Therapy of Stable Angina Pectoris
The Uncomplicated Patient
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Case study: A 62-year-old male smoker with type 2 diabetes mellitus and hypertension presents with a 4-month history of exertional chest pain. Physical examination shows a blood pressure of 152/90 mm Hg but is otherwise unremarkable. The ECG is normal, and laboratory tests show a fasting blood glucose value of 110 mg/dL, glycosylated hemoglobin 6.0%, creatinine 1.1 mg/dL, total cholesterol 160, LDL 120, HDL 38, and triglycerides 147 mg/dL. He exercises for 8 minutes, experiences chest pain, and is found to have a 2-mm ST-segment depression in the inferolateral leads at the end of exercise.

Pathophysiology and Natural History
Chronic stable angina (CSA) is defined as the predictable occurrence with exertion or emotional upset of pressure or a squeezing sensation in the substernal area of the chest and adjacent areas due to transient myocardial ischemia. Anginal equivalents (exertional breathlessness, fatigue, and/or nausea) may also occur with physical activity or emotional stress. Early onset of angina during exercise after a heavy meal or in cold weather is common. Symptoms may worsen in the presence of thyrotoxicosis, tachycardia, aortic stenosis, poorly controlled hypertension, or severe anemia.

An imbalance between myocardial oxygen demand and supply is the usual cause of angina resulting from myocardial ischemia. In most patients with CSA, the underlying cause is severe atherosclerotic narrowing (≥70%) of 1 or more coronary arteries, which paradoxically may constrict during exercise because of endothelial dysfunction (Figure). In addition, the coronary arteries in patients with CSA may also contain nonobstructive lesions; such non–flow-limiting plaques progress at variable rates, may remain "silent," and may rupture unpredictably, manifesting as an acute coronary syndrome (myocardial infarction [MI], unstable angina [UA], or ischemic sudden death [ISD]; Figure).

The annual death rate of patients with CSA is 1.6% to 3.2%. Principal determinants of prognosis include left ventricular ejection fraction (LVEF), the extent and severity of coronary artery disease (CAD), exercise duration or effort tolerance, and comorbid conditions. The ability to complete stage 2 or more of a Bruce exercise protocol and a normal LVEF denote a relatively good prognosis. Patients with an early and/or a strongly positive stress test result, those whose systolic blood pressure falls during or after exercise, and those with LV cavity dilation or a large ischemic burden during exercise imaging should be further stratified by diagnostic coronary angiography to exclude or confirm the presence of significant left main or severe triple-vessel disease, as well as to establish or exclude a diagnosis of CAD.

Treatment Strategies
The goals of therapy of CSA are (1) amelioration of anginal symptoms and improved angina-free exertion capability and (2) prevention or reduction of subsequent acute MI, UA, or ISD.

While initiating treatment, the physician must also decide whether further investigations (eg, coronary angiography) are indicated. Stress echocardiographic or radionuclide studies are not usually indicated in subjects who can exercise and who have a normal ECG. Such expensive tests should be reserved for patients who either cannot exercise or have baseline ECG abnor-
SEVERE OBSTRUCTIVE LESIONS

Prevents an increase in coronary blood flow during exercise

Paradoxical constriction due to endothelial dysfunction may occur

Reduced Coronary Blood Flow (myocardial oxygen supply)

↑Myocardial Oxygen Demand

Reversible Myocardial Ischemia

Anginal Pain or Angina equivalent

LV Dysfunction (Dyspnea)

ST-segment Changes (ST segment depression)

Metabolism Changes Increased lactate production

STRESS (Exercise)

↑HR

↑BP

↑Contractility

NON-OBSTRICTIVE LESIONS

Silent Progression

Atheroma Expansion

Endothelial Erosion

Platelet Aggregation and Deposition ± Thrombosis

Unstable Angina

Asymptomatic (silent)

Asymptomatic (silent)

Acute MI

Sudden Death

Pathophysiological mechanisms of myocardial ischemia and angina and of adverse outcomes in stable angina (modified with permission from Thadan3). HR indicates heart rate; BP, blood pressure.

malities that preclude interpretation of ST-segment data. Resting LVEF should be determined by either radionuclide ventriculography or quantitative echocardiography; a normal LVEF indicates a good prognosis. Although high levels of the biomarkers high-sensitivity C-reactive protein or brain natriuretic peptide indicate a poor prognosis, at present, routine measurement is not recommended.4 The patient in our case study has well-controlled diabetes mellitus; however, his blood pressure and dyslipidemia are not well controlled. His exercise capacity, despite a 2-mm ST-segment depression, suggests a relatively good prognosis.

Strategies to Control Anginal Symptoms

Antianginal Medications

β-Blockers, long-acting organic nitrates, and calcium channel blockers (CCBs) are effective antianginal and anti-ischemic agents, with β-blockers being the most potent anti-ischemic and antianginal drugs.2−4,9−11 There is no evidence that any of these drugs prolong life or reduce the incidence of MI in patients with CSA.4

The patient in our case study has no contraindications to β-blocker therapy, has high blood pressure, and, in addition to exercise-induced angina, experiences occasional episodes of angina induced by anxiety. Therefore, the initial drug of choice is a β-blocker; these drugs blunt exercise-induced increases in heart rate and blood pressure and control exertionally and emotionally induced angina.2−4 An alternative to a β-blocker would be a CCB or a long-acting nitrate. Continuous therapy with nitrates produces rapid tolerance. Intermittent therapy, with daily nitrate-free intervals, prevents clinical nitrate tolerance.3,4

Optimal doses of antianginal drugs should be used, and often 2 agents are necessary.2−4 If the patient does not respond adequately to monotherapy, combination therapy of a β-blocker with a long-acting dihydropyridine CCB or a long-acting nitrate should be tried.

Therapy with 3 drugs is often used in clinical practice, but there are few objective data to support the idea that treatment with 3 drugs is superior to that with 2 agents.2−4 It is important to use the maximum dose(s) of antianginal agent(s) that the patient can tolerate.

Coronary Artery Revascularization

An initial trial of antianginal drugs is indicated for the majority of patients with stable angina. Revascularization procedures should be considered for patients who do not respond adequately to optimal antianginal therapy; for those who lead an active lifestyle; for subjects with a large burden of ischemia; and for those with severe CAD, especially with decreased LV function.4−7 Relief of angina after revascularization is greater than with medical therapy, but often angina recurs after percutaneous coronary intervention or coronary artery bypass grafting (CABG).

Percutaneous coronary revascularization (angioplasty with or without stenting) and CABG surgery relieve angina in 80% to 90% of patients. However, compared with medical therapy, these procedures do not prolong life or reduce the incidence of MI2−4,9−11 except in patients with severe left main CAD and
in those with 2- or 3-vessel disease with decreased LV function, for whom CABG surgery (in retrospective sub-group analyses of the published data) has demonstrated improved survival.12

Clinical restenosis occurs in 20% to 30% of patients after angioplasty with bare metal stents; restenosis rates are higher in patients with diabetes. Restenosis is considerably lower with drug-coated stents (10%), but long-term outcome data, especially in those patients with diabetes, are not available, and late subacute thrombosis remains a concern.4 Occlusion of venous grafts occurs in >50% of grafts by 10 years after CABG surgery; arterial conduits are thus generally preferred.12

**Strategies to Reduce Adverse Clinical Outcomes (MI, UA, and ISD)**

Some data suggest that optimal medical therapy compared with percutaneous coronary revascularization in CSA patients with 1- or 2-vessel disease may be associated with lower rates of serious clinical adverse outcomes.13

Although antianginal drugs and revascularization procedures provide symptomatic relief, they do not reduce the incidence of ISD, MI, or UA, which occur frequently in patients with CSA.3,5,7,9-11 Adverse outcomes occur at random and are typically caused by disruption of nonobstructive atherosmas.5 To reduce these undesirable clinical outcomes, vasculoprotective strategies must be used in addition to antianginal drugs.

**Smoking Cessation**

Smoking cessation is critical for all patients with CSA and reduces the risk of coronary artery mortality by up to 50% in 1 year.14 It also has a positive effect on exercise performance in CSA.

**Aspirin**

Daily aspirin is recommended for all patients with CSA, unless there is a definite contraindication, such as aspirin allergy or a history of an upper gastrointestinal (GI) hemorrhage. In patients with CSA, daily aspirin (325 mg) reduced cardiovascular mortality and morbidity with an absolute reduction of 12 additional deaths for every 1000 patients treated during a 15-month period.15 Other data have shown beneficial effects of daily aspirin for patients with acute MI and UA.3,4 Thus, aspirin is an inexpensive and effective way to reduce adverse clinical outcomes in CSA. Low-dose aspirin (81 to 100 mg) is generally recommended.

**Clopidogrel**

There are no outcome studies with clopidogrel in patients with CSA who have not undergone percutaneous coronary revascularization with stents. Current guidelines recommend the use of clopidogrel in patients with known allergic reactions to aspirin or upper GI bleeding. However, in a study of patients with a history of upper GI bleeding due to ulcers, the recurrence of bleeding was 12 times greater during clopidogrel treatment compared with treatment with aspirin and a proton pump inhibitor (PPI).16 Treatment with clopidogrel plus a PPI was not evaluated, and whether this combination treatment would result in similar, better, or worse clinical outcomes compared with treatment with aspirin plus a PPI remains to be studied. Until such data are available and given the cost considerations of clopidogrel, if cardiac prophylaxis is necessary in patients with a history of an upper GI bleed, 81 mg aspirin with twice-daily administration of a PPI should be used.16

**Lipid-Lowering Therapy**

No specific trials with lipid-lowering agents have been conducted in patients with CSA. However, in the Scandinavian Simvastatin Survival Study, many patients had CSA and experienced a reduction in angina as well as in major CAD events.17 Furthermore, most of the major statin randomized, controlled trials have demonstrated a decrease in on-trial revascularization, clearly suggestive of a decrease in chest pain during the study.

In the British Heart Protection Study of 20 536 patients >55 years old and with a history of coronary disease, diabetes, or a major cardiovascular risk factor and a fasting total cholesterol level >135 mg/dL, a fixed dose of simvastatin (40 mg) resulted in a significant reduction in total mortality, vascular morbidity, and the need for revascularization procedures.18 The benefits of simvastatin were seen in both men and women and in the elderly, irrespective of baseline LDL levels, which in many patients were <100 mg/dL. Current guidelines recommend a target fasting LDL cholesterol level of <100 mg/dL in patients with CSA.11 The most recent NCEP-ATP III directive suggests a target of <70 mg/dL for high-risk CAD patients.19

In men with CAD, HDL <40 mg/dL, and LDL <130 mg/dL, treatment with gemfibrozil reduced cardiovascular mortality and morbidity.20 However, gemfibrozil should not be prescribed with a statin; fenofibrate is the recommended fibrate for use with a statin. Combination treatment with a statin and fibrates or nicotinic acid has not been adequately studied in patients with CSA. The combination of a statin plus a fibrate should be used with caution because the incidence of rhabdomyolysis is increased. There are no outcome studies evaluating the beneficial effects of this combination therapy.

The patient in our case study has a low HDL and a slightly elevated LDL level. Overwhelming outcome data confirm that a statin decreases adverse outcome events, no matter the level of LDL-C, and therefore, this patient should be treated with a statin. However, initial treatment with a fibrate alone is an acceptable alternative if he wishes not to be on statin therapy.

**Treatment of Hypertension**

We recommend aggressive control of blood pressure to <135/85 mm Hg in hypertensive patients and to <120/80 mm Hg in those with diabetes mellitus. Lowering blood pressure may reduce stroke rates by 40% to 52% and car-
diovascular morbidity by 18% to 20%.21

Exercise Training
A small study from Europe reported that supervised daily exercise training for up to a period of 1 year improved clinical outcomes compared with intervention by percutaneous coronary revascularization.22 Patients with CSA should be encouraged to exercise daily to their anginal threshold.

Angiotensin-Converting Enzyme Inhibitors
Angiotensin-converting enzyme (ACE) inhibitors should be used in all post-MI patients with CSA. Patients with CSA who have diabetes, hypertension, proteinuria, or chronic renal disease or those with impaired LV systolic function (LVEF <40%) should also be treated with an ACE inhibitor. In older patients with CAD, routine use of ACE inhibitors has been recommended on the basis of the positive results of the HOPE and EUROPA trials.23 However, in the PEACE trial, in patients with documented CAD and an LVEF ≥40%,trandolapril, a tissue-specific ACE inhibitor, was not superior compared with placebo.24 Furthermore, in the ALLHAT study, ACE inhibitors were not superior to initial treatment with a diuretic in hypertensive patients who had increased cardiovascular risk factors or diabetes.25 Therefore, there is room for disagreement regarding routine ACE inhibitor therapy in CSA patients who have not had an MI, are diabetic, have proteinuria or chronic renal disease, or have an LVEF <40%.

β-Blockers
β-Blockers have been shown to improve survival and reduce hospitalization in heart failure patients with an LVEF ≤40% and in survivors of acute MI. These drugs should be used as first-line therapy in patients with CSA who have reduced LV systolic function, provided that such patients are on background treatment with ACE inhibitors. Practice guidelines recommend that β-blockers are the first choice of therapy for uncomplicated CSA.4,7,11

Alcohol Intake
There are no placebo-controlled studies showing beneficial effects of alcohol on cardiovascular morbidity and mortality in patients with CSA. However, alcohol consumption in moderation (up to 2 glasses of wine per day) has been shown to reduce the incidence of MI in multiple observational studies.

Recommendations
The majority of patients with CSA can be managed medically; the suggested treatment is outlined in the Table.

Disclosure
Dr Abrams has a modest ownership interest in Merck and Pfizer. Dr Thadani has served on the speakers’ bureaus of and/or received honoraria from Merck, GlaxoSmithKline, AstraZeneca, Pfizer, Bristol Myers Squibb, Bayer, and Eli-Lilly, and has served as a consultant to and/or on the advisory boards of Pfizer, Bristol Myers Squibb, Bayer, Berlex, GlaxoSmithKline, and Chugai. The University of Oklahoma receives research grants from AstraZeneca, Sanofi-Synthelabo, Pfizer, Aventis, Berlex, and Bayer for studies for which Dr Thadani acts as local principal investigator. Drs Abrams and Thadani are on the Cardiovascular Therapeutics (CVT) advisory board.

References
14. Modla with permission from Thadani.34 *Triple therapy is not always superior to treatment with combination treatment with 2 agents.