Angina: management options overview

Around 330,000 new cases of angina are diagnosed in the UK each year. This article looks at the range of treatment options currently available and advice for patients.

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ANGINA occurs commonly in the UK with an estimated prevalence around 8 per cent of men and 3 per cent of women aged 55–64 years, and around 14 per cent and 8 per cent of men and women aged 65–74 years, respectively. This equates to over two million patients.¹

A diagnosis of angina can have a significant impact on a person’s quality of life, restricting daily work and leisure activities. In addition, patients with established coronary artery disease are at an increased risk of cardiovascular events such as myocardial infarction (MI).

**Terms**

Angina pectoris is a clinical syndrome caused by insufficient oxygen delivery to the heart muscle leading to ischaemia. It usually, although not exclusively, occurs as a result of an atheromatous narrowing (stenosis) in one or more of the coronary arteries.

Stable angina occurs predominantly as a consequence of exercise (“effort-induced angina”, which may include walking uphill or climbing stairs) or emotional stress. It can also be precipitated by extremes of temperature. This is the most common form of angina and can usually be well managed in primary care. Common features are listed in Panel 1. Pain will typically respond to sublingual glyceryl trinitrate in two to three minutes.

Patients can also experience “unstable angina” where there is a sudden deterioration in angina symptoms without any prognostic electrocardiogram changes or increases in cardiac enzymes that may indicate more severe myocardial damage. The pain during an attack of unstable angina is often more severe, persists longer and is less responsive to sublingual nitrates, and it can occur at rest. Despite the use of standard therapies, the risk of death, infarction, refractory angina or readmission to hospital following an episode of unstable angina is as high as 30 per cent within six months.²

Other, rarer, conditions also badged as angina are described in Panel 2.

**Interventions**

All patients with new onset angina need cardiological assessment to confirm the diagnosis and develop an individualised management plan. For most patients with stable (or unstable) angina the first step of treatment is drug therapy; but in selected high-risk patients early revascularisation may be appropriate, such as coronary artery bypass grafting or percutaneous coronary intervention (angioplasty, with or without coronary stent insertion).

In the long term, all patients with angina should be advised to make lifestyle changes (see Panel 3, p712) and be treated with standard secondary prevention therapies to reduce their long-term cardiovascular risk.

National Institute for Health and Care Excellence guidance for the management of stable angina sets out key elements of optimal angina care. It focuses on:

- Interventions to improve prognosis, using agents that...
have been shown to reduce cardiovascular risk (primarily antiplatelet agents and statins).

- Interventions to control symptoms, using anti-anginal therapies such as beta-blockers and calcium channel blockers to prevent episodes of chest pain.

These primary care strategies also apply following an episode of unstable angina.

**Improving prognosis**

All patients with angina due to atherosclerotic stenoses should be offered secondary prevention strategies to reduce their risk of future cardiovascular events. This should include aspirin and statin therapy, as well as control of other risk factors such as blood pressure, and blood glucose if diabetes or impaired glucose tolerance is present.

**Antiplatelet therapy**

Antiplatelet therapy, such as low-dose aspirin (75mg daily) in patients with coronary heart disease, including those with angina, reduces the risk of cardiovascular death, MI or stroke by approximately 25 per cent. This equates to approximately 22 serious vascular events avoided per 1,000 patients treated for two years. Similar results are seen with clopidogrel, which is a suitable alternative in patients unable to tolerate aspirin. All patients should be initiated on antiplatelet therapy as early as possible following diagnosis and, once initiated, antiplatelet therapy should be continued indefinitely.

**Lipid management**

Statin therapy has been shown to reduce cardiovascular mortality and morbidity in numerous trials since the publication of the 4S study in 1994. Meta-analysis of statin trials published in 2005 concluded that statin therapy reduced the risk of all-cause mortality by 12 per cent and the risk of any major vascular event by 21 per cent per mmol/L reduction in low density lipoprotein cholesterol. Over five years, statin therapy prevented approximately 23 major vascular events per 1,000 patients treated.

Patients taking statins are likely to have questions about the benefits of treatment, as well as the potential adverse effects. The most commonly prescribed statin in the UK is simvastatin, typically used at a dose of 40mg daily. This delivers on average a 1.8mmol/L (40 per cent) reduction in LDL cholesterol (from a baseline LDL of 4.8mmol/L). Doses of 10 and 20mg would deliver around 88 and 94 per cent of the efficacy of 40mg simvastatin, respectively (ie, between 1.5 and 1.7mmol/L reduction on average), so lower doses are still worth using if a patient cannot tolerate a higher dose. However, because atorvastatin is now off patent, it is likely that this agent will also be prescribed commonly — atorvastatin 10–80mg daily reduces LDL cholesterol by between 1.8 and 2.6mmol/L (40–55 per cent) from the same baseline LDL. Over several years of treatment, it has been estimated that a reduction in LDL cholesterol of 2–3mmol/L would reduce ischaemic heart disease events by 40–50 per cent.6 Be aware of the interaction between simvastatin and amiodarone, which is also commonly used in this patient group — the simvastatin dose should be reduced accordingly or an alternative agent considered.

Muscle aches and pains (myalgia) are commonly reported during statin therapy — myalgia itself (characterised by muscle weakness, cramps and spasms) is rare but is a severe adverse effect that can lead to the development of potentially life-threatening rhabdomyolysis (breakdown of muscle fibres). Myopathy can be excluded by measuring the creatine kinase (CK) levels in the blood, which become excessively raised with myopathy, and indicate that the statin should be stopped. If CK levels are normal, myalgia can be diagnosed — this is not dangerous, but can have an impact on patient adherence to therapy. Where myalgia is a substantial problem, switching to an alternative statin can help. Anecdotally, atorvastatin causes less myalgia than simvastatin. Where atorvastatin is also not tolerated — consider a water-soluble agent such as pravastatin or rosuvastatin.

Other common issues with statins include:

- Gastrointestinal side effects (Immediate effects, such as nausea after the dose, may be reduced by taking with or after food; for example with the evening meal.)
- Insomnia (Recommend the patient takes the statin earlier in the day. For shorter-acting agents, such as simvastatin, morning dosing reduces the efficacy by a small margin, but if quality of life is significantly enhanced as a result, this may be acceptable.)

**Controlling symptoms**

The symptoms of stable angina result from an imbalance between the oxygen requirements of the heart muscle and the supply it receives. Treatments are, therefore, aimed at:

- Improving myocardial oxygen supply and/or
- Reducing cardiac workload and hence myocardial oxygen demand

**GTN**

Sublingual GTN is indicated for the rapid symptomatic relief of acute angina symptoms as well as for prophylaxis against the development of predictable exertional chest pain. All patients with a diagnosis of angina should be supplied with sublingual GTN and counselled in how it should be used (see Panel 4 for a reminder of useful points). Patients using sublingual GTN more frequently than twice per week should be considered for regular prophylactic anti-anginal therapy.

NICE guidance clearly supports the use of one or two anti-anginal drug therapies first-line in most patients with stable symptoms. A beta-blocker or calcium channel blocker, or a combination of the two, should be considered before other options, but where these are contraindicated or not tolerated nitrates, nicorandil, ivabradine or ranolazine can all be used alone or as adjunctive therapies.

If patients cannot be controlled on two anti-anginal therapies, referral for revascularisation (CABG or PCI) should be considered.7

**Beta-blockers**

Beta-blockers have two main effects on the cardiac muscle, reducing both the rate and force of contraction, while also reducing arterial blood pressure. The net effect is a reduction in cardiac workload and myocardial oxygen requirements. Beta-blockers improve coronary perfusion when the heart muscle relaxes (ie, during diastole), which improves myocardial blood supply. Most episodes of angina are accompanied by increased...
Nicorandil has similar effects to nitrates (being largely a nitrate-like compound) but without the problem of tolerance.

Heart rate (tachycardia), and the rate-controlling effect of beta-blocker therapy is thought to contribute to the benefits in such cases.

Beta-blockers have been shown to be at least as effective as other anti-anginal drug therapies in reducing the frequency and severity of anginal symptoms in patients with effort-induced angina. However, beta-blockers may confer additional benefits over dihydropyridine agents, and may be particularly useful in patients unable to take beta-blockers. CCBs may also be considered for use in combination with other anti-anginal therapies by patients for whom monotherapy is ineffective. Dihydropyridine agents are safer in combination with beta-blockers due to a low risk of precipitating bradycardia or heart block. The combination of verapamil and beta-blockers is relatively contraindicated, and must not be used in the setting of left ventricular dysfunction. Neither verapamil or diltiazem should be used in combination with ivabradine (see later) due to an increased risk of bradycardia. Common adverse effects include constipation (especially with verapamil and diltiazem), headaches and flushing, swelling of the ankles (especially with dihydropyridines) and bradycardia (especially with non-dihydropyridine agents).

Other nitrates Nitrates mimic the effects of endogenous nitrous oxide (previously known as endothelium-derived relaxing factor), resulting in powerful vasodilatory effects. The net effect is to improve coronary blood flow and to reduce afterload and preload. This reduces the myocardial workload with a concurrent reduction in myocardial oxygen demand. Nitrates protect against exercise-induced ischaemia by preventing coronary spasm and coronary arterioconstriction induced by exercise.

Nitrates have been shown to reduce the frequency and severity of angina attacks if taken long-term at appropriate doses. Single doses of nitrates of between 15mg and 120mg have been shown to protect against effort-induced angina for up to eight hours, although nitrate tolerance has been observed when given regularly at these doses. Higher doses may be required to reduce angina frequency — one study using a longer-acting nitrate showed that only doses of 120–240mg once daily had a significant effect on effort-induced chest pain.

Glyceryl trinitrate relaxes the blood vessels and makes it easier for the heart to work. It can be used to relieve angina pain or to prevent an attack if used immediately before trigger events (eg, exposure to cold or exercise).

Make sure you keep your GTN with you at all times but it is best kept not directly next to the body (eg, keep it in a bag).

You may need to use your GTN spray urgently or in the dark, so you may wish to practise its use by spraying a few puffs into the air. You may also wish to make sure the pump is working properly by spraying it into the air if you have not needed to use it for a week.

Avoid alcohol — it increases the effects of GTN, including side effects.

A tablet should be allowed to dissolve slowly under the tongue. Repeat after five minutes if symptoms do not improve.

A second and third dose (tablet or spray) can be taken if pain is not alleviated but if pain persists seek immediate medical advice.

Once opened, the tablets keep for eight weeks only. (Some manufacturers say that fresh tablets should produce a slight burning sensation under the tongue and advise patients to obtain a new supply if this does not occur.)

Make sure you get a new spray (or tablets) before the old one runs out or expires.

If you find your GTN has become less effective, speak to your doctor or pharmacist — don’t increase the dose.

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prescribed twice daily, a suitable schedule would be to give the first dose at 8am and the second dose before 4pm. Long-acting nitrate preparations incorporate an in-built nitrate-free period releasing nitrate slowly over 15–20 hours.

Nitrate-induced headache caused by cerebral vasodilatation is a common problem and may be a factor in poor compliance, particularly at initiation. Tolerance to this effect develops rapidly with regular dosing (within three to seven days of initiation of therapy) and patients should, therefore, be encouraged to persevere with the therapy, using simple paracetamol-based analgesics where required.

Potassium channel activators
Nicorandil 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 without the problem of nitrate tolerance. As with other anti-anginal therapies, nicorandil has been shown to reduce the frequency of attacks, and has been used successfully as monotherapy as well as in combination with other agents to control symptoms. It should be considered for patients unable to tolerate beta-blockers or calcium channel blockers and for use in combination with beta-blockers, calcium channel blockers or other anti-anginals by patients for whom monotherapy is insufficient to control symptoms. Nicorandil must be used twice daily, at 12-hourly intervals, to ensure a full 24-hour effect. Small doses such as 5mg bd may be prescribed initially to limit the occurrence and severity of headaches. Doses should be titrated to a maximum of 30mg twice daily to ensure adequate control of anginal symptoms.

Ivabradine
Ivabradine (Procoralan) is purely a heart rate lowering agent. It slows the rate of firing of the sino-atrial node (the heart’s pacemaker) by blocking the If channel. Slowing the heart rate in this way reduces the myocardial oxygen demand and hence protects against episodes of angina. The agent has no effect on the force of contraction or on blood pressure. Ivabradine is licensed for use by patients with chronic stable angina who are in sinus rhythm and have a contraindication or intolerance to beta-blockers, or in combination with beta-blockers for patients inadequately controlled with an optimal beta-blocker dose and whose heart rate is over 60bpm. It has been shown to be as effective as beta-blockers in anti-anginal and anti-isaemic activity.

Ivabradine is listed by NICE as an option for the treatment of chronic stable angina, where first-line strategies (ie, beta-blockers and CCBs) are contraindicated or not tolerated. It is usually initiated at a dose of 5mg bd, increasing to 7.5mg bd after three to four weeks if required for greater symptom control and where heart rate remains over 60bpm. If the patient is elderly or 5mg is not tolerated, the dose can be reduced to 2.5mg bd. Ivabradine should not be used in combination with verapamil or diltiazem due to increased risk of bradycardia. One common side effect of ivabradine is the occurrence of luminous phenomena (or “phosphenes”): — brief moments of increased brightness — because there are Ih channels in the retina which are similar to sinus node If channels. Phosphenes are reported in up to 15 per cent of patients and patients newly prescribed ivabradine should be warned about this potential transient effect. Other potential side effects include bradycardia, first degree atrio-ventricular block, ventricular extrasystoles, headache and dizziness.

Ranolazine
At a cellular level, ischaemia causes impairment to myocardial sodium channels and leads to calcium overload, resulting in diastolic relaxation failure which, in turn, increases myocardial oxygen consumption and exacerbates ischaemia. Ranolazine (Ranexa) mediates this effect by reducing the intracellular accumulation of sodium and lowering intracellular calcium load. This facilitates myocardial relaxation and reduces diastolic stiffness, resulting in symptom relief.

Ranolazine is licensed as an adjunct to first-line anti-anginal therapies to improve symptomatic relief in patients with chronic stable angina and has been shown to be effective a reducing the frequency of angina episodes and improve exercise tolerance. As a result of its mode of action, ranolazine does not reduce heart rate or blood pressure, so it can be useful where other anti-anginal therapies are limited by bradycardia (heart rate <50bpm) or hypotension (systolic blood pressure <90mmHg). It may also be useful where first-line anti-anginal therapies are contraindicated or not tolerated.

Ranolazine should be initiated at a dose of 37.5mg bd, increasing to 500mg bd after two to four weeks of therapy. If episodes of anginal chest pain still occur after two to four weeks’ therapy, a further dose increase to a maximum of 750mg bd may be considered.

Commonly reported side effects include dizziness and headache, constipation, nausea and vomiting and asthenia. There is an increased risk of dose-related adverse effects in the elderly, patients weighing 60kg or less, and those with mild to moderate renal impairment. Down-titration of the ranolazine dose to 500mg or 37.5mg bd should be considered in patients with dose-related side effects. Ranolazine is also associated with a number of drug interactions, in particular with potent CYP3A4 inhibitors and inducers and this should be considered before initiation.

Role for pharmacists
There are many opportunities for pharmacists to support patients with a angina. This can start with encouraging a healthy lifestyle to minimise risk of future cardiovascular events.

Optimising medicines use is key to long-term outcomes, from educating on the correct use of GTN to treat acute chest pain to addressing issues with secondary prevention, such as statin side effects or underlying adherence issues and ensuring suitable anti-anginal therapies are prescribed to minimise the severity and frequency of angina attacks.

References available online.