HEART DISEASE

(2) CHRONIC STABLE ANGINA

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Chapter 4 of the National Service Framework for Coronary Heart Disease targets stable angina. This article focuses on the use of anti-anginal therapies to manage the symptoms.

**Identify gaps in your knowledge**

1. What are the aims of managing stable angina?
2. What factors may influence the type of beta-blocker prescribed to prevent attacks of angina?
3. What is the rationale behind the use of combined therapy?

This article relates to the Royal Pharmaceutical Society’s core competency of “common disease states and their drug therapies” (see “Medicines, ethics and practice — a guide for pharmacists”, number 26, July 2002, pp105–6). You should consider how it will be of value to your practice.

**Symptom control**

Symptom control can be achieved either by improving myocardial oxygen supply or reducing cardiac workload (thus reducing myocardial oxygen demand) or both.

The NSF recommends that acute chest pain is treated initially with sublingual nitrate therapy.2 Background (prophylactic) therapy with beta-blockers, other nitrates or calcium channel blockers is indicated in all patients to prevent recurrence of an attack, except in those with minimal and predictable symptoms manageable with sublingual nitrates alone.3 There is little clinical trial data demonstrating conclusively the benefits of one class of agent over another, although some classes have theoretical benefits and data can be extrapolated from studies of other manifestations of coronary heart disease.

**Beta-adrenoceptor blocking agents** Beta-blockers should be considered as first-line therapy for all patients with angina in the absence of contraindications.4 Beta-blockers reduce the rate and force of cardiac contraction, and reduce arterial blood pressure. The net effect is a reduction in cardiac workload. Beta-blockers also improve coronary perfusion during diastole and therefore myocardial blood supply is improved. Furthermore, they protect against exercise-induced vasoconstriction (by preventing the sympathetic response to exercise or stress), have anti-arrhythmic properties, anti-hypertensive effects and a cardioprotective function.

Beta-blockers have been shown to be at least as effective as other anti-anginal drugs in reducing the frequency and severity of attacks in patients with effort angina. A number of trials have compared beta-blockers with calcium channel blockers and a recent meta-analysis concluded that beta-blockers and calcium channel blockers were equally effective at preventing exercise-induced chest pain, but that beta-blockers were better tolerated5 (although the latter assertion has been refuted by other studies).

The ASIST study demonstrated increased event-free survival at one year with atenolol treatment in patients with “silent” ischaemia.
(angina symptoms presenting with little or no pain) when compared with placebo. Moreover, beta-blockers have been shown to reduce the risk of reinfarction in patients with previous MI and also to reduce the risk of first infarction in patients with angina. In addition, because most episodes of angina are accompanied by tachycardia, the rate-controlling effect of beta-blocker therapy is thought to contribute to their benefits in this setting. When prescribed at an adequate dose, all beta-blockers have anti-anginal effects. The dosage should be titrated to achieve a resting heart rate of between 50 and 60 beats per minute (maximal beta-blockade). Half-life will determine the duration of action and frequency of administration, and once-daily agents are often preferred to aid concordance. Patients should be counselled to avoid abrupt cessation of beta-blocker therapy because this has been associated with increased risk of cardiovascular events.

There is no evidence to suggest that one beta-blocker has more efficacious anti-anginal effects than any other, although some patients may respond better to a particular agent in clinical practice. Agents can be distinguished in terms of characteristics such as degree of cardioselectivity, clearance method and lipid solubility. Since beta-receptors are also found in the lungs and peripheral tissues (predominantly beta1-receptors) as well as in cardiac muscle (predominantly beta2-receptors), beta-blockers can cause bronchospasm. The Committee on Safety of Medicines has warned against the use of beta-blockers in patients with a history of asthma or bronchospasm but a recent Cochrane collaboration review has concluded that there is no strong evidence to support withholding cardioselective beta-blockers (eg, atenolol, bisoprolol) from patients with mild to moderate reversible airways disease. 

Cardioselective agents may be preferred in the presence of other co-morbidities such as peripheral vascular disease or diabetes.

Agents with greater lipid solubility are likely to be metabolised by the liver, and water soluble-agents are generally excreted via the kidneys unchanged. Concurrent liver or renal impairment may therefore determine the most appropriate agent.

Since control of heart rate is an important aspect of beta-blocker therapy in angina, agents with intrinsic sympathomimetic activity (eg, oxprenolol, celiprolol) are no longer routinely prescribed. Sotalol should not be prescribed for the management of angina due to pro-arrhythmic adverse effects and is licensed only for the treatment of supraventricular arrhythmias.

Common adverse effects of beta-blockers include bradycardia and hypotension (dose reduction may be necessary), cold extremities, lethargy, fatigue and impotence (patients should be reassured that not all patients suffer with this adverse effect, and therapy can be reviewed if it becomes a problem for them). Agents with greater lipid solubility (particularly propranolol) penetrate the blood brain barrier and can cause central adverse effects (eg, insomnia, depression), compared with water soluble agents (eg, atenolol, celiprolol).

**Calcium channel blockers** Calcium channel blockers inhibit the flow of calcium ions through open calcium channels into cells. This calcium influx is responsible for mediating the contraction of cardiac muscle. Calcium channel blockers can be subdivided into the dihydropyridines (eg, nifedipine, amlodipine, felodipine) and non-dihydropyridines (diltiazem and verapamil). These subtypes have distinctive properties which determine their use in clinical practice.

Calcium channel blockers have three main effects: peripheral vasodilatation (especially the dihydropyridines), coronary vasodilatation (all agents but particularly verapamil and diltiazem) and reducing the rate and force of cardiac contraction (diltiazem and verapamil). Calcium channel blockers have been shown to be effective anti-anginal agents, producing a reduction in angina episodes compared with placebo, and a recent meta-analysis concluded that these agents were as effective as beta-blockers in the prevention of effort-induced angina. However, there remains some debate over the relative tolerability of these two classes, with conflicting conclusions drawn in the two large-scale meta-analyses undertaken to date. 

Also, data showing a reduction in cardiac events in patients with CHD treated with calcium channel blockers are lacking although post-MI studies indicate that the non-dihydropyridines verapamil and diltiazem, may reduce mortality and reinfarction.

Calcium channel blockers should therefore be considered as first-line therapy in patients with angina, in whom beta-blocker therapy is contraindicated or not tolerated. Short-acting dihydropyridines (eg, nifedipine) have been linked to increased mortality and morbidity and therefore longer-acting agents (eg, amiodipine, felodipine) or modified release formulations are preferred. The rate-controlling effects of verapamil and diltiazem are believed to confer similar advantages as are seen with beta-blocker therapy and may confer additional benefits over dihydropyridines.

Calcium channel blockers should also be considered for use in combination with beta-blockers, nitrates or nicorandil in patients for whom monotherapy is ineffective. Dihydropyridines are safer in combination with beta-blockers due to the lower risk of precipitating bradycardia or heart block. Furthermore, increases in heart rate have been associated with some dihydropyridines, an effect that can be offset by use in combination with beta-blockers. The combination of diltiazem and beta-blockers may be used with caution, but co-prescribing of verapamil and beta-blockers should be avoided (due to risks of bradycardia and heart block). Verapamil must not be used in the setting of left ventricular dysfunction.

Common adverse effects seen with calcium channel blockers include constipation (especially with verapamil and diltiazem), headaches and flushing, swelling of the ankles (especially with dihydropyridines) and bradycardia (especially with non-dihydropyridine agents).

**Nitrates** Nitrates mimic the effects of endogenous nitrous oxide (previously known as endothelium derived relaxing factor) resulting in powerful vasodilatory effects. The net effect of nitrate therapy is to improve coronary blood flow, and to reduce preload (venodilation decreases the return of blood to the heart) and afterload (arterial dilatation reduces the peripheral vascular resistance). Nitrates protect against exercise-induced ischaemia by preventing coronary spasm and coronary arterial vasoconstriction induced by exercise. Sublingual nitrates are the treatment of choice in patients suffering an acute episode of chest pain.

As with all agents used to prevent angina, there are little data to show significant clinical outcomes although surrogate markers, such as increased exercise tolerance, are frequently used to assess efficacy. Short-acting tablets have been the traditional choice in the prevention of angina. These agents have a duration of effect of up to five hours and need to be taken twice or three times daily. Longer-acting oral nitrate preparations (eg, Imdur, Elantan LA) need only...
be administered once daily. These preparations are increasingly popular because of perceived improved patient compliance with once daily regimens and improved therapeutic control.

To avoid the development of nitrate tolerance with chronic use, it is essential that dosing schedules allow for a nitrate-free period. This is when the nitrate levels in the body are allowed to fall to a low level for at least eight hours in each 24-hour period. Without this, tolerance to continuous dosing of nitrates can develop rapidly — within just a few days. The nitrate-free period can be planned for a time when the patient is least likely to suffer from chest pain, for example, at night when the patient is at rest (this will be patient specific). A suitable dosing regimen where isosorbide mononitrate is prescribed twice daily, would be to give the first dose at 8am and the second dose no later than 4pm leaving a nitrate-free period overnight (this is known as eccentric or asymmetric dosing). Some slow release preparations release nitrate slowly over 15 to 20 hours, allowing for an in-built nitrate-free period every 24 hours. Such preparations should therefore not be prescribed twice daily for angina prophylaxis.

Oral nitrates should be considered as adjunctive therapy for the prophylaxis of anginal attacks and may be used in combination with a beta-blocker, a calcium channel blocker or nicorandil therapy to improve symptom control. Oral nitrates are generally not suitable as monotherapy, due to the problem of tolerance, failure to give full 24-hour control and the potential to precipitate reflex tachycardia.

Headache is a common adverse effect and may contribute to poor compliance, particularly at initiation of therapy. Nitrate-induced headache is due to cerebral vasodilatation and is usually transient, typically lasting three to seven days into treatment. Patients should therefore be encouraged to persevere with the therapy for at least seven days, using simple paracetamol-based analgesics when required to control any headaches.

**Potassium channel activators** Nicorandil, a potassium channel activator, relaxes vascular smooth muscle resulting in dilation of the coronary and peripheral vasculature. It has similar effects to nitrates (being largely a nitrate-like compound) but there are no tolerance problems. As with other anti-anginal therapies, nicorandil has been shown to reduce the frequency of anginal episodes. It must be used twice daily, at 12-hourly intervals, to ensure a full 24-hour effect. Small doses such as 5mg twice daily may be prescribed initially to limit the occurrence and severity of headaches. Doses should be titrated to ensure adequate control of anginal symptoms.

Nicorandil has been used successfully as monotherapy and in combination with other agents to control symptoms. The drug should be considered for monotherapy in patients intolerant to beta-blockers or rate-limiting non-dihydropyridine calcium channel blockers. Nicorandil should be considered for use in combination with beta-blockers, calcium channel blockers or nitrates in patients in whom monotherapy is ineffective.

It has been postulated that nicorandil may have cardioprotective effects. A recent large-scale study (IONA) reported significant reductions in the combined endpoint of mortality and morbidity in patients randomised to receive nicorandil in addition to standard therapy, compared with placebo. In view of these favourable results nicorandil prescribing for the management of stable angina is likely to increase.

**Drug choice for symptom control**

As already discussed, each drug class has specific advantages and disadvantages. Drug choice should be tailored to the individual patient. Although beta-blockers are the first-line choice in the majority of patients, they may be contraindicated or poorly tolerated, or co-morbidities may make other options more favourable.

The addition of a second drug is appropriate in all patients remaining symptomatic despite monotherapy (see Panel 1 above). The combination of more than two agents is not evidence-based, and may confer no additional benefit over dual therapy. Referral for specialist investigation and management should be considered for all patients, but particularly for those requiring multiple anti-anginal therapies.

**Secondary prevention** Secondary prevention strategies to address cardiovascular risk in patients with established ischaemic disease will be covered by a later article in this series.

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**References**