CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Chronic Stable Angina

E. Magnus Ohman, M.B.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 73-year-old farmer with a 15-month history of stable angina presents for consultation. He has curtailed his farming activity to avoid chest discomfort, for which he uses nitroglycerin (0.4 mg sublingually) approximately 3 times per month. His heart rate is 59 beats per minute, and his blood pressure is 132/72 mm Hg. He had unstable angina 12 years earlier, and a drug-eluting stent was implanted in his left anterior descending artery; no other obstructive coronary artery disease was noted at that time. His medications include aspirin, lisinopril (20 mg daily) for hypertension, and atorvastatin (40 mg daily). How should this case be evaluated and managed?

THE CLINICAL PROBLEM

Chronic stable angina pectoris is a common manifestation of coronary artery disease, which is the leading cause of death worldwide. An estimated 15.5 million American adults have chronic coronary artery disease, and more than 7 million have angina.[1] Angina is the initial manifestation in approximately half of all patients who present with coronary artery disease. The presence of chronic angina approximately doubles the risk of major cardiovascular events.[2,3] Studies with 1 to 9 years of follow-up data have shown that among patients with angina, factors associated with an increased risk of myocardial infarction or death include advanced age, severe forms of angina, coexisting illnesses (including chronic kidney disease and diabetes), abnormal heart function, and the inability to perform a stress test.[4-6] Patients with angina also have substantial rates of complications,[7] with associated increases in health care expenditures.[6]

Angina is traditionally defined as substernal chest discomfort (pain or tightness) of less than 10 minutes' duration. This discomfort is provoked by exertion or emotional stress and is relieved by rest or by administration of nitroglycerin. In this typical form, angina is suggestive of obstructive coronary artery disease,[8,9] but other common conditions such as anemia and valvular heart disease may mimic typical angina.[10] Angina may also be atypical, manifesting with less characteristic symptoms such as dyspnea or jaw pain; atypical presentations are more common among women and elderly persons than among men and younger persons. The severity of angina can be classified with the use of the Canadian Cardiovascular Society (CCS) scale (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[8,9]

STRATEGIES AND EVIDENCE

Establishing a diagnosis of chronic angina should be pursued in parallel with managing symptoms and initiating preventive therapies. Preventive therapies are

From the Program for Advanced Coronary Disease, Division of Cardiology, Duke University and Duke Clinical Research Institute, Durham, NC. Address reprint requests to Dr. Ohman at Duke University Medical Center, Box 3126 DUMC, Durham, NC 27710, or at ohman001@mc.duke.edu.

N Engl J Med 2016;374:1167-76.
DOI: 10.1056/NEJMcp1502240

An audio version of this article is available at NEJM.org

KEY CLINICAL POINTS

CHRONIC STABLE ANGINA

- In patients with suspected angina, it is important not only to make a diagnosis, but also to assess the prognosis.
- Management of angina should include lifestyle changes and pharmacotherapy to reduce cardiovascular risks, including those associated with high blood pressure and elevated lipid levels.
- Standard antianginal medications include beta-blockers, long-acting nitrates, and calcium-channel blockers; ranolazine is a new agent approved by the Food and Drug Administration for angina.
- Relief of angina should be assessed again within 2 weeks after the initiation of therapy.
- An invasive strategy is a reasonable option in patients who do not have a response to medical therapy.
- Physiological assessment of the target lesion is useful to guide decisions regarding revascularization.

warranted even without a firm diagnosis and should focus on blood-pressure control and cholesterol management. The recent Systolic Blood Pressure Intervention Trial (SPRINT) showed that the risk of the primary composite outcome (myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes) was 25% lower among participants who were assigned to a target systolic blood pressure of less than 120 mm Hg than among those who were assigned to a target systolic blood pressure of less than 140 mm Hg.[11]

Furthermore, a recent study suggests that addressing all risk factors (by encouraging smoking cessation and reducing non–high-density lipoprotein cholesterol, triglyceride, blood-pressure, and blood sugar levels) in patients who have diabetes and stable coronary artery disease is associated with reduced mortality.[12] This study highlights the importance of treating multiple risk factors adequately.

EVALUATION

The first step in the evaluation of chronic angina is to assess the likelihood of clinically significant coronary artery disease on the basis of the following factors: the character of the chest pain (typical, atypical, or nonanginal); the patient's age, sex, and smoking status; the presence of diabetes or hyperlipidemia; and Q-wave or ST-T wave changes on electrocardiography (ECG).[8,9] Severe angina, advanced age, female sex, smoking, coexisting illnesses, and abnormal heart function on ECG have been correlated with the presence of clinically significant coronary artery disease as assessed with the use of standard angiography.[13,14] More recent studies that use coronary computed tomographic angiography (CTA) suggest that prediction based on these risk factors, however, may substantially overestimate the prevalence of coronary artery disease.[15] This discrepancy is not surprising, since the studies that established these pretest probability criteria were performed in an era of high smoking rates and limited prevention therapies.

Several tests that are used to diagnose coronary artery disease can also provide prognostic information (Table 1). The standard exercise ECG stress test is the least sensitive test for coronary artery disease and cannot define its extent, but the duration of exercise, presence of ST-segment changes, and occurrence of angina confer prognostic information.[16]

As compared with the routine exercise ECG stress test, stress tests that involve imaging typically have a superior ability to detect coronary artery disease without an appreciable loss of specificity.[9] The exercise ejection fraction is one of the most important prognostic variables in patients with coronary artery disease.[17] Imaging stress tests allow evaluation of left ventricular performance and assessment of the extent of ischemia during stress.

U.S. guidelines have recommended the use of the exercise ECG stress test as a first-line test, although in practice it is used infrequently.[8] A recent review article recommends the use of the exercise ECG stress test to detect coronary artery disease in low-risk patients (young patients with normal ECG findings and good exercise tolerance).[18] An inability to perform an exercise test is associated with a poor cardiac prognosis.[8,9] Pharmacologic stress testing with imaging is useful for determining the diagnosis and assessing the prognosis in patients who cannot exercise.[19]

CTA can also be used to evaluate patients with suspected coronary artery disease, and it can effectively rule out obstructive coronary artery disease, but it may overestimate the extent of this disease.[20,21] In a large randomized trial

Table 1. Tests to Diagnose and Assess the Prognosis of Clinically Significant Coronary Disease.*

Test	Sensitivity	Specificity	Provides Prognostic Information†	Considerations
	percent			
Exercise stress test				
ECG	45–50	85–90	Yes	Easy to perform; can be used only with normal baseline ECG findings
Echocardiography	80–85	80–88	Yes	Cannot be used in patients with left bundle-branch block or right bundle-branch block; interpretation may be limited in overweight patients
Nuclear test	73–92	63–87	Yes	Radiation exposure
Pharmacologic stress test				
Dobutamine				
Echocardiography	79–83	82–86	Yes	Limited to patients who cannot exercise; can induce arrhythmias
MRI	79–88	81–91	Yes	Limited use in overweight patients and those with metal implants; can induce arrhythmias
Adenosine				
Echocardiography	72–79	92–95	Yes	Cannot be used in patients with left bundle-branch block or right bundle-branch block; interpretation may be limited in overweight patients; can cause wheezing and heart block
Nuclear test	90–91	75–84	Yes	Radiation exposure; can cause wheezing and heart block
MRI	67–94	61–85	Yes	Limited use in overweight patients and those with metal implants; can cause wheezing and heart block
PET	81–97	74–91	No	Limited availability; can cause wheezing and heart block

* Modified from Montalescot et al.[9] ECG denotes electrocardiography, MRI magnetic resonance imaging, and PET positron-emission tomography.
† Most tests evaluate the risk of death, myocardial infarction, or both to assess prognosis.

comparing CTA with functional testing (with the specific type of stress testing chosen by the provider) in patients with symptoms that suggested coronary artery disease,[22] the primary composite outcome (death, myocardial infarction, hospitalization for unstable angina, or a major procedural complication) occurred in 3.3% of the patients in the CTA group and in 3.0% of the patients in the functional-testing group during 25 months of follow-up (adjusted hazard ratio, 1.04; 95% confidence interval, 0.83 to 1.29). A secondary end point of a composite of the primary end point plus invasive angiography showing no obstructive coronary artery disease occurred in fewer patients in the CTA group than in the functional-testing group. However, overall radiation exposure was higher in the CTA group than in the functional-testing group because a third of the patients in the latter group had no exposure to radiation. These findings favor stress testing as the first diagnostic strategy, reserving CTA to rule out coronary artery disease when a false positive test is suspected.

MANAGEMENT

In patients in whom stable angina is suspected, preventive therapies, including aspirin, should be started immediately if they are not already in use.[8,9] A meta-analysis of primary-prevention trials showed that the rate of cardiovascular events was 18% lower among persons who took aspirin than among controls (P<0.001), owing predominantly to a 23% lower rate of myocardial infarction among those who took aspirin. However, aspirin did not have a significant effect on the rate of death from cardiovascular causes. Among patients who took aspirin, as compared with controls, the rates of intracranial bleeding (0.04% vs. 0.03%) and gastrointestinal bleeding (0.10% vs. 0.07%) were modestly higher, although these events were rare.[23]

Blood pressure should be reduced to below 120/85 mm Hg if possible,[11] and a moderate-to-high-intensity statin (that reduces low-density lipoprotein [LDL] cholesterol levels by >30% from pretreatment levels) should be used. Randomized, placebo-controlled trials have suggested that

high-intensity statins (that reduce LDL cholesterol levels by >50%) can reduce episodes of angina[24] and improve exercise tolerance[25] in patients with chronic angina who are already receiving antianginal therapy. Furthermore, a randomized trial comparing high-intensity statin therapy with percutaneous coronary intervention (PCI) in patients with stable coronary artery disease showed a lower rate of ischemic cardiac events among the patients who received atorvastatin therapy than among those who underwent PCI, although between-group differences did not meet prespecified criteria for statistical significance.[26]

Changes in lifestyle behaviors should also be recommended. These changes include weight loss in overweight or obese patients, dietary changes to reduce fat and sugar intake, and smoking cessation.[8,9]

Antianginal therapy should be initiated as soon as the diagnosis is suspected. The goal of therapy is to reduce angina symptoms and exercise-induced ischemia.[27] Sublingual nitrates should be prescribed to all patients with suspected angina, and patients should be instructed in how to use them and told to seek medical attention if symptoms are not relieved after they have used 3 such tablets. Long-term antianginal therapies should also be initiated, with attention to the patient's resting heart rate and blood pressure.[27] A suggested approach for the use of various types of antianginal therapies is shown in Figure 1.[27]

Standard Antianginal Therapies

In patients with stable angina, beta-blockers, calcium-channel blockers, and long-acting nitrates reduce angina similarly and appear to have a similar safety profile (except for short-acting calcium-channel blockers).[27-29] All these agents were approved before more formal evaluation of efficacy for angina was implemented by the Food and Drug Administration.[30]

The choice of initial standard antianginal therapy should be individualized, taking into account the desired physiological effect and any coexisting conditions and side effects in the patient.[27] Beta-blockers have been advocated as primary therapy for angina because of data indicating a reduction in mortality when they are used after myocardial infarction.[8] However, two observational studies showed no significant association between beta-blocker use and mortality among patients with chronic coronary artery disease, although a possible reduced risk of recurrent myocardial infarction was observed with beta-blocker use.[31,32]

Guidelines have recommended that the most appropriate medical therapy for angina is a combination of two antianginal therapies in different drug classes (beta-blockers, calcium-channel blockers, or long-acting nitrates); this combination therapy has been recommended because of synergistic physiological effects (Table 2).[8,9] However, randomized trials have not shown that such combination therapy is more effective in reducing ischemia or angina symptoms than beta-blocker monotherapy.[27,33]

Doses of antianginal therapies should be increased, as needed, to achieve symptom control and improvements in heart rate and blood-pressure levels. If symptoms are not relieved within 2 weeks after the initiation of therapy, cardiac catheterization may be indicated.

Emerging Antianginal Therapies

Although all standard antianginal therapies have a physiological effect (i.e., they affect heart rate or blood pressure), three emerging therapies (i.e., therapies that are becoming more widely used) that have a physiological effect and four that have a direct effect on myocardial metabolism are also available worldwide.[7] Three of these therapies are available in the United States and are described below (Table 2).[27]

Ranolazine is a metabolic antianginal agent that is approved for the treatment of chronic angina. It diminishes myocardial ischemia by reducing calcium overload caused by inhibition of the late sodium current.[34] It does not affect heart rate or blood pressure[35] and thus may be considered as a first-line agent for patients with slow heart rate or low blood pressure. Among patients with stable angina who could perform an exercise ECG stress test, exercise duration was longer and angina episodes were fewer among patients who received ranolazine therapy than among those who received placebo, without the use of background therapy[36] or standard antianginal therapy.[37] It has been evaluated in two studies of outcomes in patients with angina, with mixed results. In a study involving patients who had diabetes and angina, the weekly frequency of angina was 12% lower over time with ranolazine than with placebo (P=0.008), and the

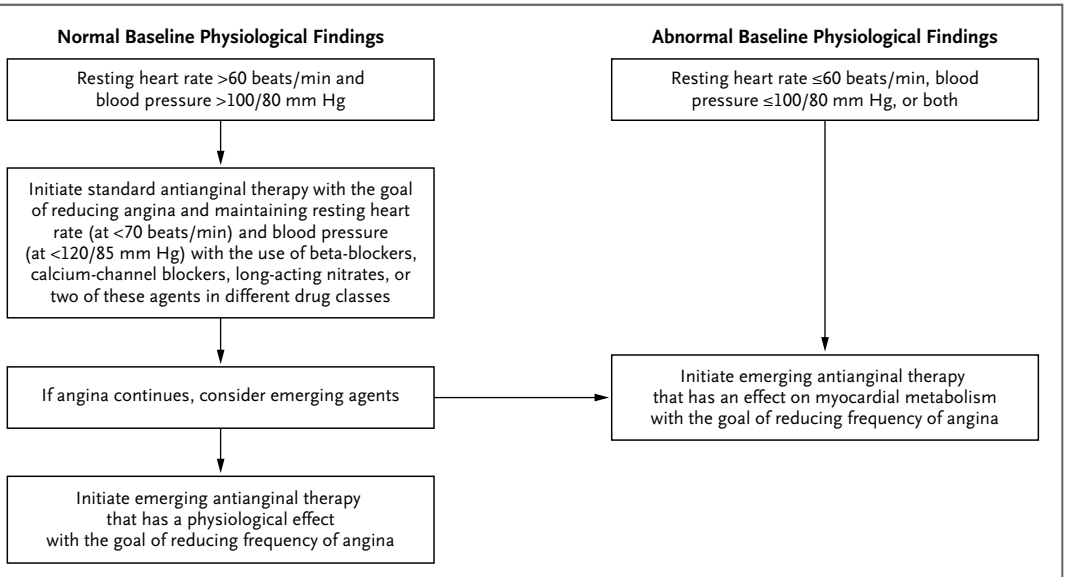

Figure 1. Approach to the Use of Antianginal Therapy, According to Baseline Physiological Findings.

Standard antianginal agents that have a physiological effect include beta-blockers, calcium-channel blockers, and long-acting nitrates. Emerging antianginal agents that have a physiological effect include ivabradine, which is used only in patients with heart failure. Emerging agents that affect myocardial metabolism include ranolazine and possibly allopurinol. Outside the United States, emerging agents that have a physiological effect include nicorandil and molsidomine; emerging agents that affect myocardial metabolism are trimetazidine and perhexiline maleate. Adapted from Husted and Ohman.[27]

use of nitrates was 19% lower with ranolazine than with placebo (P=0.003) during an 8-week period.[38] In a recent trial involving patients with chronic angina who had incomplete revascularization after PCI, ranolazine did not result in a significantly lower need for repeat revascularization or hospitalization for ischemia[39] or in fewer angina symptoms at 1 year.[40] Patients who received ranolazine were more likely than patients who received placebo to discontinue therapy, and the nonadherence rate (27% at 1 year) may have contributed to the lack of observed efficacy.

Side effects of ranolazine are dose-dependent and include dizziness (in 5% of patients who receive it), nausea (in 2%), and constipation (in 2%).[34] Ranolazine prolongs the QT interval in a dose-dependent manner[34]; however, no increase in significant arrhythmias has been observed with its use in multiple safety studies.[27] In a trial involving patients with non–ST-elevation acute coronary syndrome,[41] significant arrhythmias were less common in the ranolazine group than in the placebo group; these findings suggest that prolongation of the corrected QT (QTc) interval is not a safety concern. Still, caution is warranted regarding prescription of other drugs that cause QT-interval prolongation, as well as regarding other drug–drug interactions (Table 2).

Ivabradine is a selective heart-rate–lowering (physiological) agent that inhibits the *If* current in the pacemaker cells in the sino-atrial node.[27] It is approved for treatment of heart failure with a goal of preventing hospitalization in patients who have an increased heart rate despite adequate beta-blocker therapy. It has also been reported to be effective in improving exercise duration in patients with chronic angina who are not receiving background therapy.[27,41] However, the results of a large randomized trial involving patients who had both stable coronary artery disease without heart failure and a resting heart rate of 70 beats per minute or more have aroused concern about the use of ivabradine for chronic angina.[42] In a prespecified subgroup of approximately 12,000 patients with chronic angina (class >II on the CCS scale, which ranges from I to IV, with higher classes indicating greater limitations on physical activity owing to angina), the rates of death and nonfatal myocardial infarction were higher among patients who received ivabra-

Table 2. Antianginal Agents.*

Agent	Common Side Effects	Contraindications	Potential Drug Interactions
Agents that have a physiological effect			
Short-acting and long-acting nitrates	Headache, flushing, hypotension, syncope and postural hypotension, reflex tachycardia, methemoglobinemia	Hypertrophic obstructive cardiomyopathy	Phosphodiesterase type 5 inhibitors (sildenafil and similar agents), alpha-adrenergic blockers, calcium-channel blockers
Beta-blockers	Fatigue, depression, bradycardia, heart block, bronchospasm, peripheral vasoconstriction, postural hypotension, impotence, masked signs of hypoglycemia	Low heart rate or heart conduction disorder, cardiogenic shock, asthma, severe peripheral vascular disease, decompensated heart failure, vasospastic angina; use with caution in patients with COPD (cardioselective beta-blockers may be used if patient receives adequate treatment with inhaled glucocorticoids and long-acting beta-agonists)	Heart-rate–lowering calcium-channel blockers, sinus-node or AV conduction depressors
Calcium-channel blockers			
Heart-rate–lowering agents	Bradycardia, heart conduction defect, low ejection fraction, constipation, gingival hyperplasia	Cardiogenic shock, severe aortic stenosis, obstructive cardiomyopathy	CYP3A4 substrates (digoxin, simvastatin, cyclosporine)
Dihydropyridine	Headache, ankle swelling, fatigue, flushing, reflex tachycardia	Low heart rate or heart rhythm disorder, sick sinus syndrome, congestive heart failure, low blood pressure	Agents with cardiodepressant effects (beta-blockers, flecainide), CYP3A4 substrates
Agent that affects myocardial metabolism			
Ranolazine	Dizziness, constipation, nausea, QT-interval prolongation	Liver cirrhosis	CYP3A4 substrates (digoxin, simvastatin, cyclosporine), drugs that prolong the corrected QT interval

* Modified from Husted and Ohman.[27] A full list of prescribing information is provided in the Food and Drug Administration–approved label of each agent. COPD denotes chronic obstructive pulmonary disease, and CYP3A4 cytochrome P-450 3A4.

dine than among those who received placebo (7.6% vs. 6.5%, P=0.02). Although no clear explanation was provided for these findings, ivabradine should not be used to treat angina in the absence of heart failure.[27]

Allopurinol, a xanthine oxidase inhibitor that is used to prevent gout, has also been proposed as an antianginal metabolic agent. Potential mechanisms include decreased demand for myocardial oxygen and improved vascular endothelial function.[27] In a study involving 65 patients with chronic angina, the time to ischemia with an exercise ECG stress test was longer among persons who received high-dose allopurinol than among those who received placebo.[43] Because of limited clinical data, U.S. guidelines do not recommend allopurinol for the treatment of angina,[8] but it is recommended in the European guidelines.[9]

Invasive Treatment Strategies

Although invasive angiography has become a very safe diagnostic procedure, particularly with radial access, serious complications occasionally occur.[44] Visual interpretation of the severity of the coronary lesions identified varies considerably,[45] and determination of severity by visual interpretation can lead to overdiagnosis and overtreatment. The decision about whether to perform angiography should therefore be separated from the decision about whether to revascularize.[46]

The measurement of fractional flow reserve, a hemodynamic assessment of the severity of a lesion by measurement of the pressure difference across a lesion in a patient with drug-induced hyperemia, is useful in defining the clinical significance of borderline lesions.[46] In randomized trials that involved the use of this test, clinical outcomes were better when only lesions with a

fractional flow reserve of 0.80 or less were treated with PCI than when treatment was based on visual assessment.[46,47] A patient-level meta-analysis of several randomized trials suggested that routine use of fractional flow reserve during diagnostic angiography could reduce the need for revascularization (predominantly PCI) by 50%, with a relative reduction of 20% in rates of death, myocardial infarction, and subsequent revascularization procedures.[47]

The decision regarding whether and how to revascularize (with PCI or coronary-artery bypass grafting [CABG]) or whether to continue medical therapy should ideally involve a heart-team approach[8,9] incorporating input from interventional cardiologists and cardiothoracic surgeons. The decision should take into account clinical risk factors, characteristics of the lesion, and hemodynamic factors, and it may be informed by the use of validated risk scores to refine the selection of patients for PCI versus CABG.[46] In patients selected for revascularization, the goal should be complete revascularization if possible; patients with more extensive coronary disease derive more benefit from CABG.[46] Figure 2 shows an algorithm with associated recommendations by the American College of Cardiology and the American Heart Association, and by the European Society of Cardiology.[8,9,46]

Randomized trials involving patients who were eligible for either medical therapy or revascularization have shown that PCI is effective in reducing angina in patients with chronic angina,[46,48] but it does not result in a lower risk of death or myocardial infarction than that with medical therapy.[49] These observations suggest that medical therapy alone is a reasonable starting point if it has an acceptable side-effect profile. Revascularization should be considered for patients who have ongoing angina despite adequate medical therapy; this group includes as many as 50% of patients with chronic angina.[46] For patients who have angina and are treated medically without revascularization, referral to a structured cardiac rehabilitation program should be considered.[8]

AREAS OF UNCERTAINTY

Data from large randomized outcome trials involving patients with chronic angina are limited. The ongoing International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA; ClinicalTrials.gov number, NCT01471522) is comparing conservative management (medical therapy without angiography) with invasive management (angiography and revascularization) in patients with chronic angina and at least moderate ischemia on stress testing.[50] There are few large randomized trials of medical therapies for chronic angina to inform long-term safety and efficacy[27]; the role of allopurinol and other emerging antianginal therapies remains uncertain.

GUIDELINES

American and European guidelines have been published to guide the diagnosis and management of chronic angina.[8,9] Although these guidelines share many common approaches, they differ in several ways. The European guidelines[9] are less prescriptive regarding the type of stress test to pursue, whereas U.S. guidelines[8] recommend an exercise ECG stress test as the first-line stress test. U.S. guidelines make specific recommendations regarding the survival benefit of CABG over PCI for extensive coronary disease, whereas European guidelines recommend PCI more broadly than do U.S. guidelines for chronic angina.[8,9,46]

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has stable angina and known coronary artery disease. Since a long time has passed between his prior PCI and current stable symptoms, I would begin by prescribing antianginal therapy. I would not prescribe beta-blockers, given his slow resting heart rate. A long-acting nitrate would be a reasonable first-line therapy. Maintaining blood-pressure control with a higher dose of lisinopril and continued statin therapy is warranted. Stress testing is also warranted, since the extent and distribution of ischemia would guide further decision making. If there was ischemia in the proximal left anterior descending coronary artery distribution or reduced heart function, I would favor cardiac catheterization with consideration of revascularization, depending on the anatomical features. Stress test results that show low risk are associated with a good prognosis and

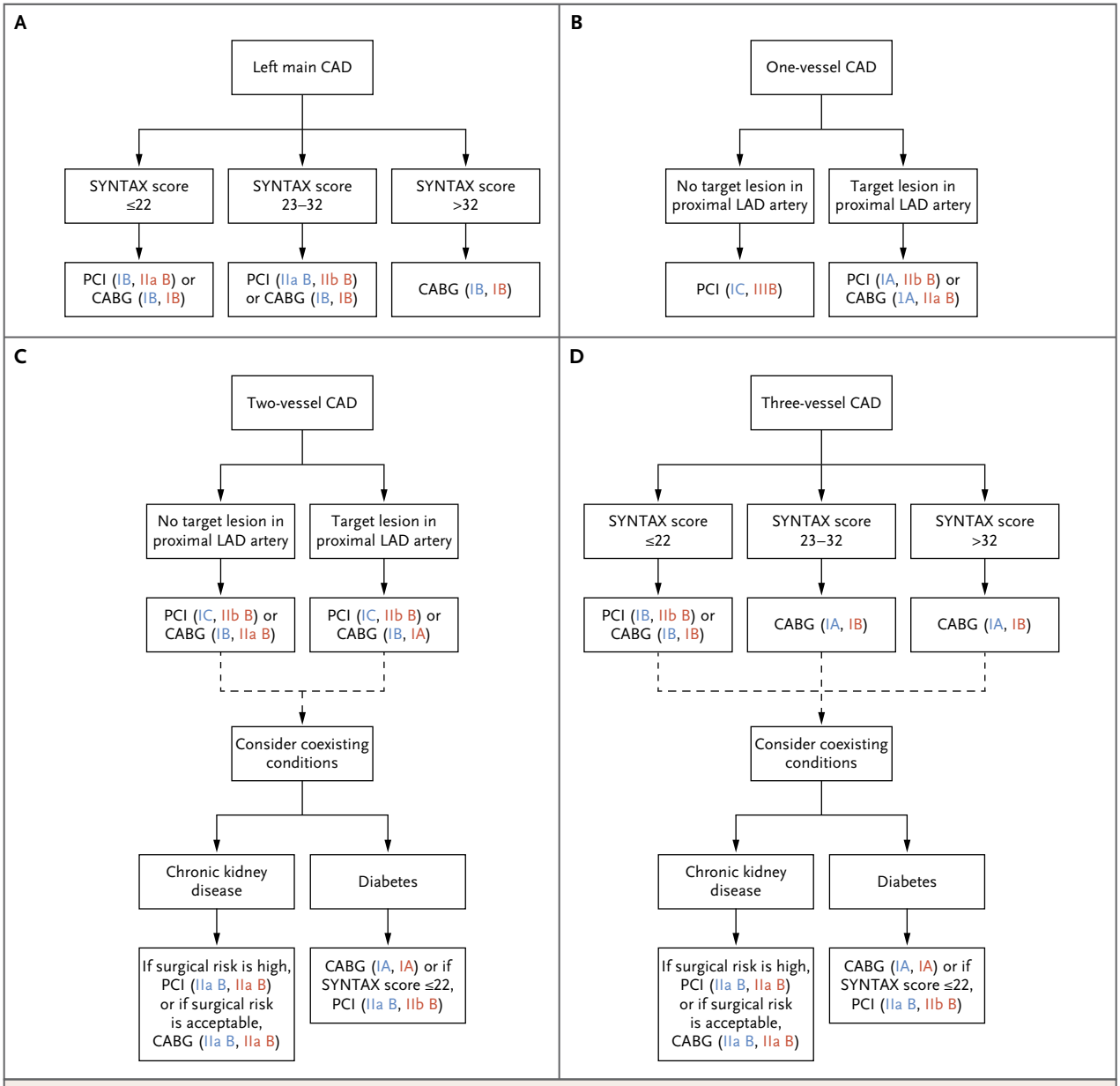

Figure 2. Algorithm for the Selection of a Revascularization Strategy.

Selection of a revascularization strategy is based on the presence of left main coronary artery disease (CAD) (Panel A), one-vessel CAD (Panel B), two-vessel CAD (Panel C), or three-vessel CAD (Panel D). In patients with two-vessel or three-vessel CAD, the coexisting conditions shown should also be considered. Class recommendations are based on the European Society of Cardiology[9] (blue) and the American College of Cardiology and the American Heart Association[8] (red) guidelines for revascularization. The European class recommendations shown are class IA; class IB; class IC; and class IIa, level of evidence B. The U.S. class recommendations shown are class IA; class IB; class IIa, level of evidence B; class IIb, level of evidence B; and class IIIB. The U.S. guidelines[8] have adopted two tiers for recommendations (symptomatic relief and survival benefit); the recommendations in this figure were simplified to reflect survival benefit. The Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score is a validated angiographic score to guide decisions about revascularization for patients with multivessel coronary disease, according to estimated outcomes. Scores range from 0 to 83, with higher scores indicating more complex disease.[46] Adapted from Piccolo and colleagues.[46] CAD denotes coronary artery disease, CABG coronary-artery bypass grafting, LAD left anterior descending, and PCI percutaneous intervention.

would provide support for continued medical therapy.

If the patient continues to have angina with strenuous exertion (in a stress test that shows low risk) despite standard medical therapy, I would discuss with the patient the options of receiving additional antianginal therapy (e.g., a calcium-channel blocker or a metabolic agent [ranolazine]) (Fig. 2) or pursuing catheterization, with potential revascularization. Decisions should be guided by the patient's preferences. If catheterization is performed, the physiological characteristics of the lesion should be evaluated (by means of fractional flow reserve) to ensure that only clinically significant lesions are subjected to PCI; this approach has been shown to reduce the risk of periprocedural complications and improve clinical outcomes.

Dr. Ohman reports receiving consulting fees from Abiomed, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Janssen, Stealth Peptides, the Medicines Company, Angel Medical Systems, Biotie Therapies, Faculty Connection, Merck, and Medscape, and grant support through his institution from Daiichi Sankyo, Eli Lilly, Gilead Sciences, and Janssen. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

I thank Penny Hodgson of Duke Clinical Research Institute for editorial assistance with an earlier version of the manuscript and Betty Summers of Duke University Medical Center for editing and checking references in an earlier version of the manuscript.

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics — 2015 update: a report from the American Heart Association. Circulation 2015; 131(4):e29-322.
2. Bhatt DL, Eagle KA, Ohman EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. JAMA 2010;304:1350-7.
3. Jones M, Rait G, Falconer J, Feder G. Systematic review: prognosis of angina in primary care. Fam Pract 2006;23:520-8.
4. Daly CA, De Stavola B, Sendon JL, et al. Predicting prognosis in stable angina — results from the Euro heart survey of stable angina: prospective observational study. BMJ 2006;332:262-7.
5. Henry TD, Satran D, Hodges JS, et al. Long-term survival in patients with refractory angina. Eur Heart J 2013;34:2683-8.
6. Povsic TJ, Broderick S, Anstrom KJ, et al. Predictors of long-term clinical endpoints in patients with refractory angina. J Am Heart Assoc 2015;4(2):e001287.
7. Cavender MA, Alexander KP, Broderick S, et al. Long-term morbidity and mortality among medically managed patients with angina and multivessel coronary artery disease. Am Heart J 2009;158:933-40.
8. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2012;60(24):e44-164.
9. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34:2949-3003.
10. Pepine CJ. Multiple causes for ischemia without obstructive coronary artery disease: not a short list. Circulation 2015; 131:1044-6.
11. The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103-16.
12. Bittner V, Bertolet M, Barraza Felix R, et al. Comprehensive cardiovascular risk factor control improves survival: the BARI 2D Trial. J Am Coll Cardiol 2015;66:765-73.
13. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med 1979;300:1350-8.
14. Pryor DB, Shaw L, McCants CB, et al. Value of the history and physical in identifying patients at increased risk for coronary artery disease. Ann Intern Med 1993; 118:81-90.
15. Cheng VY, Berman DS, Rozanski A, et al. Performance of the traditional age, sex, and angina typicality-based approach for estimating pretest probability of angiographically significant coronary artery disease in patients undergoing coronary computed tomographic angiography: results from the multinational coronary CT angiography evaluation for clinical outcomes: an international multicenter registry (CONFIRM). Circulation 2011;124: 2423-32.
16. Mark DB, Hlatky MA, Harrell FE Jr, Lee KL, Califf RM, Pryor DB. Exercise treadmill score for predicting prognosis in coronary artery disease. Ann Intern Med 1987;106:793-800.
17. Upton MT, Rerych SK, Newman GE, Port S, Cobb FR, Jones RH. Detecting abnormalities in left ventricular function during exercise before angina and ST-segment depression. Circulation 1980;62: 341-9.
18. Bourque JM, Beller GA. Value of exercise ECG for risk stratification in suspected or known CAD in the era of advanced imaging technologies. JACC Cardiovasc Imaging 2015;8:1309-21.
19. Rozanski A, Gransar H, Hayes SW, et al. Temporal trends in the frequency of inducible myocardial ischemia during cardiac stress testing: 1991 to 2009. J Am Coll Cardiol 2013;61:1054-65.
20. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med 2008;359:2324-36.
21. Meijboom WB, Meijs MFL, Schuijf JD, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. J Am Coll Cardiol 2008;52:2135-44.
22. Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med 2015;372:1291-300.
23. Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849-60.
24. Deanfield JE, Sellier P, Thaulow E, et al. Potent anti-ischaemic effects of statins in chronic stable angina: incremental benefit beyond lipid lowering? Eur Heart J 2010; 31:2650-9.
25. Stone PH, Lloyd-Jones DM, Kinlay S, et al. Effect of intensive lipid lowering, with or without antioxidant vitamins, compared with moderate lipid lowering on myocardial ischemia in patients with stable coronary artery disease: the Vascu-

lar Basis for the Treatment of Myocardial Ischemia Study. Circulation 2005;111:1747-55.
26. Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. N Engl J Med 1999;341:70-6.
27. Husted SE, Ohman EM. Pharmacological and emerging therapies in the treatment of chronic angina. Lancet 2015;386:691-701.
28. Heidenreich PA, McDonald KM, Hastie T, et al. Meta-analysis of trials comparing β-blockers, calcium antagonists, and nitrates for stable angina. JAMA 1999;281:1927-36.
29. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. II. Unstable angina, heart failure, primary prevention with aspirin, and risk factor modification. JAMA 1988;260:2259-63.
30. Jolicoeur EM, Ohman EM, Temple R, et al. Clinical and research issues regarding chronic advanced coronary artery disease. Part II: Trial design, outcomes, and regulatory issues. Am Heart J 2008;155:435-44.
31. Bangalore S, Steg G, Deedwania P, et al. β-Blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. JAMA 2012;308:1340-9.
32. Bangalore S, Bhatt DL, Steg PG, et al. β-blockers and cardiovascular events in patients with and without myocardial infarction: post hoc analysis from the CHARISMA trial. Circ Cardiovasc Qual Outcomes 2014;7:872-81.
33. Pehrsson SK, Ringqvist I, Ekdahl S, Karlson BW, Ulvenstam G, Persson S. Monotherapy with amlodipine or atenolol versus their combination in stable angina pectoris. Clin Cardiol 2000;23:763-70.
34. Chaitman BR. Ranolazine for the treatment of chronic angina and potential use in other cardiovascular conditions. Circulation 2006;113:2462-72.
35. Stone PH, Gratsiansky NA, Blokhin A, Huang IZ, Meng L. Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. J Am Coll Cardiol 2006;48:566-75.
36. Chaitman BR, Skettino SL, Parker JO, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. J Am Coll Cardiol 2004;43:1375-82.
37. Chaitman BR, Pepine CJ, Parker JO, et al. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. JAMA 2004;291:309-16.
38. Kosiborod M, Arnold SV, Spertus JA, et al. Evaluation of ranolazine in patients with type 2 diabetes mellitus and chronic stable angina: results from the TERISA randomized clinical trial (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina). J Am Coll Cardiol 2013;61:2038-45.
39. Weisz G, Généreux P, Iñiguez A, et al. Ranolazine in patients with incomplete revascularisation after percutaneous coronary intervention (RIVER-PCI): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2016;387:136-45.
40. Alexander KP, Weisz G, Prather K, et al. Effects of ranolazine on angina and quality of life after percutaneous coronary intervention with incomplete revascularization: results from the Ranolazine for Incomplete Vessel Revascularization (RIVER-PCI) Trial. Circulation 2016;133:39-47.
41. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, et al. Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. JAMA 2007;297:1775-83.
42. Fox K, Ford I, Steg PG, Tardif JC, Tendera M, Ferrari R. Ivabradine in stable coronary artery disease without clinical heart failure. N Engl J Med 2014;371:1091-9.
43. Noman A, Ang DS, Ogston S, Lang CC, Struthers AD. Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomised, placebo controlled crossover trial. Lancet 2010;375:2161-7.
44. Bashore TM, Balter S, Barac A, et al. 2012 American College of Cardiology Foundation/Society for Cardiovascular Angiography and Interventions expert consensus document on cardiac catheterization laboratory standards update: a report of the American College of Cardiology Foundation Task Force on Expert Consensus documents developed in collaboration with the Society of Thoracic Surgeons and Society for Vascular Medicine. J Am Coll Cardiol 2012;59:2221-305.
45. Leape LL, Park RE, Bashore TM, Harrison JK, Davidson CJ, Brook RH. Effect of variability in the interpretation of coronary angiograms on the appropriateness of use of coronary revascularization procedures. Am Heart J 2000;139:106-13.
46. Piccolo R, Giustino G, Mehran R, Windecker S. Stable coronary artery disease: revascularisation and invasive strategies. Lancet 2015;386:702-13.
47. Johnson NP, Tóth GG, Lai D, et al. Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. J Am Coll Cardiol 2014;64:1641-54.
48. Windecker S, Stortecky S, Stefanini GG, et al. Revascularisation versus medical treatment in patients with stable coronary artery disease: network meta-analysis. BMJ 2014;348:g3859.
49. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503-16.
50. Reynolds HR, Picard MH, Hochman JS. Does ischemia burden in stable coronary artery disease effectively identify revascularization candidates? Ischemia burden in stable coronary artery disease does not effectively identify revascularization candidates. Circ Cardiovasc Imaging 2015;8:9.