abstract

Chronic stable angina is a common condition in older patients. Although lifestyle modifications such as weight loss, smoking cessation, and risk factor control remain fundamental components of the management strategy, pharmacological agents are necessary to prevent and control anginal symptoms. Sublingual nitroglycerin (either as tablets or a spray) is the most effective agent to terminate an episode of anginal pain. Anginal frequency and exercise tolerance are improved with beta-adrenergic blockers, calcium channel blockers, and long-acting nitrate preparations. A strategy for the optimal use of these agents both alone and in combination is discussed.

Key words: angina pectoris, nitrates, beta-blockers, calcium channel blockers

ABCs of Prescribing Antianginal Therapy in Chronic Stable Angina

David Fitchett MD, FRCP(C), Cardiologist, St Michael's Hospital, Associate Professor of Medicine, University of Toronto, ON.

Introduction

Chronic stable angina is usually the consequence of atherosclerotic narrowing of the coronary arteries. The arterial narrowing results in a reduced ability for coronary blood flow to increase when the metabolic demands of the heart are greater, such as when the patient exerts. It is the imbalance between an inadequate blood supply for myocardial oxygen needs that causes myocardial ischemia. Myocardial ischemia can provoke the symptoms of angina pectoris or occur without symptoms (silent ischemia). In addition, myocardial ischemia can cause atypical symptoms that are not immediately recognized as being due to coronary heart disease.[1] The older patient with chronic ischemic heart disease may develop typical symptoms of angina pectoris, such as retrosternal chest pain provoked by exertion (with radiation to the jaw or arms) and relief from both rest and the use of sublingual nitroglycerin. Yet many older patients with myocardial ischemia do not develop chest discomfort as their principal symptom but instead complain of dyspnea. If pressed, they will admit to having a mild chest discomfort in association with the dyspnea. The absence of anginal chest pain in older patients with myocardial ischemia has been attributed to their limited exertional capacity.

Management of Angina Pectoris

The goals of treatment of the older patient with angina are to relieve symptoms, reduce the risk of fatal and nonfatal myocardial infarction, and identify high-risk patients who may have a better outcome with coronary revascularization. Drug therapy to reduce the frequency of anginal pain is a small, albeit important, part of the initial management of the patient with angina (Table 1).[2]

The older patient with stable angina pectoris should have a risk assessment to identify high-risk individuals who may benefit from coronary artery revascularization by either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) at an early stage. A full medical history and physical examination are necessary to identify high-risk individuals as well as factors that may have aggravated or provoked the onset of angina.

Lifestyle modification (such as cessation of cigarette smoking and weight loss) and recognition of predisposing factors (such as anemia, aortic stenosis, or uncontrolled atrial fibrillation) may eliminate the need for antianginal medications. Furthermore, it is important to initiate risk factor modification (such as blood pressure control and cholesterol lowering medication) and other measures (such as acetylsalicylic acid [ASA][3,4] and angiotensin-converting enzyme [ACE] inhibition) that have proven benefit in the prevention of fatal and nonfatal myocardial infarction and stroke.

Antianginal Therapy

Antianginal therapy aims to increase the threshold where the imbalance between myocardial oxygen demands exceeds the supply (Figure 1). Medications such as nitroglycerin favourably restore the balance by reducing oxygen demands as a consequence of venodilatation and the resulting reduction of left ventricular volume. A smaller heart has lesser energy

demands. Vasodilating the larger coronary arteries, and preventing vasospasm associated with a coronary stenosis, thereby increases oxygen supply.

Nitrates

Nitrates can be used both to abort an anginal attack as well as to reduce the frequency of symptomatic angina. All patients with angina should be given nitroglycerin tablets or spray to shorten an episode of chest pain. Nitroglycerin spray is the preferable format. Although more expensive in the short-term, the spray contents remain active for up to two years (or until the expiry date on the canister). In contrast, once a bottle of nitroglycerin tablets is opened the nitroglycerin rapidly evaporates from the tablets. Consequently, nitroglycerin tablets need replacing within two months of initial usage.

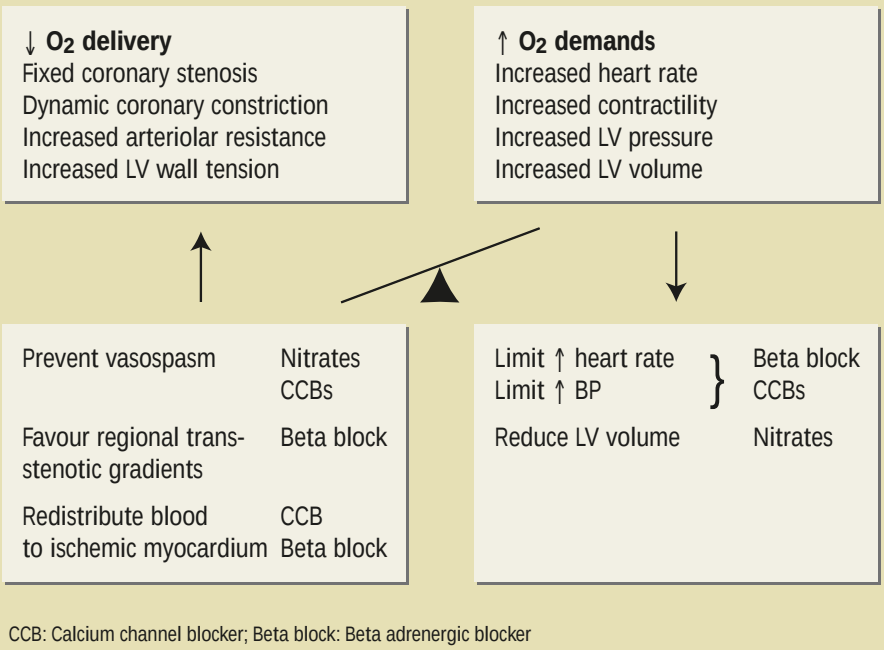
Patients need to have clear instructions about the use of sublingual nitroglycerin. They should be instructed to take one tablet or one spray (only one spray and not multiple puffs) under the tongue as soon as they feel the onset of chest discomfort. If the chest discomfort persists after five minutes a second dose can be taken. A third dose may be taken after a further five-minute period. If the chest pain persists five minutes after the third dose, the patient should be advised to seek medical advice at the nearest hospital emergency department or call for emergency medical services. Sublingual nitroglycerin tablets and spray can also be used prophyllactically in circumstances when angina may be provoked.

Sublingual nitroglycerin can cause hypotension and postural syncope that is relieved by lying down and elevating the lower limbs. However, most patients only have a small and transient fall in systolic blood pressure, and nitroglycerin is more likely to relieve angina if the patient is seated rather than supine. Yet patients should be advised to remain seated for several minutes after taking sublingual nitroglycerin to avoid postural hypotension.

Long-acting nitrate preparations, such as isosorbide dinitrate or mononitrate, and slow-release formulations such as transdermal nitroglycerin patches, are equally beneficial in preventing recurrent anginal episodes. However, because of side effects and the need for intermittent treatment, they should only be considered for patients who cannot tolerate, or fail to adequately respond to, beta-blockers or calcium channel blockers. Nitrate tolerance appears rapidly when continuous nitrate treatment is administered and can be prevented given a sufficiently long nitrate-free interval. For the transdermal nitroglycerin patch, it is recommended that it only be applied for 12 hours. The timing of the patch application should coincide with the most frequent occurrence of anginal attacks. Patients with nocturnal angina often have relief by wearing the patch at night rather than during the day. Newer long-acting mononitrates have the advantage of improved bioavailability, as they avoid first-pass hepatic elimination and are at least as effective as isosorbide dinitrate in relieving angina. Headache can be an important limitation of nitrate therapy in some older patients. Often the headache is worst during initiation of treatment, and will diminish after seven to 10 days. Starting with the smallest dose of nitrate, and encouraging the patient to persist with the help of ASA or acetaminophen, will usually result in success.

Nitrates must not be taken if the patient is using PDE-5 inhibitors—e.g., sildenafil, tadalafil, or vardenafil—as the combination can cause life-threatening hypotension. Sublingual nitroglycerin should not be taken until 12–18 hours after taking sildenafil or vardenafil, and 36 hours after tadalafil. As the PDE-5 inhibitors are metabolized by the cytochrome P450 system, agents such as ketoconazole, erythromycin, and the protease inhibitors will prolong the duration of action and the risk of a serious interaction.

Figure 1: Oxygen Demand Imbalance and Mechanisms of Antianginal Medications



CCB: Calcium channel blocker; Beta block: Beta adrenergic blocker

Beta-Adrenergic Blockers

In the absence of contraindications, beta-adrenergic blockers (β-blockers) should be used as the initial medication to reduce anginal symptoms in all patients, including the aging. Beta-blockers, by blocking β1 adrenergic receptors on the myocardium, reduce stress- induced heart rate, contractility, and blood pressure, all of which are major determinants

Table 1: Management of the Older Patient with Stable Chronic Angina Pectoris

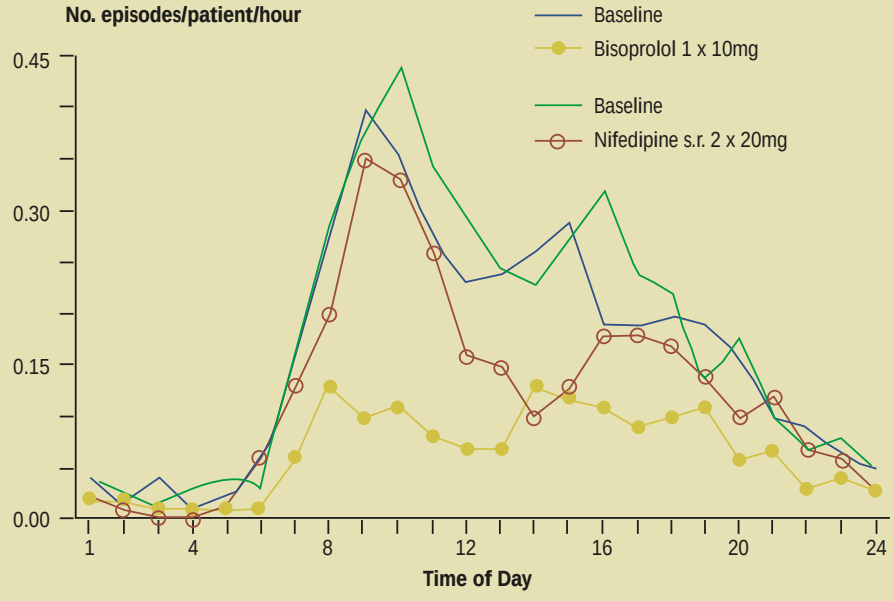
Risk assessment	Severity of angina Recent myocardial infarction History of heart failure Comorbidity (e.g., diabetes, renal failure) Noninvasive stress testing
Identify and control precipitating factors	Anemia, hypertension, hyperthyroidism, uncontrolled atrial fibrillation, valvular heart disease (aortic stenosis)
Lifestyle modification	Weight loss, smoking cessation, regular exercise, avoidance of strenuous effort known to precipitate angina
Risk factor modification/vascular protection	Cholesterol lowering, blood pressure control, acetylsalicylic acid, ACE inhibition, glycemic control
Antianginal (anti-ischemic) medication	Nitroglycerin, beta-blockers, calcium channel blockers

of myocardial oxygen requirement (Figure 1). They also may improve blood flow delivery to ischemic heart muscle by prolonging diastolic perfusion time. Beta-blockers improve survival after a myocardial infarction and in patients with hypertension. Whether they improve survival for patients with stable exertional angina that have not had a myocardial infarction is unclear. However, β-blockers appear to provide a better reduction of ischemic episodes (both symptomatic and silent) than slow release nifedipine, especially during the high-risk morning peak of ischemic activity (Figure 2).[5]

All β-blockers have a similar efficacy in reducing anginal symptoms. However, highly specific β1-blockers such as bisoprolol, atenolol, and metoprolol may be better tolerated than the nonselective agents such as propranolol and nadolol. It is wise to start at a low dose and titrate β-blockers to a therapeutic dose over a two to four week period to avoid excessive bradycardia and severe adverse effects. The optimal dose of β-blocker should limit the increase in heart rate during exercise to 75% of the rate that provokes ischemia.[6] Resting heart rate is a poor measure of the adequacy of beta-blockade as the heart rate at rest is often more dependent on vagal than sympathetic tone. Consequently, it is preferable to gradually increase the dose of β-blocker to an initial maximal target dose (e.g., metoprolol 100mg b.i.d., bisoprolol 10mg daily, or atenolol 100mg daily), assessing for symptoms and adverse effects at each increment, especially excessive bradycardia. If anginal control is inadequate, then a decision is made whether to add other agents or to repeat the exercise test to determine the adequacy of beta-blockade. As renal dysfunction is frequent in the older patient, care should be exercised when using a β-blocker with renal clearance, such as atenolol and sotalol.

The most serious adverse effects of β-blockers are the provocation of asthma in patients with reactive airways and excessive bradycardia in patients with sinus or AV node disease. Absolute contraindications for β-blockers, unless a pacemaker is in place, include severe

Figure 2: Myocardial Ischemic Episodes Peak in the Early Morning



This study shows how the long acting beta-blocker bisoprolol is more effective in reducing the early morning surge of ischemia than the slow-release nifedepine preparation.

bradycardia (resting rates <50 beats/minute), sick sinus syndrome, and high-degree AV block. Patients with chronic obstructive pulmonary disease often have little reversible bronchospasm and can usually tolerate β-blockers. Asthma is a relative contraindication to β1-blockers and probably only applies when severe. Peripheral vascular disease is not an absolute contraindication as there is little evidence that selective β1-blockers cause any worsening of symptoms or threat to an ischemic limb. However, they ought to be avoided in patients with vasospastic disorders such as Raynaud's disease, rest pain with severe peripheral vascular disease, or nonhealing lesions. β1-blockers should be prescribed for diabetic patients with angina to minimize the chance of masking hypoglycemic symptoms. Only unstable diabetics with frequent hypoglycemic episodes should be denied β-blockers to control anginal symptoms. The adverse CNS symptoms of fatigue, depression, insomnia, and nightmares may be minimized by using a hydrophyllic agent, such as atenolol or nadolol, that is less likely to cross the blood brain barrier.

Calcium Channel Blockers

Calcium channel blockers are divided into three principal classes: i) the dihydropyridines (such as nifedipine, amlodipine, and felodipine), ii) the benzothiazepine derivatives (such as diltiazem), and iii) the papaverine derivatives (such as verapamil). The major difference between the classes of calcium channel blockers relates to their electrophysiological properties. Whereas the nondihydropyridine agents diltiazem and verapamil depress sinus and AV nodal function, the dihydropyridines have almost no electrophysiological effects. All calcium channel blockers vasodilate vascular smooth muscle and have negative inotropic effects to varying degrees. The second generation dihydropyridine agents amlodipine and felodipine appear to have less negative inotropic effect and are relatively well tolerated in older patients with controlled heart failure. At the other extreme, verapamil not only slows the heart rate but with important negative inotropic properties, and is poorly tolerated in patients with poor cardiac function. Diltiazem has less negative inotropic properties, but remains a potent inhibitor of sinus node activity and AV nodal conduction.

All three groups of calcium channel blockers have similar antianginal properties. When patients undergo exercise studies after taking diltiazem, the submaximal exercise heart rate blood pressure product (HRxBP) is lower for each level of effort, suggesting that diltiazem reduces myocardial oxygen demand for a given work load. Furthermore, the HRxBP is increased at the onset of angina and myocardial ischemia, indicating that myocardial blood flow has increased. When calcium channel blockers were compared to beta-blockers,[7] an analysis of 61 studies suggested mortality and myocardial infarction rates were similar. Beta-blockers were more effective in reducing the frequency of angina and increasing exercise time than calcium channel blockers. However, the calcium channel blockers appeared to be better tolerated than the β-blockers.

For patients unable to take β-blockers, either a dihydropyridine such as a slow-release nifedipine and amlodipine, or diltiazem (as a slow-release preparation) offer symptomatic relief. Both diltiazem and verapamil should be avoided in patients with heart failure, severe left ventricular systolic dysfunction, or sinus node or AV conduction abnormalities.

A combination of β-blockers and calcium channel blockers may be effective in reducing the frequency of anginal attacks. Theoretically, the benefits of the two classes of agents should work synergistically. In six controlled studies of calcium channel blockers (two with nifedipine, two with verapamil, and two with diltiazem), the combination with β-blockers was effective in reducing anginal frequency and exercise duration.[8] However, the response from the combination was only slightly better than that observed with the calcium channel blocker alone. The combination of a β-blocker and diltiazem should be used with extreme caution, especially in older patients who have a high incidence of conduction abnormalities and left ventricular dysfunction.

Choosing a Therapeutic Regimen

Management of stable angina includes eliminating or controlling specific coronary risk factors (e.g., hypertension and hyperlipidemia), implementing lifestyle changes (e.g., cessation of smoking, exercise) to reduce the risk of coronary artery disease, controlling precipitating factors (e.g., anemia, rapid atrial fibrillation), and prescribing appropriate anti-ischemic medicines. The anti-ischemic medical regimen should not only reduce the frequency of chest pain and improve exercise tolerance, but also lessen the likelihood of silent episodes of myocardial ischemia. Treatment needs to be sufficiently long-acting to cover the early morning surge of myocardial ischemia and symptomatic angina that begins when the patient arises (Figure 2). In the QUART study,[9] the use of long-acting preparations of anti-ischemic medication resulted in improved symptom control, more treatment satisfaction, a better quality of life, yet no increase in exercise performance.

An anti-ischemic therapeutic regimen (Table 2) should always include

Table 2: The ABCs of Antianginal Medication

First-line	ASA and sublingual nitroglycerin prn for all patients Risk factor modification
Second-line	Beta-adrenergic blockers (β-blockers)
Third-line	Calcium channel blockers (either alone or with β-blockers) Long-acting nitrates or topical nitroglycerin

Table 3: Choice of Antianginal Medication with Coexistant Medical Condition

	Recommended Use	Use with caution or avoid
Hypertension	CCB β-blocker	–
Heart failure or severe LV dysfunction	Nitrate β-blocker (with care) DHP CCB	non DHP CCB
Post AMI	β-blocker (without ISA)	non DHP CCB
SVT	β-blocker Non DHP CCB	DHP CCB
VT	β-blocker	–
Asthma/COPD	CCB	β-blocker
Raynaud's disease	DHP CCB	β-blocker

Severe LV dysfn: left ventricular ejection fraction <30%; Post AMI: after acute myocardial infarction; SVT: supra ventricular tachycardia; VT: ventricular tachycardia; COPD: chronic obstructive pulmonary disase; DHP CCB: dihydropyridine calcium channel blocker; NON DHP CCB: nondihydropyridine calcium channel blocker.

acetylsalicylic acid and sublingual nitroglycerin (tablets or spray). This may be adequate anti-ischemic medication for the patient with occasional angina and ischemia at a higher level of exercise. For the patient with more than the occasional episode of exertional angina, a β-blocker should be prescribed and titrated to an adequate dose. Coexistent medical conditions may make a β-blocker an undesirable choice (Table 3) and a calcium channel blocker then becomes the preferred choice.

If the patient has angina that persists despite reasonable medical therapy, revascularisation by percutaneous coronary intervention (PCI) should be considered. Unless a coronary angiogram is performed it is not possible to determine whether PCI is an option. An invasive approach should be considered in nearly all patients (whatever the age) if medical treatment has not adequately controlled the angina. When coronary bypass surgery is not a feasible option, it is important that the patient understands that a coronary angiography may not lead to revascularisation if the anatomy is not suitable for PCI.

Conclusions

The majority of patients with angina can be managed effectively with antianginal medication. The choice of antianginal medication depends upon angina frequency, provocation, and timing, as well as any underlying comorbidity.

Coronary risk factor management is likely to have the greater impact on future cardiovascular outcomes than antianginal medication. Referral for coronary angiography and revascularization should be considered in high-risk patients at the time of initial presentation and those who fail to achieve adequate control with pharmacological treatment and lifestyle modification.

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