Management of stable angina involves symptomatic relief of chest pain, longer-acting control of symptoms and prevention of cardiovascular complications. This article looks at NICE’s approach to angina treatment.

Stable angina management

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The number of patients being treated for angina in the UK is on the rise. Generally, there are three inter-related goals for their ongoing management:1

- To limit the number, severity and sequelae of angina attacks (including psychological consequences), thereby improving quality of life
- To protect against future — and potentially more severe — ischaemic syndromes, such as sudden death, myocardial infarction and cardiogenic shock
- To reduce the risk of atherosclerosis progression

Because of advances in medical and interventional strategies that are available to manage stable angina, the National Institute for Health and Clinical Excellence has recently updated its guidance for the management of the condition.2

The clinical guideline (CG126) recommends the use of a short-acting nitrate and optimal drug treatment — ie, one or two antiangina drugs as necessary (see below) — plus treatments for the secondary prevention of cardiovascular disease. Revascularisation, using either coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI), should usually be considered only if symptoms are not adequately controlled with optimal drug treatment. CABG may also be beneficial for certain patients with multivessel disease who are adequately controlled on optimal drug treatment.3

Medical management of stable angina can be divided into three main areas, based on the aforementioned goals of treatment:

- Short-acting relief
- Longer-acting symptom control
- Secondary prevention

Pharmacists can educate patients with stable angina around the purpose of treatment, why it is important to take the prescribed medicines regularly and how side effects of treatment might affect daily activities.

Short-acting relief

Short-acting nitrates can be used to alleviate the immediate symptoms of angina (chest tightness and pain). They can also be used before patients take part in activities that they know will cause angina symptoms.

SUMMARY

According to guidance issued by the National Institute for Health and Clinical Excellence, treatment for stable angina should include the use of short-acting nitrates for the relief of the immediate symptoms. Patients should also be offered antiangina medicines for longer-acting symptom control. A beta-blocker or calcium channel blocker is used first line and, if symptoms are not adequately controlled, another medicine (eg, a long-acting nitrate or nicorandil) can be added. Revascularisation should be reserved for patients whose symptoms are poorly controlled despite optimal medical management. Secondary prevention of cardiovascular events should be considered for all patients with stable angina.
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**Glyceryl trinitrate (GTN)** is a prodrug that is metabolised to produce nitric oxide (NO). NO is a potent activator of guanylyl cyclase, which, in turn, increases the level of cyclic guanosine monophosphate and leads to arterial and venous dilation. This results in reduced diastolic filling and improved myocardial perfusion.

Short-acting GTN formulations have a rapid onset of action and should relieve symptoms of stable angina rapidly. Guidance on the use of short-acting GTN, and advice about when to seek further medical help, has been developed by the British Heart Foundation (see Box 1).

Patients who have had a previous myocardial infarction (MI) and experience chest pain or tightness should call an ambulance immediately because it is unlikely that their symptoms are an episode of stable angina.

GTN is available in two short-acting formulations: tablet and spray, which are each administered sublingually. Choice of formulation should be discussed with the patient. The tablets lose potency on exposure to air and should be discarded eight weeks after the bottle is opened. An advantage of the tablet is that it can be removed from the mouth when only partially dissolved, once angina symptoms have resolved or side effects (such as headache, flushing or dizziness) become problematic.

The spray is easy to use and has the advantage of a longer shelf-life (usually two to three years), so may be more appropriate for patients who do not often require short-acting GTN.

**Longer-acting symptom control**

Generally, treatment for the initial management of stable angina consists of one or two antiangina drugs. Doses should be titrated up to the maximum tolerated dose, based on control of symptoms (not according to heart

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**Box 1: Advice for patients suffering chest pain**

The information below has been published by the British Heart Foundation for patients with coronary artery disease who have been prescribed short-acting glyceryl trinitrate (GTN).

Sometimes you will experience pain or discomfort and, often, this will be angina that you can manage at home with your GTN. However, it could be a heart attack. Here is what to do if you feel:

1. A crushing pain, heaviness or tightness in your chest
2. A pain in your arm, throat, neck, jaw, back or stomach
3. Sweaty, light-headed, sick or short of breath
4. Stop what you are doing and sit down and rest
5. Take your GTN spray or tablets, according to your doctor or nurse’s instructions. The pain should ease within a few minutes* — if it does not, take a second dose
6. If the pain does not ease within a few minutes* after your second dose, call 999 immediately
7. If you are not allergic to aspirin, chew one 300mg tablet. If you do not have any aspirin or you are not sure if you are allergic to aspirin, you should rest until the ambulance arrives

* Guidance published by the National Institute for Health and Clinical Excellence specifies waiting for five minutes between the first and second doses of GTN and between the second GTN dose and calling an ambulance

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Beta-blockers versus CCBs Beta-blockers alleviate angina symptoms by competitively inhibiting beta adrenoceptors, thereby reducing heart rate, blood pressure and contractility of the myocardium. Reduction in heart rate prolongs diastole and therefore increases the period of coronary blood flow and perfusion; this reduces myocardial oxygen consumption and improves the oxygen supply-to-demand balance.

CCBs can be divided into three main groups — dihydropyridines (eg, amlodipine), benzothiazepine (eg, diltiazem) and phenylalkylamines (eg, verapamil) — each with distinct pharmacodynamic properties. Diltiazem and verapamil predominantly suppress cardiac conduction and heart rate. The dihydropyridines relax smooth muscle and induce dilation of coronary and peripheral arteries. These differences are important with regard to drug-drug interactions and side effects. For example, it is important that diltiazem and verapamil are not given to people with heart block or used concurrently with beta-blockers (see below).

The European Society of Cardiology and the Scottish Intercollegiate Guidelines Network recommend the use of beta-blockers first line and CCBs second line.1, 7 Largely this is because data suggest that beta-blockers can reduce mortality for patients who have had a heart attack or have heart failure.

NICE’s CG126 recommends using either a beta-blocker or a CCB first line and advises that choice should be based on patient factors (such as comorbidities, contraindications and patient preferences).2 This recommendation is based on the fact that there are no

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**First-line treatment should be with a beta-blocker or calcium channel blocker (CCB). For people taking either a beta-blocker or a CCB alone, whose symptoms are not controlled, and the other option is contraindicated or not tolerated, adding one of the following medicines should be considered:**

- A long-acting nitrate
- Nicorandil
- Ivabradine
- Ranolazine

The addition of a third antianginal medicine should only be considered if patients’ symptoms are not adequately controlled with two drugs and they are waiting for revascularisation or revascularisation is not considered appropriate.7

It should be noted that there are limited trial data looking at combinations of two versus more than two antianginal medicines for symptomatic relief and prevention of cardiovascular events. Furthermore, none is licensed to be used as part of triple antiangina therapy and, as such, informed consent should be obtained and documented before using this approach. Based on the lack of data supporting triple antiangina therapy, drug combinations should be based on comorbidities, contraindications, patient preference and drug costs.

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Strong data to suggest a difference between the two treatments for patients with stable angina.6, 7

If patients are unable to tolerate a beta-blocker then a CCB should be tried instead (or vice versa). If use of one of these medicines does not adequately control a patient’s symptoms, consider switching to the other option or using a combination of the two. If a beta-blocker and a CCB are to be used together, a dihydropyridine CCB (eg, slow-release nifedipine, amlodipine or felodipine) should be selected, since the addition of a rate-controlling CCB (eg, diltiazem or verapamil) can induce severe bradycardia.2

Long-acting nitrates As described previously, nitrates reduce myocardial oxygen consumption through dilation of blood vessels. Short-acting nitrates are used to relieve symptoms of angina. The use of longer-acting nitrates is limited by the development of tolerance, which can be prevented by ensuring a reduction in nitrate levels for four to eight hours each day (eg, by removing patches at night).7

Commonly experienced side effects include a pulsing headache (due to vasodilation), which can be minimised by slow introduction and dose titration and prophylactic analgesia with paracetamol. Other symptoms related to vasodilation, such as facial flushing and dizziness, will usually subside as the patient develops tolerance to the nitrate.

A profound drop in blood pressure can occur with concomitant use of phosphodiesterase type-5 inhibitors (eg, sildenafil) and therefore these medicines should not be used within 24 hours of a nitrate dose.

Nicorandil Nicorandil is a potassium channel activator with a nitrate component. It is thought that its antianginal action is twofold: it opens adenosine triphosphate-sensitive potassium channels in vascular smooth muscle cells, thereby dilating arterial vessels in peripheral and coronary circulation; and the nitrate component works as previously described for other nitrate medicines.

There are few studies comparing nicorandil with other therapies but the largest, the IONA study, showed a significant reduction in the composite end point of cardiac death, non-fatal MI or unplanned hospital admission for cardiac chest pain.

Side effects of nicorandil are similar to those of nitrates and gradual dose titration is advised. Similarly, due to its nitrate moiety, there is a potential interaction with phosphodiesterase type-5 inhibitors and concomitant use should be avoided.

Gastrointestinal ulceration can occur with nicorandil treatment, but this is rare. Although such ulceration can occur in any area of the gastrointestinal tract, mouth ulcers occur most often. The Medicines and Healthcare products Regulatory Agency issued a safety update about this side effect and highlighted that these ulcers are refractory to treatment but respond to withdrawal of nicorandil.9

Ivabradine Ivabradine is a selective sinus node inhibitor. It is a valuable treatment option for patients requiring a reduction in heart rate, but for whom beta-blockers and rate-controlling CCBs are contraindicated or not tolerated. It has a novel action on the pacemaker activity of the sinoatrial node — it selectively lowers the heart rate without the inotropic consequences of the other rate-slowing medicines.

Ivabradine is licensed for symptomatic treatment of chronic stable angina pectoris in adults with coronary artery disease (CAD) and normal sinus rhythm. It is also indicated for adults who are unable to tolerate (or who have a contraindication to) beta-blockers. It can also be used in combination with a beta-blocker for patients who are inadequately controlled with an optimal beta-blocker dose and whose heart rate is >60 beats per minute.

The licensed dose of ivabradine is 5–7.5mg twice daily, although a lower dose of 2.5mg twice daily can be used for elderly patients or those who experience persistently low heart rate (<50 beats per minute) or symptoms of bradycardia.

To date, ivabradine has been shown to be more effective than placebo at reducing episodes of angina and hospital admissions, and has been shown to be at least as good as atenolol and amlodipine for symptom control.10–12 When compared with atenolol, ivabradine (at 5mg, 7.5mg and 10mg twice-daily doses) increased total exercise duration.12 These studies were only powered to demonstrate non-inferiority against existing treatments. Importantly none of the clinical trials conducted to date
are large enough to demonstrate cardiovascular mortality benefits with ivabradine.

Ivabradine is extensively metabolised by the liver and gut by cytochrome P450 3A4 and therefore concomitant use of potent inhibitors and inducers of this isoenzyme may affect ivabradine plasma concentrations substantially. Ivabradine does not induce or inhibit CYP3A4.

Visual symptoms were the most common adverse effect associated with ivabradine in clinical trials (although the reported incidence appears to be lower in practice). In one study, 14.5% of patients receiving the drug reported experiencing transient enhanced brightness in a limited area of the visual field (luminous phenomena). The impact of these visual symptoms on the patients’ daily life was low and most (76%) of these effects resolved during treatment.

Due to the mechanism of action of ivabradine, bradycardia is an expected side effect of treatment. Symptoms such as dizziness, fatigue or hypotension should prompt clinicians to check a patient’s pulse and adjust the dosage accordingly.

**Ranolazine** Ranolazine is a relatively new antianginal medicine. The mechanism of action is not well understood, but it is thought that it improves relaxation of the myocardium, reduces left-ventricular diastolic stiffness and improves cardiac reperfusion (these effects are thought to be mediated through inhibition of the late inward sodium current in cardiac cells, which reduces cellular sodium and calcium ions).

Unlike other antianginal medicines, ranolazine does not substantially alter heart rate or blood pressure, making it a suitable option for patients with hypotension or bradycardia who experience angina symptoms. Although there have been several randomised control trials evaluating ranolazine use, only one has assessed the medicine within its licensed indication (adjunctive therapy for the treatment of stable angina in patients inadequately controlled with or intolerant of first-line antianginal therapies). The CARRISA study looked at the addition of placebo or ranolazine (750mg or 1,000mg twice daily) to existing treatment with either a beta-blocker, a CCB or a long-acting nitrate. Both doses of ranolazine were shown to increase exercise tolerance compared with placebo (P<0.03 for both). It should be noted that the doses of other antianginals used in the study were not maximised.

Ranolazine is metabolised extensively by CYP3A4 and partially by CYP2D6 and, therefore, it has the potential to interact with a large number of other medicines. Simvastatin clearance is highly dependent on CYP3A4 and increased levels of simvastatin have been shown with concomitant ranolazine use.

**Secondary prevention**
It is important for patients with established CAD to receive treatment to prevent future cardiovascular events, such as MI.

A diagnosis of stable angina does not automatically infer a high risk of future events and not all patients will have the same level of cardiovascular risk. For example, a 45-year-old patient with newly diagnosed angina who is otherwise relatively fit will have a substantially lower risk of cardiovascular events than a 45-year-old smoker who has type 2 diabetes and a strong family history of CAD.

**Aspirin** The benefits of aspirin for primary prevention is the subject of much debate, with some sizeable patient groups, including women and people with diabetes, failing to achieve a reduction in ischaemic events while being exposed to a significant (albeit small) risk of bleeding complications. In any case, it should be noted that aspirin does not currently have a licence for primary prevention.

A meta-analysis has identified an absolute increase per year of 0.12% for major gastrointestinal bleeding with low-dose aspirin versus placebo (number needed to harm [NNH] = 833) and 0.03% (NNH = 3,333) for intracranial bleeding. This risk will vary depending on comorbidities and concomitant use of medicines known to increase bleeding risks, but can be borne in mind when considering a patient’s risk-benefit for initiating long-term, low-dose aspirin.

Patients with a diagnosis of angina are considered to have established cardiovascular disease and, as such, aspirin 75mg daily is indicated for secondary prevention. In studies, aspirin use has been associated with a reduction in non-fatal MI and vascular events, although all-cause mortality and vascular deaths have not been reduced significantly. Accordingly, aspirin should be considered for all patients with angina but only offered to those where expected benefits outweigh the perceived risks.

**Statins** The use of statins for secondary prevention has been shown to confer a relative risk reduction of 0.79 for...
all-cause mortality and 0.75 for cardiovascular mortality, although event rates are relatively low. The reduction in risks and low price make statins a cost-effective intervention for patients with stable angina; statins should be offered to all such patients for secondary prevention.15 Simvastatin is recommended at a starting dose of 40mg daily. An alternative preparation or lower dose can be used if there are clinical contraindications or drug interactions. NICE’s clinical guideline for lipid modification (CG67) suggests that if levels of total cholesterol <4mmol/L or low-density lipoprotein cholesterol <2mmol/L are not achieved at the initial dose, simvastatin can be increased to 80mg daily (or a statin of similar potency and acquisition cost can be prescribed).17 Simvastatin is recommended at a starting dose of 40mg daily. An alternative preparation or lower dose can be used if there are clinical contraindications or drug interactions. NICE’s clinical guideline for lipid modification (CG67) suggests that if levels of total cholesterol <4mmol/L or low-density lipoprotein cholesterol <2mmol/L are not achieved at the initial dose, simvastatin can be increased to 80mg daily (or a statin of similar potency and acquisition cost can be prescribed).17

Blood pressure Blood pressure should be managed according to NICE hypertension management guidance (CG127).18 However, patients with angina are likely to be already taking a beta-blocker or a CCB (which will also help with blood pressure control). Angiotensin converting enzyme (ACE) inhibitors can be considered for patients with diabetes and stable angina.19

Lifestyle Lifestyle interventions are known to have a positive effect on cardiovascular health. As such, clinicians should assess a person’s need for advice on lifestyle interventions, such as weight control, improving diet, smoking cessation and exercise. NICE guidance does not advocate prescribing vitamins or fish oil supplements to treat stable angina because of the lack of evidence of benefit in this patient group. There is also insufficient evidence to support the use of comprehensive cardiac rehabilitation programmes (similar to those used post-acute coronary syndrome) for patients with stable angina.

References