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Angina and Its Management

Robert A. Kloner, MD, PhD[1,2] and Bernard Chaitman, MD[3]

Abstract

Angina pectoris is defined as substernal chest pain, pressure, or discomfort that is typically exacerbated by exertion and/or emotional stress, lasts greater than 30 to 60 seconds, and is relieved by rest and nitroglycerin. There are approximately 10 million people in the United States who have angina, and there are over 500 000 cases diagnosed per year. Several studies now show that angina itself is a predictor of major adverse cardiac events. In addition, angina is a serious morbidity that impedes quality of life and should be treated. In the United States, pharmacologic therapy for angina includes β-blockers, nitrates, calcium channel blockers, and the late sodium current blocker ranolazine. In other countries, additional pharmacologic agents include trimetazidine, ivabradine, nicorandil, fasudil, and others. Revascularization is indicated in certain high-risk individuals and also has been shown to improve angina. However, even after revascularization, a substantial percentage of patients return with recurrent or continued angina, requiring newer and better therapies. Treatment for refractory angina not amenable to usual pharmacologic therapies or revascularization procedures, includes enhanced external counterpulsation, transmyocardial revascularization, and stem cell therapy. Angina continues to be a significant cause of morbidity. Therapy should be geared not only to treating the risk factors for atherosclerotic disease and improving survival but should also be aimed at eliminating or reducing the occurrence of angina and improving the ability of patients to be active.

Keywords

angina pectoris, coronary artery disease, nitrates, β-blockers, calcium channel blockers, revascularization.

Definition, Cause, Epidemiology

Angina pectoris is defined as a substernal chest pain, pressure, or discomfort that is typically exacerbated by exertion and/or anxiety or other emotional or mental stress, lasts greater than 30 to 60 seconds, and is relieved by rest and/or nitroglycerin. The pain or discomfort may radiate down the arms, up into the neck, into the lower jaw, into the epigastrium, and sometimes into the back. It typically lasts between 5 and 15 minutes. Sometimes it is described as an ache or a burning. In women and the elderly population, angina may present in a more atypical fashion or as an anginal equivalent and can be characterized by dyspnea, fatigue, weakness, palpitations, or dizziness. It is estimated that ~10 million people in the Unites States have angina pectoris and that there are over 500 000 newly diagnosed cases per year in this country. The primary cause of angina is an imbalance between oxygen supply and oxygen demand in the heart. The most usual cause is coronary artery disease in which atherosclerotic plaque has narrowed the lumen of the vessel that supplies oxygen and nutrients to cardiomyocytes. When there is an increase in oxygen demand, as occurs with exertion, there is an oxygen supply–demand mismatch, such that the oxygen demand is greater than the supply through the narrowed vessel. Even vessels that are in an earlier phases of atherosclerosis, before a severely flow-limiting lesion is present, can contribute to ischemia if the plaque is vulnerable and ruptures. Some patients experience angina due to a reduced oxygen supply when the coronary arteries undergo vasospasm. Although coronary artery disease is usually thought of as disease of the large epicardial coronary arteries that course along the surface of the heart, there is now evidence that small intramural coronary arteries or microvessels can be diseased and contribute to myocardial ischemia. Other causes of angina include hypertrophic cardiomyopathy, valve disease, and especially aortic stenosis; in these cases, again there is a mismatch between supply of oxygen and demand for oxygen by the heart.

Angina is more common in the elderly population (> 65 years), who account for about a half of all cases. Elderly patients tend to have more severe coronary artery disease and do not always tolerate traditional antianginal therapies. There is

[1] Huntington Medical Research Institutes, Pasadena, CA, USA
[2] Keck School of Medicine at the University of Southern California, Los Angeles, CA, USA
[3] Saint Louis University School of Medicine, St. Louis, MO, USA

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Corresponding Author:
Robert A. Kloner, Huntington Medical Research Institutes, 10 Pico Street, Pasadena, CA 91105, USA.
Emails: kloner@hmri.org; robert.kloner@hmri.org

an increase in the prevalence of angina with age in both men and women. Women tend to manifest coronary artery disease at a later age than men. However, ischemic heart disease and stroke remain the leading causes of death in women. Of note, angina is often a more common initial presentation of coronary artery disease in women than men; in men, acute coronary syndromes may be more likely to be the presenting manifestation. Women are more likely to present with angina at an older age, and the symptoms are more likely to be atypical; they are therefore less likely to be diagnosed and treated. Several studies suggest that women who have coronary artery disease have a higher cardiovascular mortality then men. Patients with angina are more likely to have certain common comorbidities such as hypertension, diabetes, chronic obstructive pulmonary disease, peripheral vascular disease, and congestive heart failure. These comorbidities can complicate treatment regimens, as described later in this article.

Is Angina a Predictor of Adverse Cardiac Events?

Is angina itself a predictor of major adverse cardiovascular events? Spertus et al described a large VA cohort study of data from the Ambulatory Care Quality Improvement Project, assessing outpatients with stable ischemic coronary artery disease (>4400).[1] Patients with severe angina, based on responses to the Seattle Angina Questionnaire, had higher 1-year mortality than patients with moderate angina; those with moderate angina had higher mortality than those with mild or minimal angina. The Heart and Soul Study investigated a prospective cohort of over 1000 patients with stable ischemic heart disease and characterized angina as absent, monthly, daily, or weekly, and then followed the patients for a median of 8.9 years. The end points were hospitalization for angina or heart failure, revascularization, myocardial infarction, or all-cause mortality. Those patients with daily or weekly angina frequency were more likely to have angina-related hospitalization, revascularization, and all-cause mortality than those who either did not have angina or had the symptoms only monthly.[2] Scirica has pointed out that chronic angina not only impacts quality of life but also increases the risk of major adverse cardiovascular events, including death and recurrent myocardial infarction.[3] Jespersen et al found that a reference population without ischemic heart disease and who were asymptomatic had better major adverse cardiac event–free survival than patients who had angina (including patients with 1-, 2-, 3-vessel coronary artery disease, diffuse, nonobstructive coronary disease, and even in patients whose epicardial coronary arteries appeared normal, suggesting that this later group may have had microvascular disease).[4] In other words, the presence of angina, despite the coronary anatomy, resulted in worse outcome compared to patients without angina. Besides predicting worse major adverse cardiac events, angina is a considerable morbidity. Hlatky et al showed that over a course of 10 years, patients with angina reported a diminished quality of life compared to patients who were free of angina.[5] Angina was associated with lower quality of life in other studies as well.[6]

There have been recent analyses of clinical outcomes in patients with heart failure, with and without angina. In the Candesartan in Heart Failure Assessment of Reduction of Mortality and Morbidity (CHARM) study, it was reported that the NYHA functional class was worse both in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction in those patients with angina pectoris versus those without. Patients with current angina had a higher risk of major adverse cardiovascular events (composite of myocardial infarction, unstable angina, need for percutaneous coronary intervention [PCI], or coronary artery bypass grafting [CABG]) than those without but did not demonstrate an increase in all cause death.[7] Mentz et al compared long-term outcome of patients with ischemic cardiomyopathy who had versus did not have angina pectoris. Following a multivariate adjustment, patients with angina had higher rates of cardiovascular death or cardiovascular hospitalization, but rates of death, death or myocardial infarction, and death or hospitalization did not differ between those with versus those without angina.[8] These studies suggest that the presence of angina, which represents active ischemia, reduces quality of life further in patients with ischemic cardiomyopathy, although angina does not appear to impact all-cause mortality. The presence of angina predicts worse outcomes in the setting of ischemic cardiomyopathy.

The authors have observed that angina can sometimes go into remission. Practitioners have certainly observed patients with angina who have been receiving medical therapy for over 10 to 20 years and then go into complete remission. Potential mechanisms might include induction of hibernation in the ischemic segments, recruitment of new collaterals, possibly chronic ischemic conditioning, or reduction in active lifestyle (purposefully limiting oxygen demand). Certainly, angina can have remissions but also exacerbations. Secondary and often treatable causes of exacerbations of angina include poorly controlled hypertension, anemia, tachycardia, hyperthyroidism, infections with fevers and chills, hypoglycemia, and heavy meals, all factors that increase oxygen demand.

Angina and Ischemic Preconditioning

While the presence of angina is in general associated with worse outcomes, there are some exceptions where angina might actually serve in a protective role. The concept of ischemic preconditioning was first described in experimental studies in the mid-80s, whereby brief coronary artery occlusions and reperfusions (short enough that they mimic to some extent angina but not long enough to cause tissue necrosis) of a proximal coronary artery protected the myocardium when the coronary artery was subsequently occluded for a more prolonged interval. This ischemic preconditioning was shown to markedly reduce the size of myocardial infarctions. The phenomenon of ischemic preconditioning has been verified in every species in which it was tested. As part of the TIMI 4 trial, we studied the effect of a history of angina on myocardial infarction assessed by enzymes. Total creatine kinase-MB units were significantly

smaller in patients with ST-segment elevation myocardial infarction (STEMI) who had histories of previous angina prior to their infarctions. In addition, patients with histories of previous angina had lower rates of in-hospital death and severe congestive heart failure and/or shock. These benefits were not due to better coronary artery collateral development in the angina group.[9] In TIMI 9, we observed similar findings but narrowed the protective effect of angina to preinfarct angina occurring during the 24 hours prior to the STEMI.[10] There now have been numerous clinical studies showing the benefits of preinfarct angina on myocardial infarction size, left ventricular function, and other parameters. This preinfarct angina may represent the clinical equivalent of ischemic preconditioning. Although these are interesting observations, it is difficult, if not impossible, to apply ischemic preconditioning as a therapy in the setting of STEMI. However, a related phenomenon, called remote ischemic conditioning, in which a remote organ, such as a limb, is made ischemic for brief periods of time and then reperfused, can be applied clinically in the setting of STEMI. A regimen of brief repeated brachial artery occlusions induced with a blood pressure cuff, started in the ambulance, was shown to improve myocardial salvage in the setting of STEMI, and now, there are several clinical trials showing the effectiveness of this type of therapy for limiting myocardial infarct size.[11] The mechanism remains to be fully elucidated but might involve release of a protective humoral substance from the preconditioned limb into the circulation that then protects the heart, or it might involve protective neural reflexes that are stimulated by the preconditioning episode.

Table 1. Antianginal Therapies.

Anti-ischemic medications for patients with stable ischemic heart disease (SIHD) as recommended by Consensus Panel[a]
Level of recommendation, I(B). Beta-blockers should be prescribed as initial therapy for relief of symptoms
Level of recommendation, I(B). Calcium channel blockers or long-acting nitrates should be prescribed for relief of symptoms when β-blockers are contraindicated or cause unacceptable side effects, or when initial treatment with β-blockers is unsuccessful
Level of recommendation, I(B). Sublingual nitroglycerin or nitroglycerin spray is recommended for immediate relief of symptoms
Level of recommendation, IIa(B). Ranolazine can be useful when prescribed as a substitute for β-blockers for relief of symptoms if initial treatment with β-blockers leads to unacceptable side effects, or ineffective or contraindicated
Level of recommendation, IIa(A). Ranolazine in combination with β-blockers can be useful when prescribed for relief of symptoms when initial treatment with β-blockers is not successful
Anti-ischemic medications used in some countries outside the United States
Trimetazidine, mildronate, perhexiline
Ivabradine
Nicorandil
Fasudil
Revascularization
Percutaneous coronary intervention (stenting and/or angioplasty)
Coronary artery bypass surgery
Treatments for refractory angina
Enhanced external counterpulsation
Transmyocardial revascularization
CD 34+ stem cell therapy
Gene therapy
Spinal cord stimulation

[a]Adapted from Fihn et al.

Therapy for Chronic, Stable Angina*

Therapy for angina is based on the effort to improve overall survival and limit major adverse cardiovascular events associated with atherosclerotic coronary artery disease and also on treating the angina itself, attempting to either totally eliminate it or reduce its frequency and severity. The morbidity of angina is significant and interferes with quality of life. Lifestyle modification should be offered to all patients with angina and includes smoking cessation programs, healthy diet such as the Mediterranean diet, limiting dietary fats and cholesterol, diabetic diet if appropriate, avoiding excess salt, weight loss programs where appropriate, and exercise programs. Pharmacologic therapies that might reduce major adverse cardiovascular events in patients with coronary artery disease, many of whom can have angina, include statins, aspirin, and other oral antiplatelet agents and β-blockers, especially in patients who have postmyocardial infarction, heart failure, reduced ejection fraction, or hypertension. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are indicated for hypertension, diabetes, and/or heart failure. These agents help to treat coronary artery disease, but of these, only the β-blockers are approved as antianginal agents. Although statins have been shown to limit the progression of and in some cases even induce regression of atherosclerotic lesions, and in some studies reduce angina symptoms, in general, they are not considered effective antianginal drugs.

Fihn et al and Qaseem et al have described the guideline-directed medical therapy for the relief of angina symptoms as per recent guidelines from the American College of Cardiology and the American Heart Association (Table 1).[12,13] Initial therapy for immediate relief of an angina attack is sublingual nitroglycerin tablets or nitroglycerin spray. β-Blockers are also considered as first-line therapy for chronic angina, especially if there was a prior myocardial infarction, heart failure, or other indications, such as hypertension. If the patient has a contraindication to β-blockade or develops unacceptable side effects, then a calcium channel blocker and/or long-acting nitrate can be added or substituted. If there is a contraindication or unacceptable side effects to calcium channel blocker or long-acting nitrate, then add or substitute the late sodium current blocker, ranolazine. If there are persistent angina symptoms despite an adequate trial of guideline-directed medical therapy (eg, maximum doses of at least 2 antianginal classes), then consider coronary revascularization (PCI, angioplasty and/or stenting, or CABG surgery).

What effect does coronary revascularization have on survival and angina symptoms? The well-known COURAGE trial

compared outcomes in patients with stable ischemic heart disease who were randomized to optimal medical therapy versus optical medical therapy plus PCI. Overall, at 5 years, there was no difference in death or myocardial infarction between the 2 groups. By a modest amount, patients who received optimal medical therapy plus revascularization were more likely to be free of angina compared to the optimal medical therapy group alone at 1 and 3 years. However, this benefit was no longer seen at 5 years.[14] There have been some subgroups of high-risk patients in stable ischemic heart disease clinical trials that have had better clinical outcomes, free of major adverse cardiovascular events, with revascularization as recently reviewed,[15] including patients with left main coronary disease, large perfusion defects, and severe Syntax scores, but for many patients with stable ischemic heart disease, revascularization has not been shown to improve survival or prevent myocardial infarctions. Coronary revascularization does reduce angina symptoms. In the guideline papers by Fihn and Qaseem, coronary revascularization to improve survival is recommended for patients with significant ($\geq$50%) left main coronary artery stenosis, significant ($\geq$70% stenosis) in 3-vessel disease with or without proximal left anterior descending coronary artery disease, survivors of sudden death with presumed ischemia-mediated ventricular tachycardia caused by a significant ($\geq$70%) stenosis in a major coronary artery, 2-vessel disease with a proximal left anterior descending lesion, and others.[12,13]

The same guidelines suggest coronary artery revascularization to improve symptoms only when there is significant anatomic ($\geq$50% left main stenosis or $\geq$70% non-left main stenosis) or physiologic (fractional flow reserve of $\leq$0.8) coronary artery stenosis, when there is 1 or more significant stenoses amenable to revascularization and unacceptable angina despite guideline-directed medical therapy, and complex 3-vessel coronary artery disease with a SYNTAX score of >22 with or without involvement of the left anterior descending coronary artery. Coronary artery bypass surgery would be preferred over PCI in certain situations, including left main disease, severe 3-vessel disease, situations where the anatomy is not amenable to percutaneous intervention, and diabetic patients with a high coronary atherosclerotic burden. In general, the more extensive and complex the coronary anatomy is, the greater the preference for coronary artery bypass surgery, because surgery can more often provide a more complete revascularization than coronary angioplasty in patients who are suitable for either procedure. There is less enthusiastic endorsement of revascularization for other conditions.

These same guidelines stress the importance of risk stratification and their therapeutic implications in patients with stable ischemic heart disease. Low risk is defined by patients with <1% annual mortality. Based on noninvasive testing, these are patients with a low Duke treadmill score ($\geq$5), minimal or no perfusion defects on nuclear stress imaging, and no wall motion abnormalities on stress testing. These patients should initially be treated with guideline-directed medical therapy. The second category are those patients who are at intermediate risk, with a 1% to 3% annual mortality. These are patients who have a reduced left ventricular ejection fraction (35%-49%), intermediate Duke treadmill score ($-$11 to 5), and moderate defects without left ventricular dilatation or lung uptake during a nuclear study. These patients are recommended to have guideline-directed medical therapy with or without coronary angiography depending on the symptoms and clinical suspicion. The final risk category is high risk with >3% annual mortality. These patients have a low ejection fraction of <35%, a high Duke treadmill test score of equal to or more negative than $-$11, large and/or multiple defects on nuclear stress testing and left ventricular dilatation, and increased lung uptake on nuclear study. The recommendation is that these patients receive guideline-directed medical therapy and angiography. Depending upon the results of angiography, revascularization might be indicated.

Angina May Persist Despite PCI

Although PCI has reduced angina, in some cases, angina persists or returns over time. This may be related to the progression of the atherosclerotic process in the native epicardial coronary arteries, incomplete revascularization, development of microvascular disease, or in some cases restenosis in the area where the procedure was performed. The later situation is less frequent with modern drug-eluting stents. Holubkov et al showed in an NHLBI Dynamic Registry that at 1 year of follow-up after PCI, 25.6% of patients had persistence of angina.[16] Stergiopoulos and Brown showed that 29% of patients who underwent coronary stent implantation demonstrated persistent angina at $\sim$4 years.[17] Marzilli et al showed, in patients with stable angina undergoing PCI, deemed "successful" by the interventional cardiologist, that 52% of patients had a positive stress test 4 weeks following the procedure. Of the 66% of patients who experienced angina before the procedure, one-third still had angina.[18] Thus, 21% of the study population had persistent angina despite revascularization. Huqi et al found that 29% of patients who underwent PCI had abnormal exercise tests at 1 month after the procedure. At 6 and 12 months, 31% and 29% had abnormal exercise stress tests, respectively.[19] These studies suggest that there is an unmet need to develop new therapies for angina pectoris, including patients who have persistent angina and/or evidence of ischemia following what is deemed successful PCI.

The Pharmacology of the Currently Approved Antiangina Agents

Angina is a manifestation of myocardial ischemia, which is the imbalance between oxygen supply and demand. Most of the classic antianginal drugs work by either reducing oxygen demand or improving oxygen supply or some combination of both. Usually, this involves a change in hemodynamics such as a decrease in heart rate, a reduction in blood pressure, a reduction in contractility, or some combination of the above. Here, we review the major classes of antianginal agents and say a few words about their advantages and disadvantages. Although we

review the drugs separately, many patients need to be on combinations of antianginal agents. Since most have hemodynamic effects, health-care providers should monitor heart rate and blood pressure to be sure that their patients with angina (who are not infrequently already on drugs that lower blood pressure and/or heart rate due to comorbid conditions such as hypertension or heart failure) are not becoming hypotensive or bradycardic.

Nitrates

Agents such as sublingual nitroglycerin tablets and sprays are useful to treat an acute episode of angina. Nitrates work primarily by decreasing oxygen demand. They reduce preload by causing vasodilation of the venous system, thereby decreasing return of blood to the heart, which decreases volume of the ventricle and ventricular wall stress, and hence oxygen demand. In addition, they cause a small decrease in systemic arterial pressure that also decreases oxygen demand. They also dilate the coronary arteries, which can improve oxygen delivery and help reduce coronary artery vasospasm. Usually, they help relieve angina within a few minutes of administration. It is important to educate patients about what they can expect when they take a sublingual nitroglycerin tablet or use the sublingual spray.[20] Patients may experience a slight stinging or tingling under the tongue. They need to be educated not to chew or swallow the tablets. Within a few minutes of taking the nitroglycerin, patients may feel a sense of warmth in the head or a throbbing or headache, which means that the cerebral vessels are dilating. We usually tell patients to expect this and that this is a good sign as it means that the drug is working to dilate the cerebral vessels, and if those vessels are dilating, then the coronary artery vessels are likely dilating as well and improving supply of oxygen and nutrients to the heart. 20 Patients might find that taking the nitroglycerin prophylactically, 5 to 10 minutes prior to onset of forms of exertion known to exacerbate their angina, might help prevent the angina. There are several forms of long-acting nitrates. Isosorbide mononitrate is given once a day, and isosorbide dinitrate is given up to 3 times a day. Nitroglycerin patches are also available, as well as less commonly used oral and buccal preparations. The long-acting nitrates have been shown to decrease the frequency of angina attacks and improve exercise tolerance during exercise stress tests. A problem with chronic nitrate administration is that a nitrate-free interval, which is usually built into the dosing recommendation, is needed in order to prevent nitrate tolerance, which can develop rapidly. Some patients may not be able to tolerate nitrates due to headache, but often this adverse event diminishes with continued use, and sometimes simple analgesics, such as acetaminophen help the patient get through the first few weeks of therapy. Nitrates for the sole treatment of chronic stable angina, in general, have not been shown to reduce major adverse cardiovascular events, but they are effective for treating the morbidity of angina. They are contraindicated in patients taking PDE 5 inhibitors such as sildenafil (Viagra) due to the potential for severe hypotension. Conversely, if patients need to be on nitrates, they should not take PDE 5 inhibitors.

β-Blockers

β-Blockers are effective antianginal agents, and their mechanism of action is primarily a reduction in oxygen demand. They decrease heart rate, cardiac contractility, and secondarily reduce blood pressure, which all contribute to a reduction in oxygen demand. They have been shown to reduce the frequency of angina and improve exercise tolerance during stress tests. Not all β-blockers are Food and Drug Administration (FDA) approved for the use of angina. The current FDA-approved agents are atenolol, metoprolol, nadolol, and propranolol; others might be effective but are not approved for this indication. Other cardiovascular indications for β-blockers include hypertension, heart failure, or history of myocardial infarction to preserve cardiac function and reduce arrhythmias. They are also used for hypertrophic obstructive cardiomyopathy. β-Blockers are listed as one of the first-line pharmacologic therapies for angina by recent guidelines. Side effects of β-blockers include bradycardia, conduction abnormalities, bronchospasm, fatigue, lethargy, depression, nightmares, erectile dysfunction, gastrointestinal upset, worsening of insulin-induced hypoglycemia, cold extremities due to peripheral vasoconstriction, and β-blocker withdrawal syndrome, whereby β-blockers are stopped suddenly and the patient develops worsening angina. β-Blockers have been shown to improve clinical cardiovascular outcome after myocardial infarction (reducing arrhythmias, preventing adverse left ventricular remodeling and heart failure) in patients with heart failure who can tolerate β-blockers and in patients with hypertension. β-Blockers have not been shown to reduce major adverse cardiovascular events in patients with stable angina pectoris who are receiving the β-blocker solely for the therapy of angina. Care must be used when combining β-blockers with certain other antianginal agents that also slow the heart rate and affect the conduction system (the calcium channel blockers verapamil and diltiazem). β-Blockers are a heterogeneous group of drugs—some are cardioselective (eg, atenolol, metoprolol). Noncardioselective β-blockers (eg, propranolol, nadolol) might be metabolized through different pathways; some have α- and β-blocking activity and therefore are more suitable for patients with hypertension, and third-generation β-blockers are associated with fewer perturbations of glucose metabolism.

Calcium Channel Blockers

The calcium channel blockers inhibit the movement of calcium across the L-type calcium channels found in cardiac muscle and the smooth muscle of blood vessels. The dihydropyridine calcium channel blockers, such as nifedipine, amlodipine, nisoldipine, felodipine, and nitrendipine, work primarily upon the calcium channels in the smooth muscle of the blood vessels to induce vasodilation. Nondihydropyridine calcium channel blockers such as verapamil and diltiazem also affect the

conduction system of the heart, slowing the heart rate, and they can cause bradycardia or conduction abnormalities. Thus, the calcium channel blockers have several mechanisms in regard to treating angina. By relaxing the smooth muscle cells of the coronary arteries, they reduce vasospasm and reduce coronary artery vascular resistance, hence improving oxygen delivery. By vasodilating the systemic arteries, they decrease afterload and reduce oxygen demand. Some of the calcium channel blockers such as verapamil and diltiazem also slow the heart rate and hence decrease myocardial oxygen demand through their chronotropic effect. Calcium channel blockers can also reduce cardiac contractility, and this is most likely to be seen with verapamil and diltiazem, especially in patients whose cardiac function is already compromised. Not all calcium blockers are approved for treating angina. In general, those that are approved have been shown to reduce angina and improve exercise tolerance during exercise stress testing. These include diltiazem, verapamil, amlodipine, nifedipine, nicardipine, and nisoldipine. Others are approved only for hypertension. Adverse effects of diltiazem and verapamil include bradycardia, conduction disturbances, constipation, peripheral edema (usually due to vasodilation and not heart failure), worsening of heart failure in some patients, flushing, hypotension, headache, and dizziness. A rare side effect is gingival hyperplasia. The dihydropyridine calcium blockers may cause headache, dizziness, flushing, hypotension, peripheral edema, and gastrointestinal side effects. Short-acting nifedipine is avoided in acute coronary syndromes as it can sometimes cause reflex tachycardia.

Ranolazine (Late Sodium Current Blocker)

Ranolazine has been on the US markets for about 10 years for the treatment of angina. It is an antianginal agent that does not work through the usual hemodynamic methods to improve oxygen supply or reduce oxygen demand. It blocks the late sodium current toward the later phase of the action potential, reducing intracellular sodium, and subsequently reduces sodium–calcium exchange, having the net effect of reducing calcium overload, which is known to occur in ischemic cardiomyocytes. By reducing calcium overload, the myocardial cells basically relax better during diastole, which improves microvascular perfusion. The drug does not reduce heart rate or blood pressure like β-blockers or calcium channel blockers. Ranolazine was shown in clinical studies to improve exercise times during stress testing when used as monotherapy[21] or when added to β-blockers or to calcium channel blockers.[22] In these studies, it was shown to reduce the frequency of angina and the use of nitroglycerin when added to a β-blocker or calcium channel blocker.[22,23] In patients who were admitted with non-ST-segment elevation acute coronary syndromes, long-term use of ranolazine did not significantly reduce major adverse cardiovascular events (cardiovascular death or MI) but did reduce recurrent ischemia.[24] In a subset of patients who had a history of prior chronic angina, ranolazine did reduce the primary outcome of cardiovascular death, myocardial infarction, or recurrent ischemia.[25] In this same study (MERLIN), ranolazine reduced arrhythmias, assessed by Holter monitoring during the first week of admission, and there is ongoing interest in the potential of ranolazine to have an antiarrhythmic effect. In the recent RIVER-PCI study, Weisz et al described patients with a history of chronic angina who had incomplete PCI (1 or more lesions with $\geq$50% diameter stenosis in a coronary artery greater or equal to 2 mm in diameter) and were then randomized to placebo or ranolazine 1000 mg twice daily. The primary outcome was the time to first occurrence of ischemia-driven revascularization or ischemia-driven hospitalization without revascularization. There was no difference in freedom from the primary end point event between groups over about 30 months (hazard ratio [HR]: 0.95; $P = .48$).[26] In the overall participants, there was no difference in the Seattle Angina Frequency scores between groups; however, there was an improvement in this score among diabetic patients who received ranolazine.[27] Of note, in the CARISA Diabetes substudy, ranolazine reduced HbA_{1c} (at 1000 mg, twice daily, there was a 0.72% fall in HbA_{1c} from baseline). Potential mechanisms might be increased insulin sensitivity or increased physical activity. Notably, ranolazine did not lower fasting plasma glucose levels.

Table 1 reviews the FDA-approved types of antianginal agents in the United States and provides guidelines on when and how to use them. Table 2 lists specific antianginal preparations.

Table 2. Specific Antianginal Agents Approved by FDA in the Major Categories of drugs.

Beta-blockers
Atenolol
Metoprolol
Nadolol
Propranolol
Calcium channel blockers
Amlodipine
Diltiazem
Nifedipine
Verapamil
Nitrates
Nitroglycerin (glyceryl trinitrate)—sublingual tablets or spays, buccal, oral, transdermal
Isosorbide dinitrate—oral, sublingual
Isosorbide mononitrate—oral
Late calcium current inhibitor
Ranolazine

Novel Antianginal Agents Not Approved in the United States for the Treatment of Angina

There are a number of antianginal drugs that are approved in other countries but are not available in the United States that often involve novel mechanisms of action. The purpose of this section is to briefly review these intriguing agents.

Trimetazidine

This antianginal agent partially inhibits fatty acid oxidation and therefore shifts energy metabolism toward the utilization of glucose, which is a positive effect. Myocardial cell oxygen requirement of the glucose pathways is lower than that of the free fatty acid pathway. It is known that during ischemia, oxidized free fatty acid levels rise within the cardiomyocyte, and this blunts the glucose pathway. Trimetazidine blocks Acyl-CoA β oxidation to Acetyl-CoA, thus favoring the breakdown of glucose to pyruvate to form Acetyl-CoA. In the TACT study, trimetazidine reduced angina frequency, reduced the use of nitroglycerin, and improved exercise duration at trough levels compared to placebo, when used in addition to either long-acting nitrates or β-blockers.[28] Other metabolic agents including perhexiline and mildronate have shown similar benefits.[29]

Ivabradine

This antianginal agent is a sinus node inhibitor that slows down the heart rate but does not affect cardiac contractility or have a primary effect on blood pressure. It is approved for angina in many countries, but not in the United States, where it is approved only for heart failure. Ivabradine selectively inhibits the hyperpolarization-activated, mixed Na^+/K^+ inward I_f current. This reduces the rate of diastolic depolarization of the pacemaker cells in the sinus node, which decreases rest and exercise heart rate responsiveness. Ivabradine causes on average about 10 beats per minute drop in heart rate. Borer et al showed that in patients with chronic stable angina, ivabradine increased time to 1-mm ST-segment depression, increased time to limiting angina, increased time to angina onset, and increased total work performed during exercise stress tests, compared to placebo.[30] In the ASSOCIATE study, ivabradine, added to atenolol, improved total exercise duration, increased time to limiting angina, increased time to angina onset, and increased time to 1-mm ST-segment depression on exercise stress testing.[31] In that study, the most common causes for withdrawal were bradycardia (1.1% ivabradine vs 0% placebo) and unstable or aggravated angina (0.7% ivabradine vs 0.2% placebo). Ivabradine is also associated with a peculiar side effect called phosphenes, described as flashes or increased brightness of light in limited areas of the visual field, which usually are reported to be mild and diminish over time. They probably occur because of similarity of the I_f channel to other channels in the retina. In the SIGNIFY trial, Fox et al studied the addition of ivabradine to standard background therapy in over 19 000 patients who had stable coronary artery disease without heart failure and a heart rate of at least 70 beats per minute. The primary outcome was the composite of death from cardiovascular causes or nonfatal myocardial infarction. At 3 months, heart rate in the control group was 70.6 beats per minute, and in the ivabradine group, it was 60.7 beats per minute. At a median of 28 months of follow-up, the incidence of the primary end point was similar in the placebo (6.4%) and the ivabradine group (6.8%; $P = .20$). In a subgroup of patients with activity-limiting angina, ivabradine was associated with a significantly higher rate of the primary end point ($P = .02$). As expected, bradycardia was more common with ivabradine (18.0%) than placebo (2.3%; $P < .001$). Thus, this drug appears to reduce the morbidity of angina but did not have a significant effect on reducing major adverse cardiac events.[32] In the United States, the drug is not approved for treating angina but is approved to reduce the risk of hospitalization for worsening heart failure (patients with a left ventricular ejection fraction of 35% or less who are in sinus rhythm and whose resting heart rate is at least 70 beats per minute). Ivabradine should be used only by patients who are taking a maximally tolerated dosage of a β-blocker or have a contraindication to β-blocker use.

Nicorandil

Nicorandil is an antianginal agent with a dual mode of action. One is that it activates ATP-sensitive potassium channels causing dilatation of coronary and peripheral resistance vessels, and by activating these channels, it may promote a cardioprotective effect along the same pathways as ischemic preconditioning. In addition, nicorandil has a nitrate moiety that results in systemic arterial and venous vasodilatation. Thus, it reduces preload and afterload (reduction in oxygen demand) at the same time it dilates the coronary arteries (increase in oxygen supply). Meany et al showed, in patients with chronic stable angina, that nicorandil increased time to 1-mm ST-segment depression, time to angina, and increased exercise duration and total workload during exercise stress testing.[33] In a very intriguing study, called the Impact Of Nicorandil in Angina study, nicorandil given to patients with chronic stable angina over about 2.5 years reduced the primary composite outcome of coronary heart disease death, nonfatal myocardial infarction, or unplanned hospital admission for cardiac chest pain (HR = 0.83; 95% confidence interval: 0.72-0.97; $P = .014$). Nicorandil also reduced the composite of coronary heart disease death, nonfatal myocardial infarction, or unstable angina in this study.[34] These findings are important as they reflect one of the only studies to show that an antianginal agent given specifically to patients for stable chronic angina reduced major adverse cardiovascular events. However, the effectiveness of nicorandil as an antianginal drug is controversial, with some studies showing no advantage over other antianginal agents. In a meta-analysis from Japan, the short-term efficacy of nicorandil did not differ from β-blockers, calcium blockers, or nitrates, when evaluating frequency of angina and time to onset of ischemic changes on an exercise stress test. However, a limitation of this meta-analysis is a lack of a placebo group in some of the studies that were included.[35] Tolerance to nicorandil can develop with chronic dosing, similar to nitrate therapy, although cross-tolerance does not seem to be an issue.

Fasudil

Fasudil is an inhibitor of the Rho kinase pathway, which is an intracellular signaling pathway involved in increasing coronary

tone and vasospasm. In a study examining acetylcholine-induced coronary vasospasm, Fasudil further dilated the site of coronary vasospasm already treated with nitroglycerin.[36] Vicari et al studied 84 patients with stable angina randomized to placebo versus fasudil over 8 weeks. Patients were allowed to continue on nitroglycerin and β-blocker or calcium channel blocker as needed. Exercise tests were performed at baseline and at 2, 4, 6, and 8 weeks after treatment. Fasudil improved Seattle Angina Questionnaire scores and increased time to ST-segment depression on the exercise tests. However, it did not alter the frequency of angina or the use of nitroglycerin.[37] In another study, Fasudil was shown to reduce pacing-induced ischemia in patients with effort angina.[38]

Treatment of Refractory Angina

Enhanced External Counterpulsation

If the patient is experiencing continued angina after maximizing the medical regimen and undergoing revascularization where appropriate, there are some other forms of the therapy to consider. One is enhanced external counterpulsation (EECP). A set of inflatable bilateral cuffs are wrapped around the calves, lower thighs, upper thighs, and buttocks, attached to air hoses, and are then inflated and deflated based on the cardiac cycle. During early diastole, the cuffs are inflated from calves to buttocks (in a cranial direction) to 100 to 300 mm Hg, which creates retrograde aortic flow in diastole, increasing coronary artery perfusion pressure and hence coronary flow during diastole (diastolic augmentation).[39] At the completion of diastole, the pressurized air in the cuffs is rapidly removed inducing an afterload-reducing effect. The inflation deflation cycles are typically performed over 1-hour sessions that occur 5 days a week for about 7 weeks. Clinical studies have shown that EECP reduces angina, reduces use of nitrates, increases exercise tolerance, improves quality of life, improves endothelial function as determined by flow mediated dilatation studies, and improves coronary perfusion. Enhanced external counterpulsation has not been shown to reduce major adverse cardiovascular events, and it is a very time-consuming process (much like dialysis). Enhanced external counterpulsation is FDA approved for angina in the United States.[39-47]

Transmyocardial Revascularization

Another therapy that has been used for refractory angina and is sometimes combined with coronary artery bypass surgery is transmyocardial revascularization (TMR). The initial concept was that drilling laser holes from epicardium to endocardium would create a situation similar to certain reptilian hearts whereby oxygenated blood from the left ventricular cavity would then supply the wall of the left ventricle through channels or sinusoids that traversed the wall. Theoretically, this was an exciting concept. However, in reality, our group and others found that these laser-created holes thrombosed, became fibrotic, and caused damage to surrounding muscle. However, new blood vessels are formed around the healing laser lesions that can improve perfusion.[48] As recently reviewed, TMR alone, compared to medical therapy, does reduce angina[49]; some but not all studies have shown improvements in other outcomes such as perfusion, quality of life, reduced hospitalizations and coronary events, and improved exercise times. None of the TMR versus medical therapy studies showed a reduction in 1-year mortality; 1 study did show a reduction in 5-year mortality versus medical therapy.[50] However, none of these studies was double-blinded. The TMR has also been used as an adjunctive therapy to CABG, especially in areas that are not amenable to placing bypass grafts. Allen et al reported improved clinical outcome with the combination TMR versus CABG alone.[51]

Percutaneous myocardial revascularization is the technique whereby the laser holes are created by placing the laser-containing catheter into the ventricular cavity and then creating the holes from endocardium to epicardium. Some double-blind studies failed to show an improvement in angina compared to sham procedure, whereas 1 study was positive for a reduction in angina, so this technique is rarely used.[52-54]

Spinal Cord Stimulation

Another nonpharmacological therapy that has shown some promise in patients with refractory angina is spinal cord stimulation.[55] As recently reviewed, some studies showed small improvements in angina, but results have been mixed and there is a lack of large, well-designed randomized controlled trials.[56] This technique should be reserved for those patients in whom all other treatment options have been exhausted.

Stem Cell Therapy

Experimental studies showed that human $CD34^+$ stem cells could improve angiogenesis within ischemic myocardium and improve ventricular perfusion and cardiac function. In a clinical trial called ACT34-CMI, patients with coronary artery disease who were treated with intramyocardial autologous $CD34^+$ stem cells demonstrated improved exercise tolerance and less angina at 6 and 12 months compared to patients receiving placebo. Two-year outcome data were recently reported.[57] There were 167 patients with refractory angina pectoris who completed the injection procedure, using an intramyocardial delivery system injected into the ischemic area of the left ventricle as identified by NOGA mapping. At 24 months, patients receiving both a low and high dose of the cells had significant reductions in the frequency of angina. The low-dose group also had a significant improvement in exercise tolerance compared to placebo at 6 and 12 months. There was a nonsignificant trend toward reduced mortality with cell therapy. At 2 years, death rates were 12.5% in the placebo group versus 1.8% in the low-dose and 3.6% in the high-dose cell groups ($P = .08$). Other prior techniques to improve myocardial perfusion involved the concept of gene therapy; however, this approach largely failed in clinical trials.[15]

Conclusion

Angina pectoris continues to cause significant morbidity and is associated with major adverse cardiovascular events. Therapy should be geared to not only treating the risk factors for atherosclerotic disease, many of which have shown reductions in major adverse cardiovascular events, but also geared to minimize or eliminate angina itself. Standard therapies such as nitrates, β-blockers, calcium blockers, and ranolazine work, but even these agents do not always fully eliminate angina. Revascularization is indicated in certain high-risk cases and in situations where guideline-directed medical therapy is not fully working to eliminate angina. There is a need for newer, novel antianginal agents, because even after revascularization, a significant percentage of patients will have angina 1 year later.

Authors' Note

Dr Peter Stone is the guest editor to this article.
*This paper focuses on chronic stable angina; not unstable angina which is a separate topic.

Author Contributions

R. A. Kloner and B. R. Chaitman contributed to conception and interpretation, drafted the manuscript, critically revised the manuscript, and final approval and also agree to be accountable for all aspects of work ensuring integrity and accuracy.

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