Angina Pectoris: A Review of Current and Emerging Therapies

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Abstract

Angina pectoris is a debilitating indication of the presence of ischemic heart disease that affects millions of Americans. Although a number of pharmacologic treatments are available, the annual number of revascularization surgeries continues to rise in the United States. Other management strategies, such as spinal cord stimulation, enhanced external counterpulsation, metabolic modulators, and gene therapy, are being explored.

(Am J Manag Care. 2004;10:S332-S338)

Ischemic heart disease is the leading cause of death in the United States[1] and angina pectoris is a common symptom of this disease.[2,3] "Angina" is used to describe clinical symptoms such as discomfort in the chest, jaw, shoulder, back, or arms that are induced by physical exertion or emotional stress and subside with rest or treatment with nitroglycerin.[4] Some patients do not experience discomfort but complain of breathlessness or tire with activity. These symptoms are the result of underlying myocardial ischemia and are sometimes called anginal equivalents.

The American Heart Association (AHA) estimates that 6.8 million Americans suffer from angina and that 400 000 new patients present with stable angina each year.[1] Significantly more women have the condition than men, both in total numbers and as an age-adjusted percentage.[1] Angina limits normal daily activities; thus, it has a negative impact on quality of life (QOL). It has been shown that 1 year after coronary revascularization, roughly one third of patients with angina are not able to return to work.[5] Not surprisingly, the societal impact and economic costs of angina are staggering. In the American College of Cardiology (ACC)/AHA 2002 Guideline Update for the Management of Patients with Chronic Stable Angina, Gibbons and colleagues state, "angina affects many millions of Americans with associated annual costs that are measured in tens of billions of dollars."[4]

Angina treatment involves a number of strategies.[4] In general, the first step in angina management includes assessing patient risk factors, such as smoking, hypertension, dyslipidemia, diabetes mellitus, obesity, and physical inactivity. While alterations in these risk factors may improve symptoms and reduce cardiac events, the majority of patients with chronic stable angina require specific antianginal medications. It is recommended that beta-adrenergic blocking drugs be used as first-line therapy for patients with angina because these agents have been shown to have cardioprotective effects.[4] Other standard therapies for chronic angina include calcium channel blocking agents and organic nitrates,[4] but such medical therapy often does not provide adequate symptomatic relief. A number of novel therapies are directed at angina treatment, including new pharmacologic agents, gene therapy, enhanced external counterpulsation (EECP), spinal cord stimulation, and innovations in revascularization therapy. This article reviews the classification of angina pectoris and briefly describes standard and novel treatment strategies for this debilitating health problem.

Understanding Angina. Whereas there has been considerable research regarding angina, the exact mechanism of pain perception in patients with myocardial ischemia is still poorly understood. However, cardiac ischemic discomfort may be perceived in the heart, chest wall, arms, and back because of the

close proximity of the spinal nerve receptors to these areas.[6] Chest pain caused by myocardial ischemia is classified as stable or unstable angina.[4] Patients with unstable angina have a much higher risk of acute cardiac events than patients with stable angina pectoris. Such risk can be further stratified as low, moderate, or high, depending on the frequency and severity of pain and on the presence of certain electrocardiographic abnormalities. Unstable angina is commonly described based on the way it presents. This includes new onset angina or angina that has increased in frequency and severity despite medical therapy, or angina that occurs at rest (**Table 1**). Angina is frequently defined using Canadian Cardiovascular Society (CCS) functional class (**Table 2**),[7] a system that has been used for more than 3 decades. In 2002, a new CCS definition for grade IV angina was suggested that includes a set of detailed activities, "angina occurs while walking less than 1 block...or while walking in the house, or doing light chores or personal care" rather than the previous description: "Inability to carry on any physical activity without discomfort—anginal symptoms may be present at rest."[8] While other grading systems have been defined, the CCS functional classification has been the most widely used by clinicians and investigators.

Treatment of Angina Pectoris. Decreasing the frequency and severity of angina improves QOL for patients with angina. Although smoking cessation, weight control, stress management, moderate exercise, and appropriate management of hypertension, dyslipidemia, and diabetes mellitus may reduce symptoms and ischemic events, pharmacotherapy with antianginal agents is usually required. Beta-adrenergic blocking agents, calcium channel blocking agents, and short- and long-acting nitrates are the foundation of medical therapy for patients with chronic angina.[4] Although each has a different mechanism of action, these agents have multiple effects that tend to decrease cardiac workload and, therefore, lower myocardial energy requirements and/or increase coronary blood flow or improve its distribution. These effects help lessen the mismatch between myocardial oxygen requirements and oxygen supply. Unfortunately, many patients require more than 1 drug to control symptoms,[9] and patients with comorbid conditions often require a host of other medications as well. Indeed, a variety of agents, including antiplatelet/antithrombotic agents, angiotensin-converting enzyme inhibitors, and lipid-lowering drugs, are important therapeutic adjuncts in the treatment of patients with chronic angina.[4] Ultimately, the potential for adverse drug interactions and side effects associated with polypharmacy may limit the ability of a patient with chronic angina to tolerate appropriate medical therapy.

Table 1. Three Principal Presentations of Unstable Angina

Rest angina	Angina occurring at rest and usually prolonged more than 20 minutes occurring within 1 week of presentation
New onset angina	Angina of a least CCS III severity with onset within 2 months of initial presentation
Increasing angina	Previously diagnosed angina that is distinctly more frequent, longer in duration, or lower in threshold (ie, increased by at least 1 CCS class within 2 months of initial presentation to at least CCS III severity)

CCS indicates Canadian Cardiovascular Society.
Source: Reference 4.

Beta-adrenergic blocking agents are recommended as first-line therapy in the ACC/AHA guidelines.[4] These drugs, however, have absolute or relative contraindications in patients with asthma, chronic obstructive pulmonary disease, severe peripheral vascular disease, and in some patients with diabetes mellitus. In such cases, calcium channel blocking agents are often prescribed and certain calcium channel blockers, such as the dihydropyridines, may be associated with flushing and peripheral edema.[4] Diltiazem has been associated with heart failure in patients with abnormal left ventricular systolic function.[10] Sublingual nitroglycerin, either as a tablet or spray, is effective in the treatment of acute episodes of angina and is also beneficial for short-term prophylaxis. However, the oral and transdermal organic nitrate preparations, although effective, are associated with the development of tolerance when prescribed in a fashion designed to provide

Table 2. Grading of Angina Pectoris by the Canadian Cardiovascular Society Classification System

Class I	Ordinary physical activity, such as walking or climbing stairs, does not cause angina. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.
Class II	Slight limitation of ordinary activity. Angina occurs when walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold weather, in the wind, or under emotional stress, or only during the few hours after awakening. Angina occurs after walking more than 2 level blocks and climbing more than 1 flight of ordinary stairs at a normal pace and under normal conditions.
Class III	Marked limitations of ordinary physical activity. Angina occurs when walking 1-2 level blocks and climbing 1 flight of stairs at a normal pace under normal conditions.
Class IV	Inability to perform any physical activity without discomfort. Symptoms of angina may be present at rest.

Source: Reference 7.

therapeutic effects for 24 hours each day.[11] A more detailed review of the efficacy of drug therapy for management of chronic angina is available in the ACC/AHA guidelines.[4] Overall, using traditional therapies to manage pain in patients with chronic angina is commonly associated with inadequate symptom control, poor tolerance, and limited compliance. The treatment shortcomings for patients who suffer from chronic angina have resulted in the development of innovative therapies that are now being studied.

New Pharmacologic Agents. Metabolic modulators represent a potential new class of drugs with a novel approach to the treatment of angina symptoms in the United States.[12,13] In the presence of myocardial ischemia, glucose oxidation is a more efficient way of generating energy units adenosine triphosphate than free fatty acid oxidation.[14] Unlike most current classes of angina therapy, metabolic modulators may be effective without depending on reductions in heart rate or blood pressure.[13,15]

Trimetazidine, a metabolic modulator available outside of the United States, has demonstrated anti-ischemic effects in a number of studies of patients with angina. The drug has been shown to increase effort tolerance and to delay the appearance of ischemic symptoms and electrocardiographic (ECG) changes.[12,14,16,17] In addition, patient safety and tolerance with trimetazidine has been good.[18,19] The efficacy of trimetazidine has also been demonstrated in patients with diabetes, who showed improved exercise capacity and duration after 4 weeks of treatment.[20] Left ventricular dysfunction has improved during therapy with trimetazidine.[21,22]

Gene Therapy. Therapeutic angiogenesis regimens have focused mainly on the administration of a single growth factor with select isoforms of the vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF). At present, VEGF and FGF have been the most extensively studied angiogenic agents.[23] Growth factor proteins may be given directly or through gene-based approaches using naked plasmid deoxyribonucleic acid or a viral vector that encodes the gene so that it can be taken up by the recipient endothelial cells. These endothelial cells offer the potential for persistent expression of the angiogenic gene.[23,24] These agents may be administered directly to the myocardium by epicardial, endocardial, or intracoronary injection. Some trials have shown beneficial effects in patients with angina,[24] but adequately powered, randomized, placebo-controlled clinical studies must be completed to clarify the effectiveness of such therapy.

Enhanced External Counterpulsation. EECP is another novel treatment for patients with ischemic heart disease who have chronic angina and are unresponsive to other therapies. EECP is carried out by encircling the legs with compression devices, inflating them during diastole to 300 mm Hg, and deflating them during systole.[25] This unloads the left ventricle during ventricular systole, and this augmentation of pressure is thought to improve coronary blood flow during diastole. In the only published randomized clinical trial of EECP,[25] which involved 139 patients with class II to III angina, the control group was treated by compressing the lower extremities at 75 mm Hg, and the experimental group was treated by compressing the lower extremities at 300 mm Hg. While clinical symptoms and treadmill exercise times improved and a variable effect on

myocardial perfusion imaging studies was reported, the absence of proper blinding during this study makes the results uncertain. The mechanisms thought to be responsible for the improvement of symptoms include enhancement of endothelial function, promotion of collateral flow, improvement in ventricular function, and peripheral effects similar to those seen with physical exercise.[26] For EECP to be effective, patients require daily in-clinic treatments over several weeks, which is a schedule that might be difficult for many patients to maintain.

Spinal Cord Stimulation. Spinal cord stimulation, another proposed method for pain relief in patients with angina, involves placing a stimulating electrode in the dorsal epidural space at the C7-T1 level. Although the mechanism of action is complex and not fully elucidated, it has been proposed that spinal cord stimulation exerts beneficial effects by decreasing pain and sympathetic tone, yielding reductions in myocardial oxygen consumption and improved myocardial microcirculatory blood flow.[27] Early results with implanted spinal cord stimulators indicate improvements in exercise duration, time to angina, and perceived QOL.[28] In another trial, anginal symptoms decreased even after discontinuation of therapy, perhaps indicating a long-term, primary analgesic effect of this treatment.[29]

Revascularization Strategies. Revascularization strategies have expanded to include new techniques for coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI). Another approach is transmyocardial revascularization (TMR).

CABG. The standard CABG procedure revolutionized treatment of coronary artery disease (CAD) in the 1960s and incorporates midline sternotomy with cardiopulmonary bypass. While traditional CABG procedures are still in use, off-pump CABG has been shown to reduce operative morbidity, operative mortality, and length of hospital stay compared with on-pump CABG.[30] More recently, minimally invasive bypass techniques that use a small, anterior thoracotomy have been developed as well. Although the saphenous vein was the vessel of choice for graft repair during the first 2 decades of CABG surgery, long-term survival was shown to be consistently higher when the internal mammary artery was used.[31] Since the late 1980s, arterial grafts from the internal mammary, gastroepiploic, inferior epigastric, and radial arteries have all been used for arterial revascularization. Whether the CABG benefits of increased QOL and decreased angina frequency persist long term remains unclear because data from some studies suggest that these benefits subside over time.[32,33]

PCI. Advances in PCI technology have had a significant impact on the way coronary and vascular diseases are treated. The introduction of percutaneous transluminal coronary angioplasty by Gruentzig[34] in the late 1970s revolutionized the treatment of CAD, even though outcomes were limited by restenosis, dissection, and acute vessel closure. Later, coronary stents were shown to be superior to balloon angioplasty,[35,36] and each year they are being used more often than angioplasty alone. At present, there is a wide range of stents, with the latest designs offering drug-eluting coatings with antiproliferative agents, such as sirolimus and paclitaxel. In addition, stents that incorporate synthetic coverings have been introduced to treat a variety of lesions, including saphenous vein grafts. A recent study, however, indicated no benefit of the covered stent over a conventional stent with respect to acute results, restenosis, or clinical event rates.[37] For patients with angina seeking symptom relief, the long-term benefits associated with PCI and CABG remain to be determined.[32,38,39]

TMR. TMR involves the use of laser energy to create a series of transmural endomyocardial channels. There are 2 types of procedures in use. The first, TMR, is performed surgically using an epicardial approach, and, the second, percutaneous myocardial revascularization, employs an endocardial approach. Both procedures have been associated with a reduction in angina symptoms, improved exercise tolerance, and enhanced QOL, although sham-controlled trials do indicate evidence of a placebo effect with these therapies.[40] The basis for improvements reported with TMR remains unclear. The initial hypothesis was that the channels provided additional blood flow to

the myocardium, but this no longer appears to be the case. It has also been suggested that clinical improvement may be secondary to angiogenesis or to myocardial denervation.[41]

Discussion

Although there are many therapies available to treat angina and many more being studied, finding an effective solution that relieves symptoms and improves QOL may be difficult in some cases. Although a medical management approach is preferable, many patients remain symptomatic when taking traditional antianginal agents, even when multiple agents are taken. Failure of medical management in patients with refractory angina has led to the introduction of more invasive treatments such as CABG and PCI, although some reports seem to indicate that these invasive procedures are often considered before medical therapy has been given an adequate trial.[42]

Surgical and percutaneous interventions are costly, and many patients have comorbid conditions that put them at high risk for such procedures. Data from the latest Healthcare Cost and Utilization Project indicate that the mean charge for a CABG procedure is $60 853 and $28 558 for PCI.[1] Despite concerns about long-term results, the number of percutaneous interventions in the United States has increased dramatically in the past 20 years. In 2001, an estimated 571 000 PCI procedures were performed, representing a 266% increase over the number of procedures performed in 1987.[1]

Although CABG and PCI may improve angina in some patients, studies have shown that within 1 year of a CABG procedure, approximately 10% to 26%[5,43-45] of patients have recurrent pain and many require antianginal medications.[5,44,45] Similar results have been seen with PCI—29% to 34%[5,44,45] of patients had their angina recur within 1 year, and the majority of patients were still taking antianginal medications.[44,45] Fewer than 30% of patients in a 5-year multicenter study were working 5 years after coronary revascularization and, at that time, more than 20% of patients rated their health as poor or fair.[5] The results of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, in which aggressive medical therapy is being compared with aggressive medical therapy plus PCI, are expected to help delineate the usefulness of revascularization in patients with angina.[46]

Conclusion

Angina is a serious, debilitating health problem that signals the presence of CAD and may foreshadow myocardial infarction or stroke. While there have been considerable advances in medical management, surgical and percutaneous revascularization strategies, many patients remain symptomatic at substantial personal and societal cost. Given the inadequacy of current medical management and the expense and disappointing long-term efficacy associated with surgical and percutaneous revascularization, further study of new treatments is warranted.

REFERENCES

1. **American Heart Association.** *Heart Disease and Stroke Statistics—2004 Update.* Dallas, Tex: American Heart Association; 2003.

2. **Elveback LR, Connolly DC, Melton LJ 3rd.** Coronary heart disease in residents of Rochester, Minnesota VII. Incidence, 1950-1982. *Mayo Clin Proc.* 1986;61:896-900.

3. **Kannel WB, Feinleib M.** Natural history of angina pectoris in the Framingham study. Prognosis and survival. *Am J Cardiol.* 1972;29:154-163.

4. **Gibbons RJ, Chatterjee K, Daley J, et al.** ACC/AHA 2002 guideline update for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines 2002. Available at: www.acc.org/clinical/guidelines/stable/stable.pdf. Accessed April 7, 2004.

5. Five-year clinical and functional outcome comparing bypass surgery and angioplasty in patients with multivessel coronary disease. A multicenter randomized trial. Writing Group for the Bypass Angioplasty Revascularization Investigation (BARI) Investigators. *JAMA.* 1997;277:715-721.

6. **Braunwald E, Zipes DP, Libby P, eds.** *Heart Disease. A Textbook of Cardiovascular Medicine.* 6th ed. Philadelphia, Pa: WB Saunders Co. 2001.

7. **Campeau L.** Letter: grading of angina pectoris. *Circulation.* 1976;54:522-523.

8. **Campeau L.** The Canadian Cardiovascular Society grading of angina pectoris revisited 30 years later. *Can J Cardiol.* 2002;18:371-379.

9. **Pepine CJ, Abrams J, Marks RG, Morris JJ, Scheidt SS, Handberg E.** Characteristics of a contemporary population with angina pectoris. TIDES Investigators. *Am J Cardiol.* 1994;74:226-231.

10. **Goldstein RE, Boccuzzi SJ, Cruess D, Nattel S.** Diltiazem increases late-onset congestive heart failure in

postinfarction patients with early reduction in ejection fraction. The Adverse Experience Committee; and the Multicenter Diltiazem Postinfarction Research Group. *Circulation.* 1991;83:52-60.

11. Parker JD, Parker JO. Nitrate therapy for stable angina pectoris. *N Engl J Med.* 1998;338:520-531.

12. Detry JM, Sellier P, Pennaforte S, Cokkinos D, Dargie H, Mathes P. Trimetazidine: a new concept in the treatment of angina. Comparison with propranolol in patients with stable angina. Trimetazidine European Multicenter Study Group. *Br J Clin Pharmacol.* 1994;37:279-288.

13. 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;291:309-316.

14. Stanley WC, Marzilli M. Metabolic therapy in the treatment of ischaemic heart disease: the pharmacology of trimetazidine. *Fundam Clin Pharmacol.* 2003;17:133-145.

15. Chaitman BR, Skettino SL, Parker JO, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in severe chronic angina. *J Am Coll Cardiol.* 2004;43:1375-1382.

16. Sellier P, Audouin P, Payen B, Corona P, Duong TC, Ourbak P. Acute effects of trimetazidine evaluated by exercise testing. *Eur J Clin Pharmacol.* 1987;33:205-207.

17. Detry JM. Clinical features of an antianginal drug in angina pectoris. *Eur Heart J.* 1993;14:18-24.

18. Monpere C, Brochier M, Demange J, Ducloux G, Warin JF. Combination of trimetazidine with nifedipine in effort angina. *Cardiovasc Drugs Ther.* 1990;4:824-825.

19. Michaelides AP, Vyssoulis GP, Bonoris PE, et al. Beneficial effects of trimetazidine on men with stable angina under beta-blocker treatment. *Curr Ther Res.* 1989;46:565-576.

20. Szwed H, Pachocki R, Domnzal-Bochenska M. The antiischaemic effects and tolerability of trimetazidine in coronary diabetic patients. A substudy from TRIMPOL-1. *Cardiovasc Drugs Ther.* 1999;13:217-222.

21. Brottier A, Barat JL, Combe C, Boussens B, Bonnet J, Bricaud H. Therapeutic value of a cardioprotective agent in patients with severe ischaemic cardiomyopathy. *Eur Heart J.* 1990;11:207-212.

22. Belardinelli R, Purcaro A. Effects of trimetazidine on the contractile response of chronically dysfunctional myocardium to low-dose dobutamine in ischaemic cardiomyopathy. *Eur Heart J.* 2001;22:2164-2170.

23. Sellke FW, Ruel M. Vascular growth factors and angiogenesis in cardiac surgery. *Ann Thorac Surg.* 2003;75:S685-S690.

24. Grines C, Rubanyi GM, Kleiman NS, Marrott P, Watkins MW. Angiogenic gene therapy with adenovirus 5 fibroblast growth factor-4 (Ad5FGF-4): a new option for the treatment of coronary artery disease. *Am J Cardiol.* 2003;92(9B):24N-31N.

25. Arora RR, Chou TM, Jain D, et al. The multicenter study of enhanced external counterpulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes. *J Am Coll Cardiol.* 1999;33:1833-1840.

26. Bonetti PO, Holmes DR Jr, Lerman A, Barsness GW. Enhanced external counterpulsation for ischemic heart disease: what's behind the curtain? *J Am Coll Cardiol.* 2003;41:1918-1925.

27. Latif OA, Nedeljkovic SS, Stevenson LW. Spinal cord stimulation for chronic intractable angina pectoris: a unified theory on its mechanism. *Clin Cardiol.* 2001;24:533-541.

28. Hautvast RW, DeJongste MJ, Staal MJ, van Gilst WH, Lie KI. Spinal cord stimulation in chronic intractable angina pectoris: a randomized, controlled efficacy study. *Am Heart J.* 1998;136:1114-1120.

29. Norrsell H, Pilhall M, Eliasson T, Mannheimer C. Effects of spinal cord stimulation and coronary artery bypass grafting on myocardial ischemia and heart rate variability: further results from the ESBY study. *Cardiology.* 2000;94:12-18.

30. Reston JT, Tregear SJ, Turkelson CM. Meta-analysis of short-term and mid-term outcomes following off-pump coronary artery bypass grafting. *Ann Thorac Surg.* 2003;76:1510-1515.

31. Loop FD, Lytle BW, Cosgrove DM, et al. Influence of the internal mammary artery graft on 10-year survival and other cardiac events. *N Engl J Med.* 1986;314:1-6.

32. Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med.* 2001;344:1117-1124.

33. van Domburg RT, Foley DP, Breeman A, van Herwerden LA, Serruys PW. Coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty. Twenty-year clinical outcome. *Eur Heart J.* 2002;23:543-549.

34. Gruentzig AR, Myler RK, Hanna EH, et al. Coronary transluminal angioplasty. *Circulation.* 1977;55-56(suppl III):III-84.

35. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *N Engl J Med.* 1994;331:496-501.

36. Serruys P, de Jaegere P, Kiemeneji F, et al. A comparison of balloon expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med.* 1994; 331:489-495.

37. Schachinger V, Hamm CW, Munzel T, et al. A randomized trial of polytetrafluoroethylene-membrane-covered stents compared with conventional stents in aortocoronary saphenous vein grafts. *J Am Coll Cardiol.* 2003;42:1360-1369.

38. Holubkov R, Laskey WK, Haviland A, et al. Angina 1 year after percutaneous coronary intervention: a report from the NHLBI Dynamic Registry. *Am Heart J.* 2002; 144:826-833.

39. Henderson RA, Pocock SJ, Clayton TC, et al. Seven-year outcome in the RITA-2 trial: coronary angioplasty versus medical therapy. *J Am Coll Cardiol.* 2003;42: 1161-1170.

40. Saririan M, Eisenberg MJ. Myocardial laser revascularization for the treatment of end-stage coronary artery disease. *J Am Coll Cardiol.* 2003;41:173-183.

41. Huikeshoven M, Beek JF, van der Sloot J, Tukkie R, van der Meulen J, van Gemert MJ. 35 years of experimental research in transmyocardial revascularization: what have we learned? *Ann Thorac Surg.* 2002;74: 956-970.

42. Samuels BA, Diamond GA, Mahrer PR, Denton TA. Intensity of antianginal therapy in patients referred for coronary angiography: a comparison of fee-for-service and health maintenance organization therapeutic strategies. *Clin Cardiol.* 2000;23:165-170.

43. Cameron AA, Davis KB, Rogers WJ. Recurrence of angina after coronary artery bypass surgery: predictors and prognosis (CASS Registry). Coronary Artery Surgery Study. *J Am Coll Cardiol.* 1995;26:895-899.

44. Hamm CW, Reimers J, Ischinger T, Rupprecht HJ, Berger J, Bleifeld W. A randomized study of coronary angioplasty compared with bypass surgery in patients with symptomatic multivessel coronary disease. German Angioplasty Bypass Surgery Investigation (GABI). *N Engl J Med.* 1994;331:1037-1043.

45. The SoS Investigators. Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): a randomised controlled trial. *Lancet.* 2002;360:965-970.

46. Department of Veterans Affairs Cooperative Studies Program #424. Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE). Available at: http://www.couragetrial.gov. Accessed February 2, 2004.