Stable angina: management

Clinical guideline
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Your responsibility

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.
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**Introduction**

Angina is pain or constricting discomfort that typically occurs in the front of the chest (but may radiate to the neck, shoulders, jaw or arms) and is brought on by physical exertion or emotional stress. Some people can have atypical symptoms, such as gastrointestinal discomfort, breathlessness or nausea. Angina is the main symptom of myocardial ischaemia and is usually caused by atherosclerotic obstructive coronary artery disease restricting blood flow and therefore oxygen delivery to the heart muscle. The Health Survey for England (2006) reported that around 8% of men and 3% of women aged between 55 and 64 years currently have or have had angina. The figures for men and women aged between 65 and 74 years are around 14% and 8% respectively. It is estimated that almost 2 million people in England currently have or have had angina. Being diagnosed with angina can have a significant impact on a person's quality of life, restricting daily work and leisure activities.

Stable angina is a chronic medical condition with a low but appreciable incidence of acute coronary events and increased mortality. The aim of management is to stop or minimise symptoms, and to improve quality of life and long-term morbidity and mortality. Management options include lifestyle advice, drug treatment and revascularisation using percutaneous or surgical techniques.

Analysis of the comparative efficacy of different treatments for people with stable angina is difficult because of the advances in drug treatment and revascularisation strategies over several decades. Trials of drug treatment versus coronary artery bypass surgery were carried out more than 25 years ago and showed a survival advantage with surgery in patients with severe coronary artery disease. Statins and other secondary prevention treatments were not used when the trials were carried out and these treatments have a significant effect on morbidity and mortality. Percutaneous revascularisation techniques have developed, from balloon angioplasty to bare metal stents and drug eluting stents and each is associated with reduced rates of repeat revascularisation compared with the previous technique. All trials, including trials of revascularisation strategies, have been limited to people considered suitable for the intervention rather than being representative...
of the whole population with angina.

The recommendations in this guideline relate only to people with a diagnosis of stable angina. Coronary artery disease can also present as acute coronary syndromes, such as unstable angina or myocardial infarction. The NICE guideline on recent-onset chest pain of suspected cardiac arrest origin, covers the diagnosis of stable angina and should be read in conjunction with this guideline.

The guideline will assume that prescribers will use a drug’s summary of product characteristics to inform decisions made with individual patients.

This guideline recommends some drugs for indications for which they do not have a UK marketing authorisation at the date of publication, if there is good evidence to support that use. Where recommendations have been made for the use of drugs outside their licensed indications ('off-label use'), these drugs are marked with a footnote in the recommendations.
Key priorities for implementation

The following recommendations have been identified as priorities for implementation.

- Explore and address issues according to the person's needs, which may include:
  - self-management skills such as pacing their activities and goal setting
  - concerns about the impact of stress, anxiety or depression on angina
  - advice about physical exertion including sexual activity.

- Offer people optimal drug treatment for the initial management of stable angina. Optimal drug treatment consists of one or two anti-anginal drugs as necessary plus drugs for secondary prevention of cardiovascular disease.

- Consider revascularisation (coronary artery bypass graft [CABG] or percutaneous coronary intervention [PCI]) for people with stable angina whose symptoms are not satisfactorily controlled with optimal medical treatment.

- When either procedure would be appropriate, explain to the person the risks and benefits of PCI and CABG for people with anatomically less complex disease whose symptoms are not satisfactorily controlled with optimal medical treatment. If the person does not express a preference, take account of the evidence that suggests that PCI may be the more cost-effective procedure in selecting the course of treatment.

- When either procedure would be appropriate, take into account the potential survival advantage of CABG over PCI for people with multivessel disease whose symptoms are not satisfactorily controlled with optimal medical treatment and who:
  - have diabetes or
  - are over 65 years or
  - have anatomically complex three-vessel disease, with or without involvement of the left main stem.
• Consider the relative risks and benefits of CABG and PCI for people with stable angina using a systematic approach to assess the severity and complexity of the person's coronary disease, in addition to other relevant clinical factors and comorbidities.

• Ensure that there is a regular multidisciplinary team meeting to discuss the risks and benefits of continuing drug treatment or the revascularisation strategy (CABG or PCI) for people with stable angina. The team should include cardiac surgeons and interventional cardiologists. Treatment strategy should be discussed for the following people, including but not limited to:
  – people with left main stem or anatomically complex three-vessel disease
  – people in whom there is doubt about the best method of revascularisation because of the complexity of coronary anatomy, the extent of stenting required or other relevant clinical factors and comorbidities.

• Ensure people with stable angina receive balanced information and have the opportunity to discuss the benefits, limitations and risks of continuing drug treatment, CABG and PCI to help them make an informed decision about their treatment. When either revascularisation procedure is appropriate, explain to the person:
  – The main purpose of revascularisation is to improve the symptoms of stable angina.
  – CABG and PCI are effective in relieving symptoms.
  – Repeat revascularisation may be necessary after either CABG or PCI and the rate is lower after CABG.
  – Stroke is uncommon after either CABG or PCI, and the incidence is similar between the two procedures.
  – There is a potential survival advantage with CABG for some people with multivessel disease.
Discuss the following with people whose symptoms are satisfactorily controlled with optimal medical treatment:

- their prognosis without further investigation
- the likelihood of having left main stem disease or proximal three-vessel disease
- the availability of CABG to improve the prognosis in a subgroup of people with left main stem or proximal three-vessel disease
- the process and risks of investigation
- the benefits and risks of CABG, including the potential survival gain.
Guidance

People have the right to be involved in discussions and make informed decisions about their care, as described in NICE's information on making decisions about your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

Recommendations 1.5.2 and 1.5.12 partially update recommendation 1.2 of the NICE technology appraisal guidance on myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction.

The following guidance is for people who have a diagnosis of stable angina and is based on the best available evidence. The full guideline gives details of the methods and the evidence used to develop the guidance.

1.1 Diagnosis

1.1.1 Diagnose stable angina according to the NICE guideline on recent-onset chest pain of suspected cardiac origin. Diagnose and manage unstable angina and NSTEMI according to the NICE guidelines on recent-onset chest pain of suspected cardiac origin, unstable angina and NSTEMI and acute coronary syndromes.

1.2 Information and support for people with stable angina

1.2.1 Clearly explain stable angina to the person, including factors that can provoke angina (for example, exertion, emotional stress, exposure to cold, eating a heavy meal) and its long-term course and management. When relevant, involve the person's family or carers in the discussion.
1.2.2 Encourage the person with stable angina to ask questions about their angina and its treatment. Provide opportunities for them to voice their concerns and fears.

1.2.3 Discuss the person's, and if appropriate, their family or carer's ideas, concerns and expectations about their condition, prognosis and treatment. Explore and address any misconceptions about stable angina and its implications for daily activities, heart attack risk and life expectancy.

1.2.4 Advise the person with stable angina to seek professional help if there is a sudden worsening in the frequency or severity of their angina.

1.2.5 Discuss with the person the purpose and any risks and benefits of their treatment.

1.2.6 Assess the person's need for lifestyle advice (for example about exercise, stopping smoking, diet and weight control) and psychological support, and offer interventions as necessary.

1.2.7 Explore and address issues according to the person's needs, which may include:

- self-management skills such as pacing their activities and goal setting
- concerns about the impact of stress, anxiety or depression on angina
- advice about physical exertion including sexual activity.

1.3 General principles for treating people with stable angina

1.3.1 Do not exclude people with stable angina from treatment based on their age alone.

1.3.2 Do not investigate or treat symptoms of stable angina differently in men and women or in different ethnic groups.
Preventing and treating episodes of angina

1.3.3 Offer a short-acting nitrate for preventing and treating episodes of angina. Advise people with stable angina:

- how to administer the short-acting nitrate
- to use it immediately before any planned exercise or exertion
- that side effects such as flushing, headache and light-headedness may occur
- to sit down or find something to hold on to if feeling light-headed.

1.3.4 When a short-acting nitrate is being used to treat episodes of angina, advise people:

- to repeat the dose after 5 minutes if the pain has not gone
- to call an emergency ambulance if the pain has not gone 5 minutes after taking a second dose.

Drugs for secondary prevention of cardiovascular disease

1.3.5 Consider aspirin 75 mg daily for people with stable angina, taking into account the risk of bleeding and comorbidities.

1.3.6 Consider angiotensin-converting enzyme (ACE) inhibitors for people with stable angina and diabetes. Offer or continue ACE inhibitors for other conditions, in line with relevant NICE guidance.

1.3.7 Offer statin treatment in line with the NICE guideline on lipid modification.

1.3.8 Offer treatment for high blood pressure in line with the NICE guideline on hypertension.

Dietary supplements

1.3.9 Do not offer vitamin or fish oil supplements to treat stable angina. Inform people that there is no evidence that they help stable angina.
1.4  Anti-anginal drug treatment

General recommendations

1.4.1 Offer people optimal drug treatment for the initial management of stable angina. Optimal drug treatment consists of one or two anti-anginal drugs as necessary plus drugs for secondary prevention of cardiovascular disease.

1.4.2 Advise people that the aim of anti-anginal drug treatment is to prevent episodes of angina and the aim of secondary prevention treatment is to prevent cardiovascular events such as heart attack and stroke.

1.4.3 Discuss how side effects of drug treatment might affect the person's daily activities and explain why it is important to take drug treatment regularly.

1.4.4 Patients differ in the type and amount of information they need and want. Therefore the provision of information should be individualised and is likely to include, but not be limited to:

- what the medicine is
- how the medicine is likely to affect their condition (that is, its benefits)
- likely or significant adverse effects and what to do if they think they are experiencing them
- how to use the medicine
- what to do if they miss a dose
- whether further courses of the medicine will be needed after the first prescription
- how to get further supplies of medicines. [This recommendation is from the NICE guideline on medicines adherence.]

1.4.5 Review the person's response to treatment, including any side effects, 2 to 4 weeks after starting or changing drug treatment.
1.4.6 Titrate the drug dosage against the person's symptoms up to the maximum tolerable dosage.

**Drugs for treating stable angina**

1.4.7 Offer either a beta blocker or a calcium channel blocker as first-line treatment for stable angina. Decide which drug to use based on comorbidities, contraindications and the person's preference.

1.4.8 If the person cannot tolerate the beta blocker or calcium channel blocker, consider switching to the other option (calcium channel blocker or beta blocker).

1.4.9 If the person's symptoms are not satisfactorily controlled on a beta blocker or a calcium channel blocker, consider either switching to the other option or using a combination of the two.

When combining a calcium channel blocker with a beta blocker, use a dihydropyridine calcium channel blocker, for example, slow release nifedipine, amlodipine or felodipine.

1.4.10 Do not routinely offer anti-anginal drugs other than beta blockers or calcium channel blockers as first-line treatment for stable angina.

1.4.11 If the person cannot tolerate beta blockers and calcium channel blockers or both are contraindicated, consider monotherapy with one of the following drugs:

- a long-acting nitrate or
- ivabradine or
- nicorandil or
• ranolazine.

Decide which drug to use based on comorbidities, contraindications, the person's preference and drug costs.

Since this guidance was produced, the Medicines and Healthcare products Regulatory Agency (MHRA) have published new advice about safety concerns related to ivabradine (June 2014 and December 2014) and nicorandil (January 2016).

1.4.12 For people on beta blocker or calcium channel blocker monotherapy whose symptoms are not controlled and the other option (calcium channel blocker or beta blocker) is contraindicated or not tolerated, consider one of the following as an additional drug:

• a long-acting nitrate or
• ivabradine or
• nicorandil or
• ranolazine.

Decide which drug to use based on comorbidities, contraindications, the person's preference and drug costs.

Since this guidance was produced, the Medicines and Healthcare products Regulatory Agency (MHRA) have published new advice about safety concerns related to ivabradine (June 2014 and December 2014) and nicorandil (January 2016).

When combining ivabradine with a calcium channel blocker, use a dihydropyridine calcium channel blocker, for example, slow release nifedipine, amlodipine, or felodipine.

1.4.13 Do not offer a third anti-anginal drug to people whose stable angina is controlled with two anti-anginal drugs.

1.4.14 Consider adding a third anti-anginal drug only when:
• the person's symptoms are not satisfactorily controlled with two anti-anginal drugs and

• the person is waiting for revascularisation or revascularisation is not considered appropriate or acceptable.

Decide which drug to use based on comorbidities, contraindications, the person's preference and drug costs.

1.5 Investigation and revascularisation

People with stable angina whose symptoms are not satisfactorily controlled with optimal medical treatment

1.5.1 Consider revascularisation (coronary artery bypass graft [CABG] or percutaneous coronary intervention [PCI]) for people with stable angina whose symptoms are not satisfactorily controlled with optimal medical treatment.

1.5.2 Offer coronary angiography to guide treatment strategy for people with stable angina whose symptoms are not satisfactorily controlled with optimal medical treatment. Additional non-invasive or invasive functional testing may be required to evaluate angiographic findings and guide treatment decisions. [This recommendation partially updates recommendation 1.2 of the NICE technology appraisal guidance on myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction.]

1.5.3 Offer CABG to people with stable angina and suitable coronary anatomy when:

• their symptoms are not satisfactorily controlled with optimal medical treatment and

• revascularisation is considered appropriate and

• PCI is not appropriate.
1.5.4 Offer PCI to people with stable angina and suitable coronary anatomy when:

- their symptoms are not satisfactorily controlled with optimal medical treatment and
- revascularisation is considered appropriate and
- CABG is not appropriate.

1.5.5 When either procedure would be appropriate, explain to the person the risks and benefits of PCI and CABG for people with anatomically less complex disease whose symptoms are not satisfactorily controlled with optimal medical treatment. If the person does not express a preference, take account of the evidence that suggests that PCI may be the more cost-effective procedure in selecting the course of treatment.

1.5.6 When either procedure would be appropriate, take into account the potential survival advantage of CABG over PCI for people with multivessel disease whose symptoms are not satisfactorily controlled with optimal medical treatment and who:

- have diabetes or
- are over 65 years or
- have anatomically complex three-vessel disease, with or without involvement of the left main stem.

1.5.7 Consider the relative risks and benefits of CABG and PCI for people with stable angina using a systematic approach to assess the severity and complexity of the person's coronary disease, in addition to other relevant clinical factors and comorbidities.

1.5.8 Ensure that there is a regular multidisciplinary team meeting to discuss the risks and benefits of continuing drug treatment or revascularisation strategy (CABG or PCI) for people with stable angina. The team should include cardiac surgeons and interventional cardiologists. Treatment strategy should be discussed for the following people, including but not limited to:
• people with left main stem or anatomically complex three-vessel disease

• people in whom there is doubt about the best method of revascularisation because of the complexity of the coronary anatomy, the extent of stenting required or other relevant clinical factors and comorbidities.

1.5.9 Ensure people with stable angina receive balanced information and have the opportunity to discuss the benefits, limitations and risks of continuing drug treatment, CABG and PCI to help them make an informed decision about their treatment. When either revascularisation procedure is appropriate, explain to the person:

• The main purpose of revascularisation is to improve the symptoms of stable angina.

• CABG and PCI are effective in relieving symptoms.

• Repeat revascularisation may be necessary after either CABG or PCI and the rate is lower after CABG.

• Stroke is uncommon after either CABG or PCI, and the incidence is similar between the two procedures.

• There is a potential survival advantage with CABG for some people with multivessel disease.

1.5.10 Inform the person about the practical aspects of CABG and PCI. Include information about:

• vein and/or artery harvesting

• likely length of hospital stay

• recovery time

• drug treatment after the procedure.

People with stable angina whose symptoms are satisfactorily controlled with optimal medical treatment

1.5.11 Discuss the following with people whose symptoms are satisfactorily
controlled with optimal medical treatment:

- their prognosis without further investigation
- the likelihood of having left main stem disease or proximal three-vessel disease
- the availability of CABG to improve the prognosis in a subgroup of people with left main stem or proximal three-vessel disease
- the process and risks of investigation
- the benefits and risks of CABG, including the potential survival gain.

1.5.12 After discussion (see 1.5.11) with people whose symptoms are satisfactorily controlled with optimal medical treatment, consider a functional or non-invasive anatomical test to identify people who might gain a survival benefit from surgery. Functional or anatomical test results may already be available from diagnostic assessment. [This recommendation partially updates recommendation 1.2 of the NICE technology appraisal guidance on myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction.]

1.5.13 After discussion (see 1.5.11) with people whose symptoms are satisfactorily controlled with optimal medical treatment, consider coronary angiography when:

- functional testing indicates extensive ischaemia or non-invasive anatomical testing indicates the likelihood of left main stem or proximal three-vessel disease and
- revascularisation is acceptable and appropriate.

1.5.14 Consider CABG for people with stable angina and suitable coronary anatomy whose symptoms are satisfactorily controlled with optimal medical treatment, but coronary angiography indicates left main stem disease or proximal three-vessel disease.

1.6 Pain interventions

1.6.1 Do not offer the following interventions to manage stable angina:
- transcutaneous electrical nerve stimulation (TENS)
- enhanced external counterpulsation (EECP)
- acupuncture.

1.7 **Stable angina that has not responded to treatment**

1.7.1 Offer people whose stable angina has not responded to drug treatment and/or revascularisation comprehensive re-evaluation and advice, which may include:

- exploring the person's understanding of their condition
- exploring the impact of symptoms on the person's quality of life
- reviewing the diagnosis and considering non-ischaemic causes of pain
- reviewing drug treatment and considering future drug treatment and revascularisation options
- acknowledging the limitations of future treatment
- explaining how the person can manage the pain themselves
- specific attention to the role of psychological factors in pain
- development of skills to modify cognitions and behaviours associated with pain.

1.8 **Cardiac syndrome X**

1.8.1 In people with angiographically normal coronary arteries and continuing anginal symptoms, consider a diagnosis of cardiac syndrome X.

1.8.2 Continue drug treatment for stable angina only if it improves the symptoms of the person with suspected cardiac syndrome X.

1.8.3 Do not routinely offer drugs for the secondary prevention of
cardiovascular disease to people with suspected cardiac syndrome X.
Recommendations for research

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

1 Adding a newer anti-anginal drug to a calcium channel blocker

What is the clinical and cost effectiveness of adding a newer anti-anginal drug (nicorandil, ivabradine or ranolazine) to a calcium channel blocker for treating stable angina?

Why this is important

We do not know the long-term clinical and cost effectiveness of adding a newer anti-anginal drug to a calcium channel blocker in people with stable angina. We propose a double-blind placebo-controlled randomised trial comparing the addition of a newer anti-anginal drug to a calcium channel blocker with a calcium channel blocker alone in people with stable angina whose symptoms are not being controlled. Endpoints would include symptom severity, quality of life, long-term morbidity and mortality, and cost effectiveness. The results of the trial would influence clinical practice and inform future updates of key recommendations in this guideline.

2 Management of stable angina in people with evidence of ischaemia on non-invasive functional testing

Do people with stable angina and evidence of reversible ischaemia on non-invasive functional testing who are on optimal drug treatment benefit from routine coronary angiography with a view to revascularisation?

Why this is important

Revascularisation has traditionally been offered to people with stable angina who have evidence of reversible ischaemia on non-invasive functional testing. Recent trials in people
with stable angina (COURAGE, BARI-2D, MASS II) have not shown survival benefit from revascularisation compared with drug treatment. In the nuclear substudy of COURAGE (n = 314), PCI was shown to be more effective in treating ischaemia than optimal drug treatment, and in multivariate analyses reduction of ischaemia was associated with greater event-free survival. It is unclear, however, whether people on optimal drug treatment who have evidence of inducible ischaemia on non-invasive functional testing should routinely have coronary angiography and revascularisation. This question is particularly relevant for people who have responded adequately (for example Canadian Cardiovascular Class 1 or 2) to optimal drug treatment and in whom, based on symptoms alone, revascularisation is not indicated. To answer this question we recommend a randomised trial of interventional management versus continued drug treatment in people with stable angina and myocardial ischaemia on non-invasive functional testing, with all-cause mortality and cardiovascular mortality as the primary endpoints.

### 3 Early revascularisation strategy for people with angina and multivessel disease

In people with stable angina and multivessel disease (including left main stem disease) whose symptoms are controlled with optimal drug treatment, would an initial treatment strategy of revascularisation be clinically and cost effective compared with continued drug treatment?

#### Why this is important

Research is needed to determine whether early investigation and revascularisation can improve longer term survival. People with stable angina may be disadvantaged if they do not have tests to identify whether they have a higher risk profile for early cardiac death, which could be reduced by revascularisation. This disadvantage could be magnified when people who are deemed to fall into very high risk groups (for example, left main stem stenosis > 50% in the MASS II trial) are excluded from randomised trials, resulting in the benefits of revascularisation being underestimated. We propose a randomised trial comparing an initial strategy of revascularisation (CABG or PCI) with an initial strategy of continued drug treatment in people with multivessel disease (including left main stem disease) in whom revascularisation is not needed for symptom relief. The trial should use drug-eluting stents and wider inclusion criteria than BARI-2D and COURAGE.
4 Cardiac rehabilitation

Is an 8-week, comprehensive, multidisciplinary, cardiac rehabilitation service more clinically and cost effective for managing stable angina than current clinical practice?

Why this is important

Cardiac rehabilitation programmes are an established treatment strategy for certain heart conditions, such as for people who have had a heart attack. However, there is no evidence to suggest that cardiac rehabilitation is clinically or cost effective for managing stable angina. Research to date has looked at short-term outcomes, such as a change in diet or exercise levels, but the effect on morbidity and mortality has not been studied. A randomised controlled trial is required to compare comprehensive cardiac rehabilitation with standard care in people with stable angina, with measures of angina severity (exercise capacity, angina frequency, use of a short-acting nitrate), and long-term morbidity and mortality as endpoints.

5 Patient self-management plans

What is the clinical and cost effectiveness of a self-management plan for people with stable angina?

Why this is important

Stable angina is a chronic condition. Evidence suggests that addressing people's beliefs and behaviours in relation to angina may improve quality of life, and reduce morbidity and use of resources. Self-management plans could include: educating people with stable angina about the role of psychological factors in pain and pain control; and teaching people self-management skills to modify cognitions, behaviours and affective responses in order to control chest pain. These skills may include pacing of physical activities, modifying stress using cognitive reframing and problem-solving techniques, and relaxation training or mindfulness techniques. The proposed study is a randomised controlled trial in primary care that would assess the clinical and cost effectiveness of self-management plans. This research would inform future updates of key recommendations in the guideline. Furthermore the research would be relevant to a national priority area (National service framework for coronary heart disease [NSF CHD] chapter 4: stable angina and chapter 7: cardiac rehabilitation) as well as the Coalition White Paper 2010 (Equity and excellence: liberating the NHS) that emphasise the importance of increasing people’s choice and
control in managing their condition.
Finding more information and committee details

To find NICE guidance on related topics, including guidance in development, see the NICE webpage on acute coronary syndromes.

For full details of the evidence and the guideline committee's discussions, see the full guideline. You can also find information about how the guideline was developed, including details of the committee.

NICE has produced tools and resources to help you put this guideline into practice. For general help and advice on putting our guidelines into practice, see resources to help you put NICE guidance into practice.
Update information

**August 2016:** Added a footnote to recommendations 1.4.11 and 1.4.12 covering the new advice from the Medicines and Healthcare products Regulatory Agency (MHRA) about safety concerns related to ivabradine ([June 2014](#) and [December 2014](#)) and nicorandil ([January 2016](#)).

**Minor changes since publication**

**December 2012:** The licensing information for nicorandil was updated.

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Accreditation

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