Stable angina: current guidelines and advances in management

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Our Drug Review discusses the current recommended management of stable angina, focussing on secondary prevention and the control of symptoms, followed by sources of further information and an analysis of prescription data.

Stable angina pectoris is a common and limiting condition present in 10–15 per cent of women and 10–20 per cent of men aged 65–74 years with between 20 000 and 40 000 individuals per million suffering from angina in most European countries.¹

In patients with stable angina the incidence of nonfatal MI and coronary heart disease death at two years is 14.3 and 5.5 per cent in men and 6.2 and 3.8 per cent in women, respectively.² However, the prognosis of patients with stable angina can vary widely and by up to 10-fold depending on clinical, functional and anatomical factors.¹

**Diagnosis of stable angina**

Typical angina is characterised as constricting discomfort in the chest, jaw or arms that is reproducible on physical exertion and relieved by rest or fast-acting vasodilators.

In addition to a resting 12-lead ECG indicated in all patients with suspected angina, the latest NICE guidelines advocate two further forms of testing for evaluating patients: anatomical testing to assess the degree of arterial narrowing and functional testing for myocardial ischaemia. Furthermore the investigation of choice (see Figure 1) depends on the pretest probability of coronary artery disease depending on the age, sex, symptoms and pre-existing risk factors and stratified as low (<10 per cent), intermediate (10–90 per cent) and high (>90 per cent).³

The latest NICE guidelines now recommend invasive angiography in those patients with a high intermediate (61–90 per cent) risk and noninvasive functional testing (nuclear myocardial perfusion scan, stress echocardiography or stress cardiac magnetic resonance imaging) in those with a 30–60 per cent intermediate risk.² More controversially the NICE guidelines now recommend computed tomography (CT) calcium scoring and CT coronary angiography in those patients with a low intermediate (10–29 per cent) risk.

It is important to note that exercise ECG stress testing has now been omitted as a measure of evaluating myocardial
ischaemia. However, despite its limitations pertaining to low sensitivity and specificity, exercise ECG testing is widely available and is currently used across the general medical and cardiology departments, especially in nontertiary centres, and provides rapid assessment of ischaemic threshold in patients with stable angina.

Replacing exercise ECG testing with more resource-intensive imaging techniques will have significant cost implications across health services. 4

Management of stable angina

Evaluation of the management of stable angina has not been as rigorous in randomised controlled trials as therapies for the treatment of acute coronary syndrome. Therapy for stable coronary disease can be broadly divided into pharmacotherapy, nonpharmacotherapy and lifestyle measures.

This review primarily outlines the scope of pharmacological management in stable angina. The role of lifestyle intervention is of critical importance but is beyond the scope of this review.

Secondary prevention

Antiplatelet therapy

Aspirin acts primarily by cyclo-oxygenase inhibition (see Table 1) and has been evaluated in both primary and secondary prevention trials aimed at reducing the risk of vascular events (nonfatal MI, nonfatal stroke and vascular death) in patients with established coronary disease. 5

The dosage of aspirin in secondary prevention is debated. The Clotidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions (CURRENT-OASIS 7) trial failed to show improved clinical efficacy with high-dose (300–325mg per day) compared to low-dose (75–100mg) aspirin. There were fewer GI bleeds in patients on low-dose aspirin and current ESC and NICE guidelines recommend low-dose aspirin in patients with stable coronary disease. 6

Clopidogrel (75mg per day) can be used in those unable to tolerate aspirin, but there is no convincing evidence to combine aspirin with clopidogrel in patients with stable angina. 7

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**Figure 1.** Investigative pathway in the diagnosis of stable angina (CTCA = computed tomography coronary angiography)
Lipid-lowering therapy

Statins inhibit HMG-CoA reductase, preventing the hepatocytic conversion of acetyl-CoA into cholesterol (see Table 1). The benefits of statin therapy in secondary prevention are substantial and unequivocal: every 1 mmol reduction in low-density lipoprotein reduces the annual rate of vascular events by 20 per cent.\(^8\)

Statins are usually well tolerated but myalgia is frequently reported (although in clinical trials statins have not been shown to significantly increase the risk of myalgia compared to placebo).\(^9\) Rarely statins can induce rhabdomyolysis.

Occasionally statins also cause liver dysfunction and should be used cautiously in patients with chronic liver disease and those with alcohol dependence. Liver function should be monitored prior to commencement of statins and three months after initiation. Following this, liver function should be checked biannually.

Renin-angiotensin-aldosterone system modulators

ACE inhibitors block production of angiotensin II, a potent vasoconstrictor (see Table 1). The mortality benefits of chronic ACE inhibition have been well documented in patients following MI or with significant left ventricular dysfunction but its role in stable angina is less clear. Two studies have shown that ACE inhibition significantly reduced mortality and recurrent MI in patients with vascular disease.\(^10,11\) In contrast, the more recent Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial showed no benefit with addition of an ACE inhibitor.\(^12\)

The current guidelines therefore recommend ACE inhibitor therapy in patients with stable angina and co-existing diabetes, hypertension and ventricular dysfunction (Class IA evidence).

### Treatment of angina episodes

**Beta-blockers**

Beta-blockers reduce the heart rate and thus myocardial oxygen demand as well as increasing diastolic time and therefore coronary perfusion and myocardial oxygen supply (see Table 2). In stable angina beta-blockers are the recommended first-line therapy for symptom control, but there is no evidence for a reduction in cardiovascular death or MI.

Absolute contraindications to the use of beta-blockers include severe bradycardia including pre-existing high-degree atrioventricular (AV) block, uncontrolled heart failure and reversible airways disease. Relative contraindications include peripheral vascular disease.

**Calcium-channel blockers**

Calcium-channel blockers (CCBs) can be divided into those that act peripherally (the dihydropiridines) and centrally (verapamil and diltiazem, see Table 2). They reduce the influx of calcium into cells of the conducting system within the heart, reducing myocardial contractility and heart rate, as well as myocardial and vascular smooth muscle causing coronary and peripheral vasculature dilatation.

Long-acting dihydropiridines reduce the need for revascularisation but do not confer any mortality benefit in patients with stable coronary disease.\(^13\)

Verapamil and diltiazem are recommended as first-line therapy in patients in whom beta-blockade is not possible or in rare patients with angina due to coronary artery spasm.

It should be noted that beta-blockers and centrally acting CCBs (verapamil and diltiazem) should not be co-administered because of an increased risk of heart block.

**Nitrates**

Nitrates are endothelium-independent vasodilators that reduce cardiac preload and afterload. Hence they decrease myocardial oxygen demand and improve myocardial blood flow (see Table 2). Sublingual and buccal nitrates provide rapid relief of anginal symptoms and should be available to all patients. They do not reduce mortality or the risk of MI.

No strong evidence exists for the use of long-acting nitrates for angina prophylaxis.\(^14\) They should be considered as first-line therapy for patients in whom beta-blockers or CCBs are contraindicated, or as a second-line therapy where breakthrough symptoms occur despite optimal first-line therapy.

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### Table 1. Drugs used in secondary prevention in stable coronary disease

<table>
<thead>
<tr>
<th>Class of drug</th>
<th>Mechanism of action</th>
<th>Contraindications</th>
<th>Cautions</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong></td>
<td>inhibits platelet aggregation and activation</td>
<td>active peptic ulcer disease (PUD)</td>
<td>bleeding disorders previous PUD</td>
<td>gastrointestinal haemorrhage renal impairment concomitant diuretics previous angioedema</td>
</tr>
<tr>
<td><strong>Statins</strong></td>
<td>reduce LDL cholesterol</td>
<td>acute or severe liver disease</td>
<td>previous liver disease</td>
<td>reversible myositis gastrointestinal upset altered liver enzymes</td>
</tr>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td>block angiotensin II-dependent vasoconstriction</td>
<td>ACE inhibitor hypersensitivity LV outflow tract obstruction severe renal impairment renal artery stenosis</td>
<td>renal impairment concomitant diuretics previous angioedema</td>
<td>renal impairment gastrointestinal upset persistent dry cough angioedema</td>
</tr>
</tbody>
</table>

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One of the main limitations of long-acting nitrates is the development of tolerance. This can be avoided by ensuring a daily nitrate-free period of six to eight hours.

Potassium-channel openers
Nicorandil causes arteriolar and venous dilatation reducing preload and improving myocardial oxygen supply. It is currently recommended as third-line therapy and dual therapy where CCBs are not tolerated. One large trial failed to show a mortality benefit in patients randomised to nicorandil versus placebo. Nicorandil also has significant gastrointestinal side-effects including mucosal ulceration. Other side-effects include hypotension (see Table 2).

Sinus node modulators
Ivabradine (Procoralan) is a selective blocker of the I\(_f\) channel; this is present only in the sinus node and hence it is a pure heart

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**Table 2. Properties of drugs used for symptom control**

<table>
<thead>
<tr>
<th>Class of drug</th>
<th>Mechanism of action</th>
<th>Contraindications</th>
<th>Cautions</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-blockers</strong></td>
<td>reduce heart rate and increase diastolic filling</td>
<td>asthma, severe bradycardia, pre-existing high-degree AV block, sick sinus syndrome, severe uncontrolled heart failure</td>
<td>hypotension, bradycardia</td>
<td>bronchospasm, bradyarrhythmias, fatigue, impotence</td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td>centrally reduce myocardial contractility and heart rate and induce coronary vasodilatation</td>
<td>severe bradycardia, pre-existing high-degree AV block, sick sinus syndrome, concomitant beta-blocker therapy</td>
<td>hypotension</td>
<td>peripheral oedema, fatigue, constipation, erectile dysfunction</td>
</tr>
<tr>
<td>– nndihydropyridine, mainly verapamil and diltiazem</td>
<td>peripherally causes arterial vasodilatation reducing afterload</td>
<td>cardiogenic shock, recent MI (less than 1 month), advanced aortic stenosis</td>
<td>hypotension</td>
<td>reflex tachycardia, flushing, headaches, peripheral oedema</td>
</tr>
<tr>
<td>– dihydropyridine, mainly nifedipine, amlodipine and lercanidipine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nitrates</strong></td>
<td>coronary artery vasodilatation</td>
<td>left ventricular outflow tract obstruction, concomitant use of phosphodiesterase inhibitors (sildenafil) within 24 hours</td>
<td>severe hypotension</td>
<td>headache</td>
</tr>
<tr>
<td><strong>Potassium channel activators (nicorandil)</strong></td>
<td>arteriolar and venous dilatation</td>
<td>cardiogenic shock</td>
<td>hypotension</td>
<td>headache, flushing, mucosal ulceration</td>
</tr>
<tr>
<td><strong>Sinus node inhibitors (ivabradine)</strong></td>
<td>blocks I(_f) channel on the sinus node reducing heart rate</td>
<td>heart rate &lt;60bpm, cardiogenic shock, sick sinus syndrome, acute MI, heart failure</td>
<td>intraventricular conduction defects, severe hypotension</td>
<td>headache, dizziness, luminous phenomena</td>
</tr>
<tr>
<td><strong>Ranolazine</strong></td>
<td>modulates sodium-dependent calcium channels involved in myocardial contractility</td>
<td>hepatic cirrhosis</td>
<td>long QT on ECG</td>
<td>constipation, dizziness, headaches</td>
</tr>
</tbody>
</table>

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rate-lowering agent (see Table 2). Patients must therefore be in sinus rhythm.

The antianginal properties of ivabradine have been examined in two randomised control trials. In a head-to-head comparison ivabradine was as effective as atenolol in reducing frequency of angina attacks.\(^\text{16}\) When used as additional therapy to beta-blockade and compared to placebo, ivabradine increased exercise duration but had no effect on the frequency of angina attacks.\(^\text{17}\)

**Ranolazine**

Ranolazine (Ranexa) is another agent used in the management of chronic stable angina. It has been evaluated in two randomised
controlled trials. In a head-to-head comparison with placebo, both 750mg and 1g twice daily reduced the number of weekly angina attacks (2.1 vs 2.5 vs 3.3).18

Revascularisation
Percutaneous coronary intervention
One of the uncertainties in managing patients with stable angina is deciding if and when revascularisation should be offered. Percutaneous coronary intervention (PCI) consists of balloon angioplasty, usually with stent deployment.

Although PCI improves symptoms, the evidence for PCI on prognosis in stable angina has not been established. Two large randomised trials showed no advantage of PCI over optimal medical therapy19,20 in contrast, another study comparing medical therapy versus intervention in patients with coronary disease and severe stenosis showed reduction in the composite end-point of death, recurrent MI and revascularisation.21 However, this difference was primarily driven by revascularisation.

Therefore, whether intervention confers a significant prognostic benefit remains unclear and further studies are underway to address this question.

Coronary artery bypass grafting
In contrast to PCI, evidence exists for improved survival in certain high-risk groups of patients undergoing coronary artery bypass grafting (CABG) for stable coronary disease. A systematic review of seven randomised trials showed a lower mortality in the CABG groups at 5, 7 and 10 years. This risk reduction was particularly marked in patients with left main-stem disease.22 Since then two further studies have shown superiority of CABG over PCI,23,24 especially in patients with diabetes.23

More recently a study has compared medical and bypass surgery in patients with left ventricular impairment and stable coronary disease.25 Due to significant crossover the study was underpowered but showed a nonsignificant trend towards improved survival in the CABG arm.

Summary
Diagnosis of stable angina still remains challenging and guideline-recommended imaging techniques are still not readily accessible in many centres. Management of stable angina should focus on prevention and symptom control. Lifestyle measures to modify risk are critical in improving prognosis in patients with stable angina and should complement secondary-prevention pharmacotherapy.

References

Declaration of interests
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Dr Shah is cardiology research fellow and Keith Fox is professor of cardiology in the University/BHF Centre for Cardiovascular Science, University of Edinburgh

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In 2012, GPs in England wrote 7.3 million scrips for nitrates at a cost of £35 million. The volume of prescribing has changed little in recent years but spending has fallen and is now 80 per cent of the 2009 level.

Isosorbide mononitrate (ISMN) remains the most frequently prescribed nitrate, accounting for 71 per cent of scrips and 78 per cent of costs. The majority of nitrate prescribing is for generic preparations but branded ISMN m/r 60mg still accounts for 40 per cent of spending on ISMN preparations. With no fewer than 20 brands of ISMN 60mg m/r tablets and capsules, glyceryl trinitrate 400µg spray was the single most frequently prescribed preparation with 79 per cent of GTN scrips and 65 per cent of spending.

There were 66 000 scrips for GTN patches at a cost of about £1 million. Transiderm Nitro was the most popular brand (48 per cent of scrips and 61 per cent of spending).

Table 3. Number and cost of prescriptions for the most frequently prescribed nitrates, England, 2012

<table>
<thead>
<tr>
<th>Most frequently prescribed GTN formulations (all packs)</th>
<th>No. scrips (000s)</th>
<th>Cost (£000s)</th>
<th>NIC per scrip (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTN sublingual spray 400µg</td>
<td>1 609</td>
<td>4 522</td>
<td>2.64–3.70</td>
</tr>
<tr>
<td>Nitrolingual spray 400µg</td>
<td>141</td>
<td>523</td>
<td>3.71</td>
</tr>
<tr>
<td>GTN tabs 500µg</td>
<td>73</td>
<td>191</td>
<td>2.60</td>
</tr>
<tr>
<td>all GTN preparations</td>
<td>2 046</td>
<td>6 994</td>
<td>3.42</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Most frequently prescribed ISDN formulations</th>
<th>No. scrips (000s)</th>
<th>Cost (£000s)</th>
<th>NIC per scrip (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISDN tabs 10/20mg</td>
<td>54</td>
<td>690</td>
<td>11.61–13.37</td>
</tr>
<tr>
<td>Isoket Retard 20/40mg</td>
<td>29</td>
<td>105</td>
<td>2.59–5.69</td>
</tr>
<tr>
<td>all ISDN preparations</td>
<td>85</td>
<td>785</td>
<td>9.28</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most frequently prescribed ISMN formulations</th>
<th>No. scrips (000s)</th>
<th>Cost (£000s)</th>
<th>NIC per scrip (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISMN tabs 10/20/60mg</td>
<td>2 035</td>
<td>2 609</td>
<td>1.21–1.61</td>
</tr>
<tr>
<td>branded ISMN m/r 60mg</td>
<td>1 674</td>
<td>10 943</td>
<td>3.58–25.02</td>
</tr>
<tr>
<td>ISMN m/r 60mg</td>
<td>1 121</td>
<td>10 897</td>
<td>5.98–14.07</td>
</tr>
<tr>
<td>total for ISMN preparations</td>
<td>5 185</td>
<td>27 422</td>
<td>5.29</td>
</tr>
</tbody>
</table>
**CPD: Management of stable angina**

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**For each section, one of the statements is false – which is it?**

1. Stable angina pectoris is a common and limiting condition that:
   a. is present in 10–15 per cent of women aged 65–74 years.
   b. is associated with nonfatal MI at two years in 14.3 per cent of affected men.
   c. is associated with death from coronary heart disease at two years in 12 per cent of affected women.
   d. should be diagnosed by resting 12-lead ECG supported by anatomical and functional testing.

2. In patients with stable angina:
   a. the dose of aspirin for secondary prevention should be 325mg per day.
   b. there is no convincing evidence to support combining aspirin with clopidogrel in patients with stable angina.
   c. the recommended dose of clopidogrel is 75mg per day.
   d. in clinical trials statins have not been shown to significantly increase the risk of myalgia compared to placebo.

3. In the treatment of patients with stable angina:
   a. liver function should be checked biannually during long-term statin therapy.
   b. liver function should be measured before beginning a statin and then 6–12 months after initiation.
   c. current guidelines recommend ACE inhibitor therapy in patients with stable angina and co-existing diabetes, hypertension and ventricular dysfunction.
   d. the mortality benefits of chronic ACE inhibition in patients with stable angina are unclear.

4. In the treatment of angina episodes in patients with stable angina:
   a. beta-blockers are the recommended first-line therapy for symptom control.
   b. there is good evidence that beta-blockers reduce the risk of cardiovascular death or MI.
   c. long-acting dihydropiridines reduce the need for revascularisation.
   d. verapamil and diltiazem are recommended as first-line therapy in patients in whom beta-blockade is not possible.

5. Regarding treatment with a nitrate for a patient with stable angina:
   a. nitrates improve myocardial blood flow.
   b. long-acting nitrates should be considered first-line therapy for patients in whom beta-blockers or CCBs are contraindicated.
   c. long-acting nitrates should be considered second-line therapy where breakthrough symptoms occur despite optimal first-line therapy.
   d. tolerance can be avoided by ensuring a daily nitrate-free period of at least 12 hours.

6. In patients with stable angina:
   a. treatment with a beta-blocker plus ivabradine reduces the frequency of angina attacks.
   b. the impact of percutaneous coronary intervention on the prognosis is unclear.
   c. the mortality reduction due to coronary artery bypass grafting is particularly marked in patients with left main-stem disease.
   d. nicorandil is recommended as third-line therapy and dual therapy when a CCB is not tolerated.

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