

# Stable angina: a balanced approach

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### Abstract

Coronary artery disease is a chronic medical condition associated with high mortality and morbidity. Among individuals with coronary artery disease, more than 50% have chronic stable angina. Recent evidence supports initial treatment with medical therapy, followed by revascularization, if indicated, in patients with chronic stable angina. The successful management of patients with chronic stable angina involves a combination of proven secondary preventative strategies, conventional medications for symptom relief, and, in some selected suitable patients, revascularization therapy.

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**Keywords:** coronary artery disease, angina, management strategies

### Introduction

Diseases caused by atherosclerosis are widespread chronic conditions, among which coronary artery disease (CAD), in particular, is associated with high mortality and morbidity, and is the leading cause of death worldwide [1]. It is very prevalent in Western industrialized countries. For example, approximately 13 million Americans have CAD, with more than 50% having angina pectoris [2].

Angina is a clinical manifestation of CAD resulting from transient myocardial ischemia secondary to flow-limiting coronary atherosclerosis. Individuals may present with effort or stable angina, unstable angina, or acute coronary syndromes. Data on outcomes from randomized clinical trials for treatment of these clinical syndromes vary greatly and the evidence is much clearer in the treatment of the more acute and severe coronary syndromes. Conversely, there are much fewer trial data on management of patients with chronic stable angina, who form the majority of individuals with CAD. The three commonly used classes of anti-ischemic drugs –  $\beta$ -blockers, calcium channel blockers, and nitrates – are known to be effective in reducing the severity and frequency of stable effort angina, but there are no data on the effectiveness of these agents on outcomes such as death or myocardial infarction in the treatment of these patients. Patients with chronic stable

angina commonly receive a combination of conventional anti-ischemic medications for symptom relief, proven secondary prevention drugs, and, in selected suitable patients, revascularization therapy. These treatment strategies are based on extrapolation of trial data from patients after myocardial infarction and with acute coronary syndromes. Although secondary prevention strategies with  $\beta$ -blockers, antiplatelet agents, lipid-decreasing agents, and angiotensin converting enzyme inhibitors are recommended in high-risk individuals with a previous history of myocardial infarction and other vascular diseases, irrespective of whether or not they have current angina, the role of and contributions from other strategies such as routine revascularization or use of some of the newer anti-anginal medications are still being evaluated. A balanced approach to the appropriate stepwise management of patients with stable angina would be helpful for clinicians.

### Case presentation

A 55-year-old man is referred to a community cardiologist with symptoms consistent with stable Canadian Cardiovascular Society (CCS) class II/III angina that he has experienced for the previous 12 months without changes in severity and frequency. His only cardiac risk factor is hypertension. He has

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had no history of myocardial infarction or congestive heart failure. His current medications include enteric-coated aspirin 81 mg daily, atorvastatin 10 mg daily, and bisoprolol 2.5 mg daily. His resting heart rate is 84 beats/min, his blood pressure is 150/70 mm Hg, and his body mass index is 30 kg/m<sup>2</sup>; otherwise, his examination findings are within normal limits. His baseline electrocardiogram demonstrates voltage criteria for left ventricular hypertrophy with strain pattern.

Because the baseline electrocardiogram is abnormal, an exercise sestamibi nuclear perfusion scan is performed. He achieves a target heart rate of 85% and the exercise is stopped because of limiting chest pain. The nuclear imaging reveals a normal ejection fraction without transient ischemic dilatation. A reversible perfusion defect of moderate size in the distribution of the distal left anterior descending artery is noted.

### Clinical questions

Given that this patient's angina is limiting his day-to-day activities, and that there is no evidence of proximal flow-limiting coronary artery disease on exercise perfusion imaging, what is the next appropriate step in his management? Are further investigations required? What does the evidence suggest?

### Discussion

The treatment of angina is multifaceted. Secondary prevention strategies are crucial in the management of CAD, but some of the drugs used often offer limited relief of anginal symptoms. Angiotensin-converting enzyme inhibitors and statins do not directly reduce angina, but have beneficial indirect anti-ischemic effects. Lifestyle modification counseling should be provided; however, although cessation of smoking, weight loss, balanced healthy-heart diet, and regular exercise are important in reducing the mortality and morbidity associated with CAD [3], poor uptake and compliance with lifestyle counseling are major issues. In patients with established CAD, strong evidence supports the use of medications aimed at platelet inhibition with aspirin, decreasing cholesterol by means of a statin, and blood pressure control, particularly with a  $\beta$ -blocker, and an angiotensin converting enzyme inhibitor [4,5].

Conventional anti-ischemic medical therapies with  $\beta$ -blockers, calcium channel blockers, and nitrates improve symptoms by easing the balance between myocardial oxygen demand and supply in stable angina. Many studies have demonstrated the effectiveness of these agents. A meta-analysis of 90 randomized controlled trials comparing nitrates,  $\beta$ -

blockers, and calcium channel blockers demonstrated no significant difference between them, with respect to cardiac death or myocardial infarction, in the treatment of stable angina [6].  $\beta$ -Blockers tended to be better tolerated and to reduce the frequency of angina [6], and as  $\beta$ -blockers are also indicated for secondary prevention in patients who have suffered myocardial infarction, the use of these agents is particularly appropriate. The choice of which of these agents to use as initial treatment is usually made by considering the patient's other associated comorbidities. The choice for  $\beta$ -blockers can be made if the patient has suffered myocardial infarction, or has heart failure or hypertension; however,  $\beta$ -blockers are contraindicated if the patient has reactive bronchospastic airway disease. Calcium channel blockers may be used in situations in which  $\beta$ -blockers are not effective when used as sole therapy or are contraindicated. Nitrate monotherapy is usually inadequate, and there is concern about development of nitrate tolerance associated with long-term use. Often, a combination of nitrates,  $\beta$ -blockers, or calcium channel blockers is required for better control of symptoms compared with monotherapy [7].

Coronary revascularization, usually reserved for angina that is intractable to medical therapy, has made numerous advances in the past decade. With improving surgical techniques, rates of in-hospital mortality less than 1.8% for all patients undergoing coronary artery bypass grafting have been reported [8]. However, in the absence of high-risk features on the coronary angiogram (left main or multivessel disease, including stenosis of the proximal left anterior descending artery combined with left ventricular dysfunction), surgical revascularization fails to offer a prognostic benefit [9].

Percutaneous coronary intervention (PCI) has also been shown to be effective in reducing angina. With the advent of drug-eluting stents, PCI offers significantly reduced rates of target lesion revascularization up to 4 years of follow-up when compared with bare-metal stents (20% compared with less than 8%, depending on the type of drug-eluting stent,  $P < 0.001$ ) [10] and, presumably, this advance will prevent recurrence of angina as a result of restenosis of the treated lesions. However, the procedure does not affect other lesions in the coronary tree. Clinicians and patients are often under the impression, from extrapolation of the trial data on PCI in acute coronary syndromes and myocardial infarction, that PCI will similarly improve the prognosis for myocardial infarction or death in patients with stable angina. There are no data to support this belief. The role of routine PCI as an initial strategy as a background to optimal medical therapy for the treatment of chronic stable angina in patients has been evaluated by the Clinical Outcomes Utilizing Revascularization and Aggressive Drug

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Evaluation (COURAGE) trial, which allocated 2287 patients with stable CAD and angina randomly to groups to receive either PCI and optimal medical therapy or optimal medical therapy alone, in order to determine whether PCI would have the additional advantage of conferring a better prognosis [11]. At a median follow-up of 4.6 years, the cumulative primary event rates of death and non fatal myocardial infarction were 19.0% for the PCI group and 18.5% for the optimal medical therapy group (hazard ratio 1.05, 95% confidence interval [CI] 0.87 to 1.27,  $P=0.61$ ). Rates for the combined endpoint of death, myocardial infarction and stroke were 20.0% and 19.5%, respectively (hazard ratio 1.05, 95% CI 0.87 to 1.27,  $P=0.62$ ). There were no significant differences between the groups with respect to other clinical outcomes. Patients from both groups had substantial improvements in angina control from the start of the trial although the proportion of angina free patients in the PCI group were significantly higher than the optimal medical therapy group during the early phase of follow-up. At year one of follow-up, the proportion of patients who were free of angina in the group given PCI plus optimal medical therapy was 66%, compared with 58% in the group receiving optimal medical therapy alone ( $P < 0.001$ ), compared with 12% and 13%, respectively, who were free of angina at baseline. Such between-group differences in angina were not observed after the first 2 years. At 5 years of follow-up, approximately 73% of patients were free of angina in both groups, without a difference between the groups. Given these findings, an initial approach with medical therapy for the treatment of chronic stable angina for all patients should be undertaken. In patients with persisting symptoms of angina, PCI can be considered for treatment of the angina, in the knowledge that there is no added benefit in reducing the risk of death or myocardial infarction.

A proportion of patients with angina do not respond adequately to conventional antianginal treatments and are not amendable to revascularization, but may still experience limiting chest pain. A number of new antianginal treatments and interventions are currently being investigated.

Metabolically acting agents such as trimetazidine and ranolazine have protective anti-ischemic effects by increasing glucose metabolism relative to that of fatty acids. They both act through inhibition of fatty acid oxidation to increase cardiac metabolic efficiency and, more importantly, by preventing calcium overload in ischemic myocytes resulting in decreased diastolic tension [12,13]. For the past 20 years, trimetazidine has been used throughout Europe and over 90 countries worldwide for the treatment of stable angina. In stable effort angina, it affords improvements in exercise tolerance and increases ischemic

threshold at least as great as those obtained with  $\beta$ -blockers or calcium antagonists [14,15]. A meta-analysis of 12 randomized, controlled, clinical trials confirmed that trimetazidine is an effective antianginal agent when used alone or in combination with traditional hemodynamic agents [16].

In placebo-controlled clinical trials involving more than 1500 patients, ranolazine has been demonstrated clinically to increase exercise duration and reduce the frequency of angina when used alone or in combination with other antianginal drugs [17–19]. However, in a large randomized controlled trial in more than 6500 patients with non ST-elevation acute coronary syndromes, ranolazine did not offer a benefit over placebo in the primary endpoint of cardiovascular death, myocardial infarction, or recurrent ischemia [20]. Despite this finding, its effectiveness in angina relief is a welcome addition in management of angina.

Ivabradine, recently licensed by the European Medicines Agency (EMA), offers an innovative approach to the management of stable angina thanks to its selective and specific inhibition of the  $I_f$  current of the myocardial sinus node, thus providing pure reduction in heart rate and antianginal efficacy [21,22]. The efficacy of ivabradine in improving prognosis is currently being evaluated in a large morbidity–mortality trial (The Morbidity–Mortality Evaluation of the  $I_f$  Inhibitor Ivabradine in Patients with Coronary Disease and Left Ventricular Dysfunction [BEAUTIFUL] Study) [23].

Non pharmaceutical strategies that have demonstrated interesting trends toward symptom improvement, increased exercise duration, and reduced admissions to hospital in a few small trials and registries include transmyocardial laser revascularization, enhanced external counterpulsation, and spinal cord stimulation [24–26]. However, the only blinded, placebo-controlled trial evaluating the benefits of transmyocardial laser revascularization did not demonstrate improvements in anginal class, survival, and quality of life [27]. Such interventions are not standard practice, and further studies are required [28].

### **Back to the case study**

The next appropriate step in the management of this patient involves three components.

First, aggressive secondary preventative strategies need to be introduced. Lifestyle modifications, including counseling on weight loss, nutrition, and regular exercise, while difficult to implement and maintain, are essential for the comprehensive care of patients with CAD. Medical treatments, including continued antiplatelet therapy with aspirin, decreasing

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cholesterol by means of a statin, and control of blood pressure with an angiotensin converting enzyme inhibitor,  $\beta$ -blocker, or both, are important for conferring long-term clinical benefit. The doses of these medications should be adjusted to achieve maximal benefits.

Secondly, antianginal treatments can be maximized to improve quality of life. A stepwise approach, first with a  $\beta$ -blocker (giving mortality and antianginal benefits), then with calcium channel blockers, nitrates, or both, should be uptitrated to obtain relief of symptoms.

Finally, should the patient still experience limiting angina despite maximal medical treatment, revascularization therapy with either coronary artery bypass grafting or PCI should be considered. This approach follows the current standard guidelines [28].

In the very unlikely event that the patient develops intractable angina despite these interventions, alternative and newer antianginal treatment modalities may be considered. ■

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