UPDATE
Module 1723

This module covers:

- Incidence, causes and symptoms of angina
- The difference between stable and unstable angina
- The management of stable angina including short- and longer acting treatments
- The use of aspirin and statins for secondary prevention of angina
- Overview of anti-anginal medication

October
Cardiovascular month

Acute heart failure	October 4
Arrhythmias	October 11
Angina	October 18*
Thrombosis	October 25

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Managing stable angina

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Angina is a common and disabling disorder and, like many cardiovascular conditions, prevalence increases with age. It is estimated that in England about 8 per cent of men and 3 per cent of women aged 55 to 64 years have angina or a history of the condition. For men and women aged 65 to 74 years the figures are higher: 14 per cent and 8 per cent respectively.[1]

Angina is caused by myocardial ischaemia, without cell necrosis occurring, when there is an imbalance between myocardial oxygen supply and consumption. The supply of oxygen to the heart cannot meet the demands on the heart to pump blood and oxygen around the rest of the body.[2]

The presence of atherosclerotic plaques within the vessel walls contributes to the imbalance when myocardial oxygen demands rise through increasing heart rate or myocardial contraction, for example, in increased physical activity (exercise, sex), emotional stress (anger, fright, stress) or other factors such as cold, overeating and fever.[2]

The classic clinical feature of angina is retrosternal heaviness or pressure, with or without radiation to the top of the arms (primarily the left arm), neck, jaw, mid-abdomen or shoulders. It should be noted that shortness of breath is also very common (especially on exercising and climbing stairs) and is often the only complaint in patients with peripheral neuropathy.

The average frequency of angina attacks is about two per week and many patients curtail their activities to avoid attacks.[2]

Angina is generally divided into stable and unstable, with stable angina having defined activities that provoke symptoms, whereas in unstable angina symptoms can occur at any time. Typically, the onset of symptoms of stable angina follows activities that increase myocardial demand and these symptoms resolve with rest.[2]

Short-acting GTN sprays have a long shelf-life so are appropriate for patients who rarely need relief

Management of stable angina

The Nice guideline CG95[3] recommends the use of a short-acting nitrate and optimal drug treatment, ie one or two anti-anginal drugs as necessary, 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 poorly controlled with optimal drug treatment.

CABG may also be beneficial for certain patients with multi-vessel disease who are not adequately controlled on optimal drug treatment.[3]

Medical management of stable angina can be divided into three main areas:

- short-acting relief
- longer acting symptom control
- secondary prevention.

Short-acting relief

Short-acting glyceryl trinitrate (GTN) formulations have a rapid onset of action and should relieve symptoms of stable angina quickly. 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. A card to remind patients how to use GTN can be obtained from the United Kingdom Clinical Pharmacy Association (UKCPA).[4] 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 and the following points addressed.

Tablets lose potency on exposure to air, so bottles once opened need to be replaced after eight weeks. However, tablets can be taken out of the mouth when only partially dissolved, with the advantage that once angina symptoms have resolved, or if side effects (such as headache, flushing or dizziness) become problematic, the tablet can be removed. This is beneficial for patients who are sensitive to the side effects of nitrates.

Conversely, 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. In any case, patients should be encouraged to carry their GTN with them and/or obtain sufficient supplies (eg keep one in their coat pocket and one in the car).

Longer acting symptom control

Generally, treatment for the initial management of stable angina consists of one or two anti-anginal drugs. Doses should be titrated up to the maximum tolerated dose, based on control of symptoms (not according to heart rate) and side effects. Response to treatment and side effects should be reviewed two to four weeks after starting or changing drug treatment.

First-line treatment should be with a beta blocker (BB) or calcium channel blocker (CCB), the choice being agreed with the patient based on comorbidities, contraindications and patient preference. If the patient cannot tolerate one, then switching to the other should be considered.[3] If symptoms are not satisfactorily controlled on either a BB or CCB, then switching or using a combination of the two should also be considered. When combining a CCB with a BB, a dihydropyridine (eg amlodipine) is recommended.[3]

For people taking either a BB or a CCB alone or in combination, whose symptoms are not controlled, and the other option is contraindicated or not tolerated, adding a long-acting nitrate, nicorandil, ivabradine or ranolazine should be considered.[2]

The addition of a third anti-anginal 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.[2] It should be noted that there is limited trial data looking at combinations of two versus more than two anti-anginal medicines for symptomatic relief and prevention of cardiovascular events.[2]

Overview of anti-anginals

- **BBs** alleviate angina symptoms by competitively inhibiting beta adrenoceptors, thereby reducing heart rate, blood pressure and contraction 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. In general, BBs can commonly cause cold peripheries that can lead to tingling in the hands and feet. Patients with circulatory problems (eg those with Raynaud's or peripheral artery disease) are more prone to these and should potentially avoid BBs.

When titrating doses patients often feel fatigued and should be counselled to be aware of this. For those who are physically active, BBs can limit exercise capacity and so may not be an acceptable choice in younger, fit patients. In males, impotence due to BB can lead to discontinuation.

For patients with concomitant heart failure, the choice of a BB would be highly recommended due to significant mortality benefits in this patient group.

- **CCBs** can be divided into two main groups — dihydropyridines (eg amlodipine), and non-dihydropyridines (eg diltiazem and verapamil) — each with distinct pharmacodynamic properties. Dihydropyridines relax smooth muscle and induce dilation of coronary and peripheral arteries. Diltiazem and verapamil predominantly suppress cardiac conduction and heart rate. 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 BBs.
- **Long-acting nitrates** reduce myocardial oxygen consumption through dilation of blood vessels. Side effects of nitrates are related to this dilation of blood vessels and can include facial flushing and throbbing headache. Slow dose titration can often alleviate or minimise these symptoms and perseverance in taking nitrates should overcome the side effects. If headaches are problematic, then taking paracetamol 30 to 60 minutes prior to taking the nitrate can often overcome this.

It should be noted that concomitant use of phosphodiesterase type 5 inhibitors (such as sildenafil and tadalafil) can cause a profound drop in blood pressure and patients should be advised against their use within 24 hours of a nitrate dose.

- **Nicorandil** is a potassium channel activator and its side effects are similar to those of long-acting nitrates. Although rare, gastrointestinal ulceration has been associated with its use. Patients should be made aware of this and appropriate referrals made if they should exhibit symptoms.[5]
- **Ivabradine** is a selective sinus node inhibitor and acts to reduce heart rate, thereby relieving anginal symptoms. Ivabradine is extensively metabolised in the liver by cytochrome enzymes (CYP450 and CYP3A4) and has the potential to interact with potent inhibitors and inducers of this enzyme. Visual disturbance, specifically transient enhanced brightness in a limited area of the visual field (luminous phenomena) should be highlighted to patients. This is often reversible once the drug is withdrawn.
- **Ranolazine's** mechanism of action is largely unknown, although it is thought to be due to improving myocardium relaxation. Unlike other anti-anginals, ranolazine does not substantially lower blood pressure or heart rate, making it a suitable option in those with hypotension or bradycardia. It too is metabolised by CYP3A4 (and CYP2D6) meaning that it has the potential to interact with a number of strong inhibitors and inducers of these enzymes.

Secondary prevention of angina

It is important for patients with established coronary artery disease to receive treatment to prevent future cardiovascular events, such as myocardial infarction (MI) and stroke. Patients with a diagnosis of angina are considered to have established cardiovascular disease and 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.[2] 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.

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. 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.[1,5] More recently, with the publication of Nice lipid modification guidance,[6] the recommendation is to start statin treatment in people with cardiovascular disease with atorvastatin 80mg.[6] A lower dose of atorvastatin can be considered if there are potential drug interactions, a high risk of adverse effects or patient preference.

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.

The role of the pharmacist

Community pharmacists have an essential role in supporting patients with stable angina. Pharmacists can educate patients with stable angina about the purpose of their treatment, why it is important to take prescribed medicines regularly and how side effects of treatment might affect daily activities.

Pharmacists have the opportunity to check patients are taking their short-acting nitrates correctly and if they are experiencing any side effects that might impact on their adherence. An increase in angina frequency and increased use of short-acting GTN indicates worsening symptoms and should prompt referral for review of anti-anginal therapy.

Secondary prevention is an equally important aspect of the management of angina. Pharmacists should ensure patients taking short-acting nitrates are also receiving adequate secondary prevention. Recent Nice guidance stipulates that we should be considering everyone with cardiovascular disease for high intensity statin treatment with a recommendation of atorvastatin 80mg daily.

Lastly, non-pharmacological measures are important as well and pharmacists should be able to advise patients with angina about lifestyle interventions including smoking cessation, suitable exercises and dietary and healthy eating advice.

References

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4. United Kingdom Clinical Pharmacy Association: http://www.ukcpa.net/groups/cardiology/forum/topic/new-national-gtn-advice-card-is-launched/ (accessed 2/10/2014).
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6. Nice. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. July 2014. www.nice.org.uk/cg181 (accessed 20/9/2014).

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5 minute test

■ Sign up to take the 5 Minute Test and get your answers marked online: chemistanddruggist.co.uk/update

Take the 5 Minute Test

1. Patients with stable angina have defined activities that provoke symptoms.
True or false?

2. Shortness of breath may be the only symptom of angina in patients with peripheral neuropathy.
True or false?

3. The average frequency of angina attacks is five per week.
True or false?

4. Bottles of GTN tablets, once opened, should be replaced after eight weeks.
True or false?

5. First-line treatment of angina should be with long-acting nitrates or nicorandil.
True or false?

6. Dihydropyridine calcium channel blockers should not be used concurrently with beta blockers.
True or false?

7. Side effects of nicorandil are similar to those of long-acting nitrates.
True or false?

8. Side effects of ivabradine include visual disturbances.
True or false?

9. Unlike many other anti-anginals, ranolazine is not metabolised by CYP enzymes.
True or false?

10. Aspirin should be considered for all patients with angina.
True or false?

Tips for your CPD entry on managing stable angina

Reflect **How common is angina? What do the Nice guidelines recommend for its treatment? What are the side effects of ivabradine?**

Plan **This article focuses on the management of stable angina. It includes information about the symptoms, short-acting relief and longer acting symptom control of angina and considers secondary prevention of further cardiovascular events. The role of the pharmacist in supporting patients with angina is also discussed.**

Act **Read the Update article and the suggested reading (below), then take the 5 Minute Test (above). Update and Update Plus subscribers can then access answers and a pre-filled CPD logsheet at chemistanddruggist.co.uk/mycpd.**

Find out more about angina from the NHS Choices website
http://tinyurl.com/angina11

Read the MUR tips for angina on the C+D website. Identify any patients who might benefit from an MUR or advice about their angina management
http://tinyurl.com/angina12

Find out about support for patients with angina, the British Heart Foundation website has useful advice about all heart conditions and a booklet on angina
http://tinyurl.com/angina13
http://tinyurl.com/angina15

Evaluate **Are you now confident in your knowledge of angina and its symptoms and management? Could give advice to patients? Can you identify at risk patients? Do you know when to refer?**

EXPERT Q&A

Want to know more? Our cardiovascular expert is on hand to answer any further questions you may have on this month's topic. Email your queries to: **asktheexpert@updateplus.co.uk**