ABSTRACT

Chronic stable angina (CSA), a subset of chronic coronary syndrome (CCS), is most often caused by myocardial ischemia—the result of an imbalance between myocardial oxygen demand and supply. Many currently available therapeutic agents for CSA will relieve the symptoms of angina but not change the ischemic threshold. The American College of Cardiology/American Heart Association guideline was last updated in 2003 and will again be updated later this year. The guideline recommends aspirin, lipid-lowering agents, beta blockers, and angiotensin-converting enzyme inhibitors as primary preventive therapy to reduce the risk of death and myocardial infarction. Several large studies have been published to support the use of these drugs for CSA/CCS. Percutaneous coronary intervention (PCI) is being used more frequently as nonpharmacologic management, but some patients continue to have angina despite PCI and optimal doses of antianginal drugs. Refractory angina is quite common and numerous pharmacologic treatments are available. Recommended nonpharmacologic treatments include transmyocardial laser revascularization, enhanced external counterpulsation, and spinal cord stimulation. Additionally, there are now several new mechanistic approaches to managing coronary artery disease, including inhibition of late sodium channels, inhibition of free fatty acid metabolism, inhibition of rho-kinase, preconditioning, and sinus node inhibition. This article reviews some of these new drugs, which will hopefully provide additional treatment choices. Nonetheless, the importance of comprehensive management of myocardial ischemia, including symptom management, aggressive risk factor reduction, antiplatelet therapy, and lifestyle modifications, cannot be overstated.

To understand the treatments for chronic stable angina (CSA)/chronic coronary syndrome (CCS), it is important to remember its most likely cause: myocardial ischemia—the result of an imbalance between myocardial oxygen demand and supply. Oxygen supply to the heart is determined by blood flow and oxygen extraction. Myocardial ischemia may result from a disproportionate increase in myocardial oxygen demand or inappropriate decrease in coronary blood flow, and rarely reduced oxygen-carrying capacity of the blood. Therefore, any increase in myocardial oxygen demand (eg, during exercise) must be offset by a proportional increase in coronary blood flow. The direct, linear relationship between oxygen consumption and blood flow is well established in animals and humans. When there is a mismatch between myocardial oxygen demand and coronary blood flow, ischemia will result
ischemic threshold; Figure 1). Coronary stenosis or decrease in coronary flow reserve will decrease the ischemic threshold (Figure 1). As will be discussed later in this article, many therapeutic agents for CSA/CCS will relieve the symptoms of angina but will not change the ischemic threshold.

**Pharmacotherapy for CCS**

The goals of pharmacotherapy for CCS are 2-fold: to reduce the risk of myocardial infarction (MI) and death, which is presumably accomplished by several mechanisms, including reducing or stabilizing the atherosclerotic plaque and reducing the likelihood of plaque rupture and acute coronary syndrome; and to improve anginal symptoms and reduce myocardial ischemia by optimizing the myocardial oxygen supply-demand balance. Note that the goals are to increase quantity and quality of life. Recommended treatments for decreasing the risks of infarction and death include aggressive statin therapy, beta blockers, aspirin, angiotensin-converting enzyme (ACE) inhibitors, and lifestyle modifications. Drugs that improve anginal symptoms include drugs that reduce heart rate, blood pressure, contractility, and venous return to the heart (ie, beta blockers, calcium blockers, and nitrates), and there are newer agents with mechanisms of action that are different from the established antianginal drugs. The American College of Cardiology/American Heart Association (AHA) guideline recommends that treatment should include all of the elements in the A-B-C-D-E mnemonic (Sidebar). This article reviews some of the recommended treatments and discusses future directions in CCS treatment; some of the more common obstacles to the successful use of established therapies are summarized in Table 1.

**Pharmacotherapy to Prevent MI or Death**

The guideline now recommends aspirin, lipid-lowering agents, beta blockers, and ACE inhibitors as primary preventive therapy. Several large clinical trials have provided evidence to support some of these drug classes. For example, several studies have shown cardioprotective effects of ACE inhibitors, including a significant reduction in MI, stroke, and death risk in patients at increased risk for cardiovascular disease. Since the guideline was last updated, 2 other

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**Sidebar: Mnemonic for Treatment of Chronic Coronary Syndrome**

A = Aspirin and antianginal therapy
B = Beta-blocker and blood pressure
C = Cigarette smoking cessation and cholesterol
D = Diet and diabetes
E = Education and exercise

Data from Gibbons et al.

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**Figure 1. Ischemia Threshold in Stable Angina**

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**Table 1. Treatment Challenges for Coronary Artery Disease**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older antianginal drugs</td>
<td>Many patients cannot tolerate combinations at maximal doses</td>
</tr>
<tr>
<td>Disease-modifying agents</td>
<td>BP, lipid, and glucose goals are being revised downward</td>
</tr>
<tr>
<td>PCI</td>
<td>Many patients are not suitable candidates</td>
</tr>
<tr>
<td>Lifestyle modification</td>
<td>Noncompliance limits long-term benefit</td>
</tr>
</tbody>
</table>

BP = blood pressure; PCI = percutaneous coronary intervention.
Clinical trials of ACE inhibitors for CCS have been published. The EUROPA study showed a 20% relative risk reduction (95% confidence interval [CI], 9–29; \( P = .0003 \)) for cardiovascular death, MI, or cardiac arrest with perindopril in a low-risk population with stable coronary heart disease and no apparent heart failure. However, the PEACE study did not show additional benefit with ACE inhibition in patients with stable coronary artery disease (CAD) and preserved left ventricular function. Several reasons for this unexpected result have been put forth, including the lower cardiovascular baseline risk of the PEACE study population, which was more intensively treated with lipid-lowering drugs and had a greater number of patients with myocardial revascularization prior to enrollment than patients in HOPE or EUROPA; differences in clinical efficacy for cardiovascular endpoints between the ACE inhibitors in each study (trandolapril in PEACE, ramipril in HOPE, and perindopril in EUROPA); inability to reach the projected sample size in the PEACE study; and a "soft" endpoint of revascularization. Nonetheless, ACE inhibitors remain a strongly recommended treatment.

Lipid-lowering agents (ie, statins) are now recognized not only as treatments to prevent MI or death, but also as part of risk factor modification. The benefits of lowering low-density lipoprotein cholesterol for reducing coronary heart disease (CHD) events (as both primary and secondary prevention) are well established. Since the guideline was published and updated, several other trials have also now shown that statin therapy may decrease the incidence of angina and death and may decrease the frequency of angina and ischemia during exercise tolerance testing. Specifically, the ASCOT-LLA arm showed that treatment with atorvastatin in hypertensive patients significantly lowered the incidence of fatal and nonfatal stroke (89 atorvastatin vs 121 placebo; 0.73 [0.56–0.96]; \( P = .024 \)), total cardiovascular events (389 vs 486; 0.79 [0.69–0.90]; \( P = .0005 \)), and total coronary events (178 vs 247; 0.71 [0.59–0.86]; \( P = .0005 \)). The effect was so significant that the study was stopped early. Another large study comparing 10-mg and 80-mg atorvastatin in 10 001 patients with clinically evident CHD showed that more aggressive statin treatment was able to offer a 22% relative risk reduction (hazard ratio, 0.78; 95% CI, 0.69–0.89; \( P < .001 \)) in primary endpoint (occurrence of a first major cardiovascular event, defined as death from CHD, nonfatal nonprocedure-related MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke), but no additional benefit for overall mortality.

The only drugs that have shown benefit with reducing symptoms are beta blockers, calcium channel antagonists, and nitrates. Their proposed mechanisms of action are outlined in Table 2. Since the guideline was updated, a large randomized, placebo-controlled study evaluated nifedipine gastrointestinal therapeutic system in 7665 patients with stable symptomatic coronary disease. The primary endpoint was the combination of death, acute MI, refractory angina, new overt heart failure, debilitating stroke, and peripheral revascularization, with mean follow-up of nearly 5 years. Although nifedipine had no effect on major cardiovascular event-free survival, it reduced the need for coronary angiography and interventions (rate of death and any cardiovascular event or procedure: 9.32 vs 10.50 per 100 patient-years; \( P = .0012 \)).

### Table 2. Mechanisms of Action of CAD Treatments

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Proposed Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-adrenergic</td>
<td>Reduction of myocardial oxygen demand by reducing the heart rate, blood pressure, and contractility</td>
</tr>
<tr>
<td>antagonists</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin and</td>
<td>Decrease in myocardial oxygen demand by reduction of ventricular volume and blood pressure</td>
</tr>
<tr>
<td>nitrates</td>
<td></td>
</tr>
<tr>
<td>Calcium channel</td>
<td>Reduction of myocardial oxygen demand by decreasing blood pressure and contractility and with blockers</td>
</tr>
<tr>
<td>heart rate regulating agents also by decreasing heart rate</td>
<td></td>
</tr>
<tr>
<td>Calcium channel</td>
<td>Dilatation of the coronary conductance and resistance vessels; may be useful in vasospastic and mixed angina</td>
</tr>
<tr>
<td>blockers</td>
<td></td>
</tr>
<tr>
<td>Calcium channel</td>
<td>Improves exercise tolerance, usually does not change ischemia threshold</td>
</tr>
<tr>
<td>blockers</td>
<td></td>
</tr>
</tbody>
</table>


The guideline states that therapy should be staged, beginning with symptom management using beta blockers. If symptoms persist, a long-acting nitrate or calcium channel antagonist can be added, depending on the patient’s clinical characteristics. If symptoms continue, triple therapy may be necessary, provided there are no contraindications.2

**Nonpharmacologic Treatments for CCS-CSA**

Limitations of older anginal therapies and technical improvements in intervention procedures have led to increasing use of elective percutaneous coronary intervention (PCI) to treat stable CAD. Lucas et al found a 115% increase in PCI from 1993 to 2001, based on an annual cross-sectional population-based study of Medicare patients.20 By comparison, in this analysis, coronary artery bypass grafting increased only 19% and cardiac catheterization increased 69%.20 However, Katritsis and Ioannidis conducted a meta-analysis of 11 randomized trials (n = 2950) that compared PCI with conservative medical management in patients with chronic stable CAD.21 They found that although PCI effectively relieves angina, it does not offer any long-term advantage over medical management in terms of death, MI, or need for additional revascularization.21 Similarly, Spertus et al showed that patients with stable CAD and angina are more likely to have improved quality of life following PCI than those who have CAD but are free from angina.22 In this study, the majority of patients with angina (72%) reported a large improvement in quality of life following elective PCI compared to only 19% of patients who were symptom-free (Figure 2).22 Thus, the major benefit of PCI in stable CAD is angina relief.

**Treatment for Refractory Angina**

Within the spectrum of CCS lies refractory angina, defined as “Canadian Cardiovascular Society (CCS) class III or IV angina (ie, marked limitation of ordinary physical activity or inability to perform ordinary physical activity without discomfort) with objective evidence of myocardial ischemia and persistence of symptoms despite optimal medical therapy, lifestyle modification treatments, and revascularization therapies.”23,24 It is quite common, with more than 100 000 patients diagnosed per year (and prevalence estimates of approximately 300 000–900 000 in the United States). Although its prognosis remains uncertain, the 1-year rate of MI and death has been reported to be 26% to 17%, respectively.25

The updated guideline provides recommendations for patients with refractory angina who are not candidates for PCI or revascularization. Indeed, some patients experience incomplete angina relief post-PCI. A study of 1632 consecutive patients who underwent PCI showed that, at 1-year follow-up, 26% reported experiencing angina within the previous 6 weeks, despite relatively extensive use of adjunctive antianginal therapy—78.6% were using at least 1 antianginal drug (27.9% were using nitrates, 29.9% calcium channel blockers, and 60.9% beta blockers).26

The potential pharmacologic treatments for refractory angina are numerous: metabolic modulators, bradycardic agents, K+-channel activators, metformin, thiazolidinediones, preconditioning agents, vasopepti-
dase inhibitors, nitric oxide (NO)-donors, capsaicin, diuretics, gene therapy, and autologous bone marrow, in addition to rho-kinase inhibitors and ranolazine (both discussed later in this article). There are also numerous options for nonpharmacologic treatment of refractory angina: transmyocardial laser revascularization (TMLR), enhanced external counterpulsation (EECP), spinal cord stimulation (SCS), percutaneous myocardial revascularization, transcutaneous electrical nerve stimulation, programmed exercise, extracorporeal cardiac shock wave therapy, temporary sympathectomy, and cardiac transplantation. The updated guideline states Class IIa recommendations for TMLR, and Class IIb recommendations for EECP and SCS. TMLR is based on the premise that open transmyocardial channels will lead to angiogenesis. TMLR studies to date have all been open trials (ie, no sham-controlled studies). Although TMLR has shown no effect on mortality, it may improve anginal symptoms and exercise tolerance.27

Enhanced external counterpulsation has been shown to improve several measures of CAD symptoms, including angina, nitrate use, exercise tolerance, time to exercise-induced ST-segment depression, and myocardial perfusion.28-36 EECP is conducted as 35 1-hour sessions, 1 to 2 times per day. It acts by inflating/deflating cuffs, which serve to increase diastolic aortic pressure (with subsequent increase in coronary perfusion pressure) and reduce systolic pressure (thereby attenuating the cardiac workload and promoting venous return, which increases cardiac output). However, the exact mechanisms for the beneficial effects remain unclear. Bonetti et al evaluated the efficacy of EECP and its proposed mechanism using reactive hyperemia-peripheral arterial tonometry (RH-PAT), a noninvasive method to assess peripheral endothelial function. RH-PAT measures reactive hyperemic response in the finger. Based on their study results, the investigators propose that the delayed improvement in parameters of endothelial function with EECP may be due to the increased activity and expression of endothelial NO synthase from increased shear stress, which is generated by a standard course of EECP.27

Spinal cord stimulation consists of 3 1-hour stimulations per day. An epidural lead is placed at the level of C7–T1 in a subcutaneous generator. The applied electric impulse inhibits transmission of nerve impulses via the spinothalamic tract. Similar to EECP, the mechanism is not completely understood, but it may decrease ischemia and improve myocardial blood flow by decreasing sympathetic tone.

NEW MECHANISTIC APPROACHES TO MANAGEMENT OF CAD

There are now several new mechanistic approaches to managing CAD, including inhibition of late sodium channels, inhibition of free fatty acid metabolism, inhibition of rho-kinase, preconditioning, and sinus node inhibition.

Ranolazine has been studied in 4 large clinical trials. It is thought to modify the pathophysiology of CAD through several potential mechanisms: inhibition of late inward Na+ current, which is increased during ischemia and CHF; decreasing Na+ overload; decreasing Ca2+ overload; decreasing metabolic dysfunction; decreasing ischemia-induced diastolic and systolic mechanical dysfunction; and decreasing ischemia-induced electrical dysfunction. Although conventional anti-ischemic medications act by preventing development of ischemia (Figure 3), ranolazine is thought to act by preventing the consequences of ischemia, namely electrical instability and myocardial dysfunction. Importantly, the mechanisms for decreasing myocardial ischemia and angina by ranolazine are not due to a decrease in myocardial oxygen demand nor a primary increase in coronary blood flow (Table 3). The first study of ranolazine was the Monotherapy Assessment of Ranolazine in Stable
Angina trial, which was a randomized, double-blind, placebo-controlled, crossover study in 191 patients with angina-limited exercise. Patients were randomized to receive sustained-release ranolazine 500, 1000, or 1500 mg, or placebo, each administered twice daily for 1 week. The results showed significant improvements in exercise duration, time to angina, and time to 1-mm ST-segment depression. One-year survival was 96.3% ± 1.7%—an expected rate for this high-risk population. Similarly, ranolazine (400 mg immediate release, 3 times daily) was compared to atenolol (100 mg/day) or placebo in 158 patients with symptom-limited exercise in a double-blind, 3-period, crossover study. Exercise tests were administered at the end of each treatment period. Ranolazine was shown to be at least as effective as atenolol in increasing exercise duration, time to 1-mm ST-segment depression, and time to onset of angina. Ranolazine achieved these endpoints without decreasing blood pressure, heart rate, or rate-pressure product to a clinically significant degree. Ranolazine was also evaluated in combination with atenolol or diltiazem in 823 patients with angina/ischemia, despite standard daily doses of these traditional drugs. The results showed significant improvements in exercise duration, time to angina, and time to 1-mm ST-segment depression, in addition to reduced nitrate use and number of weekly anginal episodes (Figure 4), without adverse long-term survival consequences over 1 to 2 years of treatment. Ranolazine (1000 mg sustained-release, twice daily) has been evaluated as combination therapy in patients with chronic angina taking amlodipine 10 mg. Early analysis shows significant improvement in patients treated with ranolazine compared to placebo regarding number of angina episodes and nitroglycerin consumption per week, with consistent treatment effect across subgroups (ie, long-acting nitrate users vs non–long-acting nitrate users; men vs women; patients aged <64 years vs patients ≥65 years).

Trimetazidine inhibits one of the enzymes involved in fatty acid oxidation, which results in increased myocardial glucose oxidation. During ischemia, myocytes shift from glucose oxidation to fatty acid oxidation, creating ionic species within the cell. Trimetazidine is thought to protect the myocyte from these ionic and metabolic

![Figure 4. Ranolazine Improves Exercise Capacity in Combination with Standard Antianginal Therapies: The CARISA Study](image-url)

**Table 3. Pathophysiologic Effects of Ranolazine Versus Older Antianginal Drugs**

<table>
<thead>
<tr>
<th>Class</th>
<th>O₂ Supply</th>
<th>Heart rate</th>
<th>Arterial pressure</th>
<th>Venous return</th>
<th>Myocardial contractility</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-blockers</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>DHP CCB</td>
<td>↑</td>
<td>↑↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Non-DHP CCB</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Long-acting nitrates</td>
<td>↑</td>
<td>↑↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Late Na⁺ current inhibitors (ranolazine)</td>
<td>—</td>
<td>—/</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Except amlodipine.*
†Ranolazine: no direct effect but may prevent ischemia-related decline.
CCB = calcium channel blocker; DHP = 1,4 dihydropyridine.

Data from Gibbons et al; Boden et al; Kerins et al.

CARISA was a randomized, 3-group parallel, double-blind, placebo-controlled trial of 823 eligible adults with symptomatic chronic angina. Participants were randomly assigned to receive placebo or ranolazine 750 mg twice daily or 1000 mg twice daily. Patients were already taking atenolol 50 mg every day, diltiazem 180 mg every day, or amlodipine 5 mg every day. The main outcome measures were: change in exercise duration, time to onset of angina, time to onset of ischemia, nitroglycerin use, and number of angina attacks. Survival of the ranolazine-treated patients during the CARISA study or its associated long-term open-label study was 98.4% in the first year and 95.9% in the second year. Ranolazine also significantly reduced angina attacks and nitroglycerin use by approximately 1 per week compared to placebo (*P* <.02). *n* = 791.

*P* <.05.
*P* ≤.01.
*P* ≤.001 vs placebo.
BID = twice daily; CARISA = Combination Assessment of Ranolazine in Stable Angina.
changes. With established efficacy as monotherapy or in combination with beta blockers or calcium channel antagonists, the Trimetazidine in Poland study was designed to assess the efficacy and tolerability of trimetazidine in combination with metoprolol in patients with stable effort angina.44 The results showed significant improvement with trimetazidine compared to placebo in time to 1-mm ST-segment depression, total workload, time to onset of angina, maximum ST-segment depression, mean weekly number of angina attacks, mean weekly nitrate consumption, and grade of anginal pain—with no evidence of developing tolerance to trimetazidine.44 It is now widely used in Europe and India for angina.

A rho-kinase inhibitor is also being evaluated for stable angina. Rho-kinase is an intracellular signaling molecule involved in the vascular smooth muscle contractile response to agonists (eg, acetylcholine, angiotensin II, and norepinephrine). Rho-kinase phosphorylates and inactivates myosin regulatory light chain phosphatase, resulting in sustained contraction. Therefore, rho-kinase inhibition results in systemic and coronary vasodilation. A phase II, randomized, placebo-controlled clinical trial of fasudil, a rho-kinase inhibitor, in 84 patients with stable angina has recently been completed.45 The results showed that fasudil 80 mg (up to 3 times daily) significantly increased ischemic threshold and improved Seattle Angina Questionnaire scores. However, no significant differences were noted in CCS class, time to angina, or frequency of angina or nitroglycerin use between the 2 treatment groups. Because there was no change in rest or exercise heart rate and blood pressure, the effect of fasudil may be related to increase in blood flow rather than changes in oxygen demand.46 Clearly, further studies are needed.

Ivabradine is a sino-atrial node inhibitor. It is a selective, heart-rate lowering drug that inhibits the hyperpolarization-activated, mixed sodium/potassium inward I1 current, which is a primary SAN pacemaker current. Ivabradine is thought to work in stable angina by improving myocardial perfusion and reducing myocardial oxygen demand from the lowered heart rate. In a double-blind, placebo-controlled, randomized trial of 360 patients with chronic angina, ivabradine (2.5 mg, 5 mg, and 10 mg twice daily) or placebo was administered for 2 weeks, followed by an open-label 2- or 3-month extension on ivabradine (10 mg twice daily) and a 1-week randomized withdrawal to ivabradine (10 mg twice daily) or placebo. The study showed dose-dependent improvements in exercise tolerance and time to development of ischemia during exercise with ivabradine. Specifically, in the per-protocol population (n = 257), significant improvements in time to 1-mm ST-segment depression were observed in the 5- and 10-mg twice-daily groups (P < .005), in addition to time to limiting angina in the 10-mg twice-daily group (P < .05). Also, all exercise tolerance test parameters deteriorated in patients who received placebo during randomized withdrawal (all P < .02), but not in those still receiving ivabradine.46 Several other treatments are also under investigation for refractory angina. For example, gene therapy and use of recombinant proteins are used to deliver angiogenic cytokines (vascular endothelial growth factor, bFGF, aFGF, and FGF-4) to induce therapeutic myocardial angiogenesis.47-54 One study compared heparin to adenosine.55 Granulocyte macrophage colony-stimulating factor is being used to mobilize bone marrow stem cells to induce angiogenesis, with some initial promising results.56 Cell implantation therapy involves the direct intramyocardial percutaneous delivery of autologous bone marrow in patients with myocardial ischemia to induce angiogenesis. A feasibility study in 10 patients was successful with no periprocedural complications and no major cardiac events after 1 year of follow-up. Severity of angina in some patients and quality of life improved in all study patients. Myocardial perfusion of the target areas improved in 4 of 8 patients.58 Similarly, another study followed 15 patients with chronic refractory angina for 1 year who underwent transcoronary sinus administration of autologous bone marrow. No deaths or MI were observed during the follow-up. Mean angina measures improved significantly and perfusion imaging showed improvement in 12 of 15 patients, whereas coronary angiography showed more collateral vessels in 66% of the study patients.59

FUTURE DIRECTIONS IN ANTIANGINAL THERAPY

Despite various medical therapies and/or revascularization, some patients continue to experience angina. For these patients, management of their CCS in the primary care setting (where many patients are managed) appears to be suboptimal. In a cross-sectional analysis of more than 7000 veterans with self-reported coronary heart disease, 30% of the study participants experienced angina or took sublingual nitroglycerin more than twice a week. Of these
patients with frequent angina, 22% were not taking any antianginal medications, 33% were only taking 1 antianginal drug, and 50% of those taking antianginal drugs were not taking the recommended doses.\textsuperscript{60} Thus, while our current treatment options for recurrent angina are limited and/or are not being used at the recommended dosages, consensus on the role of newer treatments is pending. Thus, how do we best manage symptomatic patients?

Treatments for angina have evolved from focusing strictly on symptom relief to more disease-modifying approaches, and both have shown benefit in patients with CAD. We are now seeing data indicating that the effects of drug therapy (for symptom relief) and lifestyle changes are independent and additive.

In a study of 409 patients with CAD, Sdringola et al measured quantitatively the size and severity of perfusion defects by dipyridamole positron emission tomography at baseline and after 2.6 years of follow-up, with additional follow-up at 5 years.\textsuperscript{61} Patients received one of the following treatment regimens: “poor” treatment (no drugs or diet changes), “moderate” treatment (AHA diet and lipid-lowering drugs or strict low-fat diet), or “maximal” treatment (strict low-fat diet, exercise, and lipid-lowering drugs with specific lipid targets). The results showed “dose-dependent” effects on coronary events (5-year follow-up) and perfusion abnormalities (2.6-year follow-up). The percentage of patients experiencing coronary events after 5 years were 6.6%, 20.3%, and 30.6% in patients treated with maximal, moderate, and poor treatment regimens, respectively. Similarly, the size and severity of perfusion abnormalities increased for those receiving moderate and poor treatments, but decreased for those receiving maximal treatments ($P = .0001$ and $P = .003$, respectively).\textsuperscript{61} Although the study population was not randomized, the data strongly support a multidimensional approach to treating CAD, including pharmacologic treatments and lifestyle changes, as primary and secondary prevention.

Very recently, data have shown that more aggressive medical management provides advantages over less aggressive management, as demonstrated by less disease progression and fewer clinical events. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial tests whether PCI plus aggressive medical therapy (ie, lifestyle modification and antiplatelet, antianginal, blood pressure- and glucose-lowering, and lipid-modifying therapies) is superior to PCI alone. More than 2200 patients were randomized and will be followed for 5 years to compare the outcomes.\textsuperscript{62} Similarly, the Bypass Angioplasty Revascularization Investigation 2 Diabetes study uses a 2 x 2 factorial design to compare the effects of revascularization plus medical therapy versus medical therapy alone and insulin sensitizer-based diabetes treatment versus insulin-based treatment (with both achieving a similar goal of glycemic control). More than 2300 patients have been randomized and will be followed for 5 years. The study was undertaken because patients with diabetes respond less favorably to PCI and surgery compared to patients without diabetes.\textsuperscript{63}

**CONCLUSIONS**

The goals of antianginal therapy in CCS are to reduce myocardial oxygen supply-demand balance to improve ischemia/anginal symptoms and to provide secondary prevention therapy. Current therapies, although effective in many patients, insufficiently control symptoms/ischemia in others. New agents will hopefully provide additional choices due to mechanisms of action not previously available, but the importance of comprehensive management of MI, including symptom management, aggressive risk factor reduction, antiplatelet therapy, and lifestyle modifications, cannot be overstated.

**REFERENCES**


