

# Gavel

Evidence-Based Medicine *in practice*

## The management of stable angina

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- Chronic stable angina is a common problem that has a high risk of progression to more acute forms of myocardial ischaemia.
- Angina can generally be accurately diagnosed by a careful clinical history and examination, aided in equivocal cases by an exercise electrocardiogram.
- More sophisticated functional testing and angiography are only required in a minority of cases.
- Management hinges on the twin objectives of improving outcomes and improving symptoms.
- The routine use of aspirin and statins is both clinically effective and cost-effective as a strategy to improve outcomes. Beta-blockers are probably also effective in this respect, although the evidence is more circumstantial.
- Symptom control is equally well achieved by all the main classes of anti-ischaemic agents. Choice should generally be made according to individual patient characteristics.
- Surgical revascularisation provides highly effective short-term symptom relief, although its effect on mortality is less clearly defined.
- High costs and significant risks attached to the procedures mean that revascularisation should only be considered for those patients with severe, uncontrolled disease.

# Angina management

Improving outcomes in coronary heart disease (CHD) constitutes one of the key health priorities for the NHS and is one of the first round of National Service Framework documents to be published. Given the limited resources available, however, it is entirely reasonable that the greatest efforts should be focused on the treatment of patients who are most likely to benefit – those who already have established CHD. While primary prevention of heart disease by means of cholesterol and blood pressure lowering is effective, the large numbers needed to treat (NNTs – see Box 1, page 5) associated with these strategies mean that the economic viability of this approach must be called into question, given the limited potential gain to the population as a whole. The key government priority for the management of CHD in the UK has therefore been identified as secondary prevention. It should be remembered, however, that secondary prevention includes not only those patients with frank myocardial infarction, but also those with chronic stable angina.

## Burden of disease

Although angina is a chronic manifestation of CHD that may apparently run an uncomplicated course for many years, it is,

nonetheless, associated with a significant risk of myocardial infarction (MI) or CHD death. In one UK study of new angina patients referred to a hospital clinic, 11.2% of the patients had an MI (fatal or otherwise) over a 15-month period.<sup>1</sup> Another study followed up a cohort of 686 angina sufferers, assigned to a variety of treatments, for 22 years. Although their mean age was only 51 at the start, by the end of the study 85% of the participants had suffered an MI and 74% of them were dead.<sup>2</sup>

Angina is not only a serious problem, it is a common one. It has been estimated that there are 2 million sufferers in the UK, with a further 22,800 being diagnosed every year (a conservative estimate).<sup>1</sup> In the average 8,000-patient practice, this would equate to nearly 300 patients. Although not every angina patient will attend the practice on a regular basis, this group of patients places significant demands on primary care (Figure 1). Clearly, then, given the burden of disease that they represent, it is essential that angina patients are both accurately diagnosed and appropriately treated.

In this issue of *Gavel* we will look at the evidence base, such as it is, and try to derive a primary care management strategy that is rational, practical and cost-effective.

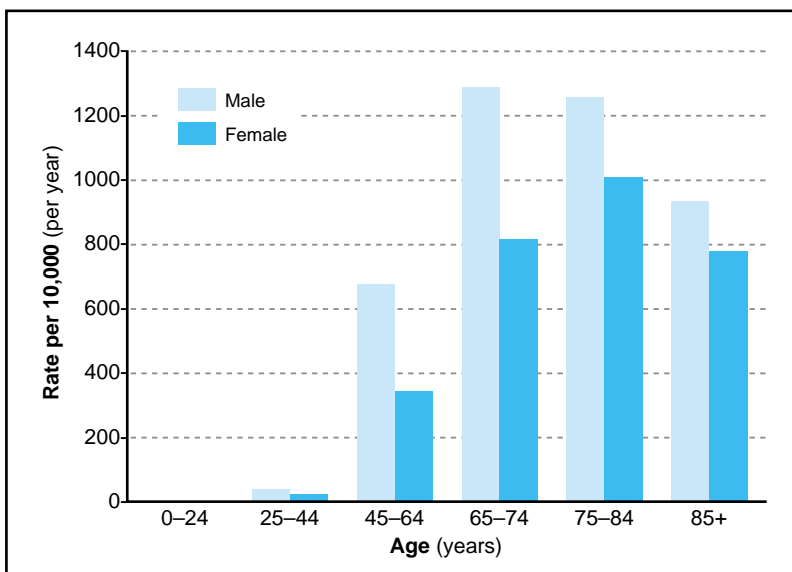
## Diagnosis and grading of angina

There are three levels of diagnostic sophistication that may be employed in the assessment of the angina patient:

1. History, examination and resting electrocardiogram (ECG).
2. Functional assessment using exercise stressed ECG.
3. Ultrasonographic, radiographic or angiographic imaging.

For most GPs, only option 1 will be readily available, perhaps combined with relatively prompt access to exercise ECG testing. Our critical assessment must therefore focus on the reliability of these relatively simple methods.

Figure 1. General practice consultations for angina<sup>3</sup>



**Table 1. Likelihood (%) of coronary artery disease based on clinical assessment<sup>4</sup>**

Age (years)	History suggestive of:					
	Typical angina		Atypical angina		Non-cardiac pain	
	Male	Female	Male	Female	Male	Female
30–39	70	26	22	4	5 (b)	1
40–49	87	55 (c)	46	13	14	3
50–59	92	79	59	32	22	8
60–69	94 (a)	90	67	54	28	19

a, b and c refer to the discussion in the text

### History, examination and resting ECG

The medical history is a very powerful predictor of significant coronary disease. Clinical examination may help to elucidate an underlying cause, but is unlikely to aid primary diagnosis. Resting ECG is important to identify prior MI and rhythm or conduction disorders, but a normal result does not exclude significant CHD. Four key aspects must be examined in the history:

- Location and radiation of pain.
- Relationship to stress and exercise.
- Character of pain.
- Duration of pain.

If all four aspects exhibit the classic signs of angina, then there is little doubt about the diagnosis. Even two clearly positive features may be sufficiently convincing to diagnose typical angina. Frequently, however, the history is less clear-cut and one may only be able to make a diagnosis of atypical angina. Where all features are absent, non-cardiac causes are more likely. The confidence that can be placed in this clinical impression will vary with the age and sex of the patient.

Table 1, drawn up by the Task Force of the European Society of Cardiology, quantifies the predictive value of this approach.<sup>4</sup> Thus, a man aged over 60 with a classic history of angina has a 94% likelihood of having significant coronary artery disease (CAD) (Table 1, a). Further diagnostic assessment is unlikely to improve on this probability and he should be treated accordingly. At the other extreme, a man under 40 with chest pain lacking the characteristic features of angina has so little risk of significant CAD that further investigation would be unwarranted (b). A woman in her 40s with a typical history, however, has a 55% chance of having

significant CAD (c). The diagnostic uncertainty is probably sufficient, here, for a more sophisticated investigation to be undertaken to form a reliable diagnosis and initiate appropriate management.

### Exercise ECG

Few GPs will have exercise ECG facilities within the surgery, so a decision has to be made on whether to refer patients for this particular investigation. Exercise ECG is not an inherently sensitive detector of CAD, when used in isolation, but can prove extremely useful in cases where there is diagnostic doubt.<sup>5</sup> Where the clinical picture is already clear-cut, however, it has little additional to offer.<sup>6</sup> To take our three patients again:

- The man in his 60s with a clear cardiac history was estimated to have a 94% chance of having significant CAD (a). A positive exercise test (ST depression >0.15 mV) would increase this likelihood to 99%, a difference that would not influence our management plan.<sup>4</sup>
- The man in his 30s with a history suggestive of a non-cardiac cause was estimated to have a 5% chance of having significant CAD (b). A positive exercise test (ST depression >0.15 mV) would increase this likelihood to 7%. Once again, this would not influence our management plan, so the investigation is unjustified.<sup>4</sup>
- The woman in her 40s with a typical angina history, on the other hand, was estimated to have a 55% chance of having significant CAD (c). A positive exercise test (ST depression >0.15 mV) would increase this likelihood to 84%, a difference with clear clinical significance that therefore justifies the investigation.<sup>4</sup>

### Functional cardiac imaging and angiography

Access to these more sophisticated facilities will generally require referral to a cardiologist. While this may be an appropriate referral if invasive management is planned, it will not necessarily be required for all patients for diagnostic purposes. As with any diagnostic test, this decision should be taken on the basis of whether or not it will alter the management plan. Patients likely to warrant referral might include:

- Those with a clear diagnosis but poorly controlled symptoms.

- Those with moderate or severe symptoms in whom diagnostic uncertainty remains.
- Those with atypical symptoms but a strongly positive exercise ECG.
- Those in whom exercise ECG is difficult to perform or where false-positive results are common (for example, young women).

In some patients, especially those with typical and severe symptoms or with prior MI or coronary intervention, direct referral for angiography may be justified.

## Management

Once the diagnosis has been made, and assuming urgent referral is not indicated, an initial management plan must be defined. This must address two separate but equally important areas:

- Prevention of progression to MI or premature death.
- Relief of symptoms and improvement of exercise capacity.

### Prevention of MI or death

There are five types of intervention that might reasonably be expected to improve long-term outcomes in stable angina patients:

- Antiplatelet agents – aspirin, dipyridamole, clopidogrel and so on.
- Control of atherogenic risk factors – smoking, cholesterol, hypertension.
- Anti-ischaemic agents – beta-blockers, nitrates, calcium antagonists.
- Revascularisation – coronary artery bypass grafting (CABG), percutaneous transluminal coronary angiography (PTCA).

### Antiplatelet agents

Although there is a substantial evidence base relating to the use of antiplatelet agents in MI, only six randomised, controlled trials have examined its role in stable angina. Five of these are small studies, using a range of antiplatelet agents in a total of 551 patients. The pooled data were suggestive of a 35% relative risk reduction (absolute risk reduction = 5.5%; NNT = 18), but the result did not achieve statistical significance.<sup>7</sup> The sixth study (SAPAT), however, looked at the benefit of 75 mg aspirin or placebo years in a large cohort of 2,035 patients with symptomatic angina.<sup>8</sup> Mean age was 67 years and the sexes were evenly represented. Over the course of

four years, 81 patients in the aspirin group suffered the primary endpoint of MI (fatal or non-fatal) or sudden death, compared with 124 in the placebo group. This is a highly significant relative risk reduction of 34% (absolute risk reduction 4.2%) and equates to an NNT of 25 (95% confidence interval (CI) 15–65) (see Box 1). A more detailed look at the figures reveals that most of this benefit reflected a reduction in non-fatal MI, there being no significant effect on mortality. Even so, on the basis of this study and the trend observed in the smaller trials, aspirin therapy must now be considered as best practice in any patient with symptomatic angina in whom such treatment is not contraindicated.

### Risk factor control

While it seems self-evident that the control of known coronary risk factors should improve the outlook for angina patients, this has only been investigated in any structured fashion for cholesterol reduction. There is a convincing body of evidence supporting the use of simvastatin and pravastatin in the prevention of coronary events. Of the four studies published, two looked at patients with prior MI,<sup>9,10</sup> one looked at patients with no apparent CAD,<sup>11</sup> and one looked at a mixed group of patients with established CAD (21% had stable angina, 17% had post-infarctional angina and 62% were asymptomatic post-infarction patients).<sup>12</sup> All four of these studies demonstrated clear reductions in coronary events. While there is no study that has evaluated statins in angina alone, this is sufficiently clear evidence to justify use of statins in stable angina where total cholesterol is greater than 5.5 mmol/l.

As an interesting footnote, simvastatin also appears to have an impact on long-term symptom control. In a sub-analysis of the 4S data,<sup>13</sup> 568 patients on simvastatin were found to have experienced new or worsening angina over the course of the trial, compared with 725 patients in the placebo group. This is a highly significant result (NNT=14; 95% CI 9–16), but should probably be regarded as a coincidental benefit rather than a new strategy for symptom control.

### Anti-ischaemic agents

There have been no specific long-term studies of the impact of anti-ischaemic agents on

morbidity or mortality in stable angina patients, so it is difficult to draw categorical conclusions about this therapeutic group. There is, however, good circumstantial evidence in support of beta-blockade.

The Beta Blocker Pooling Project collected mortality data from nine long-term secondary prevention studies, involving 13,679 patients with established CHD.<sup>14</sup> Subgroup analysis suggested that those patients with post-infarction angina pectoris seemed to benefit particularly from beta-blocker treatment. Although one must interpret such *post hoc* analyses with caution, the trend was consistent across all the constituent studies, lending the conclusions some credibility.

### Revascularisation

The use of surgical revascularisation, whether by means of CABG or PTCA, is gaining in popularity throughout Europe.<sup>15</sup> While both strategies appear to be effective for the control of symptoms (see below), individual studies disagree as to whether they are capable of reducing mortality and morbidity in chronic stable angina.

A meta-analysis published in 1994 pooled data from seven trials of 2,649 patients randomised to receive either CABG or standard medical treatment.<sup>16</sup> Over a ten-year period, there were 350 deaths in the CABG group, compared with 404 in the medical treatment group. This is a significant difference that equates to an NNT of 25,

although the 95% confidence limits are wide (13–161). Sub-analysis shows that the maximum benefit is gained by those patients with the most severe angina at baseline. Those with milder disease showed no mortality benefit.

The other confounding factor in this analysis is the age of the studies – most were started in the 1970s, at which time medical management was ill-defined and surgical techniques less sophisticated than now. Only 20% of medical patients were on aspirin and none were on statins, making extrapolation to current practice difficult.

Two long-term studies have compared PTCA with medical treatment in a total of 1,230 patients with mild to moderate stable angina.<sup>17,18</sup> Although it offers good symptomatic control, there was no outcome benefit with PTCA. In fact, in the larger of the trials,<sup>18</sup> over a 2.7-year period, there were 32 CHD events in 504 patients assigned to PTCA, compared with 17 in the 514 patients assigned to medical therapy. This is a significant difference and equates to a number needed to harm of 33, although, once again, the confidence intervals are wide (18–243).

Given the risks associated with the procedures,<sup>4,16</sup> and the uncertainty of the long-term benefits, it seems reasonable that PTCA and CABG should be reserved for those patients who remain symptomatic on medical therapy or in whom the potential benefit is considered to outweigh the potential risks.

## Box 1. How to calculate NNTs

In order to compare clinical trials in a meaningful fashion, some measure of statistical comparison is required. Published papers use a range of statistical techniques, but these are generally difficult for the non-specialist to interpret. For this reason, *Gavel*, where possible, expresses trial results in terms of number needed to treat (NNT). NNTs are an estimate of the number of patients that would need to be given a therapy, in order to achieve the desired result.

For an outcome such as cardiovascular events, it is calculated very simply:

$$\text{NNT} = \frac{1}{\text{Proportion patients with a CHD event on placebo} - \text{Proportion of patients with a CHD event on treatment}}$$

As an example, the Sapat study,<sup>8</sup> described on page 4 of this issue of *Gavel*, found the following:

- One hundred and twenty-four patients out of 1,013 on placebo experienced a CHD event (12.2%).
- Eighty-one out of 1,009 patients on treatment experienced a CHD event (8.0%).

$$\text{NNT} = \frac{1}{0.122 - 0.080} = 24.6$$

This means that, 25 patients need to be treated for four years to prevent one patient from suffering a CHD event.

### Cost implications of prevention

Aspirin must be regarded as standard therapy for all patients with established CHD, including those with chronic stable angina. Purchase costs are low, perhaps £10 per patient per year, with a significant number of patients paying for their own treatment over the counter.<sup>19</sup> Given an NNT of 25, this would suggest that an investment of £1,000 (25 patients at £10 per year for four years) will result in the prevention of one MI. One does not need a detailed economic analysis to appreciate the cost-effectiveness of this approach, yet, surprisingly, aspirin is still only used in a minority of patients. National data gathered from GPs looking after 1.4 million patients suggest that, in 1994, only 45% of men and 35% of women with established CHD were being prescribed aspirin.<sup>20</sup>

The addition of statin therapy clearly has greater cost implications, with typical annual costs of £300–£400 per patient. The associated health gains, however, are considerable. A recent economic analysis has suggested that the addition of a statin to the standard stable angina regimen is highly cost-effective. Over a ten-year period, statins incur a cost of approximately £9,000 per life-year gained overall, dropping to less than £6,000 per life-year in patients with severe angina.<sup>21</sup> Based on such clear-cut benefits, the Standing Medical Advisory Committee has advised that patients with stable angina should be specifically targeted for statin therapy, as a second priority after those with a prior MI.<sup>22</sup>

The overall costs of beta-blocker therapy are more difficult to assess, as we have no primary outcome data on which to base an

NNT calculation. Purchase costs range from about £9 per year for generic propranolol to about £120 for the more selective, modern agents. Given these relatively modest costs, and the likelihood that the patient will require symptomatic treatment anyway, it seems not unreasonable, on cost grounds, to add a beta-blocker to the standard regimen of those patients who can tolerate it.

CABG carries significant, up-front costs that make it difficult to justify as a purely preventive measure. An economic analysis showed that medical therapy was the more cost-effective approach overall, over a ten-year period. Even in more severely affected patients, where CABG potentially has an advantage, the costs are high and range from £16,000 to £30,000 per life-year saved.<sup>21</sup> Any decision to use CABG, therefore, should probably reflect its potential benefit in improving intractable symptoms, rather than as a strategy to prevent adverse outcomes.

### Symptom control

There are, once again, several strategies that can be adopted for the control of symptoms in chronic stable angina:

- Nitrates.
- Beta-blockers.
- Calcium antagonists.
- Potassium channel openers.
- Surgical revascularisation.

### Pharmaceutical strategies

Broadly speaking, every patient with symptomatic angina will require access to sublingual nitrates. These work rapidly and effectively and, in patients with milder

**Table 2. Strengths and weaknesses of anti-ischaemic treatment classes**

	Outcomes benefit?	Use in heart failure?	Use in PVD?*	Safe in combination?	Safe in coexisting disease?	Comments
<i>Nitrates</i>	No	Yes	Yes	Yes	Yes	Tolerance may develop with constant dosing
<i>Beta-blockers</i>	Probable	Caution	Caution	Not with diltiazem or verapamil	Caution in asthma/diabetes	Treatment of choice in post-MI patients
<i>Calcium antagonists</i>	No	Caution	Yes	Caution – see beta-blockers	Yes	Specifically indicated for vasospastic angina
<i>Potassium channel openers</i>	No	Caution	Yes	Yes	Yes	Limited experience

\*PVD = peripheral vascular disease

**Table 3. Symptom control – costs for 28 days' treatment at typical dose<sup>29</sup>**

Class	Regimen	Cost
Nitrates (sublingual)	prn tabs	£0.53 per 100 tablets
	prn spray	£3.24–£4.10 for 200 doses
Nitrates (oral)	bd/tds	£0.75–£8.70
	od	£7.00–£11.30
Beta-blockers	bd/tds	£0.71–£5.15
	od	£1.47–£9.08
Calcium antagonists	bd/tds	£6.29–£12.29
	od	£8.12–£13.51
Potassium channel opener	bd	£8.65–£16.44

disease, may be all that is necessary. Their benefit, however, only lasts for approximately 30 minutes and so, for many patients, additional daily treatment will be required.

There is a bewildering range of studies comparing the antianginal efficacy of the various agents, alone or in combination, with each other or placebo. Most of these studies are small and of limited duration, and the study designs often leave a lot to be desired. No one therapeutic class really emerges as being consistently superior to any other, although each has its good and bad points (Table 2, opposite). One very interesting aspect of the combination studies emerges, however. As each of the classes exerts its effect via a slightly different mechanism, one might expect that combination therapy would give improved symptom control. In fact, a review of the literature suggests that this theory is not borne out in practice and that patients may be better managed by increasing the dose of a single agent or switching to an alternative.<sup>23</sup> Where control cannot be achieved on a single agent, therefore, it is now recommended that a switch to an alternative class is tried first, before starting combination treatment.<sup>4</sup>

#### **Revascularisation**

While the impact of CABG and PTCA on clinical outcomes is difficult to quantify, their benefit in terms of symptom control is, in the short term at least, rather more clear-cut. Three large studies have compared the efficacy of CABG versus medical therapy,<sup>2,24,25</sup> while two have looked at PTCA.<sup>17,18</sup> Their consistent finding is an early improvement in the intervention group, which declines over a

period of two to five years. This benefit is greatest in patients with the most severe symptoms – in patients with mild angina the advantage may disappear over as little as a few months. When this is set against an increased short-term risk of death, MI or restenosis, it becomes apparent that surgical intervention should only be considered in patients with severe, functionally limiting angina that is resistant to medical therapy, or where the severity of CHD is so great that the short-term risk is justified (for example, three-vessel disease or impaired left ventricular function).

#### **Cost implications of pharmacological symptom control**

Symptomatic control cannot be assessed in terms of the number of life-years saved, and, given their similar efficacies, there is unlikely to be any substantial differences in the cost per QALY (quality-adjusted life-year) associated with each option. The choice is therefore likely to be made on clinical grounds, with drug choices being made to suit the individual's circumstances, as outlined in Table 2. There are, nonetheless, a few important cost considerations (Table 3).

#### **PRN nitrates**

Sublingual nitrate tablets are very cheap but have a short shelf-life, requiring replacement every eight weeks. In patients who have infrequent attacks, it may prove both cheaper and simpler to give them a nitrate spray, which will remain effective for several years.

#### **Oral nitrates**

Oral isosorbide dinitrate is very cheap (less than £1 per month) but requires three-times-daily dosing. The longer-acting isosorbide mononitrate costs significantly more but has been shown to be associated with considerably better symptom control, especially when given once daily.<sup>26–28</sup> This probably reflects a combination of improved compliance and an enforced nitrate-low period overnight, which helps to avoid tolerance. This benefit may be diminished in multidose regimens, when a dose taken too late in the day may encourage the development of tolerance.<sup>28</sup>

A recently launched product that combines once-daily isosorbide mononitrate and aspirin offers interesting possibilities to extend this compliance benefit beyond symptom control.

## Beta-blockers

Quite apart from their symptomatic efficacy, beta-blockers may also be associated with benefits in terms of outcomes (see above). They are generally cheap and, unless contraindications exist, should probably be considered the treatment of choice in stable angina. In order to minimise the risk of adverse effects, however, and to improve treatment compliance, it is probably worth the additional expense of using a once-daily selective agent, rather than older, multidose regimens.

## Calcium antagonists

All oral calcium antagonists are effective antianginal agents, with a relatively tight cost range. Side-effects and compliance may be a problem with older, multidose products and so, given the relatively small cost differential, it is probably worth using longer-acting products.

## Potassium channel openers

Currently one agent in this class – nicorandil – is licensed for use in angina. Although efficacious, it is difficult to recommend it as a first-line therapy. The cost may be justified where other treatments have failed, or when combination therapy is being considered.

## Conclusions

- All patients should be given aspirin, if it is not contraindicated, at a dose of 75 mg per day.
- All patients should be given sublingual nitrate and instructed in its use.
- All patients should have their lipids checked and, if total cholesterol is >5.5 mmol/l, be started on a statin.
- A selective, once-daily beta-blocker should be considered, where not contraindicated, especially in symptomatic angina.
- Where beta-blockers are contraindicated, ineffective or poorly tolerated, and symptomatic control is required, a once-daily nitrate or calcium antagonist should be started.
- If control is not achieved, dosage should be titrated upwards or a switch to another class tried. Potassium channel openers may be tried.
- Where angina severely limits normal activities or is uncontrolled by maximal medical therapy, or where there is impaired myocardial function, referral for revascularisation should be considered.

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