References to exertional pain in the arm or breast in relation to diseases affecting the heart can be found in ancient Egyptian and Roman literature, but it was not until the 18th century that London physician William Heberden described the condition angina pectoris. Heberden reported seeing nearly 100 people with the disorder, 94 of whom were men over the age of 50 years.

Today, coronary artery disease (CAD) is the leading single cause of mortality in the UK. In 2014, CAD was responsible for 15 and 10 per cent of all male and female deaths respectively, totalling around 69,000 deaths. Aside from the human cost, CAD also poses a significant socioeconomic burden on the UK, with a total expenditure of £954 million in England in 2013/2014. Treatment of stable CAD is aimed at minimising symptoms, slowing disease progression and improving prognosis. In this article, we summarise the current diagnostic pathway and discuss the management of stable angina, with a focus on optimal medical therapy and when to refer to specialist services.

**Diagnostic pathway**

Making a diagnosis of angina caused by CAD is not always straightforward. In some cases, clinical assessment alone may be enough to confirm or refute a diagnosis; in others, additional diagnostic testing is required. The diagnosis of angina is usually suspected from history and examination. Table 1, adapted from the 2010 NICE guideline on chest pain of recent onset, highlights the characteristics of classical anginal pain. All three features are consistent with typical angina, while two out of three constitute atypical angina. Pain is more likely to be nonanginal in the absence of these features.

Initial investigations should include a 12-lead ECG and blood tests, the latter identifying conditions that can exacerbate angina, such as anaemia. A chest X-ray is indicated in patients with an atypical presentation, suspicion of lung disease, or heart failure.
NICE recommends estimating the likelihood of CAD using clinical assessment and typicality of angina, age, sex and risk factors (diabetes, smoking and hyperlipidaemia; see Table 2).2 If there are resting ECG changes consistent with CAD, the estimated likelihood is higher. Further diagnostic testing is stratified depending on pretest probability:

- **Low risk:** If the estimated likelihood of CAD is <10 per cent, other causes of chest pain should be considered. In patients with typical anginal pain, causes other than CAD should be investigated for, including hypertrophic cardiomyopathy.
- **Intermediate risk:** When the estimated risk of CAD is 10–90 per cent, patients should be reviewed by specialist cardiology services for consideration of additional diagnostic testing. CT coronary angiography, functional imaging or invasive coronary angiography may be undertaken depending on further risk stratification. If symptoms are felt to be consistent with angina, pharmacological therapy should be initiated pending further investigation.
- **High risk:** In patients presenting with typical symptoms with an estimated risk of CAD >90 per cent, no further diagnostic testing is required.

### Management of stable angina

The management approach for patients with stable angina should be multifaceted. Patient education, risk factor modification and evidence-based pharmacological treatments all play a key role in reducing morbidity and mortality in CAD. The aims of pharmacological therapy are to relieve symptoms and to prevent future cardiovascular events by reducing progression of coronary atherosclerotic plaque disease, stabilising plaque and preventing thrombosis in the event of plaque rupture.

**Information for patients**

Patients should be offered a clear explanation of the cause of angina and should be given information regarding factors that can provoke symptoms. Discussion should highlight the circumstances in which urgent medical attention should be sought, in particular if there is a sudden worsening in symptom frequency or severity. The role of lifestyle modification and the risk-benefit profile of pharmacological treatments should also be discussed.

### Anginal pain

- Constricting discomfort in the front of the chest, or in the neck, shoulders, jaw or arms
- Precipitated by physical exertion
- Relieved by rest or glyceryl trinitrate within about five minutes

### Risk factor modification

Management of cardiovascular risk factors are central to the overall care of patients with stable angina and particular attention should be paid to addressing modifiable risk factors. Where appropriate, this should include optimisation of management for hypertension, hyperlipidaemia and diabetes. Smoking cessation, diet, weight management and physical activity should also be addressed. The European Society of Cardiology recommends annual influenza vaccination for patients with CAD, particularly the elderly.3

### Prevention of cardiovascular events

Antiplatelet and lipid-lowering agents are the cornerstone treatments in the prevention of cardiovascular events. Low-dose aspirin therapy is recommended in all patients without contraindications.3,4 In one early study comparing the use of low-dose aspirin plus sotalol with placebo plus sotalol in patients with angina, there was a 34 per cent reduction in risk of myocardial infarction and sudden death in the aspirin group.5 In patients with aspirin intolerance, clopidogrel should be offered as an alternative.

The decision whether to initiate lipid-lowering therapy should follow an informed discussion about the risks and benefits. Table 3 summarises the NICE recommendations for the use of statins as primary prevention.6 The recommended treatment in these patients is atorvastatin 20mg once daily. ACE inhibitors or angiotensin II-receptor antagonists are indicated in the presence of co-morbid conditions including left ventricular systolic dysfunction (LVSD), hypertension or diabetes.4,7

### Antianginal medications

**Beta-blockers**

Beta-adrenoceptor antagonists (beta-blockers) are the first-line agent to relieve symptoms and improve exercise tolerance. They decrease myocardial oxygen demand by reducing heart rate and blood pressure. Prolongation of diastole results in improved coronary arterial filling. The antianginal properties of beta-blockers are a class effect, with the most commonly used beta-blockers being those with predominant affinity for the beta-1 receptor, such as metoprolol, atenolol and bisoprolol. While no randomised placebo-controlled trials of beta-blockers in stable angina exist, there is strong evidence supporting a prognostic benefit from beta-blockade following myocardial infarction and in heart failure with reduced ejection fraction.8,9

Side-effects include hypotension, fatigue, bradycardia, heart block, bronchospasm, peripheral vasoconstriction, impotence, hypoglycaemia and depression. Beta-blockers are contraindicated in patients with known conduction disorders, and cardiogenic shock, and should be used with caution in patients with asthma. Beta-blockers can worsen symptoms in patients with vasospastic (Prinzmetal) angina and should therefore be avoided in these patients.

**Calcium-channel blockers**

For patients intolerant of beta-blockers, calcium-channel blockers can be used first line, or as a second-line treatment if symptoms persist despite beta-blocker monotherapy. They are considered

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**Table 1. Characteristic features of typical angina (taken from NICE 2010 guidelines on chest pain of recent onset)**2
Angina

REVIEW

Angina is the treatment of choice in vasospastic (Prinzmetal) angina. Randomised controlled trials and meta-analyses have shown them to be as effective as beta-blockers in reducing angina symptoms. They are dichotomised by their pharmacological action into dihydropyridines (amlodipine, felodipine and nifedipine) and nondihydropyridines (verapamil and diltiazem). Both groups are predominantly vasodilators, acting through selective inhibition of L-type voltage-gated calcium channels in vascular smooth muscle and in the myocardium. Dihydropyridines have a greater affinity for peripheral vasculature with minimal negatively inotropic effects (minimum effects on reducing the force of contraction of the heart), thereby making them more suitable for patients with concomitant LVSD, with the exception of nifedipine, which is contraindicated in such patients. Nondihydropyridines have the additional property of AV-nodal blockade, resulting in a slowing of the heart rate. Due to their negatively inotropic effects, nondihydropyridines are contraindicated in patients with LVSD.

Common side-effects of dihydropyridines include headache, ankle swelling and fatigue. Additional contraindications include severe aortic stenosis and hypertrophic obstructive cardiomyopathy. Nondihydropyridines increase the risk of bradycardia and conduction disorders, and they should not be used in combination with beta-blockers due to the risk of atrioventricular block. They are also known to cause constipation and gingival hypertrophy.

All calcium-channel blockers interact with potent inhibitors of the CYP3A4 enzyme and should not be prescribed in combination with azole antifungals, macrolide antibiotics, ciclosporin, or the antiretroviral drug ritonavir. The dose of simvastatin should not exceed 20mg daily when prescribed alongside amiodipine due to an increased risk of statin-induced myopathy.

Nitrates

Nitrates exert their pharmacological action through a direct effect on vascular smooth muscle. They are a class of prod-

rugs that undergo in vivo reduction to nitric oxide (NO), which activates soluble guanylate cyclase and increases levels of cyclic guanosine monophosphate (cGMP). This results in venous and arterial dilatation, which reduces myocardial preload, afterload and oxygen demand thereby alleviating anginal symptoms.

Short-acting nitrates: All patients with stable angina should be prescribed a short-acting nitrate preparation for acute symptomatic relief. Sublingual glyceryl trinitrate (GTN) spray or absorbable buccal tablets are recommended to relieve exertional symptoms. They can also be administered prophylactically in cold weather, before physical activity or after a meal. The most commonly reported side-effects are headache and hypotension. They should be avoided in patients with severe aortic stenosis and hypertrophic cardiomyopathy.

Table 2. Percentage of people estimated to have coronary artery disease, according to symptoms, age and risk factors (adapted from NICE 2010 guidelines on chest pain of recent onset)

<table>
<thead>
<tr>
<th>Nonanginal chest pain</th>
<th>Atypical angina</th>
<th>Typical angina</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td><strong>Men</strong></td>
<td><strong>Women</strong></td>
</tr>
<tr>
<td>35</td>
<td>3</td>
<td>35</td>
</tr>
<tr>
<td>45</td>
<td>9</td>
<td>47</td>
</tr>
<tr>
<td>55</td>
<td>23</td>
<td>59</td>
</tr>
<tr>
<td>65</td>
<td>49</td>
<td>69</td>
</tr>
</tbody>
</table>

High risk = diabetes, smoking and hyperlipidaemia (total cholesterol >6.47mmol/L); low risk = none of these three. For men >70 years with atypical or typical symptoms, assume an estimate of >90 per cent; for women >70 years with typical symptoms and high risk, assume an estimate of >90 per cent; for other women >70 years, assume an estimate of 61–90 per cent.

Table 3. Summary of NICE recommendations on the use of statin therapy as primary prevention

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Who to offer</th>
<th>Who to consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 10 per cent 10-year risk of developing coronary artery disease (using the QRISK2 assessment tool)</td>
<td>Age &lt;85 years or With type 2 diabetes</td>
<td>Age ≥85 years</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>Age &gt;40 years or Onset of diabetes &gt;10 years ago or Established nephropathy or Other risk factors for cardiovascular disease</td>
<td>All patients</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>All patients</td>
<td></td>
</tr>
</tbody>
</table>
Long-acting nitrates: Long-acting preparations of oral nitrates, such as isosorbide mononitrate, can be used for long-term control of angina symptoms. Although the prolonged use of long-acting nitrate preparations has the unwanted side-effect of ‘nitrate tolerance’, this can be overcome by introduction of a daily ‘nitrate-free period’ of at least eight hours, with a suggested dosing regimen in the morning and afternoon. The side-effect profile of long-acting nitrates is similar to that of short-acting preparations. They should not be prescribed for patients taking alpha-adrenergic blockers, eg doxazosin, or phosphodiesterase type 5 (PDE5) inhibitors, eg sildenafil, due to the risk of profound hypotension.

Nicorandil
Nicorandil is a nicotinamide ester that exerts its antianginal properties through a dual mode of action: activation of ATP-sensitive potassium channels in vascular smooth muscle and a direct nitrate-mediated dilatory effect. This enhances peripheral and coronary arterial dilatation and systemic venous dilatation. It is also thought to aid in the stabilisation of coronary atherosclerotic plaques.

In the Impact Of Nicorandil in Angina (IONA) randomised placebo-controlled trial, administration of nicorandil in addition to standard antianginal therapy was associated with a 17 per cent reduction in risk of coronary heart disease death, nonfatal myocardial infarction, and unplanned hospital admission for cardiac chest pain.10 Side-effects include headache, hypotension, painful ulceration and genital and gastrointestinal fistulae. Nicorandil should not be prescribed alongside PDE5 inhibitors.

Ivabradine
Ivabradine is a selective inhibitor of the sinus node If ion current (‘funny current’). It is negatively chronotropic (slows heart rate), thereby decreasing myocardial oxygen demand with no effect on myocardial contractility or systemic blood pressure.

In the morbidity-mortality EvAlUaTion of the If inhibitor ivabradine in patients with coronary disease and left-ventricular dysfunction (BEAUTIFUL) trial, ivabradine did not significantly reduce the composite primary endpoint of cardiovascular death, hospitalisation for acute myocardial infarction (MI) and hospitalisation for new onset or worsening heart failure.11 In a prespecified subgroup of patients with LVSD and a heart rate of ≥70 beats per minute, ivabradine reduced admission to hospital for fatal and nonfatal MI, and incidence of coronary revascularisation compared with placebo.

Ivabradine is not suitable for patients who are in atrial fibrillation and is contraindicated in patients with conduction disorders, acute MI and cardiogenic shock. Its use with rate-limiting calcium-channel blockers or CYP3A4 enzyme inhibitors should be avoided. Side-effects include bradycardia, hypotension and visual disturbance due to phosphenes.

Figure 1. Management of stable angina
Ranolazine
Ranolazine selectively inhibits the late inward sodium current in the myocardium, leading to a reduction in intracellular calcium levels and diastolic left ventricular wall tension, thereby reducing myocardial oxygen demand. It has been shown to improve exercise tolerance in patients with stable angina and minimises the use of short-acting nitrates. Commonly reported side-effects include dizziness, constipation and nausea. Ranolazine should be avoided in patients with a prolonged QTc interval and used with extreme caution alongside other QT-prolonging medications. It is contraindicated in patients with liver cirrhosis and should be avoided in patients with severe renal impairment (estimated glomerular filtration rate (eGFR) <30ml/min/1.73m²). Dosage should be reduced when prescribed alongside CYP3A enzyme inhibitors. Although available in other parts of the UK, it was not recommended by the Scottish Medicines Consortium (SMC) for use within NHS Scotland.

Trimetazidine
Trimetazidine is an anti-ischaemic agent that improves myocardial glucose use through inhibition of fatty acid metabolism. A Cochrane review meta-analysis found that it significantly reduced angina attacks, nitrate use, and time to onset of ST depression in patients with stable angina. Its use has been restricted by the European Medicines Agency (EMA), and it is not licensed for use within the UK.

Choice of antianginal therapy
Figure 1 summarises the recommended management pathway for stable angina. The first choice of antianginal therapy in all patients should be either a beta-blocker or calcium-channel blocker (either dihydropyridine or nondihydropyridine). Selection should be based on the presence of co-morbidities (such as asthma) and/or physiological parameters such as resting heart rate, with preference for dihydropyridines in patients with bradycardia. If symptoms are not controlled on a single agent, then consideration should be given to combination of a beta-blocker and dihydropyridine calcium-channel blocker. If this combination is not tolerated (most commonly due to hypotension), then options include the addition of another agent such as a long-acting nitrate, nicorandil, ivabradine or ranolazine.

Nonpharmacological options
The first-line treatment for stable CAD is medical therapy, aimed at modifying risk factors and relieving symptoms. While there is no evidence that percutaneous coronary intervention (PCI) reduces mortality or rates of MI in these patients, it can be highly effective in those with persisting anginal symptoms despite optimal medical therapy. Guidelines therefore suggest that PCI should be considered in patients who have ongoing symptoms despite a trial of at least two antianginal drugs. The caveats to this are patients who cannot tolerate medical therapy and those who have prognostically significant CAD such as left main stem stenosis.

Conclusion
The management of CAD and stable angina is primarily focused on the primary prevention of cardiovascular events and symptom relief. Modifiable risk factors should be identified, and advice and support given to patients to help address them. Pharmacological therapy should be tailored to a patient’s lifestyle and co-morbidities. When symptoms are not relieved by the combination of two antianginal therapies, patients should be referred for consideration of coronary angiography and revascularisation.

References

Declaration of interests
Dr Gardner is an investigator for: Alere, Biocontrol, Boston Scientific, Medtronic, Novartis and St Jude Medical. He also sits on advisory boards for Novartis and St Jude Medical, and is a consultant for Boston Scientific. Neither Dr Jackson nor Dr Docherty have any interests to declare.

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