Management of Stable Angina – Drugs, Stents and Devices for Coronary Bypass Surgery

a report by
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Stable angina pectoris is a common disorder; its prevalence increases with age. Patients with stable angina pectoris experience a pressure or a choking sensation in the chest and adjacent areas or shortness of breath (angina equivalent) associated with physical or emotional stress. Most patients with stable angina pectoris have severe obstructive atherosclerotic lesions of complex morphology in one or more coronary arteries and multiple non-obstructive lesions. Obstructive lesions limit the increase of blood flow that is required during periods of increased myocardial oxygen demand, such as exercise.

The endothelium overlying the lesions is dysfunctional and is responsible for paradoxical constriction of the stenotic site during exercise, resulting in further reduction of blood flow distal to the lesion. The resultant imbalance between myocardial oxygen supply and demand produces reversible myocardial ischaemia and its clinical consequences, such as anginal pain and/or shortness of breath. Non-obstructive lesions are lipid-rich and soft in consistency and the endothelium overlying these lesions is prone to fissuring and disruption. The exact mechanism of plaque-endothelial surface disruption remains elusive. Several mechanisms, including an active inflammatory process, have been implicated. The fissured endothelium exposes the atheromatous material inside the vessel wall to the circulating blood. This results in platelet aggregation and deposition, which may be followed by additional intraluminal thrombosis. The clinical presentation may remain silent or manifest as acute coronary syndrome (myocardial infarction (MI), unstable angina) or sudden ischaemic death.

The annual death rate of patients with stable angina is 1.6% to 3.2%. The most important determinant of prognosis is underlying left-ventricular systolic function at rest, co-morbid conditions and the severity and extent of coronary artery disease.

Treatment Goals

Treatment goals are:

- abolition or reduction of the frequency of angina attacks;
- prolongation of angina-free walking duration;
- abolition or reduction of other consequences of reversible myocardial ischaemia, such as dyspnea due to transient elevation of left-ventricular systolic and diastolic pressure; and
- prevention or reduction of serious adverse outcomes (MI, unstable angina and ischaemic sudden death) due to plaque-endothelial surface disruption.

The treatment must be applicable to a large segment of the population of stable angina. Pharmacological therapy should be devoid of intolerable adverse effects and drug interactions. Newer therapy should be either superior to or as effective as already proven therapy and should show additional beneficial effects when used in addition to currently proven and effective treatment of stable angina pectoris.

Currently available anti-anginal drugs (long-acting nitrates, beta-blockers and calcium channel blockers) and revascularisation procedures alleviate or prevent anginal symptoms but have not been shown to improve survival or reduce the incidence of MI in patients with stable angina pectoris. On the other hand, the strategies that reduce the incidence of adverse outcomes have little anti-anginal effect. Therefore, treatment of stable angina must include the use of anti-anginal drugs and/or revascularisation procedures plus strategies that reduce adverse clinical outcomes.

Treatment Aimed at Decreasing the Frequency and Severity of Anginal Symptoms and Myocardial Ischaemia

Several strategies are available to achieve the goal of decreasing the frequency and severity of anginal symptoms and myocardial ischaemia. Anti-anginal drugs (nitrates, beta-blockers and calcium channel blockers) are usually the first option. Revascularisation procedures, percutaneous balloon dilation of the coronary artery (PTCA), with or without stent placement, are being used increasingly, especially in the US, and coronary bypass surgery is now being offered only to selected patients with stable angina pectoris.

Udho Thadani was appointed Emeritus Professor of Medicine in the Division of Cardiology, Oklahoma University Health Sciences Center (OUHSC) in 2001, prior to which he was Professor of Medicine from 1983 to 2001. He has also been Consultant Cardiologist at the Oklahoma University Medical Center and Oklahoma City Department of Veterans' Affairs Medical Center (VAMC) since 1980. Professor Thadani was Associate Professor of Medicine, OUHSC, from 1980 to 1983; Assistant Professor of Medicine, Queen's University, Ontario, from 1978 to 1980; Registrar and Research Fellow at Queen's University, Ontario, and Leeds University, England, from 1969 to 1978; House Physician and Intern at Kingston General Hospital, Hull, England, and All India Institute of Medical Sciences (AIIMS) New Delhi, India, from 1965 to 1969. He is the recipient of several awards, most recently the James F Hammersten Award for Patient Care, Research and Education, VAMC, in 2003 and Provost's Senior Faculty Research Award, OUHSC, in 1995. He was a member of the Cardio Renal Advisory Committee of the US Food and Drug Administration (FDA) from 1995 to 1999 and is a Fellow of the Royal Society of Medicine, London; Royal College of Physicians and Surgeons of Canada; American College of Cardiology (ACC); and the American Heart Association (AHA). Professor Thadani is a Member of the Canadian Cardiovascular Society (CCS), American Society of Hypertension (ASH) and Heart Failure Society of America (HFSA).

Drugs

Nitrates are nitric oxide donors and predominantly reduce myocardial oxygen demand by reducing venous return. These agents also dilate stenotic coronary lesions and increase sub-endocardial blood flow to the ischaemic areas. Sublingual nitroglycerin is very effective and prolongs exercise tolerance in patients with stable angina pectoris. Long-acting and sustained-release formulations of nitrates, although used widely, do not provide 24-hour anti-anginal prophylaxis due to development of tolerance. Based on the published data, it can be concluded that none of the nitrate preparations or regimens provide continuous 24-hour anti-anginal prophylaxis. Many patients are unable to tolerate intermittent therapy with nitrates due to nitrate-induced headaches.

Beta-blockers reduce myocardial oxygen demand by reducing heart rate, myocardial contractility and exercise-induced increase in systolic blood pressure. Beta-blockers also increase coronary blood flow by increasing the diastolic filling period. These agents are the most effective anti-ischaemic agents and reduce exercise and ambulatory ischaemia to a greater extent than other anti-anginal drugs. Both non-selective and cardio-selective agents have been shown to improve exercise performance and reduce exercise-induced ischaemia in patients with stable angina pectoris.

Beta-blockers improve survival and reduce hospitalisation in patients with reduced left-ventricular function. However, there are no studies of beta-blockers on survival in patients with stable angina pectoris and normal left-ventricular function. Some patients are unable to tolerate beta-blockers due to excessive decrease in heart rate or fatigue, or due to concomitant diseases such as severe chronic obstructive pulmonary disease, bronchial asthma and severe peripheral vascular disease with resting limb ischaemia.

Calcium channel blockers act mainly by vasodilating the coronary arteries and by reducing peripheral vascular resistance. Non-dihydropyridine agents, verapamil and diltiazem, depress sinoatrial and atrio-ventricular node activity and also reduce myocardial oxygen demand. Long-acting dihydropyridine agents that are widely used to treat patients with stable angina primarily reduce myocardial oxygen demand by their predominant arterial dilating effects.

Recent studies with long-acting dihydropyridine and non-dihydropyridine groups of calcium channel blockers have shown that these agents are relatively safe and effective in patients with stable angina and preserved left-ventricular function. Calcium channel blockers should be avoided in patients with stable angina who have systolic left-ventricular dysfunction.

When used in adequate doses, all three classes of anti-anginal drugs, i.e. long-acting nitrates, beta-blockers and calcium channel blockers, have been shown to increase angina-free walking duration and total exercise time and to reduce angina frequency during daily activities. The combination of two agents from different classes (beta-blocker plus a long-acting nitrate or a calcium channel blocker, especially a dihydropyridine agent) may be more effective than monotherapy. However, triple therapy is not necessarily superior to treatment with two agents of different classes.

None of the three classes of anti-anginal drugs has been shown to reduce the frequency of serious adverse outcomes in patients with stable angina, the exception being patients with stable angina who have experienced a recent MI or who have reduced left-ventricular function; beta-blockers improve survival in these patients.

Nicorandil is a nitro-vasodilator with potassium channel-opening properties. Improvement in exercise tolerance has been reported in some studies, but not all. On the other hand, in patients with coronary artery disease, nicorandil was shown to reduce the incidence of serious adverse outcomes compared with placebo.

The metabolic agents trimetazidine (available in some countries) and ranolazine (not available as yet) are effective anti-anginal and anti-ischaemic agents and hold promise as they are devoid of circulating and haemodynamic effects.

Devices and Coronary Bypass Surgery

Revascularisation procedures increase coronary blood flow and have no effect on myocardial oxygen demand. Several studies have shown that PTCA, with or without stent placement, relieves anginal episodes in the majority of patients and increases angina-free walking time. However, the restenosis rate (20% to 30%) and recurrence of symptoms has remained a major problem especially in patients with diabetes mellitus. Drug-coated stents (sirolimus-eluting stents, paclitaxel-eluting stents) have reduced the rates of restenosis significantly. However, acute thrombosis of the stent still remains an issue. The majority of patients who undergo balloon dilation of the coronary artery with or without stent placement are currently maintained on anti-anginal drug therapy.

Compared with medical therapy (anti-anginal drugs) percutaneous coronary interventions do not reduce mortality or the incidence of MI in patients with stable angina pectoris. In a randomised study, in

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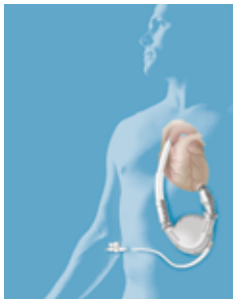

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patients with proximal left-anterior coronary artery disease, PTCA did not reduce the incidence of death or MI compared with medical therapy.

Coronary artery bypass surgery utilises venous or arterial conduits and increases the blood flow to the areas distal to the significant stenotic lesions. The procedure is effective in patients with graftable vessels and abolishes or reduces angina frequency in 70% to 80% of patients. Angina-free exercise duration also increases following surgery. In unblinded, parallel-design, randomised studies, coronary bypass surgery reduced neither the incidence of death nor the frequency of MI compared with medical therapy. Subgroup, *post hoc* analysis showed that patients with severe narrowing of the left main coronary artery and those with poor left-ventricular function and multivessel coronary artery disease (MVD) had better survival rates after surgery compared with medical treatment. Recent trials have compared coronary bypass surgery to PTCA with or without stent placement. Both strategies are equally effective in relieving angina although the need for a repeat percutaneous procedure or bypass surgery is greater in patients who have undergone a percutaneous revascularisation procedure. Currently, bypass surgery is indicated in diabetic patients with MVD.

Many of the patients who have undergone bypass surgery experience recurrence of symptoms over time due to progressive atherosclerotic occlusion of the venous conduits. This usually manifests itself 10 to 15 years after surgery and, in many of these patients, native coronary arteries are not suitable for a repeat revascularisation procedure due to disease progression.

Given the evidence that neither percutaneous interventions nor coronary artery bypass surgery improves survival or reduces serious adverse outcomes compared with medical therapy, it is preferable to try medical therapy first and consider percutaneous intervention or bypass surgery if medical therapy has failed.

Enhanced external counterpulsation (EECP) improves exercise performance with reduction in myocardial ischaemia in patients with stable angina pectoris. However, reported trials are rather small and, at present, EECP is reserved for patients who do not respond to conventional anti-anginal therapy and are not candidates for a revascularisation procedure.

At present, direct laser revascularisation procedures are only being used in patients who are not candidates for a revascularisation procedure and are refractory to medical therapy. Percutaneous transmyocardial revascularisation is not superior to a sham procedure in patients with stable angina.

Spinal cord stimulation and transcutaneous nerve stimulation are reserved for those patients who are not candidates for a revascularisation procedures and remain very symptomatic despite optimal drug therapy.

Anti-anginal drugs, PTCA with or without stents, bypass surgery and other devices do not improve survival or reduce the incidence of MI in patients with stable angina. The following strategies are, therefore, needed to improve outcome.

Treatment Aimed at Reducing Adverse Outcomes

Smoking cessation reduces the risk of coronary artery disease mortality by 50% after one year. After five to 10 years, the coronary mortality rate in ex-smokers matches that of non-smokers. Stopping smoking may increase exercise performance in patients with stable angina pectoris.

Aspirin reduces the incidence of death and acute MI in patients with stable angina pectoris. Therefore, all patients with stable angina pectoris should be treated with daily aspirin (81mg to 320mg), provided they do not have a history of allergic reaction to aspirin and do not experience intolerable gastrointestinal side effects.

There is no data to indicate that newer antiplatelet agents – clopidogrel and ticlopidine – are superior to aspirin in patients with stable angina pectoris. Large-scale trials comparing aspirin with clopidogrel in patients with stable angina pectoris are lacking.

Lipid lowering therapy, especially with statins, reduces coronary morbidity and mortality in patients with established coronary artery disease. In a small study, aggressive lowering of low-density lipoprotein cholesterol with atorvastatin plus anti-anginal therapy was superior to percutaneous interventions plus anti-anginal therapy in patients with stable angina pectoris. Gemfibrozil reduced the incidence of serious adverse outcome in male patients with stable angina and low high-density lipoprotein levels (<35mg per dl) in the Veterans' Administration Low High-density Lipoprotein Cholesterol Intervention Trial (VA-HIT).

Available data supports the aggressive treatment of lipid abnormalities in addition to daily use of aspirin and smoking cessation in patients with stable angina pectoris. ■

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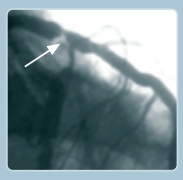
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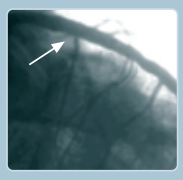
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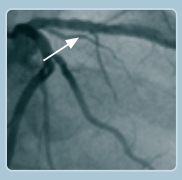
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1. Morice MC et al. N Engl J Med 2002;346:1773-80. 2. Moses J et al. N Engl J Med 2003;349:1315-23. 3. Schofer J et al. Lancet 2003;362:1093-99. 4. FIM 4-year results presented at ACC 2004.
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