Current Management of Stable Angina Pectoris

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Angina is the clinical manifestation of myocardial ischemia and is most often due to coronary stenosis. The management of stable ischemic heart disease requires treatment aimed at both symptom relief and reduction of cardiovascular morbidity and mortality related to atherosclerosis. Risk-factor modification and medical therapy to prevent acute ischemic events and disease progression should be initiated after diagnosis. Patients with symptoms refractory to medical therapy, high-risk stress test results, or anatomic findings have an indication for coronary revascularization. This article addresses evidence that supports the use of secondary prevention therapies and the various antianginal medications that are available for the management of stable angina.

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KEY WORDS

Stable ischemic heart disease • Angina pectoris • Atherosclerosis

The management of patients with stable ischemic heart disease (SIHD) aims both to relieve anginal symptoms and reduce cardiovascular morbidity and mortality related to atherosclerosis. Prognosis should be evaluated by noninvasive testing and, in high-risk scenarios, with cardiac catheterization. Upon diagnosis, aggressive modification of cardiac risk factors and medical therapy to prevent acute ischemic events and disease progression should be initiated. Antianginal medications improve exercise tolerance and decrease the frequency of anginal episodes. Patients with symptoms refractory to medical therapy, high-risk stress test results, or anatomic findings have an indication for coronary revascularization (either percutaneous or surgical), depending on anatomic disease complexity. For patients with angina refractory to standard treatment, additional therapies may be considered.

Prevalence and Classification

SIHD can have a wide spectrum of clinical presentations that can include discomfort in the chest, jaw, shoulder, back, or arms, typically elicited by exertion, emotional stress, or dyspnea on exertion, and is relieved by rest or nitroglycerin. Less typically, discomfort may occur in the epigastric area. SIHD is commonly encountered in clinical practice, affecting an estimated 9 million people in the United States (3.9% of the population).[1] The prevalence of angina assessed by the Rose questionnaire varies widely across populations and is slightly more prevalent in women than in men.[2] The health and economic burden of this syndrome, and of coronary artery disease (CAD) in general, is tremendous, in addition to its impact on quality of life.

There are several accepted classifications of angina pectoris. The one most commonly used is the Canadian Cardiovascular Society (CCS) classification based on severity of symptoms[3]:

- Class I: Ordinary activity does not cause angina. Symptoms of angina occur with strenuous, rapid, or prolonged exertion.
- Class II: Slight limitation of ordinary activity. Angina occurs when walking or climbing stairs rapidly, walking uphill, or during exertion after meals, in cold weather, when under emotional stress, or only during the first few hours after awakening.
- Class III: Marked limitation of ordinary physical activity. Angina on walking one or two blocks on level ground or one flight of stairs at a normal pace under normal conditions.
- Class IV: Inability to carry out any physical activity without discomfort or angina at rest.

Natural History and Prognosis

Prognostic data on SIHD are based on large, prospective, population-based studies. In the Framingham Heart Study, 2-year rates of nonfatal myocardial infarction (MI) and cardiac death in patients with an initial presentation of stable angina were 14.3% and 5.5% in men, and 6.2% and 3.8% in women, respectively.[4] However, this was in the era preceding widespread use of aspirin, statins, and β-blockers. Contemporary prognostic data in SIHD come from pharmacologic and revascularization trials. In the 12,218-patient European Trial on the Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA),[5] low-risk patients with stable CAD randomized to receive the angiotensin-converting enzyme (ACE) inhibitor, perindopril (8 mg/d), had a 20% reduction (8.0% vs 9.9%) of the composite endpoint of cardiovascular death, cardiac arrest, and acute MI compared with the placebo-treated group (95% confidence interval [CI], 9-29; $P = .0003$); a statistically significant reduction in nonfatal MI from 6.2% to 4.8% (odds ratio [OR] 0.78; CI, 0.67-0.90) and a nonsignificant reduction of cardiovascular mortality from 4.1% to 3.5% (OR 0.86; CI, 0.72-1.03) at a mean follow-up of 4.2 years was also noted.[5] Ischemic event rates were higher, however, in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial,[6] which enrolled low- to medium-risk patients with chronic angina and/or objective ischemia with significant obstructive CAD. During a median follow-up period of 4.6 years, despite a very high compliance to currently accepted optimal medical therapy, the MI rate was 12.3% and all-cause mortality was 8.3%.[6]

Risk Stratification

The risk of cardiovascular events in individual patients with stable angina varies significantly depending on a number of clinical, physiologic, and anatomic characteristics. Therefore, clinical, noninvasive, and invasive tools have been developed to assess prognosis and identify patients who may benefit from earlier revascularization strategies versus those patients who can be treated conservatively.

A number of clinical criteria have been shown to adversely affect prognosis of patients with established CAD through their effect on disease progression, such as type 2 diabetes mellitus (DM), smoking, hypertension, and hyperlipidemia. Characteristics such as age, previous MI, congestive heart failure, and the severity of angina are also important predictors of poor outcome.

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Noninvasive testing plays an important role in risk stratification of patients with stable angina and can serve as a gatekeeper to cardiac catheterization. The maximal exercise capacity measured during exercise electrocardiograph is one of the strongest and most consistent prognostic markers. The prognostic value of stress nuclear myocardial perfusion imaging is well established and incremental to clinical and exercise data. Patients with a normal nuclear perfusion study result have an annual risk of death

or MI of < 1%. Left ventricular (LV) function, evaluated by echocardiography, is also highly predictive of survival in these patients.[7]

Invasive testing with coronary angiography is used to confirm the diagnosis of CAD and to further risk-stratify patients. Recent guidelines from the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Task Force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons identified two clinical scenarios that have a Class I recommendation for coronary angiography as an initial testing strategy to assess risk[1]: (1) for those patients who have survived sudden cardiac death (SCD) or potentially life-threatening ventricular arrhythmias, and (2) for patients who develop signs and symptoms of heart failure. Coronary angiography is also given a Class I recommendation to assess risk following an initial noninvasive evaluation in patients with SIHD whose clinical characteristics and results of noninvasive testing indicate a high likelihood of severe ischemic heart disease, and when the benefits are considered to exceed risk (Table 1).

The extent of CAD on coronary angiography is inversely related to survival. Patients with significant left main disease have a poor prognosis when treated medically. Similarly, patients with three-vessel disease, including ≥ 95% proximal left anterior descending artery (LAD) disease, have a 5-year survival rate of 59% compared with 93% in patients with single-vessel disease (Table 2).[1]

Goals of Treatment

Treatment of stable angina should be directed at two main goals: reducing the global risk related to atherosclerosis and providing symptom relief. With continuous and marked improvements in percutaneous revascularization devices and techniques, as well as new evidence from large, prospective, randomized trials of pharmacotherapy, our understanding and available treatments for patients with stable CAD have evolved significantly over the past few decades.

Treatment of stable angina should be directed at two main goals: reducing the global risk related to atherosclerosis and providing symptom relief.

Modification of Causal Risk Factors

The comprehensive approach to reducing the global risk of atherosclerosis should begin with lifestyle modification.[8] Moderate-intensity aerobic physical activity, such as brisk walking for 30 to 60 minutes at least 5 days per week, is recommended. For high-risk patients, such as patients with recent acute coronary syndrome (ACS) or revascularization, and those with congestive heart failure, a medically supervised program is recommended. Dietary therapy should include a diet high in fresh fruits and vegetables and reduced intake of saturated fats (< 7% of total calories), trans-fatty acids, and cholesterol (< 200 mg/d). A body mass index between 18.5 and 24.9 kg/m^2 should be achieved and maintained.[8] The effect of dietary and supplemental omega-3 fatty acids in CAD is controversial. A meta-analysis of over 20,000 patients

TABLE 1

Noninvasive Risk Stratification

High Risk (> 3% annual death or MI)

1. Severe resting LV dysfunction (LVEF < 35%) not readily explained by noncoronary causes
2. Resting perfusion abnormalities ≥ 10% of the myocardium in patients without prior history or evidence of MI
3. Stress ECG findings including ≥ 2 mm of ST-segment depression at low workload or persisting into recovery, exercise-induced ST-segment elevation, or exercise-induced VT/VF
4. Severe stress-induced LV dysfunction (peak exercise LVEF < 45% or drop in LVEF with stress ≥ 10%)
5. Stress-induced perfusion abnormalities encumbering ≥ 10% myocardium or stress segmental scores indicating multiple vascular territories with abnormalities
6. Stress-induced LV dilation
7. Inducible wall motion abnormality (involving > 2 segments or 2 coronary beds)
8. Wall motion abnormality developing at low dose of dobutamine (≤ 10 mg/kg/min) or at a low heart rate (< 120 beats/min)
9. Coronary artery calcium score > 400 Agatston units
10. Multivessel obstructive coronary artery disease (≥ 70% stenosis) or left main stenosis (≥ 50% stenosis) on CCTA

CCTA, coronary computed tomography angiography; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; VT/VF, ventricular tachycardia/ventricular fibrillation.
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TABLE 2

Coronary Artery Disease Prognostic Index

Extent of CAD	Prognostic Weight (0-100)	5-Year Survival Rate (%)[a]
1-vessel disease, 75%	23	93
1-vessel disease, 50%-74%	23	93
1-vessel disease, ≥ 95%	32	91
2-vessel disease	37	88
2-vessel disease, both ≥ 95%	42	86
1-vessel disease, ≥ 95% proximal LAD	48	83
2-vessel disease, ≥ 95% LAD	48	83
2-vessel disease, ≥ 95% proximal LAD	56	79
3-vessel disease	56	79
3-vessel disease, ≥ 95% in ≥ 1 vessel	63	73
3-vessel disease, 75% proximal LAD	67	67
3-vessel disease, ≥ 95% proximal LAD	74	59

[a]Assuming medical treatment only.
CAD, coronary artery disease; LAD, left anterior descending artery.
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found that those with prior MI benefited from supplementation, whereas those with stable angina without prior MI had an increased risk of SCD when randomized to omega-3 fatty acids compared with placebo.[9] The ongoing REDUCE-IT trial (http://clinicaltrials.gov/ct2/show/NCT01492361) comparing icosapent ethyl with placebo should help answer the question about the effect of omega-3 fatty acids on cardiovascular events. Smoking cessation and avoidance of exposure to tobacco smoke is recommended. Referral to special programs and use of adjunctive pharmacotherapy is advised.

Control of cardiovascular risk factors is required. Blood pressure should be lowered to a goal of < 140/80 mm Hg (< 130/80 mm Hg in patients with DM or chronic kidney disease). Aside from lifestyle modifications, pharmacotherapy should include initial treatment with β-blockers and/or ACE inhibitors; if the patient is ACE inhibitor-intolerant, an angiotensin receptor blocker (ARB) should be prescribed. Management of DM should include measures to achieve a near-normal hemoglobin A_{1c} (HbA_{1c}; < 7%), except in the presence of brittle DM with high risk for hypoglycemia. If baseline low-density lipoprotein (LDL) cholesterol is ≥ 100 mg/dL, then LDL-lowering drug therapy should be initiated (in addition to therapeutic lifestyle changes), with the goal of achieving an LDL < 100 mg/dL, with a more aggressive goal of < 70 mg/dL in high-risk patients, including patients with DM and smokers.[1]

Reducing Atherosclerosis Progression and Cardiovascular Risk

Antiplatelet Drugs. Aspirin, 75 to 162 mg/d, should be initiated at the time of diagnosis and continued indefinitely in all patients with CAD, unless contraindicated. Dosages of 160 to 325 mg have the same protective effect, but are associated with increased risk of bleeding.[1] The Antithrombotic Trialists' Collaboration[10] meta-analysis found that aspirin reduced the risk of vascular events (vascular death, nonfatal MI, and nonfatal stroke) by approximately 25%.

Clopidogrel, a thienopyridine antiplatelet agent that inhibits adenosine diphosphate activation of platelets via the $P2Y_{12}$ receptor, was found to be slightly more effective than aspirin at reducing major adverse cardiac events in stable patients with atherosclerotic vascular disease studied in the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial.[11] However, the combination of clopidogrel and aspirin in patients with established stable atherosclerotic vascular disease or multiple risk factors was not superior to aspirin alone in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial.[12] Therefore, dual antiplatelet therapy is not recommended in patients with stable angina, unless started after an ACS or after percutaneous coronary intervention (PCI). Clopidogrel can be used in patients with chronic angina when aspirin is contraindicated. The more potent $P2Y_{12}$ inhibitors (prasugrel and ticagrelor) have not been well studied in patients with stable CAD.

Antilipid Drugs. There are several classes of medications used to treat dyslipidemia; however, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) are the only drugs shown to reduce the rates of cardiovascular death and MI in large, randomized trials of primary and

secondary prevention. The recent Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health outcomes (AIM-HIGH) trial[13] of niacin for secondary prevention as an addition to statins in patients with very well-controlled LDL cholesterol and established cardiovascular disease failed to show an incremental benefit. The Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) study,[14] a secondary prevention trial testing the addition of extended-release niacin to statin therapy, has missed its primary endpoint and has shown no clinical benefit for extended-release niacin. A recently published systematic review and meta-analysis evaluated 11 studies including 9959 subjects (primarily secondary prevention studies) treated with niacin; it concluded that treatment with niacin was associated with a significant 34% reduction in the composite endpoint of any cardiovascular disease event and a significant 25% reduction in coronary heart disease events.[15]

Inhibitors of the Renin-Angiotensin-Aldosterone System. ACE inhibitors should be given indefinitely to all stable CAD patients with LV ejection fraction ≤ 40%; those with hypertension, DM, and chronic kidney disease (Class I); and those who are not low risk. These recommendations are based on Heart Outcomes Prevention Evaluation (HOPE)[16] and EUROPA[5] trials demonstrating the efficacy of ramipril and perindopril, respectively, in reducing the rates of cardiovascular death and MI in moderate- to high-risk stable CAD populations with no heart failure. However, in a low-risk stable CAD population receiving intensive medical and revascularization treatment, trandolapril did not improve outcomes in the Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) trial.[17]

ARBs have been shown to be noninferior to ACE inhibitors and are recommended for patients who have an indication for ACE inhibitors but are intolerant. However, the combination of an ACE inhibitor and an ARB in stable CAD patients is associated with more adverse effects with no additional benefits.[18]

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Antianginal Therapies

The other aspect of stable angina management is focused on providing symptomatic relief and improving quality of life. Treatment options include medical therapy with one or more classes of antianginal drugs, revascularization strategies (either percutaneous or surgical), and other less conventional therapies, such as enhanced external counterpulsation (EECP). In recent years there has been increased scrutiny in the medical community and in the media regarding the use and possible overuse of PCI in SIHD. In response, in 2009, the Appropriateness Criteria for Coronary Revascularization were published (with an update published in 2012). These guidelines contain an extensive number of clinical scenarios with corresponding appropriateness scores (appropriate, uncertain, or inappropriate). In most scenarios the guidelines emphasize a stepwise approach to symptomatic treatment of patients with stable angina with implementation of maximal antiischemic medical therapy (defined as the use of at least two classes of therapies to reduce angina symptoms) before embarking on a revascularization strategy.[19]

Antianginal Drugs. There are four main classes of antianginal medications in current use: β-blockers, ranolazine, nitrates, calcium channel blockers (CCBs), plus a miscellaneous group of drugs currently in development. In general, therapy is directed at improving the imbalance between myocardial oxygen supply and demand, which results in cardiac ischemia (Table 3).

β-blockers are the first line of treatment in patients with SIHD. β-blockers decrease heart rate, myocardial contractility, and blood pressure, effectively reducing myocardial oxygen demand and increasing coronary perfusion time. Despite the commonly held belief that β-blockers are cardioprotective in patients with chronic angina, they have only been shown to improve survival and prevent reinfarction in patients with a history of MI. In patients with systolic heart failure (New York Heart Association Class II-IV) β-blockers (specifically bisoprolol, extended-release metoprolol, and carvedilol) have been shown to improve survival, reduce the rate of cardiovascular hospitalizations, and improve symptoms and functional class. Such benefits have not been demonstrated in SIHD patients without prior infarction or systolic

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TABLE 3

Use of Anti-ischemic Medications: Recommendations

Class I

1. β-blockers should be prescribed as initial therapy for relief of symptoms in patients with SIHD (Level of Evidence: B)
2. CCBs or long-acting nitrates should be prescribed for relief of symptoms when β-blockers are contraindicated or cause unacceptable side effects in patients with SIHD (Level of Evidence: B)
3. CCBs or long-acting nitrates, in combination with β-blockers, should be prescribed for relief of symptoms when initial treatment with β-blockers is unsuccessful in patients with SIHD (Level of Evidence: B)
4. Sublingual nitroglycerin or nitroglycerin spray is recommended for immediate relief of angina in patients with SIHD (Level of Evidence: B)

Class IIa

1. Treatment with a long-acting nondihydropyridine CCB (verapamil or diltiazem) instead of a β-blocker as initial therapy for relief of symptoms is reasonable in patients with SIHD (Level of Evidence: B)
2. Ranolazine can be useful when prescribed as a substitute for β-blockers for relief of symptoms in patients with SIHD if initial treatment with β-blockers leads to unacceptable side effects or is ineffective, or if initial treatment with β-blockers is contraindicated (Level of Evidence: 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 (Level of Evidence: A)

CCB, calcium channel blocker; SIHD, stable ischemic heart disease.
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heart failure. The only randomized, placebo-controlled trial that investigated the effect of β-blockers on angina relief was the Atenolol Silent Ischemia Study (ASIST),[20] which confirmed the beneficial antianginal effect of atenolol compared with placebo without a significant effect on serious cardiac adverse events. A meta-analysis comparing antianginal therapies found that there were 0.31 (95% CI, 0.00-0.62; $P = .05$) fewer episodes of angina per week with β-blockers than with calcium antagonists.[21] Unless absolutely contraindicated (eg, in patients with symptomatic bradycardia or severe bronchospasm), or not well tolerated, these drugs are generally continued long term. β-blocker use is limited in patients with baseline bradycardia, higher-degree atrioventricular block, borderline low blood pressure, symptomatic peripheral arterial disease, and reactive airway disease. Most β-blockers can also have negative effects on glycemic control in those with DM and pre-DM, and adversely affect the lipid profile, as well as quality of life (eg, depression, fatigue, erectile dysfunction [ED]).

Ranolazine, the first member of a newer class of medications, is a piperazine derivative that was first approved by the US Food and Drug Administration in 2006 as a treatment for chronic angina. In 2008, ranolazine received a new indication for the treatment of chronic angina allowing for first-line use. This new labeling also provided information showing that ranolazine reduced arrhythmias (including ventricular arrhythmias), new-onset atrial fibrillation, and bradycardia in patients with CAD, although it is not indicated as an antiarrhythmic agent.[22] In addition, the new labeling states that ranolazine reduces HbA_{1c} in patients with DM. Because DM is a common comorbidity in patients with chronic angina, ranolazine may be a particularly useful first-line agent in these patients, although it is not indicated for its effect on glucose. Ranolazine, an inhibitor of the late inward sodium current, decreases ischemia-induced myocyte sodium and calcium overload. The anti-ischemic effects occur without change in heart rate or blood pressure, making it a particularly useful antianginal agent in patients with baseline bradycardia, cardiac conduction defects, and lower blood pressures. In a large trial of patients after non–ST-elevation MI, the Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction (MERLIN TIMI) 36 trial,[23] ranolazine did not influence the rates of major adverse cardiac events, although recurrent ischemia was reduced, as were ventricular arrhythmias. Ranolazine was also found to be associated with lower HbA_{1c} levels. Ranolazine is currently being studied in patients with chronic angina undergoing PCI with incomplete revascularization

in the Ranolazine for Incomplete Vessel Revascularization Post-Percutaneous Coronary Intervention (RIVER-PCI) trial (http://clinicaltrials.gov/ct2/show/NCT01442038). Although it has been associated with a small increase in the QTc interval as the dose is titrated from 500 mg twice daily, it actually has been shown to have antiarrhythmic effects. Ranolazine should not be used in patients who are taking strong cytochrome P450 3A4 inhibitors and inducers. Ranolazine has received a Class IIa recommendation (Level of Evidence: B) from the 2012 SIHD guidelines as a first-line therapy for patients who do not tolerate β-blocker therapy, and a Class IIa recommendation (Level of Evidence: A) when used in combination with a β-blocker.[1]

Nitrates are available in several preparations (oral tablet, sublingual tablet, transdermal patch or ointment, oral spray). Nitrates work via nitric oxide to relax smooth muscle cells and cause vasodilatation. Improvement in coronary perfusion results from decreased pre- and afterload, as well as augmented coronary and collateral flow. Due to the immediate onset of action, short-acting sublingual nitroglycerin is the treatment of choice for acute anginal attacks. Long-acting nitrates (isosorbide dinitrate and isosorbide 5-mononitrate) improve angina symptoms and exercise performance, but have no effect on major adverse cardiac events, and commonly cause headache.[24] A nitrate-free interval of 12 hours should be maintained to avoid drug tolerance, which is a common problem with the use of nitrates. Long-term compliance with nitrate therapy is limited by the common occurrence of severe migraine-like headaches. It is also contraindicated in patients who are prescribed phosphodiesterase type 5 inhibitors for ED or pulmonary hypertension.

Dihydropyridine CCBs (nifedipine, amlodipine, felodipine) are vasoselective and do not affect atrioventricular nodal conduction and exert their antianginal effect by reducing blood pressure and increasing coronary artery blood flow.

CCBs are well-established antianginal agents. They inhibit influx of calcium through L-type calcium channels of cardiac and vascular smooth muscle cells, leading to a decrease in vascular tone and arterial dilation. Dihydropyridine CCBs (nifedipine, amlodipine, felodipine) are vasoselective and do not affect atrioventricular nodal conduction and exert their antianginal effect by reducing blood pressure and increasing coronary artery blood flow. They can be associated with reflex tachycardia, which, in some cases can exacerbate ischemic symptoms. Nondihydropyridine CCBs (verapamil, diltiazem) are nonselective and exert their effects by reducing cardiac work by reducing blood pressure as a vasodilator and negative inotropic and chronotropic effects and can cause bradycardia, particularly when used with β-blockers. The nondihydropyridine CCBs should not be used in patients with significant LV systolic dysfunction and have not been shown to reduce mortality or rates of MI, although amlodipine was shown to decrease hospitalizations for angina, need for revascularization, a composite cardiovascular adverse outcome, and slow atherosclerosis progression by intravascular ultrasound.[25,26] These agents may be particularly effective in the treatment of variant angina due to the prevention of coronary spasm.

Combination antianginal therapy can maximize anti-ischemic effects and angina relief, and may limit drug-related side effects. Compared with monotherapy with a β-blocker or CCB alone, combination therapy increases time to ST-segment depression, time to angina onset, and total exercise duration.[27] Ranolazine, when added to a β-blocker or CCB, significantly reduces anginal frequency and use of nitroglycerin and increases exercise capacity.[28,29]

PCI. PCI is used in conjunction with optimal medical therapy and represents an important therapeutic option for the management of patients with SIHD. The decision to perform PCI is based on multiple factors, including symptoms on maximal medical treatment (two antianginal drugs), high-risk noninvasive testing findings, high-risk anatomy, risk of the procedure, and the likelihood of acute procedural success and long-term durability. Because the culprit lesions in ACS are mainly non–flow-limiting coronary stenoses that are thrombotic in nature and are predisposed to becoming occlusive (leading to recurrent ischemia and infarction), PCI in stable CAD should be considered a treatment directed toward symptom relief, rather than reduction of mortality. Previous trials comparing PCI versus medical therapy for stable CAD (prior to routine use of drug-eluting stents) did not show a reduction in mortality or rates of MI, although superior angina relief, improved exercise tolerance, and better quality of life was observed with PCI (Table 4). A meta-analysis of 12 randomized clinical trials (7182 participants) comparing revascularization with PCI and optimal medical therapy in patients with stable CAD confirmed the finding of greater angina relief with PCI.[30] According

TABLE 4

Large Randomized, Controlled Trials of PCI Versus Medical Treatment in Stable Angina

Study	Population	Primary Endpoint	Results	Comments
FAME 2[32]	1220 patients; FFR-guided PCI + OMT vs OMT alone	Death, MI, or urgent revascularization	4.3% PCI vs 12.7% in OMT ($P < .001$)	Primary endpoint driven by reduction in urgent revascularization for MI or objective ischemia
COURAGE[6]	2287 patients; objective evidence of ischemia, PCI vs OMT	Death or MI	19.0% vs 18.5% ($P = .62$)	Better angina relief with PCI early on; no difference in individual MACE; 32% crossover rate; DES in only 2.6%
RITA-2[43]	1018 patients; PTCA vs drugs	Death or MI	6.3% vs 3.0% ($P = .02$) due to periprocedural MI	Greater symptomatic relief with PTCA, but excess mortality and periprocedural MI
ACME[44]	212 patients; PTCA vs drugs	Changes in exercise tolerance, frequency of angina, and use of nitroglycerin	Better exercise tolerance with PTCA	More complications with PTCA

ACME, Angioplasty Compared to Medicine; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; DES, drug-eluting stents; FAME, Fractional Flow Reserve–Guided PCI Versus Medical Therapy in Stable Coronary Disease; FFR, fractional flow reserve; MACE, major adverse cardiac events; MI, myocardial infarction; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; PTCA, percutaneous coronary angioplasty (without stenting); RITA, Randomised Intervention Treatment of Angina.

to the 2011 ACCF/AHA/Society for Cardiovascular Angiography and Interventions Guideline for PCI,[29] the only Class I recommendation for PCI to improve survival for chronic CAD is in survivors of SCD with presumed ischemic-mediated ventricular tachycardia caused by a significant (≥ 70% diameter) stenosis. In contrast, PCI has a Class I recommendation to improve symptoms in patients with one or more significant coronary artery stenoses amenable to PCI and unacceptable angina despite guideline-directed medical therapy.[31] The findings of the recently published Fractional Flow Reserve–Guided PCI Versus Medical Therapy in Stable Coronary Disease (FAME 2) trial,[32] however, may promote ischemia-guided revascularization as an adjunct to medical therapy. In FAME 2, a total of 888 stable CAD patients with ischemia demonstrated by fractional flow reserve ≤ 0.80 at the time of cardiac catheterization were randomized to medical therapy alone versus PCI plus medical therapy. Patients with fractional flow reserves > 0.80 were placed into a medical treatment registry. The primary endpoint (death, MI, or urgent revascularization) occurred in 4.3% of the PCI group and in 12.7% of the medical therapy group (hazard ratio with PCI, 0.32; 95% CI, 0.19-0.53; $P < .001$), mainly due to lower rates of urgent revascularization triggered by MI or objective ischemia.

Coronary Artery Bypass Grafting. Coronary artery bypass grafting (CABG) is indicated to improve survival in patients with stable angina and significant (≥ 50% diameter stenosis) left main disease, or in patients with severe three-vessel disease (with or without involvement of the proximal LAD), or disease in the proximal LAD plus one other major coronary artery. CABG is also indicated to improve symptoms in patients with suitable anatomic targets and unacceptable angina despite guideline-directed medical therapy.[1] The survival advantage of CABG over medical therapy was first established from three studies that enrolled patients between 1972 and 1984.[33-35] Overall, there was a 4.1% absolute risk reduction in 10-year mortality with CABG ($P = .03$).[36] The relevance of those trials now is limited because medical therapy at the time consisted mainly of nitrates and β-blockers. The recently published Surgical Treatment for Ischemic Heart Failure (STICH) trial[37] compared medical therapy alone versus medical therapy and CABG in

1212 patients with surgical CAD and ejection fraction ≤ 35%. Over a median follow-up of 56 months, 41% of the medical therapy group and 36% of the CABG group died ($P = .12$), but the difference was statistically significant following adjustment for baseline characteristics ($P = .039$). There was also a slight advantage for CABG in cardiovascular-specific causes of death: 33% of the medical therapy group and 28% of the CABG group died of an adjudicated cardiovascular cause ($P = .05$). The study also found a slight advantage for CABG in some of the composite secondary endpoints. In the medical therapy group, 68% of the patients died from any cause or were hospitalized for cardiovascular causes, compared with 58% of the CABG group ($P < .0001$). There was a 17% crossover rate after a median of 56 months of follow-up.[37]

Table 5 lists the largest trials comparing CABG with PCI for chronic CAD. Overall, CABG is associated with fewer repeat revascularization procedures with no difference in mortality or MI. Several subgroups of patients may have a survival benefit with CABG, including anatomic subset (distal bifurcation left main disease, proximal LAD disease, and depressed LV function) and patients with DM. The selection of CABG versus PCI as a method of revascularization is contingent upon several factors, including coronary anatomy, surgical candidacy, and patient preference. In general, patients with three-vessel disease (particularly if it involves the proximal left anterior descending artery or left main coronary artery) with LV systolic dysfunction and DM are considered better candidates for CABG than PCI.

Alternative Therapies for Angina. Patients who have lifestyle-limiting angina (Class III to IV) despite optimization of medical

TABLE 5

Large Randomized, Controlled Trials of CABG Versus PCI in Stable Angina

Study	Population	Primary Endpoint	Results	Comments
PRECOMBAT[45]	600 patients; isolated LM disease, CABG vs SES	MACCE at 1 and 2 years	6.7% vs 8.7% at 1 year ($P = .01$) for noninferiority; 8.1% vs 12.2% at 2 years ($P = .12$)	SES was noninferior to CABG; target vessel revascularization more common in PCI group
SYNTAX[46]	1800 patients; 3VD or LM disease, CABG vs PES	MACCE at 1 year	12.4% vs 17.8% ($P = .002$) driven by repeat revascularization	Higher stroke rates in the CABG arm (2.2% vs 0.6%; $P = .003$); at 3 years, more repeat revascularization and MI in the PCI group
SoS[47]	988 patients; multivessel CAD, CABG vs BMS	Rates of repeat revascularization, median of 2 years	6% vs 21% ($P < .001$)	Fewer deaths in CABG group (2% vs 5%; $P = .01$), maintained at 6 years
ARTS[48]	1205 patients; multivessel CAD, CABG vs BMS	Freedom from MACCE at 1 year	Event-free survival 87.8% vs 73.8% ($P < .001$) driven by repeat revascularization	No difference in the rates of death, stroke or MI; similar findings at 5 years
BARI[49,50]	1829 patients; multivessel CAD, CABG vs PTCA	All-cause mortality at mean of 5.4 years	111 vs 131 deaths (P = NS)	Cardiac mortality higher in PTCA group (8.0% vs 4.9%; $P = .022$); survival in diabetics worse with PTCA (65.5% vs 80.6%)

ARTS, Arterial Revascularization Therapy Study; BARI, Bypass Angioplasty Revascularization Investigation; BMS, bare metal stent; CABG, coronary artery bypass surgery; CAD, coronary artery disease; LM, left main; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; NS, not significant; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; PRECOMBAT, Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease; PTCA, percutaneous coronary angioplasty (without stenting); SES, sirolimus-eluting stent; SoS, Stent or Surgery; SYNTAX, Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

therapy and revascularization, or who are not candidates for revascularization, can be considered for alternative treatments for symptomatic relief. Several types of therapies exist, including EECP, transmyocardial laser revascularization (TMR), and spinal cord stimulation.

EECP treatment consists of placing pneumatic cuffs on the lower extremities that are inflated during diastole, thus increasing preload and decreasing afterload, thereby improving coronary flow. The course of outpatient treatment is typically 7 weeks, with sessions lasting 35 minutes to 1 hour. In a small, randomized trial, patients experienced improvement in exercise duration and a decrease in weekly angina episodes.[38] A more recent meta-analysis including 13 prospective studies and nearly 1000 patients found that EECP reduced angina by at least one CCS class in 86% of the patients, suggesting that EECP is a viable option for patients.[39] TMR is a procedure that uses laser energy to create channels in the myocardium that theoretically improve myocardial perfusion via creation of sinusoids.

TMR is both a surgical and catheter-based procedure. One potential mechanism by which angina is reduced is via myocardial denervation. TMR was the subject of a Cochrane Database Review in 2009. In randomized trials, compared with medical therapy, surgical TMR reduced angina frequency with similar mortality as analyzed by intention to treat. The 30-day mortality in an as-treated analysis, however, showed significantly higher mortality in the TMR group (6.8% vs 0.8%), suggesting this procedure should only be performed in the setting of clinical trials or palliative circumstances.[40]

Spinal cord stimulation uses low voltage stimulation of the spinal nerves to control pain, resulting in parasympathetic vasodilation and decreased anginal episodes. Compared with a control group, spinal cord stimulation significantly improved exercise capacity and health-related quality of life.[41] Caution is required when treating patients with permanent pacemakers and implanted cardioverter defibrillators, but the feasibility in this population has been reported.

Additional experimental therapies for refractory angina are being investigated. Although they are beyond the scope of this review, data that show therapeutic angiogenesis as a promising treatment

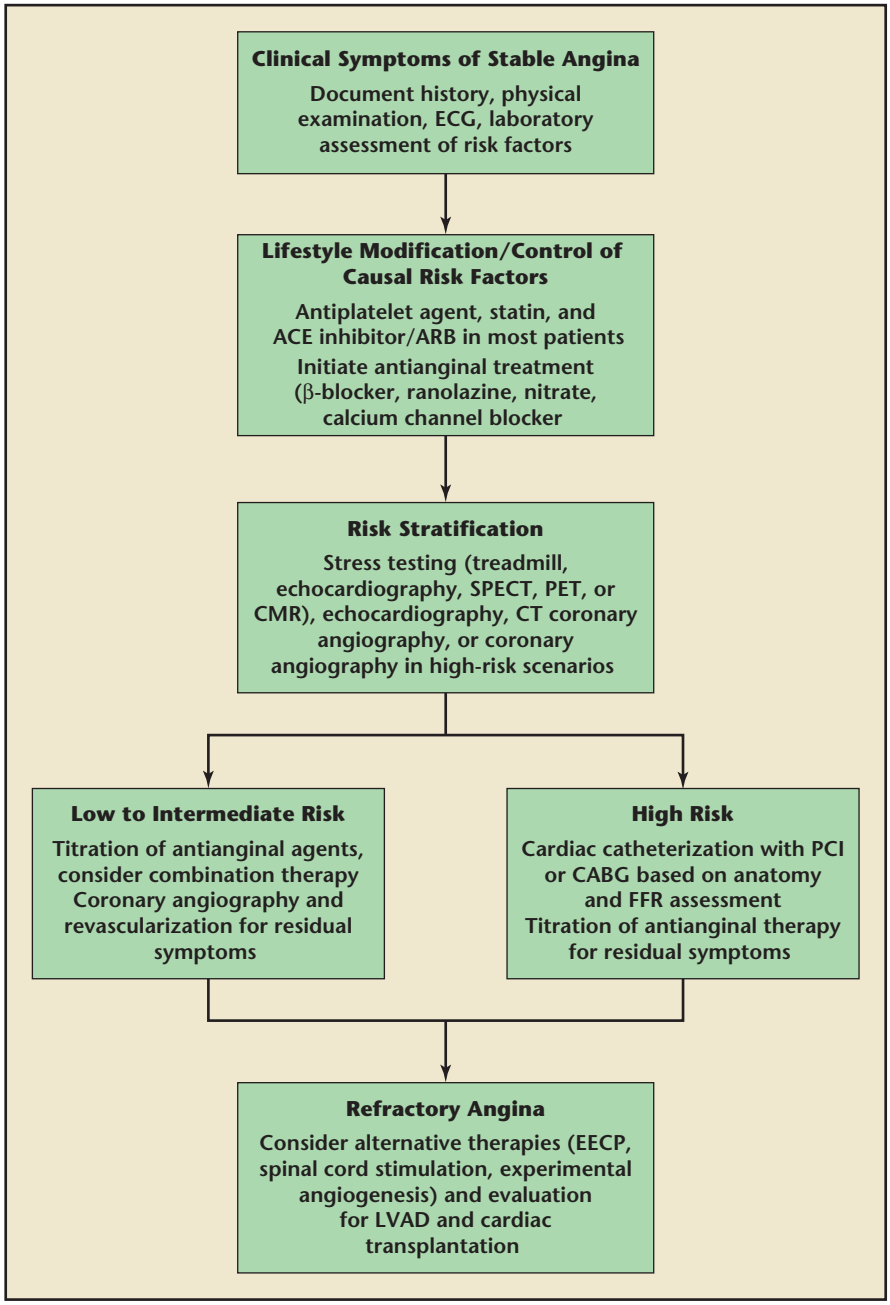

Figure 1. Proposed algorithm for evaluation and management of patients with stable ischemic heart disease. ACE, angiotensin-converting enzyme; CABG, coronary artery bypass graft; CCB, calcium channel blocker; CMR, cardiovascular magnetic resonance; CT, computed tomography; ECG, electrocardiogram; EECP, enhanced external counterpulsation; FFR, fractional flow reserve; LVAD, left ventricular assist device; PCI, percutaneous coronary revascularization; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

are accumulating. The goal of this therapy is to reduce ischemia and angina by inducing the formation of blood vessels. Therapeutic angiogenesis has been accomplished by administration of growth factors (vascular endothelial growth factor and fibroblast growth factor), gene therapy, and cell therapy with endothelial progenitor cells.[42] In addition, for selected patients, referral to a cardiac transplant program for evaluation of a LV support device or transplantation should be considered.

Conclusions

SIHD remains a condition that is underappreciated and undertreated. The primary goals of therapy are to reduce cardiovascular events (eg, cardiovascular death and MI) and eliminate symptomatic episodes. Statins, antiplatelet agents, and mediators of the renin-angiotensin-aldosterone axis are used to reduce cardiovascular events. Antianginal therapy is often sufficient to control symptoms but may require a combination of agents. In this regard, ranolazine represents an important addition to the armamentarium of antianginal therapies. Revascularization strategies are reserved for patients with persistent angina on optimal medical therapy or for those with high-risk noninvasive or angiographic findings. Figure 1 contains a simplified algorithm for evaluation and management of patients with SIHD. ■

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MAIN POINTS

- The management of stable ischemic heart disease requires treatment aimed at both symptom relief and reduction of cardiovascular morbidity and mortality related to atherosclerosis. Upon diagnosis, aggressive modification of cardiac risk factors and medical therapy to prevent acute ischemic events and disease progression should be initiated.
- Antianginal medications improve exercise tolerance, decrease the frequency of anginal episodes, and enhance quality of life, which is an important consideration in those with symptoms of angina.
- Reduction of atherosclerosis progression and cardiovascular risk can be achieved through lifestyle modification and medical therapy, which includes the use of drugs such as antianginals, antiplatelets, and antilipids, among others.
- Patients with symptoms refractory to medical therapy, high-risk stress test results, and/or anatomic findings have an indication for coronary revascularization (either percutaneous or surgical), depending on disease complexity.

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