ABSTRACT

Coronary artery disease (CAD) is a principal cause of morbidity and mortality around the globe. An important indicator of CAD is angina pectoris, defined as a syndrome of substernal chest discomfort, with a characteristic quality and duration that is provoked by exertion or emotional stress, and is relieved by rest or the administration of nitroglycerin. The main pathologic abnormality in stable angina is the presence of an intimal plaque within the coronary artery lumen that limits flow to a portion of the left ventricle. Inflammatory processes are a major driving force of atherosclerosis and are involved in the disruption of plaques and the resulting thrombosis. Anginal pain is most likely mediated by adenosine released from the ischemic myocardium that activates sensory nerves in the heart. The exact location of ischemia in the myocardium (subendocardial vs transmural) is related to whether or not patients with CAD experience angina. Asymptomatic patients do not have the traditional endpoints of disease and the development of a cardiac event is often the initial manifestation of CAD. Unstable angina presents as a change in the usual pattern of stable angina and usually occurs at rest. Treatment options available for the management of chronic stable angina are plentiful and include pharmacologic, nonpharmacologic, and alternative therapies. Unfortunately, there are many patients with angina refractory to current medical treatment strategies or who are not candidates for surgical or catheter-based revascularization. There is a need for new effective therapies for these patients with angina who are not receiving full benefit from current therapies.


A full review of ischemic heart disease can be a daunting task. There is much that can be written about atherogenesis, plaque biology, risk factors for atherosclerosis, and the natural history of coronary atherosclerosis. Indeed, entire books and reviews can and have been written about each of these areas. The focus of this monograph is to develop a conceptual framework for understanding angina pectoris, the most common symptom of myocardial ischemia experienced by individuals with coronary atherosclerosis. This paper will briefly describe the magnitude of the problem of atherosclerotic cardiovascular disease (CVD) in general and coronary artery disease (CAD) in particular, and then move quickly to a focus on angina pectoris.

MAGNITUDE OF THE PROBLEM

CAD remains a major healthcare problem in the United States and around the globe, despite dramatic advances in medicine. The reasons for this are multifactorial and are largely due to the advancing age of our population.1 It has been estimated that CVD and stroke will cost the United States $368.4 billion in 2004. Coronary heart disease (CHD) is expected to consume more than one third of this expenditure at $133.2 billion.

CHD affects 6.4% of the US population, or more than 13 million Americans.1 The prevalence of CHD...
increases with age for both males and females and is more prevalent in men at each age group, except from age 25 to 44 years. Atherosclerotic CVD is the leading cause of death in men and women in the United States with CAD accounting for more than half (54%) of those deaths. CVD is also a major cause of morbidity and can result in myocardial infarction (MI) with resulting impairment in cardiac function and congestive heart failure, loss of limbs with reduction in mobility, and stroke with its devastating effects on mobility, communication, and other cognitive functions. These diseases have taken on increasingly global importance as the epidemic of obesity and type 2 diabetes mellitus spreads to large countries such as India and China. Patients with type 2 diabetes seem to develop an especially aggressive form of CVD and CAD. The World Health Organization projects that in 2020, CAD will account for 6% of the total global disease burden, of which only 11% will be in developed regions, the rest being in developing nations.

SUBSTRATE FOR ANGINA

Atherosclerosis is a systemic disease. Indeed, patients with this disease may experience problems due to CAD, atherosclerotic peripheral arterial disease, and atherosclerotic cerebrovascular disease. In each instance, it is the reduction in flow to the specific vascular bed that results in symptoms such as angina pectoris, intermittent claudication, and various central nervous system symptoms (such as transient ischemic attacks or strokes).

WHAT IS ANGINA PECTORIS?

Angina pectoris is a discomfort that individuals experience when the supply of blood flow to the myocardium is inadequate to meet the metabolic needs of the myocardium. Although most patients experience discomfort in the chest, others may experience symptoms exclusively in the back, throat, neck, jaw, shoulders, elbows, forearms, wrists, or gums. Some patients experience discomfort that is limited to only one of these areas. It is a visceral discomfort that assorted patients say is “hard to describe.” Many patients, when asked if they have “chest pain,” will deny “pain.” It is for this reason that the physician should ask the patient if he or she has discomfort (not pain) in the chest or in the other locations where angina may be felt. Women often have very atypical symptoms, which can be especially difficult to interpret.

Table 1 lists the conditions that may provoke or exacerbate angina pectoris. There are 2 important points to be made from this table. First, conditions exist in which angina occurs in the presence of anatomically normal coronary arteries. Perhaps the best example of this is aortic stenosis, where large increases in cardiac work (the stenotic valve plus exercise) with inadequate supply (relatively low coronary perfusion pressure plus limitation of coronary vasodilation) lead to myocardial ischemia and angina pectoris.

Second, the most common cause of angina pectoris, not shown on Table 1, is coronary atherosclerosis. Angina in CAD also results from an imbalance between supply and demand. It is the supply that is affected by CAD. The supply of oxygen to the myocardium and removal of metabolites are dependent on coronary blood flow. Normally, incremental increases in myocardial oxygen demand are met almost

<table>
<thead>
<tr>
<th>Condition</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Oxygen Demand</td>
<td>Decreased Oxygen Supply</td>
</tr>
<tr>
<td>Noncardiac</td>
<td>Noncardiac</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>Anemia</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Hypoxemia</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Asthma</td>
</tr>
<tr>
<td>Arteriovenous fistulas</td>
<td>COPD</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>Interstitial pulmonary fibrosis</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Syndromimetic toxicity</td>
</tr>
<tr>
<td>Ventricular</td>
<td>(eg, cocaine use)</td>
</tr>
<tr>
<td>Supraventricular</td>
<td>Hyperviscosity</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Polycythemia</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>Thrombocytosis</td>
</tr>
</tbody>
</table>

Table 1. Conditions That May Provoke or Exacerbate Ischemia

COPD = chronic obstructive pulmonary disease.
entirely by a balanced increase in coronary blood flow; not so in CAD.

**WHAT IS THE SUBSTRATE FOR ANGINA PECTORIS?**

Angina pectoris in CAD is due to impingement of the lumen by atherosclerotic plaque in the coronary artery, thereby restricting coronary blood flow. The development of this plaque may begin early in life. Indeed, many young soldiers who died in the Korean War who were autopsied were shown to have surprisingly advanced CAD. The atherosclerotic plaque is composed of a fibrous cap that covers the surface. Beneath the cap is the soft portion of the plaque, filled with lipid-laden macrophages, oxidized low-density lipoprotein (LDL) cholesterol, and other cellular waste products. Often there is bone-like calcification in the plaque.

Based on studies with intracoronary ultrasound, angina tends to be mainly stable and reproducibly provoked by exertion when the plaque is “hard” and composed mainly of fibrous plaque and calcification with relatively low lipid content. “Soft” plaques, which have a thin fibrous cap and high lipid content, are prone to rupture. Features associated with plaque rupture are listed in Table 2. Rupture exposes the contents of the plaque, which are highly thrombogenic, to the blood in the vicinity of the rupture. The thrombus that develops at the site of plaque rupture can be fully occlusive resulting in a transmural infarction. The thrombus may also be partially occlusive resulting in acute coronary syndromes such as unstable angina or non–ST-segment elevation nontransmural MI. On the contrary, the plaque and related thrombus may not be sufficiently occlusive to cause immediate symptoms but may “heal” in such a way as to increase the degree of structural occlusion, only to repeat this process at a later date leading to any of the sequelae outlined here.

There are many anginal syndromes. Stable angina is the most common and is reproducibly provoked by exertion and oftentimes by emotion. In contrast, unstable angina may occur at rest, thereby indicating restriction in coronary blood flow so severe as to prevent sufficient coronary blood flow to meet metabolic needs of the myocardium when the patient is inactive. Angina may occur after meals, especially when walking, and is termed postprandial angina. In these circumstances, the cardiac work of supplying the exercising muscle plus the gut that is in the absorptive/digestive state may require more coronary blood flow than the diseased coronaries can deliver. Other episodes of angina may awaken the individual from sleep (nocturnal angina), or occur when the patient becomes recumbent (angina decubitis). These and other anginal syndromes have unique factors that contribute to the provocation of angina, but share the common characteristic of inadequate coronary blood flow in relationship to metabolic demands. The chest discomfort associated with the full range of ischemic insults from acute MI to stable exertional angina tends to differ, not in character, but in

---

**Table 2. Features Associated with Plaque Rupture**

<table>
<thead>
<tr>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Large eccentric soft lipid core</td>
</tr>
<tr>
<td>2. Thin fibrous cap</td>
</tr>
<tr>
<td>3. Inflammation in the cap and adventitia</td>
</tr>
<tr>
<td>4. Increased plaque neovascularity</td>
</tr>
<tr>
<td>5. Outward or positive vessel remodeling</td>
</tr>
</tbody>
</table>


---

**Figure 1. Regulation of Coronary Flow**

![Figure 1. Regulation of Coronary Flow](image-url)
severity. As the amount of myocardium that is ischemic increases, there is more likely to be radiation of the discomfort to other areas like the arms, as well as associated symptoms of dyspnea, diaphoresis, and nausea.

**What Causes the Sensation of Angina?**

The discomfort of angina is transmitted to the central nervous system by nerve fibers that travel with the sympathetic nerves. Bilateral stellate block eliminates angina. Although it is difficult to study basic mechanisms of angina in humans, experimental data suggest that the nerve endings responsible for angina are activated by adenosine, probably by stimulation of adenosine A₁ receptors.5-8 Consistent with this concept is the finding that administration of aminophylline, a non-selective adenosine receptor antagonist that blocks A₁ receptors, prolongs the time to exercise-induced angina without reducing myocardial ischemia. Based on ambulatory electrocardiogram monitoring, two thirds of all episodes of myocardial ischemia that occur during activities of daily life are symptomless (ie, “silent ischemia”). Although the precise mechanism for this is not clear, myocardial ischemia during activities of daily life is mainly subendocardial, thus involving the inner portions of the left ventricular (LV) myocardium. Experimental data suggest that the nerve endings responsible for the sensation of angina may be preferentially distributed to the outer portions of the LV myocardium. Thus, during activities of daily life, the stimulus (probably adenosine) is remote from the fibers that are activated by myocardial ischemia.

**What Is the Relationship Between the Severity of Coronary Artery Stenosis and the Development of Myocardial Ischemia?**

In a normal coronary circulation, coronary blood flow can be increased 3- to 4-fold, but only by pharmacologic means. Agents such as adenosine (or its analogues) and persantine (which blocks the uptake of adenosine) have been used to induce maximal coronary vasodilation. Adenosine is the most potent naturally occurring vasodilator. Many patients who receive intravenous or intracoronary adenosine describe symptoms of chest discomfort that sound like angina, thus, providing further support for the concept that this substance, released from the ischemic myocardium in large amounts, is the main stimulus for nerve endings that detect myocardial ischemia.

The difference between normal resting coronary blood flow and the maximally dilated flow is called maximal or pharmacologic coronary flow reserve. Figure 1 illustrates the effect of increasing degrees of coronary stenosis on maximal coronary flow reserve. There is generally no reduction in maximal flow reserve in a coronary artery containing plaque until the cross-sectional area is reduced by 70% (50% diameter reduction). A highly trained athlete uses about half of his or her maximal coronary flow reserve during peak effort (maximal functional reserve). Activities of daily life generally occur at levels of coronary blood flow less than half of the maximal functional reserve (functional reserve). In Figure 1, the curve for functional reserve intersects the pharmacologic flow reserve curve far to the right on the stenosis axis. What this means is that in order to induce ischemia and thus angina, the stenosis must be severe (ie, generally >70% cross-sectional area reduction).

There are some qualifiers for what has just been outlined above. Less severe stenosis can cause myocardial ischemia when the stenosis is long. In addition, changes in vasomotor tone, the degree of constriction of vascular smooth muscle in the wall of the artery in the stenotic segment, can alter the degree of stenosis (Figure 2), thereby adding a dynamic component to the degree of stenosis that is superimposed on the structural component (ie, the plaque). Coronary stenoses that are not severe when vasomotor tone is low may become severely narrowed by constriction of...
smooth muscle in the wall of the coronary arteries. In addition, a tight stenosis creates areas of high shear that activate platelets. Platelet adhesion and aggregation at the site of stenosis can contribute to the reduction in cross-sectional area. Vasoactive substances released from platelets, such as thromboxane A₂ and serotonin, can induce vasoconstriction and reversibly worsen the severity of the stenosis. Finally, LV hypertrophy (LVH) alone reduces coronary flow reserve in the absence of coronary disease. Thus, patients with LVH may be even more susceptible to the flow-limiting effects of coronary stenoses than those without LVH, and they may develop myocardial ischemia with less severe degrees of stenosis.

The key concept to understanding coronary flow in CHD is the following: during activity, when the existing degree of vasodilator reserve is insufficient to meet the demand of the myocardium for flow and, thus, for oxygen delivery, ischemia results. The ischemia in turn provokes the symptom of angina pectoris. When the subject is inactive, then discomfort (angina) may occur at rest (Figure 2).

The initial manifestation in more than half of patients with CAD is chronic stable angina. The American Heart Association (AHA) and the American College of Cardiology (ACC) have estimated that 16.5 million Americans have stable angina. Such patients can often identify specific activities or situations that provoke angina pectoris. For those with myocardial ischemia that is symptomless (or “silent”), the initial evidence of underlying CAD may be an acute coronary syndrome, sudden death, or the conversion to symptomatic angina.

### Treatment Options

The primary goals for the treatment of chronic stable angina are to reduce the risk of mortality and morbidity and to reduce or eliminate anginal pain. The objective of therapy is to enable patients to return to normal activities. Ideally, management of ischemic heart disease should have as few side effects as is possible. The ACC and the AHA have developed guidelines for the management of patients with chronic stable angina. These guidelines focus on risk assessment and treatment of asymptomatic as well as symptomatic patients with known or suspected CAD.

### Pharmacologic

A wide array of pharmacologic agents is available for the treatment of ischemic heart disease. When selecting the most appropriate pharmacologic treatment for an individual patient, specific consideration should be given to agents that have been proven to improve prognosis. An in-depth discussion of these agents is beyond the scope of this paper; rather, a brief overview of agents used to treat ischemic heart disease is provided.

**Beta blockers.** Blockade of beta-adrenergic receptors causes cardiac slowing and decreased myocardial contractility and may lower arterial pressure. These effects serve to reduce the myocardium’s demand for oxygen, and thus flow, especially during exercise. Patients on beta blockers thus require a smaller portion of their coronary flow reserve to do a given amount of physical activity, and are, thus, less likely to have myocardial ischemia when coronary flow reserve is limited. Put another way, patients with flow-limiting coronary stenoses can do more physical activity with their available coronary flow reserve following beta blockade. Figure 3 illustrates the portion of the functional coronary flow reserve used before and after beta blockade. Note that the beta blocker curve intersects the functional flow reserve curve further to the right. Thus, after beta blockade, ischemia will occur at a higher degree of stenosis than before blockade. Not only can

![Figure 3. Effect of Beta Blockers on Coronary Blood Flow](image)
beta blockers provide symptomatic relief from angina, several trials have demonstrated that these agents can also improve survival in patients with recent or prior MI.10 Beta blockers should be considered as initial therapy for chronic stable angina, secondary prevention post-MI, and for the reduction of mortality and morbidity in hypertensive patients. Concurrent asthma or bronchospasm and atrioventricular (AV) conduction abnormalities are relative contraindications to beta blocker therapy; however, diabetes mellitus is not grounds for avoiding these antianginal agents.

**Calcium channel blockers.** Long-acting or slow-release calcium channel antagonists are able to relieve the symptoms of chronic stable angina. The nondihydropyridine calcium channel blockers, such as verapamil and diltiazem, reduce heart rate and should be administered with caution in patients receiving concurrent beta blocker therapy or with evidence of sinus node or LV dysfunction or AV block. Calcium channel blockers may exert antianginal effects by decreasing heart rate at exercise and rest. These agents work by lowering arterial pressure at rest and with exercise, thereby decreasing oxygen demand. Finally, calcium channel blockers relax vascular smooth muscle in the coronaries thereby minimizing the dynamic component of angina (Figure 4).

**Nitroglycerin.** This agent is efficacious in relieving angina by decreasing myocardial oxygen requirements (reduced preload via systemic venodilation) and by improving myocardial perfusion (by relaxing the smooth muscle in diseased and stenotic coronary arteries) (Figure 4). When combined with beta blockers or calcium channel blockers, nitrates can improve the antianginal efficacy of these agents.10 Diseased coronaries produce less nitric oxide (NO) than normal coronaries. NO is the key naturally occurring epicardial coronary vasodilator. Nitroglycerin and related long-acting nitrates are NO donors and cause relaxation of vascular smooth muscle.

**Antiplatelet therapy.** Aspirin, the most common antiplatelet therapy, has been shown to decrease the risk of nonfatal MI in chronic stable angina patients by 33% and to reduce the risk of serious vascular events by about 25%.11 The antithrombotic effect of aspirin is induced by the inhibition of cyclooxygenase and the subsequent production of thromboxane A2 and prostacyclin.8 Patients intolerant of aspirin may be treated with clopidogrel, an antiplatelet medication that prevents adenosine diphosphate-mediated activation of platelets. Clopidogrel is associated with a reduction in the combined risk of MI, vascular death, or stroke in high-risk patients with established vascular disease.12 There is little evidence that either aspirin or clopidogrel have any antianginal effect.

**Lipid-lowering therapy.** The importance of an aggressive approach to the control of lipids in patients with CAD is paramount. The use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, has been associated with a decrease in mortality of up to 30% and a reduction in major coronary events in patients with known CAD of up to 35%.13-15 These impressive results included some patients with baseline levels of LDL cholesterol levels under 100 mg/dL.15 Reducing LDL may limit progression or even induce regression of CAD, thereby having an indirect anti-ischemic effect. As discussed below, it also stabilizes plaques and thereby reduces the risk of acute coronary syndromes.

**Angiotensin-converting enzyme inhibitors.** Two recent multicenter, randomized trials—the Heart Outcomes Prevention Evaluation (HOPE) study, and the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA)—demonstrated the efficacy of angiotensin-converting enzyme (ACE) inhibitors in patients with CAD or those at risk of CAD.16,17 The
significant effect on the incidence of cardiovascular death, MI, or stroke was reported to be independent of the blood pressure-lowering effects of ACE inhibition. The results of HOPE have lead to the recommendation that ACE-inhibitor therapy is appropriate for all patients with CAD and for asymptomatic patients with CAD who have concurrent diabetes or LV dysfunction. Some controversy exists regarding the true nature of the vascular protective effects observed with ACE-inhibitor therapy in HOPE. It is possible that these cardioprotective benefits may have been due to an antihypertensive effect that is more evident when the effects of ramipril on blood pressure are examined over 24 hours rather than at a single endpoint.

**Novel agents.** Novel drug therapies for the treatment of CAD decrease anginal symptoms via optimization of myocardial energy metabolism. These therapies include carnitine derivatives, antioxidants, and fatty acid oxidation inhibitors (reviewed by Stanley in 2002). Perhaps the most clinically exciting of these novel agents are the fatty acid oxidation inhibitors, trimetazidine (available outside the United States) and ranolazine (currently under US Food and Drug Administration review). These agents have demonstrated an improvement in symptoms when used as monotherapy or when combined with traditional pharmacologic agents.

**Nonpharmacologic Therapies**

Lifestyle modifications are important in the management of patients with ischemic heart disease. Such modifications include maintenance of ideal body weight, diet, exercise, and smoking cessation. In general, lifestyle modifications should be instituted prior to or along with pharmacotherapy and should serve to complement pharmacotherapy in the control of blood pressure and dyslipidemia.

**Alternative Therapies**

Some patients with ischemic heart disease require surgical intervention in addition to lifestyle modification and pharmacotherapy. In an effort to improve the prognosis of patients with CHD, the incidence of revascularization procedures has grown dramatically over the past 2 decades. Percutaneous coronary intervention and coronary artery bypass graft surgery are the primary treatment options for those CAD patients with high-risk features or who are refractory to maximal medical management. However, many patients with CAD are not good candidates for conventional revascularization and their management remains a clinical challenge. This is especially true of diabetics in whom CAD is often both severe and diffuse. Alternative therapies for chronic stable angina in these difficult-to-treat patients include surgical laser transmyocardial revascularization (TMR), enhanced external counterpulsation (EECP), and spinal cord stimulation.

The mechanisms for improvement in symptoms in patients with chronic stable angina associated with surgical TMR are currently unclear and may include increased myocardial perfusion, denervation of the myocardium, or stimulation of angiogenesis. EECP is a nonpharmacologic technique that has been found to be associated with a decrease in angina frequency and improved time to exercise-induced ischemia. Further study of this treatment is warranted; however, widespread use of EECP is limited by significant exclusion criteria, limited availability of the device, the occurrence of adverse events, and the lack of long-term effect.

**Figure 5. Plaque Stabilization as a Means of Reduction in Clinical Events**

**Plaque Phenotype**

- Large lipid core
- Reduced SMC and collagen
- Inflammation
- Increased neovascularity
- Enhanced thrombogenicity
- Endothelial dysfunction

**Plaque Phenotype**

- Reduced lipid core
- Increased SMC and collagen
- Reduced Inflammation
- Reduced neovascularity
- Reduced thrombogenicity
- Improved endothelial function

**Plaque Instability**

- Increased thrombogenicity
- Reduced lytic activity

**Reduced clinical events**

- Reduced thrombogenicity
- Increased lytic activity

SMC = smooth muscle cells.

Spinal cord stimulation has been used since the late 1980s as a means of providing analgesia in patients with chronic angina refractory to medical, catheter-based, or surgical treatment. Although there are several studies evaluating the efficacy of this technique, there is a general lack of data on the intermediate- and long-term benefits of spinal cord stimulation. This technique is used more widely in Europe than in the United States.

**STABILIZATION OF PLAQUE**

It is well established that luminal narrowing by an atherosclerotic plaque contributes to the clinical manifestations of occlusive vascular disease. However, the development of an arterial thrombus superimposed on an underlying disrupted plaque is responsible for the most acute and potentially lethal manifestations of CAD. The majority of coronary thrombi occur at sites where the fibrous cap of an atherosclerotic plaque has fissured eroded, or ruptured. Although the exact mechanisms responsible for plaque rupture are not fully defined, several features present prior to rupture have been identified (Table 2).

Studies have demonstrated that risk factor modification leads to a decrease in the formation of new lesions, less lesion progression, and in some cases, actual regression of disease. The magnitude of clinical event reduction observed is much greater than what can be accounted for with small changes in the severity of stenosis. Therefore, it has been postulated that risk factor modification may not change plaque mass and stenosis severity, but may change the composition of the plaque thereby reducing the propensity for plaque rupture. This “plaque stabilization” brought on by lipid modification may be due to changes in the composition of plaque and therefore a reduction in the frequency of acute vaso-occlusive events (Figure 5). Some scientists have postulated that the depletion of lipids and decreased inflammation from atherosclerotic plaques may help reduce the risk of plaque rupture and subsequent thrombosis via plaque stabilization with resultant clinical benefits.

**CONCLUSIONS**

Ischemic heart disease is a prevalent disease worldwide and is associated with significant morbidity and mortality. Treatment of CHD may include lifestyle changes, pharmacological, and/or catheter-based or surgical therapy. Traditionally, pharmacologic approaches for treating ischemic heart disease have either increased the oxygen supply to the heart muscle or decreased the oxygen demand of the muscle. Novel therapies utilizing a different mechanism of action to decrease anginal symptoms via optimization of myocardial energy metabolism are an exciting option. Current drug treatments of ischemic heart disease are directed toward symptom control and prevention of disease progression and sequelae. However, many agents are associated with side effects that affect quality of life (events such as impotence, fatigue, edema, and headache). In addition, many patients need to take more than 1 antianginal agent for appropriate management, thereby increasing the risk of side effects. Regardless of the condition being treated, multidrug regimens are generally associated with lower compliance than are simple regimens.

Many patients with CAD suffer from persistent symptoms despite administration of standard therapy. Up to one fourth (26%) of CAD patients 1-year post-revascularization still experience anginal attacks, including patients who receive antianginal pharmacotherapy. Refractory patients face persistent symptoms and the risk of a cardiac event or death. There is a need for interventions that can induce plaque regression and eventually reverse ischemic heart disease itself. Until such interventions become widely available, there will continue to be a major demand for therapies that reduce angina pectoris.

We have reviewed the causation of angina as well as therapeutic options. Despite numerous choices of treatment for these patients, there are millions of patients who continue to experience angina. Many patients are not suitable for revascularization due to the extent and severity of their disease. There is a need for new effective therapies for the many patients who suffer from chronic angina and are not receiving full benefit from traditional treatment.

**REFERENCES**


