note that this does not represent tolerance or loss of antianginal effectiveness. Acetaminophen is effective in managing nitrate-induced headaches during the initial weeks of therapy. Patients using transdermal nitroglycerin may experience skin erythema and inflammation. Initiating therapy with smaller doses and rotating the application site can mitigate some of the adverse drug reactions of transdermal nitroglycerin.

8 Several formulations of nitrates are available for acute and chronic use (Table 33-7). All patients with CAD should have access to SL nitroglycerin tablets or spray for the treatment of acute episodes of angina. Patient education is critical to ensure appropriate SL nitroglycerin use (Table 33-8). The SL route of administration avoids gastrointestinal absorption and hepatic first-pass metabolism. SL nitroglycerin 300 to 400 μg typically provides relief of angina within 5 minutes of administration. SL nitroglycerin can also relieve symptoms even if the patient is chronically taking long-acting nitrates. The adverse drug reactions of flushing, headache, and postural hypotension can appear rapidly and the patient should be aware of this potential. SL nitroglycerin can also be used to prevent acute episodes of angina. When patients want to participate in activities that they know lead to angina, they can take a dose of SL nitroglycerin 2 to 5 minutes in advance. This prophylactic dose provides up to 30 minutes of protection and allows patients to participate in activities that they might otherwise be unable.

TABLE 33-7

Nitrate Products

Product	Onset (minutes)	Duration	Initial Dose
Nitroglycerin			
IV	1-2	3-5 minutes	5-10 µg/min
Sublingual*	1-3	30-60 minutes	0.3-0.4 mg
Oral	40	3-6 hours	2.5-6.5 mg three times a day
Ointment	20-60	2-8 hours	0.5-1 in. (1.3-2.5 cm)
Patch	40-60	>8 hours	0.2-0.4 mg/hour (1 patch)
Isosorbide dinitrate			
Immediate release	20-40	4-6 hours	5-20 mg three times a day
Sustained release	60	8 hours	40 mg once daily
Isosorbide mononitrate			
Immediate release	30-60	6-8 hours	20 mg twice a day
Extended release	30-60	12-24 hours	30-60 mg daily

*Sublingual nitroglycerin exists in three different formulations: tablets, spray, and powder packets.

TABLE 33-8

Appropriate Use of Sublingual Nitroglycerin

Education Point	Rationale
Keep in original dark glass container	SL nitroglycerin will interact with plastic and can lose potency when exposed to light. This is why it is packaged in a dark glass container.
Do not store in a larger plastic vial with a child-resistant safety cap	During an episode of angina, you do not want the patient struggling to figure out how to open the safety cap.
Do not store in the bathroom	SL nitroglycerin will degrade in moisture and tablets will lose their integrity and potency.
Keep SL nitroglycerin close by at all times; may need multiple vials	SL nitroglycerin does not do any good to the patient if they do not have it with them at the time of an episode of angina. The patient should consider having one at home, at work, in the garage, etc.
The patient should be sitting down and resting while taking the tablet	While the SL nitroglycerin tablets are small, the dose is not. It is likely the patient will have some flushing, may get a headache, and even become a little light-headed. They need to know this can happen.
Describe how to use a sublingual tablet	The SL nitroglycerin is administered under the tongue in order to provide rapid absorption and avoid first-pass metabolism. The patient needs to keep the tablet under the tongue until dissolved. Avoid swallowing the tablet.
Once opened, tablets need to be refilled every 6 months and spray every 3 years	Due to the instability of SL nitroglycerin tablets, they are typically only good for 6 months after the bottle is opened.[a] Shelf-life of the spray is longer. Patients need to be advised to refill SL nitroglycerin even if all doses have not been taken.
Remove the cotton plug from the bottle	Larger quantity bottles commonly have a cotton plug. During an episode of angina, you do not want the patient to be struggling with trying to get the cotton plug out of the bottle.
May be taken in advance of events known to cause chest pain	SL nitroglycerin can be used to prevent episodes of angina if taken before partaking in an exertional event known to precipitate angina/chest discomfort.
Contact 911 if first SL nitroglycerin does not relieve angina[b]	Most episodes of angina are relieved within 5-10 minutes of rest and a single SL nitroglycerin. If pain persists, the episode may be an acute coronary syndrome, not stable ischemic heart disease. This requires rapid medical attention.

[a]Product-specific.

[b]May be patient-specific based on their experience with SL nitroglycerin and angina episodes.

The development of nitrate tolerance must be considered when chronically using long-acting nitrate therapy for SIHD. Several trials have shown that continuous nitrate therapy for more than 24 hours leads to a reduction or loss of the hemodynamic and antianginal effects of nitrates. In a large study in patients receiving 24 hours of transdermal nitroglycerin, almost all patients lost control of their angina symptoms within 24 hours to 1 week, which cannot be overcome with higher doses.[63]

Nitrate tolerance is not an “all or none” phenomenon. Responsiveness is reduced in some patients while others experience a total loss of efficacy. Despite the continued use of nitrates and a loss of antianginal effect, plasma volume remains expanded and some hemodynamic effects are maintained. 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.[64,65] Consequentially, the dysfunctional enzyme is unable to produce active NO

and the angina relieving effect of nitrate agents is reduced or lost.

Why nitrate tolerance develops remains unknown, but several pharmacologic approaches have been developed to manage and prevent it. One thought is that tolerance is due to an exhausting of sulfhydryl groups needed to use organic nitrates.[64] Based on this hypothesis, acetylcysteine and ACE inhibitors such as captopril, which supply sulfhydryl groups, have been investigated as a potential strategy for preventing nitrate tolerance. Unfortunately, both agents have provided inconsistent results. ACE inhibitors may prevent nitrate tolerance through other mechanisms. The inhibition of angiotensin II production can reduce superoxide anion production, leading to reduced nitrate degradation, as well as a reduction in protein kinase C and endothelin leading to a reduction in vasoconstriction. Unfortunately, none of these approaches have shown to be effective in maintaining the antianginal effects of continuous nitrate therapy.

The preferred management of nitrate tolerance for patients with CAD is to ensure a 10- to 14-hour nitrate-free interval every day. This approach has been shown to maintain antianginal efficacy with the use of chronic nitrates. The rationale for this approach is based on the observation that although nitrate tolerance develops rapidly, it is also reversed rapidly. Unfortunately, this approach does not provide the patient with anti-ischemic coverage for a full 24 hours and places the patient at risk for angina episodes. Typically, the nitrate-free interval is provided during the nighttime hours when the patient is sleeping and, in most cases, has lower MVO_2. Several trials have used chronic nitrates with a daily nitrate-free interval and demonstrated increased exercise time, reduced exercise-induced ischemic events, and reduced need for SL nitroglycerin. Despite these benefits, a nitrate-free interval would not provide protection to the 20% to 30% of patients with SIHD who experience nocturnal episodes of angina. Moreover, it is well documented that angina episodes and MI commonly occur in the morning hours, immediately before or after awakening. Patients using chronic nitrate therapy are unlikely to have taken or applied their nitrate therapy for the day during this critical time period. Therefore, nitrates should not be routinely used as monotherapy in patients with SIHD due to the lack of 24-hour coverage, lack of protection against circadian-related ischemic events, and potential for reflex tachycardia. Trials have demonstrated that patients taking intermittent transdermal nitroglycerin did not experience rebound ischemia during the nitrate-free interval when β-blockers or diltiazem were concurrently used.

7 Several nitrate preparations can be used for chronic long-term prevention of angina episodes. Transdermal patches and isosorbide mononitrate are the most commonly prescribed chronic nitrates. Although isosorbide dinitrate is effective, the three times daily dosing regimen requires patients to take a dose every 4 to 5 hours in order to provide an adequate nitrate-free interval. Two of the isosorbide mononitrate preparations are dosed twice daily. The twice-daily preparations should be dosed 7 hours apart, such as 7 am and 2 pm. It is critical to be specific about the times each dose should be taken so that patients do not take the doses 12 hours apart, thus compromising the nitrate-free interval. One isosorbide mononitrate preparation is dosed once daily. It is an extended-release preparation that provides 12 hours of nitrate exposure. This should be followed by a 12-hour nitrate-free interval. Transdermal nitroglycerin patches are typically prescribed as “on in the am and off in the pm.” It is best to provide specific times for application and remove (eg, apply at 8 am and remove at 8 pm). Patients who work evening or night shifts need to have the timing of their nitrate doses adjusted to coincide with when they are active during the day.

Ranolazine

Unlike other agents used for angina, ranolazine does not impact HR, BP, the inotropic state, or coronary blood flow. Animal studies have demonstrated that ranolazine has little affinity for α_1, β_1, and β_2 adrenoreceptors and has minimal calcium channel blocking activity. Ranolazine reduces ischemic episodes by selective inhibition of late sodium current (I_{Na}). Total sodium entry during an action potential is comprised of an early (fast) and late (slow) component. Under normal conditions, late I_{Na} constitutes only 1% of total I_{Na}. Several preclinical studies have observed an increase in late I_{Na} in ischemic and failing hearts.[66] It is not fully appreciated if this increase in late I_{Na} is due to an increase in the density of the late Na^+ channels or dysfunction of these channels. The increase in intracellular Na^+ triggers an increase in the influx of Ca^{2+} through the reverse mode of the Na^+/Ca^{2+} exchanger, resulting in intracellular Ca^{2+} overload and eventually myocardial stunning.[66] Therefore, it is not the intracellular Na^+ concentration that produces ischemic damage, but its recognized role in Ca^{2+} accumulation via Na^+/Ca^{2+} exchange.[66] By inhibiting late I_{Na}, ranolazine produces a reduction in intracellular Na^+. The reduction in intracellular Na^+ contributes to a reduction in the magnitude of ischemia-induced Ca^{2+} overload and improves myocardial function as well as myocardial perfusion.[66]

Ranolazine is available as a sustained-release preparation dosed twice daily. With a half-life of approximately 7 hours, ranolazine achieves a steady-state within 3 days. Since ranolazine 1,000 mg twice daily significantly improves exercise tolerance more than 500 mg twice daily, titration to 1,000 mg

twice daily should be attempted. When ranolazine was added to atenolol (50 mg daily), diltiazem (180 mg daily), or amlodipine (5 mg or 10 mg daily), there was an increase in exercise duration, time to angina, time to 1 mm ST-depression, and a reduction in the number of angina episodes and SL nitroglycerin tablets used per week compared to placebo.[67,68] In these trials, the magnitude of increase in exercise duration during testing was associated with a 25% reduction in the weekly number of angina episodes and SL nitroglycerin use over placebo and almost a 50% reduction from baseline.[68,69] The improvement in exercise duration demonstrated with ranolazine is consistent with results produced with β-blockers, CCBs, and chronic nitrates.[8,70]

Patients should be initiated on ranolazine 500 mg twice daily, with the dose increased to 1,000 mg twice daily within the next 1 to 2 weeks if tolerated. Ranolazine is primarily metabolized by CYP3A4 (70%-85%) and CYP2D6 (10%-15%) in the liver and is a substrate for *P*-glycoprotein, making it prone to several clinically important drug interactions. Potent inhibitors of CYP3A4 and *P*-glycoprotein such as ketoconazole, itraconazole, protease inhibitors, and clarithromycin will significantly increase ranolazine drug concentrations. Conversely, potent CYP3A4 inducers such as phenytoin, phenobarbital, carbamazepine, rifampin, rifabutin, rifapentine, and St. John's wort significantly decrease ranolazine drug concentrations. Concurrent use of these strong inhibitors and inducers with ranolazine is contraindicated. Moderate inhibitors of CYP3A4, such as diltiazem, verapamil, erythromycin, and fluconazole, can be used with ranolazine, but the dose should not exceed 500 mg twice daily. Due to inhibition of CYP3A4 by ranolazine, doses of simvastatin should not exceed 20 mg daily. Ranolazine increases digoxin 1.4- to 1.6-fold at trough and 2-fold at peak plasma concentrations, likely through competition for intestinal and renal *P*-glycoprotein. Digoxin doses may need to be reduced to avoid toxicity. Agents that are potent inhibitors of *P*-glycoprotein, such as cyclosporine, may increase ranolazine concentrations and adverse drug reactions. The dose of ranolazine should be reduced.

Ranolazine and metformin compete for renal clearance through the organic cation transporter 2, which has the potential to increase metformin drug concentrations and increase the risk of lactic acidosis. This interaction is only clinically meaningful when both full-dose ranolazine (1,000 mg twice daily) and full-dose metformin (1,000 mg twice daily) are used together. In this setting, the metformin dose should be reduced to 850 mg twice daily. Patients on ranolazine 500 mg twice daily do not need to alter their metformin doses. Ranolazine produces reductions in A1c by 0.6% to 0.7% (0.006-0.007; 7-8 mmol/mol).[68,71] Reductions in blood glucose were observed in patients with or without diabetes, without causing hypoglycemia. While ranolazine is not a treatment for DM, clinicians may find this property useful.

The most common adverse drug reactions from ranolazine use are constipation, nausea, dizziness, and headache. At therapeutic doses, ranolazine produces a modest prolongation of QTc (15 msec or less). A linear relationship exists between ranolazine plasma concentration and the QTc interval, but the effect is modest when used at recommended doses. Patients should not receive doses of more than 1,000 mg twice daily and caution should be used in patients receiving concomitant QTc-prolonging agents.

While ranolazine is safe and effective for treating angina episodes, it would only be an option as monotherapy in patients with SIHD who cannot tolerate traditional antianginal agents due to hemodynamic or other adverse drug reactions. Ranolazine is recommended as an add-on therapy to traditional antianginal agents. In patients who have achieved HR and BP targets on maximally tolerated doses of traditional agents but continue to have exertional angina symptoms, ranolazine is a reasonable choice because it does not impact these hemodynamic parameters.

Nonpharmacologic Therapy (Revascularization)

Surgical revascularization plays a role in the treatment of SIHD. The most common revascularization procedures are coronary artery bypass grafting (CABG) surgery or PCI with or without stent placement. In 2017, more than 600,000 PCI procedures were performed in the United States and approximately a third of these were done electively (eg, in patients with SIHD).[72] Stents are placed in over 90% of patients undergoing PCI, with drug-eluting stents (DES) accounting for 82% of all stents. Bare metal stents (BMS) are placed less commonly (18%). Approximately 371,000 CABG surgeries are performed annually.[2] Other revascularization options are under development.

9 The primary goal of revascularization is to prolong life and, secondarily, to eliminate or reduce symptoms. Revascularization is recommended over medical therapy as initial management of SIHD in select patients, such as those with significant stenosis of the left main coronary artery, multivessel disease and LV dysfunction, or refractory angina. Whereas most of the pharmacologic approaches reduce MVO_2, revascularization increases myocardial oxygen supply in vessels with critical stenosis. This is accomplished by opening the vessel (PCI) or using alternative transplanted vessels to bypass a critical stenosis (CABG). While both procedures are highly effective and have advantages in certain groups of patients over pharmacologic approaches, both have limitations.

Percutaneous Coronary Intervention

The term PCI encompasses the use of balloon angioplasty with stent placement as well as other less commonly performed intracoronary procedures such as rotational atherectomy and aspiration thrombectomy. During a PCI, a catheter is guided into coronary arteries through either femoral or radial access. A sheath is placed in either the femoral or radial artery to maintain access during the procedure. A guide catheter is then introduced through the sheath and advanced to the ostium of the coronary arteries. A guidewire is then advanced through the guide catheter and across the stenosis in the coronary vessel. The deflated balloon is then slid along the guidewire and to the site of the coronary stenosis. The balloon is then inflated. The inflated balloon expands the coronary lumen by stretching and tearing the atherosclerotic plaque (see Acute Coronary Syndromes, Chapter 34 for detailed review). Most elective PCI procedures are completed in 30 to 60 minutes.

Abrupt vessel closure is a potential complication of balloon angioplasty. Abrupt vessel closure is provoked by physical disruption of the plaque on the vessel walls during the procedure. In the past, this complication occurred in 5% to 8% of cases and required emergency CABG surgery in 3% to 5% of patients. A second complication from PCI is restenosis, which can lead to recurrent symptoms and the need for another revascularization procedure in approximately 30% to 50% of patients within a year.[73] These complications have now been dramatically reduced with the use of antithrombotic therapy and intracoronary stents.

Stents are scaffolds made from stainless steel or other metal alloys placed within coronary arteries that can prevent acute vessel closure and restenosis. The stent is placed over the deflated balloon and advanced to the area of coronary stenosis. When the balloon is inflated, the stent expands into the coronary vascular wall. The balloon is then deflated, leaving the expanded stent permanently in the diseased coronary vessel. While stents have had a dramatic effect of reducing restenosis, and therefore repeat revascularization procedures, they do not prevent death or MI more effectively than balloon angioplasty alone.

Restenosis is a phenomenon characterized by a greater than 50% diameter loss in the vessel lumen at the site of the intervention. Restenosis most often occurs within the first 3 to 6 months following the procedure. The pathophysiology of restenosis involves a complex cascade of various growth factors and cytokines that promote smooth muscle cell proliferation and result in a progressive loss of luminal diameter.[73] Restenosis typically occurs through the following mechanisms: early vessel recoil, late constrictive remodeling, and neointimal proliferation.[73]

Elastic recoil is a nearly instantaneous phenomenon, occurring during the first hour after the successful dilation of the vessel. As the vessel is stretched during balloon angioplasty, the endothelium lining the vessel becomes damaged. In response to the stretching, the fibers begin to recoil back to their previous size.[73] Late constrictive remodeling, also referred to as negative remodeling, is mediated by myofibroblasts of the adventitia layer of the coronary vessel. Balloon-induced injury often results in exposure of the adventitia to the lumen. Cell proliferation begins as activated fibroblasts contribute to the enlargement of the adventitia. These activated fibroblasts differentiate into myofibroblasts that are involved in the profibrotic and remodeling effects of the vessel.[73] As the adventitia becomes thick and fibrotic, a decrease in arterial cross-sectional area results.

The scaffold-like properties of a BMS prevent restenosis by controlling elastic recoil and negative remodeling. Restenosis rates dropped from 30% to 50% with balloon angioplasty alone to 15% to 30% with the use of BMS. However, stent-induced vessel injury and inflammatory reactions around the stent struts trigger a set of events that promote neointimal hyperplasia, a normal response to vascular damage.[73] The anti-proliferative drugs used in DES target neointimal hyperplasia. DES are coated with sirolimus, paclitaxel, zotarolimus, or everolimus. These agents interrupt the cell cycle to prevent neointimal proliferation and reduce restenosis rates to 5% to 10%.[73]

Although stents can effectively reduce restenosis, the exposed stent struts can provoke thrombosis. Stent thrombosis is driven by the implantation of the stent into an atherosclerotic plaque, exposing platelet adhering proteins to the stent surface. Patients remain at risk for stent thrombosis until a thin layer of endothelial tissue can grow around the stent struts. This process is called re-endothelialization and typically occurs in 2 to 4 weeks after BMS deployment, with most adverse events occurring within the first 2 weeks. The process of re-endothelialization is significantly prolonged with the use of DES. The drugs in a DES prevent smooth muscle, neointimal, and endothelial cell growth. Therefore, while DES effectively reduces neointimal proliferation and the risk of restenosis, they also increase the period of risk for stent thrombosis.

Stent thrombosis is uncommon (<5% of cases) but catastrophic when it occurs. Stent thrombosis results in a large MI or death in two-thirds of cases. The mortality rate from stent thrombosis ranges from 20% to 45%. Stent thrombosis can be largely prevented by using DAPT.

Pharmacotherapy with PCI

The physical damage imposed on the atherosclerotic plaque during PCI with stent placement induces platelet recruitment and activation, leading to the potential for thrombus formation. Therefore, antithrombotic therapy with antiplatelet and anticoagulant agents are necessary to produce a successful outcome. Antiplatelet therapy is also used after the procedure to reduce the risk of stent thrombosis.

All patients without a contraindication should receive aspirin before PCI. Patients already on chronic aspirin therapy should take an additional 75 to 325 mg before PCI. Aspirin-naïve patients should be given a dose of 325 mg, preferably at least 2 but up to 24 hours before PCI. Chronic treatment with aspirin 81 mg daily is recommended after PCI. Patients receiving a stent should also receive a $P2Y_{12}$ inhibitor (eg, clopidogrel) before PCI. The ACC/AHA guidelines recommend against stent placement if it is believed the patient will not tolerate or comply with the recommended duration of DAPT.[1]

After elective PCI, DAPT should be continued to reduce the risk of stent thrombosis. For patients who receive a BMS, a minimum of 1 month of DAPT is sufficient.[74] In patients at high risk of bleeding, a minimum of 2 weeks can be given, as most re-endothelialization of the stent surface occurs within 2 weeks. Patients receiving a DES should receive at least 6 months of DAPT due to the delayed and somewhat unknown duration of the re-endothelialization process.[73,74] However, it is reasonable for those patients who receive a DES and are at high risk of bleeding or develop significant bleeding to stop the $P2Y_{12}$ inhibitor after only 3 months of therapy.[74] An alternative approach in patients undergoing PCI for SIHD, continuing the P2Y12 inhibitor but discontinuing aspirin 1-3 months after PCI, reduces the risk of bleeding and may be considered.[75]

The results of the DAPT (Dual Antiplatelet Therapy Trial) found that a longer duration of DAPT (up to 30 months) provides a greater reduction in CV adverse events when compared to 12 months of treatment, but also a significant increase in major bleeding.[76] Therefore, the guidelines state that a longer treatment regimen for both BMS and DES can be considered in patients who have tolerated therapy, are not at high risk of bleeding, nor have experienced any bleeding complications. This longer duration of DAPT for patients receiving a DES is a Class IIb recommendation.[74]

PCI Versus Medical Management

Despite advancements in PCI technique and stent technology, no study to date has demonstrated that PCI in patients with SIHD improves survival. This is most likely due to the advancements in pharmacotherapy and the use of GDMT. PCI resulted in fewer angina episodes when compared to medical therapy, but in these trials PCI rarely included the use of stents and medical therapy did not include the use of high-intensity statins or ACE inhibitors.[77]

Contemporary PCI and GDMT have been compared in recent clinical trials. In the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, the rate of death and MI were not different between patients who were randomized to GDMT alone compared to PCI with GDMT (19.0% in PCI group vs 18.5% in GDMT group).[78] While more patients were angina-free in the PCI group compared to the GDMT group at 1 year (66% vs 58%), there was no difference at the 5-year follow-up time point (74% vs 72%). The need for revascularization after 5 years was lower in the PCI group (21.1% vs 32.6%). This trial confirms that PCI with GDMT does not lower the risk of death and MI compared to GDMT alone, and PCI should be reserved for patients with SIHD refractory angina after receiving optimal GDMT. These data underscore the importance of aggressive, goal-oriented, pharmacotherapy in patients with SIHD. While one-third of patients in the COURAGE study randomized to the GDMT group did need to receive PCI during the 5-year study, two-thirds did not. Similar to the COURAGE trial, the incidence of CV death, MI, and CV hospitalizations (unstable angina, HF, or resuscitated cardiac arrest) was not significantly different between patients with SIHD treated with an initial invasive strategy consisting of coronary angiography, revascularization, and GDMT compared to an initial conservative strategy in, the more recent ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial.[79]

Thus, based on the available evidence, PCI cannot be supported as the initial management strategy in most patients with SIHD. Existing evidence suggests that PCI in SIHD should be reserved for patients with chest pain despite optimal GDMT often referred to as refractory angina.

Coronary Artery Bypass Graft Surgery

While PCI is the most common form of revascularization, CABG surgery is recommended to prolong survival or relieve refractory symptoms of angina in select patients.[1,80,84] In the majority of CABG surgeries, a sternotomy, and division of the sternum is done to provide the surgeons with direct access to the heart. Thus, it is often referred to as “open-heart surgery.” Once the heart is exposed, vascular conduits surgically harvested from other

areas of the body are used to “bypass” the atherosclerotic plaque. The most commonly used vascular conduits are the saphenous vein grafts (SVG) from the leg and the left internal mammary artery (LIMA) from the chest wall. The radial and gastroepiploic arteries are also occasionally used. When a LIMA graft is performed, the distal portion is detached from its insertion point behind the sternum and an anastomosis is made distal to the atherosclerotic plaque of the diseased coronary artery to restore blood flow beyond the blockage. The other vascular conduits (eg, SVG) are considered “free grafts” and are anastomosed distally to atherosclerotic plaques of the other diseased coronary arteries. The proximal ends of the free grafts are then anastomosed to the aorta restoring blood flow distal to the blockage. Prior to and during the anastomoses of the bypass grafts, patients are often placed on cardiopulmonary bypass which redirects blood from the heart to a bypass machine. In the bypass machine, venous blood is oxygenated and then returned to the systemic circulation to maintain myocardial and systemic perfusion during the surgery. The heart is then arrested allowing the surgeon to perform the surgery without the heart actively beating. After the bypass grafts have been installed, the patient is weaned from the cardiopulmonary bypass machine, the heart and lung resume their normal functioning, the cannulas are removed, and the sternum and incisions are closed.

While a critical obstruction of a native coronary vessel due to atherosclerosis usually takes five or more decades, the lifespan of an SVG is significantly shorter. This is due to the higher BP in arterial circulation compared to venous pressures. Endothelial damage and LDL-C accumulation significantly accelerate the atherosclerotic process. The use of arterial grafts provides greater long-term graft patency compared to SVG. Arterial grafts are more prone to vasospasm and require longer surgical times to harvest.

Despite the advancements in technique and patient care, CABG surgery is associated with several complications. Death, neurological impairment, MI, major bleeding, acute kidney injury, atrial fibrillation, and surgical wound infections are all potential complications following CABG surgery. Early mortality within 30 days is generally low (1%-2%) but is higher in emergent or high-risk cases (eg, multiple comorbidities, older patients).[82] Neurological complications such as stroke (1%-3%), delirium (8%-50%), and cognitive deficits can occur due to hypoxia, emboli, hemorrhage, or a metabolic abnormality during or shortly after the surgery.[82] Patients with advanced age, previous stroke or transient ischemic attack, HTN, ASCVD, atrial fibrillation, and prolonged cardiopulmonary bypass duration are at higher risk of neurological complications. Atrial fibrillation occurs in as many as 30% of patients undergoing CABG surgery but is often transient. An infection of the sternum, known as mediastinitis, occurs in 0.5%-3% of patients and may prolong hospital stays, increase recovery time, and result in repeat surgical intervention.[82] MI, major bleeding requiring surgical re-exploration, and acute kidney injury requiring hemodialysis each occur in 1% to 4% of patients following CABG surgery.[82]

New approaches to CABG surgery have been developed in an attempt to minimize complications. One of these approaches is the off-pump bypass coronary surgery that is performed while the heart is beating. By reducing the need for cardiopulmonary bypass and aortic clamping, rates of adverse neurologic and renal events are significantly lower.[82] Another approach to surgical revascularization is the use of minimally invasive direct coronary artery bypass during which a small left anterior thoracotomy is done in lieu of a sternotomy. Due to the small incision and technical difficulty of the surgery, only patients with single-vessel disease in either the left anterior descending or right coronary artery currently are candidates for the procedure. Although postoperative pain is often increased, clinical outcomes of minimally invasive direct coronary artery bypass are similar to conventional CABG but recovery time is quicker.[82]

In suitable surgical candidates, CABG surgery is the preferred revascularization strategy in several clinical scenarios. Examples include patients with left main CAD (≥50% stenosis) “unprotected” by collateral coronary blood flow or patent bypass grafts, 2-vessel CAD (≥70% stenosis in the proximal left anterior descending coronary artery and one additional major coronary artery), and multivessel CAD (≥70% stenosis in three or more major coronary arteries). CABG surgery is preferred to PCI and medical management because it is associated with prolonged survival.[84] CABG surgery is also recommended to decrease mortality in patients who survived an episode of sudden cardiac death due to ischemia from significant (≥70% stenosis) CAD in one or more arteries. In patients with SIHD whose symptoms are refractory to GDMT, CABG surgery may be considered.[1,84] However, because it is less invasive than CABG surgery, PCI is often the preferred strategy in this setting.

Pharmacotherapy with CABG

Prior to CABG surgery, attention to pharmacotherapeutic needs is important to minimize postoperative complications. Patients taking aspirin 81 to 325 mg daily preoperatively should continue taking aspirin until the time of surgery to reduce ischemic events. Although patients undergoing elective CABG who were not taking aspirin preoperatively have commonly been initiated on aspirin within 24 hours of surgery, this approach offers no benefit and is no longer recommended.[84] To reduce the risk of CABG-related major bleeding, $P2Y_{12}$ inhibitors should be discontinued well in advance of an elective

CABG surgery (5 days for clopidogrel and ticagrelor; 7 days for prasugrel) and at least 24 hours prior to urgent CABG surgery, if possible. Initiation of β-blockers or amiodarone prior to CABG surgery may be considered to reduce the risk of postoperative atrial fibrillation.[84]

Pharmacotherapy after CABG surgery includes aspirin, high-intensity statins, β-blockers, and the continuation of ACE inhibitors (ACC/AHA Class I recommendations).[1,84] Aspirin 81 to 325 mg daily should be resumed or initiated within 6 hours of CABG surgery and continued indefinitely to reduce the risk of graft closure and acute MI. If patients are truly aspirin allergic, clopidogrel is an acceptable alternative. For patients treated with DAPT following PCI who subsequently undergo CABG surgery, DAPT should be resumed postoperatively and continued for the initially recommended duration of therapy is completed.[74] Due to the accelerated atherosclerotic process in the bypass grafts, high-intensity statin therapy should be resumed or initiated in all patients following CABG surgery. β-Blockers should be initiated after CABG surgery to reduce the incidence of postoperative atrial fibrillation.[84] The safety and efficacy of initiating ACE inhibitors following CABG surgery are uncertain and may increase the risk of hypotension and acute kidney injury, particularly if administered during the early postoperative period.[81] However, the continuation of previous ACE inhibitor therapy following CABG surgery is associated with a significant reduction in nonfatal cardiac, cerebral, and renal events, whereas ACE inhibitor withdrawal following CABG surgery is associated with increased event rates.[83] Therefore, for patients taking ACE inhibitors or ARBs prior to CABG surgery, these therapies should be resumed following surgery once patients have demonstrated stable hemodynamics and renal function.[81] For ACE inhibitor-naïve patients, initiation of an ACE inhibitor should be considered in stable patients with compelling indications (eg, HFrEF, HTN, DM, and chronic kidney disease).[81] For symptomatic relief of chest pain episodes, patients need access to SL nitroglycerin after surgery. Smoking cessation and cardiac rehabilitation are also critical to successful postoperative outcomes.

Management of Angina

8 Medical management of angina episodes follows a stepwise approach (see Fig. 33-2 and Table 33-6). All patients should have access to SL nitroglycerin for the treatment of an acute episode of angina. Patients need to be adequately educated on appropriate use and storage, assuring consistent access to the tablets or spray (Table 33-8). This may require patients to have multiple vials or canisters that are in areas that they spend time (eg, home, work, car). While some patients may only need SL nitroglycerin for infrequent attacks, many patients with SIHD will need chronic therapy to prevent angina episodes. Patients experiencing frequent angina episodes or in whom angina is impacting the quality of life should receive chronic therapy. The goal of chronic therapy is to provide complete or nearly complete elimination of angina episodes while having the patient take part in normal activities.

Since increased heart rate can increase MVO_2 and precipitate angina, either a β-blocker or a non-DHP CCB (verapamil or diltiazem) can be used for the initial chronic management of angina. The goal is to lower the patient's resting HR to 50 to 60 beats per minute and an exercise HR of less than 100 beats per minute. Not all patients, especially older adults, can tolerate an HR in this range; the goal HR would be as low as the patient can tolerate above 50 beats per minute. Both β-blockers and CCBs can improve exercise duration and reduce the number of weekly angina episodes.[70]

6 β-Blockers are recommended over CCBs as initial therapy for control of angina episodes in patients with SIHD.[1] This recommendation is based on improved survival demonstrated with the use of β-blockers in patients after MI and with HFrEF. Only carvedilol, metoprolol succinate, and bisoprolol should be used in patients with HFrEF, starting with low doses and titrating up in a slow and set regimen. CCBs have not demonstrated similar benefits in patients following an MI or with HFrEF. Patients with contraindications or intolerable adverse drug reactions to β-blocker therapy may be treated with a CCB, with verapamil or diltiazem preferred in patients needing HR reduction. In patients without a history of MI or HF, the use of β-blocker therapy does not provide a survival advantage and is used purely for the control of ischemic episodes and symptoms of angina.[70]

5 If angina symptoms are controlled once the HR goal is achieved, no additional antianginal therapy is necessary and patients are monitored for continued efficacy and adverse drug reactions. Regardless of whether a β-blocker or non DHP CCB are selected as initial therapy for HR reduction, many patients will require combination therapy to attain adequate control of their symptoms. If additional therapy is required, the need for additional antihypertensive agents should be considered in the next step. Patients with angina symptoms refractory to β-blockers who continue to have elevated BP above the goal of 130/80 mm Hg should be prescribed a DHP CCB. Unlike long-acting nitrates and ranolazine, DHP CCBs decrease both MVO_2 and BP.

While not commonly combined, DHP CCB and non-DHP CCB target different calcium channels and are a rational regimen for patients with SIHD with contraindications or intolerance to β-blockers. It is important to monitor the patient for peripheral edema and signs and symptoms of reduced cardiac output.

7 In patients with continued angina episodes despite achieving BP and HR goals, a long-acting nitrate or ranolazine should be added to the regimen. Both agents have demonstrated efficacy when used in combination with SL nitroglycerin and medications to control HR and BP. While long-acting nitrates are not optimal agents when used as monotherapy due to reflex tachycardia, this is attenuated in patients who are taking a β-blocker or non-DHP CCB. Ranolazine does not reduce HR or BP, making it an option in patients who have already achieved their HR and BP goals, but still have exertional angina. The selection of a long-acting nitrate or ranolazine should be based on patient preferences, tolerability, and cost. Long-acting nitrates do not provide 24-hour angina protection, but this may not be an issue for all patients. While ranolazine provides 24 hours protection and has a more attractive adverse drug reaction profile compared to long-acting nitrates, it is more expensive and associated with numerous drug interactions.

Patients who are unable to fully participate in the activities that bring them joy in life because of inadequate control of chest pain symptoms, despite the use of maximally tolerated therapies, have refractory angina. Some patients may have refractory angina while taking relatively fewer antianginal medications or lower doses due to intolerances or contraindications. Patients with refractory angina should be referred for revascularization therapy.

Management of Vasospastic Angina

In patients where the onset of angina varies, pharmacotherapy that targets vasospasm is needed. While β-blockers are typically the agents of first choice in patients with a consistent angina threshold, they are less useful in patients with vasospasm. Although not all studies report increased chest pain episodes with β-blockers in patients with vasospasm, they can induce coronary vasoconstriction and prolong ischemia. Worsening angina is most likely due to unopposed α1-adrenergic receptor stimulation during β-blockade. A similar phenomenon may occur in patients with SIHD treated with β-blockers who also abuse cocaine or methamphetamines.

Both nitrates and CCBs reduce vasospasm. Most patients respond well to SL nitroglycerin for acute attacks. While long-acting nitrates can be used in the treatment of vasospasm, the high doses typically needed for adequate symptom control are not well tolerated. Therefore, CCBs are often used. There is no preference to which agent is selected first, but CCBs are dosed less frequently and a single agent may be sufficient to manage symptoms. Nifedipine, verapamil, and diltiazem are all equally effective for the initial management of coronary vasospasm. Dose titration is important to maximize the response with CCBs. Patients unresponsive to calcium antagonists alone may add long-acting nitrates.

EVALUATION OF THERAPEUTIC OUTCOMES

The therapeutic goals in the management of patients with SIHD are to prolong life, reduce symptoms of angina, and improve quality of life. Improving the patient's quality of life requires careful attention to the potential adverse drug reactions from medications. Surrogate endpoints such as BP goal attainment, use of high-intensity statin, A1c goal attainment, smoking cessation, and achieving a healthy weight should be used to determine progress toward the ultimate goal—reduced risk of mortality and major cardiovascular events. Patients should be evaluated every 1 to 2 months until goals are achieved. Follow-up every 6 to 12 months thereafter is appropriate.

3 Monitoring for improvements in symptoms related to angina should include asking the patients about the number and severity of angina episodes and weekly SL nitroglycerin use as well as inquiring about exercise capacity or duration of exertion needed to induce angina. It is important to ask the patient about their ability to engage in activities they want to do. It is not uncommon for patients to report reduced or no episodes of angina because they have stopped engaging in activities that bring on angina. Patients experiencing worsening angina may complain of increasing frequency and severity of symptoms, increased SL nitroglycerin use, decreased exercise capacity, or a combination of these. Once patients have received optimal medical therapy, symptoms should improve in 2 to 4 weeks and remain stable until the disease progresses. Instruments such as the Seattle Angina Questionnaire and CCS Angina Grading Scale can be used to improve the assessment of symptoms.[1] While objective tests such as an exercise tolerance test with or without cardiac imaging can be obtained to assess the adequacy of treatment, they are primarily performed in patients who do not achieve adequate symptom control. Following a revascularization procedure, the patients' symptoms should be assessed every 6 to 12 months.

ABBREVIATIONS

ACC	American College of Cardiology
ACE	angiotensin-converting enzyme

ACS	acute coronary syndrome
AHA	American Heart Association
ARB	angiotensin receptor blocker
ASCVD	atherosclerotic cardiovascular disease
BMS	bare-metal stent
BP	blood pressure
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CCS	Canadian Cardiovascular Society
CCB	calcium channel blocker
COR	class of recommendation
COX	cyclooxygenase
COPD	chronic obstructive pulmonary disease
CT	computer topography
CVD	cardiovascular disease
DES	drug-eluting stent
DHP	dihydropyridine
DM	diabetes mellitus
ECG	electrocardiogram
EDRF	endothelium-derived relaxing factor
FFR	fractional flow reserve
GDMT	guideline-directed medical therapy
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HR	heart rate

HTN	hypertension
LDL-C	low-density lipoprotein cholesterol
LIMA	left internal mammary artery
LOE	level of evidence
LV	left ventricle
MI	myocardial infarction
MVO_2	myocardial oxygen demand
PCI	percutaneous coronary intervention
SIHD	stable ischemic heart disease
SVG	saphenous vein graft

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SELF-ASSESSMENT QUESTIONS

1. A 56-year-old patient had coronary artery bypass graft (CABG) surgery performed for refractory symptoms of angina despite maximally tolerated medical therapy and multiple percutaneous coronary interventions. Which of the following medications should be initiated following CABG surgery and continued indefinitely to maintain patency of the saphenous vein grafts?

   A. Aspirin

   B. Rivaroxaban

   C. Ticagrelor

   D. Warfarin

2. Which of the following best explains why ischemia does not typically occur with exertion in patients with stable ischemic heart disease until coronary stenosis reaches 70% or more of the luminal diameter?

A. Atherosclerotic plaque rupture beyond this degree of coronary stenosis

B. Collateral circulation diminishes as coronary stenosis increases

C. Coronary flow reserve is exhausted as the degree of coronary stenosis increases

D. Vasospasm occurs once coronary stenosis exceeds 70% of luminal diameter

3. Which of the following patients with stable ischemic heart disease is more likely to experience atypical symptoms of angina? (Key Concept #2)

A. 46-year-old with hypertension, dyslipidemia, and obesity

B. 54-year-old with gastroesophageal reflux disease and dyslipidemia

C. 62-year-old with atrial fibrillation, stroke, and chronic kidney disease

D. 76-year-old with hypertension, dyslipidemia, and diabetes

4. A patient with stable ischemic heart disease is being evaluated for control of angina symptoms. The patient reports experiencing angina symptoms one to two times weekly, unchanged from baseline. Angina symptoms are typically provoked when walking up stairs, consistent with baseline. The chest discomfort is described as 5 out of 10, similar to baseline. The patient reports using 3 to 4 tablets/week of sublingual nitroglycerin compared to 1 to 2 tablets/week at baseline. His blood pressure is 132/84 mm Hg, heart rate is 70 beats per minute. Which of the following suggest worsening angina control?

A. Frequency of angina symptoms

B. Provoking factors

C. The severity of angina symptoms

D. Sublingual nitroglycerin use

5. A 63-year-old female with hypertension, diabetes, dyslipidemia, and obesity is newly diagnosed with stable ischemic heart disease. Blood pressure is 148/86 mm Hg, heart rate is 64 beats per minute. Weight is 104 kg; body mass index is 43.3 kg/m^2. LDL cholesterol is 127 mg/dL (3.28 mmol/L) and hemoglobin A1c is 8.3% (0.083; 67 mmol/mol). Which of the following risk factor modification goals is appropriate for this patient?

A. Blood pressure <130/80 mm Hg

B. Body mass index <30 kg/m^2

C. Hemoglobin A1c <6.5% (0.065; 48 mmol/mol)

D. LDL cholesterol <70 mg/dL (1.81 mmol/L)

The next two questions (#6 and #7) refer to the following case.

A 68-year-old male presents with complaints of angina when walking two flights of stairs. The pain is relieved with rest and only occasionally requires a dose of SL nitroglycerin for relief. His PMH includes a history of MI 3 years ago, HTN, and hyperlipidemia. He quit smoking 3 years ago after his MI. His home medications include aspirin 81 mg daily, metoprolol 25 mg twice daily, and atorvastatin 80 mg daily. Vital signs: BP is 158/92 mm Hg, HR 82 bpm.

6. Which of the following is most appropriate to treat this patient's angina?

A. Add lisinopril 10 mg daily

B. Add ranolazine 1,000 mg twice daily

C. Add SL nitroglycerin 1 tablet as needed for angina

D. Increase metoprolol to 50 mg twice daily

7. The patient returns for a cardiology appointment 6 weeks later and states that his angina has improved and he is feeling much better. His laboratory findings are within normal limits. Vital signs: BP is 140/88 mm Hg, HR 68 bpm. LDL 67 mg/dL (1.73 mmol/L). Which of the following is most appropriate to consider in this patient to reduce mortality?

   A. Clopidogrel 75 mg daily

   B. Lisinopril 5 mg daily

   C. Ezetimibe 10 mg daily

   D. Hydrochlorothiazide 25 mg daily

8. A 74-year-old female undergoes PCI for stable angina symptoms and receives a drug-eluting stent in her right coronary artery. Which of the following is recommended post-PCI?

   A. Aspirin 325 mg daily plus clopidogrel 75 mg daily for 6 months

   B. Aspirin 81 mg daily plus ticagrelor 90 mg twice daily for 1 month

   C. Aspirin 325 mg daily plus ticagrelor 90 mg twice daily for 1 month

   D. Aspirin 81 mg daily plus clopidogrel 75 mg daily for 6 months

9. A patient presents to his local pharmacy with a new prescription for SL nitroglycerin tablets. Which is not correct patient counseling information to give the patient?

   A. This medication is only for the treatment of acute anginal attacks.

   B. Keep the bottle in the original glass bottle as the medication is sensitive to light.

   C. Be sure to sit down before taking this medication as it may cause dizziness.

   D. It is recommended to replace the bottle every 6 months to ensure optimal potency.

10. A 75-year-old patient with SIHD presents with continued angina. His home medications include aspirin 81 mg daily, allopurinol 100 mg daily, lisinopril 20 mg daily, carvedilol 25 mg twice daily, rosuvastatin 20 mg daily, isosorbide mononitrate 60 mg daily, and acetaminophen as needed for pain. His PMH includes a history of MI, HTN, gout, dyslipidemia, and arthritis. Vital signs: BP 100/60 mm Hg; HR 62 bpm, weight 90 kg. Laboratory findings are within normal limits. Which of the following is the most appropriate option to treat this patient's angina?

    A. Change carvedilol 25 mg twice daily to amlodipine 10 mg daily

    B. Change isosorbide mononitrate to a nitroglycerin patch

    C. Increase carvedilol to 50 mg twice daily

    D. Add ranolazine 500 mg twice daily

11. A 65-year-old patient with continued angina presents to the primary care physician. Home medications include aspirin 81 mg daily, ramipril 10 mg daily, metoprolol 50 mg twice daily, atorvastatin 40 mg daily, nitroglycerin patch 0.8 mg/hr daily, SL nitroglycerin as needed for angina, dofetilide 500 mcg twice daily, and apixaban 5 mg twice daily. PMH includes a history of multiple MI's, a history of PCI with stents 5 years ago, atrial fibrillation, HTN, and dyslipidemia. Vital signs: BP 138/85 mm Hg, HR 58 bpm. LDL 70 mg/dL (1.81 mmol/L). Which of the following is the most appropriate agent to treat this patient's angina?

    A. Increase metoprolol to 100 mg twice daily

B. Add Ranolazine 500 mg twice daily

C. Add amlodipine 5 mg daily

D. Add Diltiazem ER 120 mg daily

12. A 72-year-old patient is getting ready to be discharged after undergoing a CABG procedure for his chronic, refractory angina. PMH includes HTN, CAD, diabetes, and hyperlipidemia. Discharge medications include aspirin 81 mg daily, metformin 500 mg twice daily, carvedilol 12.5 mg twice daily, and rosuvastatin 40 mg daily. Vital signs: BP 140/90 mm Hg, HR 75 bpm. Hemoglobin A1c is 6.5% (0.065; 48 mmol/mol) and LDL is 65 mg/dL (1.68 mmol/L). Which of the following medications should be added to this patient's regimen?

A. Ticagrelor 90 mg twice daily

B. Lisinopril 10 mg daily

C. Ezetimibe 10 mg daily

D. Empagliflozin 10 mg daily

13. Which of the following directly affects myocardial oxygen demand?

A. Myocardial wall tension

B. Presence of anemia

C. Large plaque burden

D. Coronary vasospasm

14. A 64-year-old patient is newly diagnosed with SIHD. PMH includes dyslipidemia. Blood pressure is 126/74 mmHg, HR 68 bpm. LDL is 110 mg/dL (2.84 mmol/L). The following medications are initiated: aspirin 81 mg daily, atenolol 50 mg daily, atorvastatin 80 mg daily, and ramipril 2.5 mg daily. Which of the following medications should also be considered?

A. Clopidogrel 75 mg daily

B. Ranolazine 500 mg twice daily

C. Nitroglycerin SL 0.4 mg PRN

D. Verapamil ER 180 mg daily

15. A 69-year-old female with diabetes complains of midepigastric discomfort that radiates to her jaw. Her symptoms are brought on by gardening and relieved with rest. Which of her symptoms is atypical?

A. Midepigastric discomfort

B. Provocation by gardening

C. Radiation to her jaw

D. Relief by rest

SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** The best answer is to initiate and continue aspirin indefinitely as it has been shown to reduce the risk of SVG closure during the first year after CABG surgery. Low-dose rivaroxaban has been evaluated in patients with both stable ASCVD and ACS undergoing CABG with no statistically

significant differences in graft failure found. Therefore, it is not recommended to maintain graft patency. Ticagrelor as a single antiplatelet agent is not recommended post-CABG as the antiplatelet agent of choice. It could be used post-CABG in combination with aspirin in patients who have had a recent stent or an ACS event, but it has not been found to be better than aspirin alone post-CABG in one trial (RKC1). Warfarin would not be indicated post-CABG unless the patient had a specific indication for anticoagulation. Thus, A is the best answer. See section "Pharmacotherapy with CABG".

2. **C.** When coronary atherosclerotic plaques exceed a critical threshold, typically approximately 70% blockage, the coronary reserve is used at rest to vasodilate the obstructed coronary artery and maintain coronary blood flow. As a result, the ability to adapt to increases in oxygen demand is diminished because coronary flow reserve is exhausted, leading to ischemia. Thus, C is the best answer. See section "Etiology and Pathophysiology"

3. **D.** Older patients, females, and those with diabetes are more likely to experience atypical symptoms of angina. Therefore, D is correct (age 76, history of diabetes). See the "Clinical Presentation" section.

4. **D.** Successful treatment of angina should reduce the frequency of angina episodes as well as the weekly use of sublingual nitroglycerin. Although the patient reports no change in provoking factors nor the frequency or severity of episodes, the increased use of sublingual nitroglycerin may indicate worsening symptoms of angina; D is the best answer. See the "Evaluation of Clinical Outcomes" section.

5. **A.** Current guidelines recommend a BP goal of <130/80 mm Hg; thus, A is correct. Although LDL goals of <70 mg/dL (1.81 mmol/L) may be targeted in "very high-risk" patients (such as those with a history of multiple ASCVD events or 1 major event and multiple high-risk comorbidities), current guidelines recommend the use of high-intensity statins in patients with clinical ASCVD such as this patient or patients who are 40 to 75 years of age and diabetes to reduce LDL by ≥ 50%. Diabetes guidelines recommend a hemoglobin A1c of <7% (0.07; 53 mmol/mol) in select patients and 7% to 9% (0.07-0.09; 53 to 75 mmol/mol) in frail or high-risk patients, not <6.5% (0.065; 48 mmol/mol). While a BMI between 18.5 and 24.9 kg/m^2 is ideal to reduce CV risk, the initial goal of weight management is to lose 5% to 10% of body weight from baseline (Table 33-5).

6. **D.** The best answer is to increase the β-blocker dose, which is a guideline-recommended first-line treatment of angina since the patient is experiencing continued angina and is on a low dose of metoprolol. Additionally, his blood pressure and heart rate are not at target levels and further lowering of BP and HR will improve the myocardial oxygen mismatch and improve his angina. See the "Pharmacotherapy to Relieve Symptoms Recommendations" section and "β-blockers" subsection.

7. **B.** The best answer is to initiate an ACE inhibitor in this patient since he has SIHD and is also post MI. The SIHD guidelines recommend the use of ACE inhibitors in all patients with SIHD who also have HTN, DM, LV dysfunction, or chronic kidney disease, unless contraindicated as well in patients post-MI. See "Angiotensin-Converting Enzyme (ACE) Inhibitors" and "Blood Pressure Management" sections (see Table 33-5).

8. **D.** The correct answer is aspirin 81 mg plus clopidogrel 75 mg daily for at least 6 months in a SIHD who receives a drug-eluting stent during an elective PCI. The guidelines recommend clopidogrel as the $P2Y_{12}$ antiplatelet of choice in SIHD patients undergoing an elective PCI. The correct dose of aspirin should be 75 to 100 mg daily. See the "Pharmacotherapy with PCI" section.

9. **A.** SL nitroglycerin can be used for the treatment of acute angina attacks but also can be used for the prevention or prophylaxis of angina if taken before partaking in an exertional event known to precipitate angina. See Education for clinicians and patients on use of sublingual nitroglycerin (see Table 33-8).

10. **D.** The correct answer in this patient with continued angina while receiving a β-blocker and chronic nitrate with low blood pressure and heart rate is to add ranolazine. Ranolazine provides relief of angina without impacting hemodynamics such as HR, BP, the inotropic state, or increase coronary blood flow. See the "Pharmacotherapy to Relieve Symptoms Recommendations" section and "Ranolazine" subsection.

11. **C.** The patient's blood pressure is not at the goal of <130/80 mm Hg and since he is continuing to experience angina, amlodipine would be the best agent to add on to his current regimen to control both angina and reduce blood pressure. Ranolazine can be added on to anginal regimens, often as third- or fourth-line options but this patient has a drug-drug interaction with the dofetilide and ranolazine; both of which can increase the QTc interval and predispose this patient to torsades de pointes. In addition, ranolazine will not address this patient's elevated blood pressure. Metoprolol is not a good option in this patient due to the low heart rate of 58 bpm on the current dose. Lastly, diltiazem is not a good option to add on in this situation since he is already taking another AV nodal blocking agent, metoprolol, and his heart rate is already low. See the

"Pharmacotherapy to Relieve Symptoms Recommendations" section.

12. **B.** The addition of an ACE inhibitor should be considered in stable patients post CABG with compelling indications (eg, HFrEF, HTN, DM, and chronic kidney disease). This patient has diabetes, and his blood pressure is not controlled. The use of dual antiplatelet therapy (DAPT) may be considered in some patients post-CABG, such as those with a recent stent ACS presentation. In a patient with stable ischemic heart disease undergoing CABG, DAPT with clopidogrel, but not ticagrelor, could be an option. There is no need for ezetimibe or empagliflozin in this patient since his LDL is < 70 mg/dL (1.81 mmol/L) and hemoglobin A1c is < 7% (0.07; 53 mmol/mol). See the "Pharmacotherapy with CABG" section.

13. **A.** The major determinants of MVO_2 include heart rate (HR), myocardial contractility, and intramyocardial wall tension. Arterial oxygen content is related to hemoglobin concentration and oxygen saturation. Consequently, patients with anemia (low hemoglobin) or hypoxia (low oxygen saturation) have lower than normal oxygen-carrying capacity. Both large atherosclerotic plaque burden inside a coronary artery and coronary vasospasm affect coronary artery oxygen supply. See the "Etiology and Pathophysiology" section.

14. **C.** All patients with SIHD should be prescribed SL nitroglycerin to treat acute symptoms of angina in the absence of contraindications (C is correct). A combination of antianginal therapies is not recommended for the initial management of patients with SIHD; therefore, neither ranolazine nor verapamil is indicated. In the case of verapamil, adding this to beta-blocker therapy (atenolol) may also increase the risk of bradycardia and should be avoided. In the absence of an ACS event or PCI within the preceding 6 to 12 months, DAPT is not indicated. Thus, clopidogrel is incorrect. See Figure 33-2 and section "Antiplatelet Therapy".

15. **A.** Atypical symptoms of angina may consist of mid-epigastric discomfort (A is correct), effort intolerance, dyspnea, and/or excessive fatigue. Radiation to the jaw or left arm (C), provocation by exertion (B), and relief by rest (D) are all typical symptoms of angina and, thus, incorrect. See the "Clinical Presentation" section.