SIGN 151 • Management of stable angina

A national clinical guideline

April 2018

http://guide.medlive.cn/
### Key to Evidence Statements and Recommendations

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### Recommendations

Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the ‘strength’ of the recommendation).

The ‘strength’ of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation.

Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence, and the balance of benefits and harms of the options.

- **R** For ‘strong’ recommendations on interventions that ‘should’ be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm. For ‘strong’ recommendations on interventions that ‘should not’ be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more harm than good.
- **R** For ‘conditional’ recommendations on interventions that should be ‘considered’, the guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person’s values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.

### Good-Practice Points

- Recommended best practice based on the clinical experience of the guideline development group.
Management of stable angina
A national clinical guideline

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1 Introduction

1.1 THE NEED FOR A GUIDELINE

Despite a steep decline in mortality from coronary artery disease (CAD) in Scotland over the last 20 years, CAD remains one of the leading causes of death in Scotland, responsible for 7,154 deaths in 2015. It is estimated that 18% of men aged 65–74 and 32% of men aged 75 and over are living with ischaemic heart disease (IHD) heart attack or angina); the prevalence in women in these age groups is substantially lower at 9% and 20% respectively.1

Accurately distinguishing patients with stable angina from patients with unstable angina is problematic due to limitations in the way angina is coded in national data. In Scotland, data from 2012/13, submitted by Scottish general practices to Information Services Division Scotland through the Practice Team Information system recorded a rate of angina for men aged 65–74 and 75 years and over of 34.3 and 59.7 per 1,000 population, respectively. The comparable figures for women in the same age groups were 23.3 and 38.5 per 1,000 of the population.4 It is likely that the majority of people consulting their General Practitioner (GP) with angina will have stable angina. The Scottish Health Survey Topic Report on Older People’s Health reported the prevalence of angina, based on combined data from 2008–2010, as 18% in men and 15% in women aged 65 and over.5

The presence of stable angina signifies underlying CAD with an associated increased risk of subsequent cardiac events that can be reduced by appropriate medical treatment or surgical intervention.

A diagnosis of angina can have a significant impact on the patient’s level of functioning. In one survey, patients with angina scored their general health as twice as poor as those who had had a stroke. In another survey, patients had a low level of factual knowledge about their illness and poor medication adherence. A Tayside study showed that in patients with angina, symptoms are often poorly controlled, there is a high level of anxiety and depression, an ongoing need for frequent medical contact and scope for lifestyle change.9

GPs should ensure that patients presenting with symptoms consistent with angina are rapidly assessed. Evidence-based diagnostic practice and the prioritisation of investigation in patients with symptoms consistent with angina are required.

1.1.1 UPDATING THE EVIDENCE

This guideline updates SIGN 96, on management of stable angina, published in February 2007, to reflect the most recent evidence.

Where no new evidence was identified to support an update, text and recommendations are reproduced verbatim from SIGN 96. The original supporting evidence was not reappraised by the current guideline development group.

1.2 REMIT OF THE GUIDELINE

This guideline covers the investigations necessary to confirm the presence of stable angina, the optimum medical treatment to relieve symptoms and the relative benefits of different interventions, including coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI). The optimum management of those patients with stable angina requiring non-cardiac surgery is also covered. The provision of patient education is covered as well as whether psychological interventions can help improve symptoms and quality of life.

1.2.1 OVERALL OBJECTIVES

This guideline provides recommendations based on current evidence for best practice in the diagnosis and management of stable angina in patients where reduced myocardial perfusion is due to arterial narrowing resulting from underlying atherosclerotic CAD. This guideline does not address the management of chest pain due to other cardiovascular or non-cardiac causes.
1.2.2 DEFINITION OF STABLE ANGINA

Stable angina is used to describe a clinical syndrome of predictable chest pain or pressure precipitated by activities such as exercise or emotional stress, which increase myocardial oxygen demand. Although classical stable angina can be predictable in onset, reproducible and relieved by rest or glyceryl trinitrate (GTN), other factors and circumstances can influence its development. Angina can be caused by various cardiovascular conditions but this guideline is restricted to the clinical situation where reduced myocardial perfusion is due to arterial narrowing resulting from underlying atherosclerotic CAD.

Stable angina is usually assessed in the outpatient setting. It is important when taking a clinical history to identify, and manage appropriately, those patients whose symptoms may be due to the more severe changes of plaque erosion and rupture occurring as part of the spectrum of acute coronary syndrome (see SIGN guideline number 148 on acute coronary syndromes).

1.2.3 TARGET USERS OF THE GUIDELINE

Effective diagnosis and management of stable angina requires co-ordination of a range of services and healthcare professionals including cardiologists, acute and emergency medicine specialists, general practitioners and other healthcare professionals in primary care, as well as patients, carers, voluntary organisations and policy makers.

1.2.4 SUMMARY OF UPDATES TO THE GUIDELINE, BY SECTION

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1.2.5 PATIENT VERSION

A patient version of this guideline is available from the SIGN website, www.sign.ac.uk.

1.3 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan.

The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at through a process of shared decision making with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be documented in the patient’s medical records at the time the relevant decision is taken.

1.3.1 INFLUENCE OF FINANCIAL AND OTHER INTERESTS

It has been recognised that financial interests in, or close working relationships with, pharmaceutical companies may have an influence on the interpretation of evidence from clinical studies.

It is not possible to completely eliminate any possible bias from this source, nor even to quantify the degree of bias with any certainty. SIGN requires that all those involved in the work of guideline development should declare all financial interests, whether direct or indirect, annually for as long as they are actively working with the organisation. By being explicit about the influences to which contributors are subjected, SIGN acknowledges the risk of bias and makes it possible for guideline users or reviewers to assess for themselves how likely it is that the conclusions and guideline recommendations are based on a biased interpretation of the evidence.

Signed copies are retained by the SIGN Executive and a register of interests is available in the supporting material section for this guideline at www.sign.ac.uk

1.3.2 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORISATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as ‘off-label’ use.

Medicines may be prescribed ‘off label’ in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose
- for a different patient population.

An unlicensed medicine is a medicine which does not have MA for medicinal use in humans.
Generally ‘off-label’ prescribing of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.

“Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers’ professional responsibility and potential liability.”

The General Medical Council (GMC) recommends that when prescribing a medicine ‘off label’, doctors should:

- be satisfied that such use would better serve the patient’s needs than an authorised alternative (if one exists)
- be satisfied that there is sufficient evidence/experience of using the medicines to show its safety and efficacy, seeking the necessary information from appropriate sources
- record in the patient’s clinical notes the medicine prescribed and, when not following common practice, the reasons for the choice
- take responsibility for prescribing the medicine and for overseeing the patient’s care, including monitoring the effects of the medicine.

Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards.

Prior to any prescribing, the licensing status of a medication should be checked in the summary of product characteristics (www.medicines.org.uk). The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.

1.3.3 HEALTH TECHNOLOGY ASSESSMENT ADVICE FOR NHSSCOTLAND

Specialist teams within Healthcare Improvement Scotland issue a range of advice that focuses on the safe and effective use of medicines and technologies in NHSScotland.

The Scottish Medicines Consortium (SMC) provides advice to NHS boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines and all new formulations and new indications of established products. NHSScotland should take account of this advice and ensure that medicines accepted for use are made available to meet clinical need where appropriate.

SMC advice relevant to this guideline is summarised in section 9.4.
2  Key recommendations

The following recommendations were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation.

2.1  DIAGNOSIS AND ASSESSMENT

- **R** Computerised tomography-coronary angiography should be considered for the investigation of patients with chest pain in whom the diagnosis of stable angina is suspected but not clear from history alone.

- **R** In patients with suspected stable angina, the exercise tolerance test should not be used routinely as a first-line diagnostic tool.

2.2  STABLE ANGINA AND NONCARDIAC SURGERY

- **R** The routine use of aspirin to reduce perioperative cardiac events in patients undergoing non-cardiac surgery, including those with known stable coronary artery disease, is not recommended.
3 Diagnosis and assessment

Angina is a symptom that suggests an individual has underlying obstructive CAD. Investigation to confirm the severity and extent of underlying CAD will allow management strategies to be developed and optimise cardiovascular risk reduction. A significant proportion of patients with chest pain will not have angina and initial assessment should try to identify alternative diagnoses for these patients at an early stage.

Patients with acute cardiac chest pain (suspected acute coronary syndrome) are outside the remit of this guideline as these patients require more urgent and immediate management (see SIGN guideline number 148 on acute coronary syndromes).

Patients with stable angina are usually managed in the primary care setting but may present in a number of healthcare settings. An initial diagnosis of angina can be made within primary care. Further assessment and risk stratification, will normally require referral for specialist input.

3.1 CLINICAL HISTORY AND ASSESSMENT

Patients with stable angina should have the diagnosis made following a carefully obtained history and clinical assessment. Clinical history is the key component in the evaluation of the patient with angina; often the diagnosis can be made on the basis of clinical history alone. While a number of scoring systems are available to assess patients with chest pain and stable angina, an accurate clinical assessment is of key importance. There are several typical characteristics which should increase the likelihood of making a diagnosis of angina. These include:

- type of discomfort – often described as tight, constricting, dull or heavy
- location – often retrosternal or left side of chest and can radiate to left arm, neck, jaw and back
- relation to exertion – angina is often brought on with exertion or emotional stress and eased with rest
- duration – typically the symptoms last up to several minutes after exertion or emotional stress has stopped
- other factors – angina may be precipitated by cold weather or after a large meal.

The predominant features described by some patients are discomfort and heaviness or breathlessness, rather than pain. Chest discomfort, irrespective of its site, is more likely to be angina when precipitated by exertion and relieved by rest. It is also characteristically relieved by glyceryl trinitrate (GTN). Not all patients will present with typical characteristics and healthcare professionals should be aware of other symptoms such as breathlessness brought on by exertion.

NICE has recommended the following list of features to help characterise patient symptoms into typical, atypical and non-anginal pain.

Chest pain is:

- a constricting discomfort in the front of the chest, or in the neck, shoulders, jaw, or arms
- precipitated by physical exertion
- relieved by rest or GTN within about five minutes.

Typical angina – presence of all three features
Atypical angina – presence of two of the three features
Non-anginal pain – presence of one or none of the three features.
Once confirmed, angina severity can be graded as a Canadian Cardiovascular Society (CCS) class of I-IV17 (see Table 1).

Table 1: Canadian Cardiovascular Society angina classification

<table>
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<tr>
<th>Class</th>
<th>Description</th>
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<tr>
<td>Class I</td>
<td>Ordinary activity such as walking or climbing stairs does not precipitate angina</td>
</tr>
<tr>
<td>Class II</td>
<td>Angina precipitated by emotion, cold weather or meals and by walking up stairs</td>
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<tr>
<td>Class III</td>
<td>Marked limitations of ordinary physical activity</td>
</tr>
<tr>
<td>Class IV</td>
<td>Inability to carry out any physical activity without discomfort - anginal symptoms may be present at rest</td>
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The likelihood of a diagnosis of angina increases with the number of cardiovascular risk factors in individual patients. These include:

- smoking
- hypertension
- diabetes
- previous history of CAD
- family history of CAD (first degree relative - male < 55 years/female < 65 years of age)
- hyperlipidaemia
- chronic kidney disease
- atherosclerotic disease in another vascular bed.

These risk factors are best initially addressed in the primary care setting where lifestyle advice can be provided and support offered, where necessary. More objective evaluation of symptoms may be necessary to establish the severity of any underlying CAD. In addition to assessment of conventional risk factors, (see SIGN guideline number 149 on risk estimation and the prevention of cardiovascular disease)18 patients with suspected stable angina should have the following evaluated:

- body mass index or waist circumference
- heart sounds
- haemoglobin level
- renal function
- lipid profile
- fasting blood glucose or HbAc
- thyroid function
- depression and social isolation
- physical activity.

A number of scoring systems have been proposed to assess the severity and prognostic impact of angina.19, 20 While these scoring systems may be accurate in the patient groups included in the cohorts studied, their use in routine clinical practice cannot be recommended, but they may have a role in influencing the clinical decision-making process.
When a GP identifies a patient with stable angina, further assessment at a cardiology outpatient clinic is desirable.

✔ Patients with suspected angina should have a detailed initial clinical assessment which includes history, examination and an assessment of blood pressure, haemoglobin, renal function, thyroid function, cholesterol and glucose levels.

✔ Those patients who should be considered for early referral to secondary care include those with new onset angina and those with established CAD and an increase in symptoms.

3.1.1 NON-CARDIAC CHEST PAIN

The diagnosis of angina can usually be made based on clinical history and assessment. Angina pain is not usually sharp or stabbing in nature. It is not usually influenced by respiration or eased with antacids and simple analgesia.

Confirmation of non-cardiac chest pain may reduce anxiety and distress and thus avoid unnecessary hospital admissions and consultations. Low-risk patients, such as young patients with atypical symptoms, should be assessed in primary care where possible. Management of these patients may include explaining symptoms, discussing concerns and providing reassurance where necessary. A diagnosis of non-cardiac chest pain should be given early and confidently as correct management may reduce morbidity.

A rehabilitation programme for patients with chest pain but normal coronary arteries, based on cognitive behavioural principles, found that those who continued to attribute symptoms to cardiac causes had worse outcomes.

✔ If the diagnosis is uncertain, clinicians should not give the impression that the patient has angina. This may lead the patient to have false beliefs, which may be difficult to change even after further investigations have ruled this out.

✔ Patients with non-cardiac chest pain do not require further investigation for myocardial ischemia.

3.2 DIAGNOSTIC AND PROGNOSTIC TOOLS

A number of cardiac investigations are available to aid the diagnosis of angina, confirm the presence of atherosclerotic CAD and help with risk stratification in patients for whom a diagnosis of stable angina is made. These investigations may be anatomical, such as computerised tomography-coronary angiography (CT-CA) and invasive coronary angiography, or functional, such as exercise tolerance testing, stress echocardiography, stress perfusion cardiovascular magnetic resonance imaging, and myocardial perfusion scintigraphy. The choice of investigation should depend on the clinical presentation, pretest probability and prior history of CAD, and may be influenced by the local availability of these investigations and resources. The tests are discussed below in order of increasing invasiveness. Diagnosis and treatment algorithms for patients with suspected stable angina and confirmed angina are included in Annex 2 and Annex 3, respectively.

In general, CT-CA and invasive coronary angiography provide anatomical information about the location and burden of atherosclerotic CAD and may identify anatomical features associated with increased cardiac risk such as left main-stem disease. Functional tests demonstrating ischaemia provide information to guide risk stratification based on ischaemic burden or a surrogate and may be helpful in the diagnosis of stable angina, particularly where there is uncertainty over the severity of underlying CAD.
A meta-analysis comparing the diagnostic accuracy of a number of non-invasive tests in patients with suspected stable angina favoured CT-CA with a sensitivity of 0.96 (95% confidence interval (CI), 0.94 to 0.97) and specificity of 0.79 (95% CI 0.72 to 0.84) for the detection of obstructive CAD.\textsuperscript{16} In addition, economic modelling suggested that CT-CA was the most cost-effective strategy, at least in the short term, with the lowest cost per correct diagnosis, irrespective of the pretest probability.\textsuperscript{16}

It should be emphasised that the diagnosis of stable angina is based on symptoms, not simply the demonstration of underlying CAD. Confirmation of a diagnosis of stable angina should trigger initiation of medical therapy (see section 4) and where appropriate, risk stratification should be considered to identify patients at high risk who may benefit from coronary revascularisation.

3.2.1 ELECTROCARDIOGRAPHY

A baseline 12-lead electrocardiogram (ECG) should be performed in every patient with suspected angina.\textsuperscript{27} A normal 12-lead ECG does not exclude a diagnosis of CAD.\textsuperscript{28} An abnormal ECG increases the likelihood of CAD but gives no indication as to the severity of any associated obstructive coronary heart disease. An abnormal resting ECG increases the probability that a patient has CAD.\textsuperscript{29} A 12-lead ECG can also highlight the presence of other conditions such as atrial fibrillation or left ventricular hypertrophy. The interpretation of resting ECGs is operator dependent.\textsuperscript{30}

3.2.2 EXERCISE TOLERANCE TESTING

The diagnostic accuracy of an exercise tolerance test (ETT) varies greatly depending on many features such as age, gender and history of known CAD, significantly limiting its utility as a diagnostic tool.\textsuperscript{31} The sensitivity and specificity of an ETT in establishing the diagnosis of CAD is dependent on the cohort of patients studied.\textsuperscript{16, 24, 25, 26} Sensitivity is higher in patients with triple-vessel disease and lower in patients with single vessel disease.\textsuperscript{32} The true diagnostic value of exercise ECG lies in its relatively high sensitivity, but it is only moderately specific for the diagnosis of CAD in women.\textsuperscript{33} An ETT has some utility in young patients with exertional symptoms who are unlikely to have obstructive CAD avoiding the need for investigations employing ionising radiation.\textsuperscript{26}

In patients who have an established diagnosis of CAD, the ETT can be useful, primarily to assess ischaemic burden and prognosis.\textsuperscript{16}

A normal exercise test may reassure many patients but it does not exclude a diagnosis of CAD. Symptoms associated with ECG changes during an ETT can aid diagnosis and a highly abnormal ETT result is an indication for urgent treatment and further investigation.

3.2.3 STRESS ECHOCARDIOGRAPHY

Stress echocardiography, either with exercise stress or pharmacological stress, is a non-invasive method of identifying inducible myocardial ischaemia by the detection of stress-induced wall motion abnormalities. Like an ETT, it has the advantage of being radiation free and is well tolerated by patients.\textsuperscript{34} In a Health Technology Assessment of stress echocardiography with contrast, sensitivity and specificity for the diagnosis of CAD ranged from 64% to 93% (82% to 93% excluding one outlier) and 65% to 97%, respectively, for patients with suspected CAD (11 studies, n=620). For patients with suspected or known CAD (12 studies, n=2,029), sensitivity and specificity varied according to whether myocardial perfusion analysis or wall motion analysis was used (sensitivity 67% to 96% and 47% to 84%, respectively; specificity 51% to 86% and 70% to 86%, respectively).\textsuperscript{35} Ultrasound imaging may be challenging in some patients (up to 5% in some studies have an inadequate acoustic window)\textsuperscript{34} but intravenous contrast agents can be used to improve endocardial definition. A negative stress echocardiogram is associated with an annual cardiac event rate of less than 1%.\textsuperscript{36}
3.2.4 STRESS PERFUSION CARDIAC MAGNETIC RESONANCE IMAGING

Stress perfusion cardiac magnetic resonance imaging (CMR) is a newer, non-invasive functional test with high sensitivity for detecting significant myocardial ischaemia and has the advantage, compared to single-photon emission computed tomography (SPECT) myocardial perfusion scintigraphy, of being radiation free. In addition to providing information on ischaemic burden, it provides accurate assessment of ventricular volumes and function and identification of previous areas of myocardial infarction/scar. It does not depend on ultrasound windows and may, therefore, be useful for imaging patients who are challenging to image using stress echocardiography. Some patients may find the claustrophobic aspect of the test unacceptable.

A systematic review and meta-analysis of 28 studies (n=2,970) of myocardial perfusion imaging using magnetic resonance imaging (MRI) reported an overall sensitivity of 91% (95% CI 88 to 93) and specificity of 80% (95% CI 76 to 83). Results were similar for those with suspected CAD (sensitivity 90%, 95% CI 78 to 96; specificity 86%, 95% CI 74 to 93).37

CMR can be used as an alternative to myocardial perfusion scintigraphy (MPS) or stress echocardiography to risk stratify patients with a diagnosis of stable angina. A negative stress perfusion CMR is associated with an annual cardiac event rate of less than 1%,38, 39 compared with a 5% annual cardiac event rate associated with a positive stress perfusion CMR.39

3.2.5 MYOCARDIAL PERFUSION SCINTIGRAPHY

Myocardial perfusion scintigraphy (MPS) with exercise or pharmacologic stress has been evaluated for the investigation of patients with suspected angina.40 In meta-analyses, the overall sensitivity and specificity of MPS with SPECT are reported as ranging from 78% to 88% and 64% to 73%, respectively.16 Myocardial perfusion scintigraphy may be the appropriate initial diagnostic test in patients with pre-existing ECG abnormalities (for example left bundle branch block) or in those unable to adequately exercise or as part of the diagnostic strategy for suspected CAD in people with lower likelihood of CAD.41 It may also be useful in females who may have a low risk of underlying CAD but a high risk of a falsely positive ETT and in patients where identification of regional ischaemia would be of value (for example prior to PCI). Myocardial perfusion scintigraphy provides valuable independent and incremental prognostic information to that provided by an ETT and enable risk stratification of patients, which can inform treatment decisions.42

3.2.6 COMPUTERISED TOMOGRAPHY-CORONARY ANGIOGRAPHY

Computerised tomography-coronary angiography is a non-invasive structural test which can detect the presence of coronary artery disease. Studies have demonstrated excellent diagnostic performance with a sensitivity of up to 99%,43-45 specificity of up to 92%,43-47 and a negative predictive value approaching 100%.44-47

A normal CT-CA is associated with an annual risk of a major adverse cardiac event of less than 0.5%, similar to the risk in a normal healthy population, making it a very useful ‘rule-out’ test.48

Computerised tomography-coronary angiography has also been shown to be useful in patients with obesity, arrhythmia and coronary calcification.49, 50 Incidental non-cardiac findings may also be seen during CT-CA. In the SCOT-Heart study, 16% of patients were found to have parenchymal lung disease, 11% a pulmonary nodule, 9% emphysema, 8% hiatus hernia, 2% liver pathology and 1% lymphadenopathy. 50

A recent multicentre study in Scotland of patients with suspected angina demonstrated that CT-CA helped to clarify the diagnosis of angina, was associated with a reduction in the need for further stress testing, and permitted targeting of treatments and interventions to those patients who gained most benefit.50

As CT scanning technology has improved, the dose of radiation associated with a CT-CA has reduced. In SCOT-Heart, the median radiation dose was 4.1mSV.50
3.2.7 CORONARY ANGIOGRAPHY

Invasive coronary angiography is the established benchmark investigation for establishing the nature, anatomy and severity of CAD. It is an invasive investigation and carries a mortality risk of around 0.1% for elective procedures.\(^5\) It requires referral to a cardiologist and is best reserved for those patients who are at high risk or continue to have symptoms despite optimal medical treatment and may require revascularisation. It may also provide valuable information regarding valvular and left ventricular function.

Assessment of coronary fractional flow reserve (FFR) at the time of coronary angiography using a coronary pressure wire can help clarify the functional significance of underlying CAD and guide treatment decision making.\(^5\)

- **R** A resting ECG should be performed in patients with suspected cardiac chest pain.
- **R** Computerised tomography-coronary angiography should be considered for the investigation of patients with chest pain in whom the diagnosis of stable angina is suspected but not clear from history alone.
- **R** Where appropriate, functional tests, including the exercise tolerance test, should be considered to aid in the risk stratification of patients with known CAD.
- **R** In patients with suspected stable angina, the exercise tolerance test should not be used routinely as a first-line diagnostic tool
- **✓** Coronary angiography should be considered after non-invasive testing where patients are identified to be at high risk or where a diagnosis remains unclear.

3.3 MODELS OF CARE

Optimum management of angina should facilitate the early detection of patients who may have severe CAD and who would benefit from early intervention, and provide reassurance for those patients at low risk.

- **✓** Following initial assessment in primary care, patients with suspected angina should have the diagnosis confirmed and risk stratification undertaken, when appropriate, in secondary care.
4 Pharmacological management

4.1 DRUG MONOTHERAPY TO ALLEVIATE ANGINA SYMPTOMS

All the studies reported were carried out on a mixed population with males as a majority and included various age groups and patient entry criteria. Populations of patients with and without past medical histories of myocardial infarction (MI), heart failure and other cardiac and non-cardiac comorbidities were reported. The populations in the trials resemble the Scottish population who are treated for chest pain resulting from CAD. Drugs that are unlicensed for the treatment of CAD in the UK are not included in the guideline.

4.1.1 BETA BLOCKERS

Beta blockers improve oxygen supply and demand balance by reducing heart rate and blood pressure, decreasing end systolic stress and contractility and prolonging diastole, allowing more coronary flow.

Meta-analyses have shown that beta blockers remain the first-line drugs for the long-term prevention of chest pain resulting from CAD. One observational study suggests a mortality benefit of beta blockers in patients with stable CAD and without a past medical history of MI or heart failure.

Most randomised controlled trials (RCTs) have used older beta blockers such as propranolol, metoprolol and atenolol for the treatment of stable angina, and newer beta blockers such as bisoprolol have also been shown to be effective. The efficacy of beta blockers is due to a class effect mediated through blocking beta adrenoceptors rather than to individual characteristics of each drug. Comorbidity, for example heart failure, and other factors such as compliance and cost should be considered when selecting an individual beta blocker.

The British National Formulary (BNF) indicates that the usual beta-blocker regimens are: atenolol 100 mg daily in single or divided dosages, metoprolol 50–100 mg two to three times daily or bisoprolol 5–20 mg once daily. Doses should be tailored individually to ensure maximum beta blockade depending on the sensitivity of the patient to specific drugs. A resting heart rate of less than 60 beats per minute is an indication of beta blockade.

Beta blockers are contraindicated in patients with severe bradycardia, second or third degree atrioventricular block, sick sinus syndrome, decompensated heart failure and severe asthma. Diabetes mellitus, chronic obstructive airways disease and peripheral vascular disease are not contraindications to beta blocker use.

4.1.2 CALCIUM CHANNEL BLOCKERS

Calcium channel blockers (CCBs) inhibit calcium transport and induce smooth muscle relaxation.

Meta-analyses and RCTs have shown that CCBs are generally as effective as beta blockers in reducing angina symptoms.

Few studies have directly compared individual CCBs using anginal symptoms as a clinical endpoint. In a small RCT diltiazem and amlodipine were similar in improving exercise tolerance in patients with CAD. The choice of CCB may depend on comorbidity and drug interactions.

Rate-limiting CCBs (verapamil and diltiazem) are contraindicated in patients with heart failure, severe bradycardia or second or third degree atrioventricular block. Patients with heart failure and angina may be safely treated with the dihydropyridine derivatives amlodipine or felodipine (see SIGN guideline number 147 on the management of chronic heart failure).

There is conflicting evidence regarding the safety of nifedipine in patients with angina. Meta-analyses have indicated that nifedipine monotherapy or short-acting nifedipine in combination with other antianginal drugs may increase the incidence of cardiovascular events, mainly angina episodes.
Prinzmetal (vasospastic) angina is a rare form of angina in which pain is experienced at rest rather than during activity. It is caused by narrowing or occlusion of proximal coronary arteries due to spasm and cannot be diagnosed by coronary angiography. Beta blockers should not be used in this form of angina because they may worsen the coronary spasm. Patients with this condition may be treated effectively with a dihydropyridine derivative CCB such as amlodipine.

4.1.3 NITRATES

These drugs act directly on the vascular smooth muscle to produce venous and arterial dilatation, reducing pre-load, after-load and oxygen demand.

Nitrates are effective drugs in the prevention and treatment of angina. In meta-analyses, there was no significant difference in the antianginal efficacy between long-acting nitrates and beta blockers or CCBs. In one RCT, the CCB amlodipine was shown to be more effective than nitrates in controlling exercise-induced angina in elderly patients with stable CAD.

Sublingual GTN is effective for the immediate relief of angina and can also be used to prevent ischaemic episodes when used before planned exertion.

Nitrate tolerance can be avoided by prescribing modified-release long-acting preparations or by asymmetric dosing. Such regimens can be confusing to patients and could lead to non-compliance and nitrate tolerance. Modified-release oral nitrates that are given once daily provide therapeutic plasma nitrate levels over the initial few hours following ingestion. Adherence has been shown to improve when transferring from multiple-dose regimens to once-daily regimens. The low plasma nitrate level at 24 hours following ingestion appears to minimise tolerance.

The main side effect of nitrates is headache, which usually wears off after continuous use, but in some patients this could become intolerable and necessitate change to another antianginal drug.

An economic model published in 1997 compared a single-daily dose regimen using a modified-release formulation with a twice-daily dose regimen, and assumed that better adherence with the single dose (88% vs 68%) would improve symptom control and result in fewer visits to GPs. The two regimens were found to have very similar annual costs (£248 vs £250). The sensitivity analysis showed that the result is highly sensitive to changes in the assumed adherence rates and drug costs. In current clinical practice in Scotland, prescription of a generic drug for the two-dose regimen would be cost saving (£14.86 per annum) compared to the single dose modified-release option (£87.99 per annum).

4.1.4 POTASSIUM CHANNEL ACTIVATORS

Potassium channel activators induce relaxation of vascular smooth muscle and have coronary vasodilator properties. There are few studies on the efficacy of nicorandil in the treatment and prevention of chest pain. One RCT showed that nicorandil was comparable to diltiazem in reducing angina. Another trial demonstrated that nicorandil was as effective as amlodipine in patients with symptomatic stable angina.

In another RCT of over 5,000 patients, nicorandil was shown to significantly reduce the combined endpoint of coronary heart disease death, non-fatal myocardial infarction, or unplanned hospitalisation for cardiac chest pain (15.5% to 13.1% hazard ratio 0.83, 95% CI 0.72 to 0.97). A cost-effectiveness analysis based on the results of this trial estimated that the additional costs of adding nicorandil to standard care for patients with angina were offset by the reduced hospitalisation costs. There are safety concerns with ulceration at any anatomical point throughout the gastrointestinal tract with nicorandil. If this occurs, nicorandil should be stopped and an alternative antianginal agent initiated, if necessary.

Following a review of safety data in 2016, the MHRA issued advice that the use of nicorandil for the treatment of stable angina should be restricted to second-line therapy where there is a contraindication or intolerance to beta blockers or calcium channel blockers.
4.1.5 SELECTIVE I\(_f\) INHIBITORS

Ivabradine, a selective I\(_f\) inhibitor, inhibits the I\(_f\) pacemaker current in the sinoatrial node and acts to lower heart rate.

In a double blind randomised parallel-group trial ivabradine was shown to have equivalent antianginal efficacy to atenolol in patients with stable angina.\(^8\) While symptomatic benefit has been clearly demonstrated, the use of ivabradine does not confer any cardioprotective benefit in patients with stable angina in the absence of heart failure. In a multicentre randomised trial enrolling over 19,000 patients with stable IHD without heart failure, the addition of ivabradine to contemporary medical therapy had no effect on all-cause mortality, death from cardiac causes or non-fatal MI. A pre-specified subgroup analysis of 12,049 participants who had symptomatic angina demonstrated a small but significant increase in the combined risk of cardiovascular death or non-fatal heart attack with ivabradine compared with placebo (3.4% vs 2.9% yearly incidence rates).\(^8\)

In Scotland, use of ivabradine is restricted by SMC to the symptomatic treatment of chronic stable angina pectoris in adults with CAD and normal sinus rhythm for whom heart rate control is desirable and who have a contraindication or intolerance to beta blockers and rate-limiting calcium channel blockers (see section 9.4).

4.1.6 RANOLAZINE

Ranolazine is an antianginal drug that acts primarily through inhibition of the inward sodium current in myocardial cells. Evidence on the efficacy of ranolazine is conflicting. In a systematic review of 17 RCTs (n=9,975) comparing ranolazine as monotherapy or add-on therapy with placebo or other antianginal agents, three studies reported a reduced number of angina episodes in patients receiving ranolazine as add-on therapy (mean difference (MD) 0.66, 95% CI -0.97 to -0.35). For all other outcomes, including all-cause mortality, fatal or non-fatal acute MI, revascularisation, and angina episode frequency with ranolazine as monotherapy, either no benefit was reported or effects were uncertain. Where non-serious adverse events were reported, for patients receiving ranolazine as monotherapy (two studies), no difference was found between groups; for those receiving ranolazine as add-on therapy (three studies), there was a higher risk of non-serious adverse events in those receiving ranolazine (relative risk (RR) 1.22, 95% CI 1.06 to 1.40).\(^8\)

A systematic review found seven studies (n=3,317) of patients with refractory chronic stable angina receiving ranolazine reported significant improvements in exercise tests in all but one trial compared to placebo. There was benefit in terms of a reduction in symptoms and use of sublingual nitrate. The review did not address the effect of ranolazine on frequency of cardiovascular events.\(^8\)

Ranolazine is not recommended by SMC for use in Scotland for the symptomatic treatment of patients with stable angina pectoris (see section 9.4).

R Sublingual glyceryl trinitrate tablets or spray should be used for the immediate relief of angina and before performing activities that are known to bring on angina.

R Beta blockers should be used as first-line therapy for the relief of symptoms of stable angina.

R Rate-limiting calcium channel blockers should be considered where beta blockers are contraindicated.

R Patients with Prinzmetal (vasospastic) angina should be treated with a dihydropyridine derivative calcium channel blocker eg (amlodipine, nifedipine).
4.2 COMBINATION THERAPY TO ALLEVIATE ANGINA SYMPTOMS

4.2.1 ADDING CALCIUM CHANNEL BLOCKERS TO BETA BLOCKERS

A meta-analysis of 22 RCTs demonstrated that the combination of a beta blocker with a CCB is more effective than monotherapy in improving exercise tolerance. Time to 1-mm ST-segment depression, total exercise duration and time to onset of anginal pain were significantly increased with the combined therapy compared to beta blocker alone (by 8%, 5% and 12%, respectively). This benefit was only shown to be significant within six hours of drug intake.84

Adding diltiazem to beta blockers produces a dose-dependent improvement in symptom control and exercise tolerance.85 The BNF suggests caution as this combination may cause severe bradycardia, heart block and hypotension in some patients.11

Dihydropyridine derivatives are safe when combined with beta blockers. The combination of metoprolol with felodipine was shown to be slightly more effective than metoprolol alone in one RCT.86 This trial showed a statistically significant improvement in time until end of exercise with felodipine-metoprolol combination (10/100 mg) compared with metoprolol 100 mg (p=0.04) and felodipine 10 mg compared with metoprolol 100 mg (p=0.03). For time until onset of pain or time until 1-mm ST-depression there were no significant differences among the treatment groups.

Other RCTs have shown that adding CCBs to beta blockers, although safe, offered very little or no benefit in relief of anginal symptoms.87-89

R When adequate control of anginal symptoms is not achieved with beta blockade, addition of a calcium channel blocker should be considered.

✓ Rate-limiting calcium channel blockers should be used with caution when combined with beta blockers.

4.2.2 ADDING NITRATES, NICORANDIL OR IVABRADINE TO OTHER ANTIANGINAL DRUGS

Adding isosorbide mononitrate to a beta blocker 90 or to a CCB 91 significantly improves performance on a range of clinical endpoints. Adding nicorandil to other antianginal drugs was effective in reducing combined cardiac events. One of these composite endpoints was hospital admission for refractory angina. There was no primary endpoint for reducing chest pain.77

Adding ivabradine to atenolol relieved symptoms of angina and improved exercise capacity in a placebo-controlled RCT in 899 patients with stable angina.92 Ivabradine was discontinued in 1% of patients due to bradycardia.

The combination of ivabradine and a beta blocker or rate-limiting calcium channel blocker is not currently recommended by SMC for use in Scotland and may be potentially harmful.

4.2.3 THE USE OF THREE DRUGS

The evidence for combining three drugs is very limited. In one study the combination of long-acting nitrates, beta blockers and CCBs was ineffective in improving exercise testing when compared to a combination of two of the drugs.88

The patients included in these trials were mostly patients who were stable and perhaps did not require another drug to control their angina. They were usually tested as to whether adding another drug would reduce their existing angina, measured by the number of angina episodes, exercise tolerance and amount of GTN used. In ‘real life’ situations patients are usually given a second or a third antianginal drug when they become refractory to one or two drugs. More randomised trials are needed to test the efficacy of prescribing a third antianginal drug to patients whose angina is not optimally controlled on a combination of two drugs.
Patients whose symptoms are not controlled on maximum therapeutic doses of two drugs should be considered for referral to a cardiologist.

4.3 DRUG INTERVENTIONS TO PREVENT NEW VASCULAR EVENTS

Patients with angina due to CAD are at risk of cardiovascular events and are eligible for secondary preventative treatments to lower their risk of cardiovascular disease (CVD). These interventions are considered in more detail in SIGN guideline number 149 on risk estimation and the prevention of cardiovascular disease.18

4.3.1 ANTIPLATELET THERAPY

Evidence from 287 studies involving a total of 135,000 patients with cardiovascular disease, including stable angina, has shown that antiplatelet therapy, mainly with aspirin, given in a dose ranging from 75 to 150 mg daily led to a significant reduction in serious vascular events, non-fatal myocardial infarction, non-fatal stroke and vascular mortality.93

In a randomised trial of 19,185 patients with stable atherosclerotic vascular disease, 22% of whom had stable angina, clopidogrel use was associated with a marginally lower annual composite risk of ischaemic stroke, myocardial infarction and vascular death compared with aspirin (5.3% v 5.8%, RR reduction 8.7%, 95% CI 0.3 to 16.5) and no difference in side effects or bleeding risk.94 These data suggest that clopidogrel monotherapy may be considered as an alternative to aspirin for the prevention of vascular events in the long-term treatment of patients with stable angina due to atherosclerotic coronary artery disease.

Enteric coated products do not prevent the major gastrointestinal complications of aspirin therapy and are significantly more expensive than the standard dispersible formulation.95-97

4.3.2 LIPID LOWERING THERAPY WITH STATINS

A meta-analysis of data from 14 randomised trials of statins involving 90,056 patients including patients with stable angina has shown the overall benefit of statin therapy. There was a significant reduction in all-cause and coronary mortality, myocardial infarction, the need for coronary revascularisation and fatal or non-fatal stroke.98

All patients with stable angina due to atherosclerotic disease should receive long-term standard aspirin and statin therapy.

4.3.3 ACE INHIBITORS

The question of whether patients with stable angina but without left ventricular systolic dysfunction benefit from angiotensin-converting enzyme (ACE) inhibition is controversial. Four large RCTs were identified which addressed this topic although the results are conflicting.99-102 When reanalysed in two meta-analyses of these and other trials, ACE inhibitors significantly reduced all cause and cardiovascular mortality.103, 104

The HOPE study involved 9,297 high-risk patients with vascular disease or diabetes plus one other cardiovascular risk factor without history of heart failure or left ventricular dysfunction. It showed that ramipril was associated with significant reductions in all-cause mortality, myocardial infarction and stroke in these patients.99 The use of perindopril in the EUROPA study involving 13,655 patients with stable CAD and no clinical evidence of heart failure reduced the risk of cardiovascular death, myocardial infarction or cardiac arrest.100 This significant reduction in cardiovascular events is mainly due to the reduction in the incidence of non-fatal myocardial infarction. Unlike the HOPE study, the effect on all-cause mortality did not reach a statistically significant level. Subgroup analysis of the trial showed that benefit from perindopril is mainly in patients with history of myocardial infarction.
Two other trials of ACE inhibitors did not show benefit in patients with stable coronary heart disease. The PEACE trial of trandolopril involving 8,290 patients with no history of clinical heart failure or echocardiographic evidence of left ventricular systolic dysfunction did not reveal any benefit on cardiovascular events although the event rate was unexpectedly low.101 The study population in this trial was of lower risk and received more intensive treatment of risk factors than those in the HOPE and EUROPA trials.

A smaller trial (QUIET) of 1,750 patients with coronary heart disease and normal left ventricular function found that the ACE inhibitor quinapril did not significantly affect clinical outcomes or the progression of coronary atherosclerosis.102 All patients recruited to this trial had undergone successful coronary angioplasty involving the revascularisation of at least one coronary artery.

A meta-analysis of six randomised trials, including 33,500 patients with CAD and preserved left ventricular systolic function showed that ACE inhibitors significantly reduced cardiovascular (RR 0.83, CI 0.72 to 0.96, absolute risk reduction (ARR) 0.86%) and all-cause mortality (RR 0.87, CI 0.81 to 0.94, ARR 1.06%).103 When the findings of the HOPE, EUROPA, and PEACE trials were combined in a meta-analysis of 29,805 patients, ACE inhibitors significantly reduced all-cause mortality (7.8% v 8.9%, p=0.0004), cardiovascular mortality (4.3% v 5.2%, p=0.0002), non-fatal myocardial infarction (5.3% v 6.4%, p=0.0001) and all stroke (2.2% v 2.8%, p=0.0004).104 Although PEACE and QUIET, which did not show benefit from ACE inhibitors among their populations, both recruited patients at apparently lower CVD risk, the authors concluded that the PEACE trial was underpowered rather than affected by low cardiovascular event rates in the study population.

Patients with left ventricular systolic dysfunction or heart failure are at higher risk than those included in HOPE, EUROPA or PEACE and will gain relatively more benefit from ACE inhibitor therapy.104 Systematic reviews of ACE inhibitor therapy in patients with chronic heart failure or left ventricular systolic dysfunction indicate absolute risk reductions ranging from 3.8% to 6%.105,106 All patients with stable vascular disease are likely to derive some benefit from these drugs, to a degree approximately proportional to the level of baseline risk.

All patients with stable angina should be considered for treatment with angiotensin-converting enzyme inhibitors.

4.4 MEDICATION CONCORDANCE

Clinical experience and data from the Prescribing Information System suggest that adherence to long-term medicines for chronic conditions is approximately 50% at two years after diagnosis. This level of adherence is very likely to have a negative impact on symptom control and prognosis and limits extrapolation from clinical trials where adherence is often tightly controlled. Information on medicines adherence and strategies to improve adherence among patients with stable angina is lacking and the applicability to a UK population of studies, for example of pharmacist-led interventions, undertaken in countries other than the UK, is unknown.

A systematic review of interventions to enhance medication adherence identified 182 trials, 21 of them in patients with CVD or relating to CV risk reduction. Only five of the 17 highest-quality trials reported improvements in both adherence and clinical outcomes. The interventions used were heterogeneous and often complex. Effects were generally small, and it was not possible to identify common beneficial components.107
5 Interventional cardiology and cardiac surgery

5.1 Coronary Artery Anatomy and Definitions

The three principal coronary arteries are the left anterior descending (LAD), circumflex and right coronary arteries. The right and left coronary arteries arise from their respective coronary ostia just above the aortic valve. The right coronary artery supplies the right side of the heart and typically terminates as the posterior descending coronary artery supplying the diaphragmatic (inferior) surface of the left ventricle. The left coronary artery continues for a variable distance up to 3 cm as the left main-stem before dividing into LAD and circumflex coronary arteries. The left coronary artery branches supply the anterior and lateral walls of the left ventricle and the majority of the septum. The clinically important distributions of CAD are:

- left main-stem disease
- single-, double- or triple-vessel CAD depending on the number of principal arteries diseased.

Multivessel disease typically refers to disease in more than one coronary artery and is not the same as triple-vessel CAD.

Following coronary angiography, and assessment of left ventricular function, patients may be considered for coronary revascularisation by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

The principal indications for revascularisation are symptomatic relief and prognostic gain (increased life expectancy). Published guidelines recommend revascularisation for prognostic and symptomatic benefit in patients with the following anatomy:

- significant left main-stem disease (greater than 50% stenosis), or
- proximal three-vessel disease, or
- two-vessel disease involving the proximal LAD.

The benefit is greatest in patients with left ventricular dysfunction and/or evidence of reversible ischaemia at low or moderate workloads on exercise testing.

Although not receiving prognostic advantage, the following groups of patients may receive symptomatic benefit from surgical revascularisation:

- those with single-vessel CAD not involving the LAD
- those with two-vessel CAD not involving the LAD

5.2 Percutaneous Coronary Intervention

Percutaneous coronary intervention defines percutaneous transluminal coronary angioplasty (PTCA) where the artery is dilated by inflating a fine balloon. In addition, PCI includes stenting which involves dilating the artery by angioplasty and then inserting a fine lattice scaffold to prevent the artery from recoiling (stent). More than 90% of PCI procedures now involve implantation of one or more coronary stents. Stent technology has developed rapidly over time and the majority of coronary stents implanted now are coated with drugs (drug-eluting stents; DES) to prevent or retard endothelialisation and reduce restenosis (see section 5.2.2). Drug-eluting balloons are PTCA balloons coated with drugs similar to those used on drug eluting-stents. Drug-eluting balloons have been developed to reduce restenosis rates whilst avoiding stent implantation, for example in small calibre vessels, or instent restenosis (see section 5.7).
5.2.1 PERCUTANEOUS CORONARY INTERVENTION VERSUS MEDICAL THERAPY

Randomised trials have consistently demonstrated that PCI, compared to medical therapy alone, improves symptoms of angina.\textsuperscript{113,114} In patients with stable angina, this symptomatic benefit lasts for up to 24 months and is greatest in patients with more severe angina.\textsuperscript{115} Conversely, where angina symptoms are well controlled on medical therapy, PCI appears to confer no additional symptomatic relief.\textsuperscript{116}

In contrast, evidence of a survival benefit is limited although no individual trial has been powered to demonstrate this. A meta-analysis of 12 RCTs (n=7,182) found no significant differences in all-cause mortality, cardiac death, non-fatal MI and revascularisation in patients receiving PCI compared with medical therapy.\textsuperscript{114} Subsequent RCTs generally supported these findings.\textsuperscript{117,119} One RCT comparing FFR-guided PCI with medical therapy versus medical therapy alone (n=888) reported a significantly lower occurrence of the combined endpoint (death from any cause, non-fatal MI or urgent revascularisation within two years) in the PCI group (8.1% v 19.5%) but the difference was largely attributable to a reduced rate of urgent revascularisation in the PCI group (4.0% v 16.3%, hazard ratio (HR) 0.23, 95% CI 01.4 to 0.38).\textsuperscript{119}

A meta-analysis of PCI versus optimal medical therapy for prevention of spontaneous MI in patients with stable CAD suggested that a reduction in spontaneous non-procedure-related MI with PCI compared to medical therapy was offset by a higher rate of procedural MI resulting in a neutral effect on MI overall.\textsuperscript{120}

5.2.2 TYPE OF STENT

Randomised controlled trials using first generation DES have shown that both sirolimus and paclitaxel coated stents reduce the need for repeat revascularisation by around 50% when compared to uncoated stents.\textsuperscript{122-124} Evidence from systematic reviews and meta-analyses is broadly consistent in demonstrating that newer generation DES are associated with reduced rates of revascularisation.\textsuperscript{121,125,126} Evidence for other benefits is mixed with one review of 47 RCTs showing no difference in death, MI or thrombosis between DES and bare-metal stents (BMS)\textsuperscript{126} and another showing decreased cardiac mortality, MI and stent thrombosis with everolimus-eluting stents compared with BMS.\textsuperscript{125} In patients with diabetes, DES were associated with lower revascularisation, in-segment restenosis and MI but no difference in mortality or stent thrombosis.\textsuperscript{127} In the treatment of failing saphenous vein grafts, DES were associated with lower rates of revascularisation but no difference in death or MI.\textsuperscript{128}

Drug eluting-stents delay re-endothelialisation and for this reason dual antiplatelet therapy (aspirin plus clopidogrel) is recommended for at least three to six months post the procedure compared with four weeks for uncoated (bare-metal) stents (see sections 5.5.2 and 6.2).

Early concerns about an increased risk of late (6–12 months after stent implantation) and very late (more than 12 months after stent implantation) stent thrombosis with DES compared to bare-metal stents have proved unfounded.\textsuperscript{126} A meta-analysis including five RCTs, reported a lower risk of late and very late stent thrombosis with newer generation DES (everolimus) when compared to bare-metal stents.\textsuperscript{125}

Antistenotic drugs are frequently bound to the surface of a stent using a polymer. Polymers may be durable (non-biodegradable) or biodegradable. Stents with durable polymers may be associated with a greater risk of restenosis and late stent thrombosis through stimulation of local inflammation although this does not appear to be the case with newer generation DES. In a network meta-analysis examining 126 trials
including 106,427 patients followed up for between six months and five years (mean 2.3 years), DES with a biodegradable polymer were associated with a reduction in target vessel revascularisation and late stent thrombosis rates when compared to early generation paclitaxel-eluting stents with a durable polymer (HR 0.66 and 0.61 respectively) but not when compared to newer generation DES with durable polymers (eg everolimus eluting).129

The cost of DES in Scotland has reduced significantly in recent years. This, combined with the availability of longer stent lengths and fewer repeat procedures with DES, has minimised the impact of any cost differential between the two stent types.

R In patients with stable angina undergoing percutaneous coronary intervention, second- or third-generation drug-eluting stent should be used unless there is a contraindication to prolonged dual antiplatelet therapy.

5.3 CORONARY ARTERY BYPASS GRAFTING

Coronary artery bypass grafting has been used for over three decades to bypass coronary stenoses. It is a major surgical procedure with a low mortality that involves bypassing of a section of coronary artery narrowed by atheroma with a section of healthy saphenous vein or internal mammary artery. In the UK Cardiac Surgical Register for 2015, the overall 30-day mortality was 0.58%.130 This includes salvage procedures performed in patients who may have died even if surgery had not been undertaken.

5.3.1 CORONARY ARTERY BYPASS GRAFTING VERSUS MEDICAL THERAPY

Evidence that CABG is superior to medical therapy in the relief of symptoms and prognosis in patients with stable angina is based largely on historical studies.131-133 One RCT (MASS II) of 611 patients with stable multivessel CAD reported greater freedom from angina (64% v 43%), a reduction in MI (10.3% v 20.7%) and a reduction in subsequent revascularisation (7.4% v 39.4%) at 10 years in patients treated with CABG compared to medical therapy. There was no difference in overall mortality, possibly due to the small sample size.134

A network meta-analysis, including 100 trials and 93,553 patients, examining the effect of revascularisation on prognosis in patients with stable CAD confirmed earlier findings that CABG, compared with medical therapy, improved survival, reduced risk of MI and reduced subsequent revascularisation (rate ratio 0.80, 95% CI 0.70 to 0.91; 0.79, 95% CI 0.63 to 0.99; 0.16, 95% CI 0.13 to 0.20, respectively).121

5.3.2 ON-PUMP VERSUS OFF-PUMP CORONARY ARTERY BY PASS GRAFTING

Coronary artery bypass grafting may be performed using cardiopulmonary bypass where a pump and oxygenator perform the role of the heart and lungs and permit the surgeon to operate on a still non-beating, protected heart. This on-pump surgery was considered to be responsible for some of the deleterious effects following CABG such as cognitive dysfunction or exaggerated systemic inflammatory response, and consequently off-pump coronary artery bypass surgery has emerged as a technique to perform CABG without cardiopulmonary bypass. Although considered minimally invasive, the procedure still involves a chest incision. Minimally invasive direct coronary bypass surgery attempts to reduce the major skin incision but its use is not widespread.

The use of off-pump surgical techniques developed, in part, as a method of reducing potential cognitive impairment after surgery (see section 5.3.4). A meta-analysis comparing off-pump with conventional on-pump CABG did not demonstrate any significant differences in 30-day mortality, myocardial infarction, stroke or renal dysfunction but did show a reduced incidence of atrial fibrillation, transfusion, inotrope requirements with reduced length of ventilation time and intensive care unit and hospital stay. The results for graft patency and neurocognitive function were inconclusive.135
Two good-quality RCTs were identified which indicate a benefit of off-pump surgery in reduction of cognitive impairment at three months for patients with one to three vessels bypassed, which is not sustained at 12 months (decline 21% in off-pump group and 29% in on-pump group at three months, 31% and 33% respectively at 12 months). A one cohort study also found a slight benefit for off-pump surgery at six months in younger patients.138

A study looking at on- and off-pump surgical groups with cardiac and healthy controls found no evidence of cognitive decline at three or 12 months on objective testing, but significant baseline differences between surgical and non-surgical control groups in self-reported cognitive problems. The authors conclude that after CABG, patients, like similar patients with long-standing coronary artery disease, have some degree of cognitive dysfunction secondary to cerebrovascular disease before surgery.139

In contrast, one RCT found no significant decline in cognitive function in either group immediately after surgery and at two and a half months. Several variables appear to influence outcomes. Age did not predict decline in cognitive function although the patients tended to be relatively young (in their sixties).140 Patients may have marked presurgical deficits which mask the potential effect on cognitive function of type of surgery.140

The five-year outcomes of the CORONARY (CABG off or on-pump revascularisation study), an RCT of over 4,000 patients with CAD assigned to undergo on- or off-pump CABG, showed no differences in the rate of the composite outcome of death, stroke, MI, renal failure or repeat revascularisation between patients who underwent off-pump compared with on-pump CABG.142

In contrast the five-years outcomes of the ROOBY (Randomised On/Off BY-pass) trial, an RCT of over 2,200 patients undergoing CABG in the USA demonstrated a higher incidence of major adverse cardiovascular events and lower 5-year survival with off-pump CABG compared to on-pump CABG. In this study, however, there was a 12.5% conversion rate from off-pump to on-pump surgery raising concerns about surgical experience with the off-pump technique (median number of cases performed by surgeons was 50).143

There is evidence that off-pump CABG might be beneficial in patients at high risk, such as those with end-stage chronic kidney disease (CKD), in whom off-pump CABG resulted in lower in-hospital mortality and need for new renal replacement therapy. Off-pump CABG appears to be associated with a reduced risk of early morbidity, such as stroke, wound and respiratory infections, and fewer transfusions and shorter hospital stays. However, surgeons’ experience and the familiarity of the surgical and anaesthetic teams with the procedure, and performance within the context of a high-volume off-pump CABG centre were important factors.145

In the subgroup of patients with atherosclerotic changes of the ascending aorta, a no-touch technique avoiding any manipulations of the ascending aorta, either on- or off-pump, may be associated with a reduced risk of stroke.148

R Off-pump coronary artery bypass graft can be considered whenever complete revascularisation may be safely achieved, especially in patients with increased risk and comorbidities.

The decision about whether to use on-pump or off-pump approaches should be based on the familiarity of the surgeon with the technique.

5.3.3 CHOICE OF CONDUIT IN SURGICAL REVASCULARISATION

Long-term patency rates in excess of 95% beyond ten years have been reported for anastomosis of the left internal mammary artery (IMA) to the LAD. This superior long-term patency compared to saphenous vein graft (SVG) leads to significant reduction in long-term mortality, subsequent myocardial infarction, the need for further operation and freedom from late cardiac events.146,150
Reports on the use of both IMAs have reinforced the benefits of arterial revascularisation. In patients where both IMAs were used, there was marginally improved long-term survival at five, ten and 15 years (94%, 84% and 67% for bilateral IMA and 92%, 79% and 64% for single IMA). This prognostic benefit was accompanied by a reduced need for reoperation and PCI.151-153

The radial artery is also a suitable conduit and may be used as a free graft applied to the aorta or as a composite ‘Y’ graft from a left IMA. Five-year angiographic patency in a small number (n=50) of asymptomatic patients was 89% for radial artery with IMA patency exceeding 94% and SVG patency of 92%.154

The results of SVG patency may reflect the importance of secondary preventative therapy. Some studies have noted an increased rate of stenosis of radial artery grafts and have cautioned on their applicability in target vessels with only moderate stenosis. Total arterial revascularisation may confer long-term benefit but application of the radial artery graft to subcritical stenoses may not confer benefit.155-157

In a meta-analysis of 28 studies, including 89,399 patients, use of both IMA has been shown to enhance overall long-term outcomes in comparison to single IMA use. Despite a relative increase in the incidence of deep sternal wound infection, the survival benefits and other morbidity advantages (MI-free survival, angina-free survival, hospital mortality, bleeding, and iterative revascularisation) outweigh this short-term risk.158

R Patients undergoing surgical revascularisation of the left anterior descending coronary artery should receive an internal mammary artery graft.

R In patients undergoing multiple coronary artery bypass grafting, use of both internal mammary arteries should be considered.

5.3.4 EFFECT ON COGNITION

Cognitive decline is relatively common in the early period following surgery, in both on-pump and off-pump surgical groups,136 and, in some patients, the initial decline may improve over the first three months. A systematic review of 12 cohort studies and 11 intervention studies found that 22% of patients had evidence of cognitive decline at two months after CABG. The relatively early follow-up period used may overestimate the longer-term severity of the problem.159

Evidence for decline in later time periods after surgery is conflicting and suggests that factors related to presence of cardiovascular disease and the ageing process, rather than surgery itself, may influence continuing decline.160, 161,162, 163

5.4 CHOICE OF REVASCULARISATION TECHNIQUE

Following a decision to undertake coronary revascularisation, the major consideration is whether this should be undertaken by PCI or surgery. Coronary artery bypass graft has historically been the first line option but with the evolution of PCI technology, the introduction of DES, and comparable clinical outcomes in specific populations, the role of surgery has been challenged.

In the 10 years up to 2015/16 the number of CABG operations carried out each year in Scotland decreased by 46% (from 2,306 to 1,252); a reduction in the age-standardised rate from 82.3 to 41.6 per 100,000 population. In the same period, the number of PCIs increased by 40% (from 5,841 to 8,228); an increase in the age-standardised rate from 127.2 to 160.7 per 100,000 population.164

The choice of revascularisation technique is often complex and involves careful consideration of medical and surgical suitability with informed patient choice at the centre of the decision making process. In the context of stable angina where any intervention is essentially elective, adequate time should be allocated to allow appropriate clinical decision making and fully informed decision making with the patient. Ideally, revascularisation options should be agreed following review by a multidisciplinary ‘Heart Team’ including cardiac surgeons, cardiac anaesthetists and interventional cardiologists, and discussion with the patient.
Patient preferences must be taken into account, especially for patient groups for whom there is no clear overall benefit of one approach over the other and where the choice may depend heavily on the relative risks of and from repeat revascularisation and stroke, as well as patient preferences relating to these risks.165

Factors influencing decision making include the extent and severity of underlying CAD (single versus multivessel disease), the presence of left main-stem disease, comorbidity including the presence of diabetes mellitus and renal impairment, and patient age. A summary of the evidence for major factors influencing decision making is provided below. When interpreting the evidence, it is important to highlight the limitations of the available data. The evidence is based largely on composite endpoints as the majority of studies were not powered for individual outcomes. Many studies included both patients with stable angina and those with unstable coronary artery disease. As with the majority of clinical studies, the study populations reflect a highly selected group of patients, the number of patients included being a very small proportion of those screened.

5.4.1 MULTIVESSEL DISEASE

In patients with multivessel CAD, CABG is consistently associated with a reduced need for subsequent revascularisation when compared to PCI. There is disagreement between meta-analyses as to whether CABG is superior to PCI in terms of prognostic benefit. This may be related in part to the burden of underlying CAD, with a higher burden of disease favouring CABG.

A meta-analysis of 20 RCTs including nine trials in patients with multivessel disease reported significantly lower rates of stroke following PCI (odds ratio (OR) 0.49, 95% CI 0.25 to 0.97) but higher rates of repeat revascularisation at 12 months with PCI compared with CABG (OR 7.18, 95% CI 4.32 to 11.93). Rates of death and MI with CABG and PCI were similar for patients with multivessel disease.166 Only three of the nine trials SYNTAX, FREEDOM and CARDia used DES and two of these were specifically in patients with diabetes.

By contrast, in a subsequent meta-analysis including 12 trials of patients with multivessel disease, all-cause mortality and repeat revascularisation were higher with PCI than with CABG (OR 1.2, 95% CI 1.0 to 1.4; OR 0.5, 95% CI 4.2 to 7.4, respectively), but there was no difference in rates of MI or stroke. Only two of the 12 trials used DES (FREEDOM - first-generation; CARDia - sirolimus in 69% of patients, BMS in 21%) and these were both in patients with diabetes.165

A recent RCT comparing CABG and PCI with everolimus-eluting stents in patients with multivessel disease reported no differences in the primary outcome of death, MI or target vessel revascularisation after two years, but found an increase in the primary outcome in the PCI group at a median of 4.6 years follow up (15.3% v 10.6%, HR 1.47, 95% CI 1.01 to 2.13). This difference was driven primarily by repeat revascularisation (11% v 5.4%, p=0.004) and spontaneous MI (4.3% v 1.6%, p=0.02).167

There is evidence to support the concept that the superiority of CABG over PCI may be related to the burden of CAD. One RCT (SYNTAX) examined clinical outcomes in patients with three-vessel CAD randomised to treatment with either CABG or PCI with paclitaxel-eluting stents.168 The burden of CAD was assessed using a validated scoring system (SYNTAX score). In a prespecified subgroup analysis, all-cause mortality, MI, and repeat revascularisation were lower with CABG than PCI in patients with more complex disease (as defined by a score of more than 22 on the original trial’s anatomic complexity or SYNTAX score).169 The exception was stroke where outcomes at five years were similar in patients undergoing PCI and CABG. In patients with low SYNTAX scores (22 or less), outcomes with PCI and CABG were similar, apart from higher rates of repeat revascularisation in the PCI group (25.4% v 12.6%).
5.4.2 LEFT MAIN-STEM DISEASE

The evidence suggests that PCI and CABG offer comparable outcomes in the short-to medium-term in patients with left main-stem disease. Increasing anatomical complexity, a higher burden of underlying CAD and longer-term outcomes would favour CABG.

A meta-analysis of four RCTs of patients with unprotected left main-stem disease reported no difference in rates of death or MI between PCI with DES (sirolimus or paclitaxel) and CABG. With PCI, a reduced risk of stroke (0.12% v 1.9%, OR 0.14, 95% CI 0.04 to 0.55) was offset by an increased rate of repeat revascularisation (11% v 5.4%, OR 2.17, 95% CI 1.48 to 3.17). A subsequent meta-analysis of the same four RCTs plus 17 observational studies found broadly similar results, although mortality was lower with PCI (RR 0.79, 95% CI 0.71 to 0.87).

Two RCTs in patients with left main-stem disease reported no difference in the composite outcome of all-cause mortality/stroke/MI/repeat revascularisation at three-year follow-up between patients receiving PCI with DES compared with CABG. In the first trial (n=705, paclitaxel-eluting stents), there was no difference between PCI and CABG for those with low or intermediate SYNTAX scores but there were higher rates of major adverse cardiac and cerebrovascular events with PCI in those with high SYNTAX scores (46.5% v 29.7%); a result consistent with that found in patients with multivessel CAD (see section 5.4.1). In the second RCT (n=1,905, everolimus-eluting stents), 53% of patients had stable angina, and all had SYNTAX scores less than 33 (low to intermediate complexity).

In contrast, an RCT comparing PCI with DES (predominantly biolimus-eluting stents) with CABG in 1,201 patients with left main-stem disease, 82% of whom had stable angina and a median SYNTAX score of 22.4, reported no significant differences between groups in the primary composite endpoint (all-cause mortality, non-procedural MI, repeat revascularisation, stroke) at one year, but a found a significant reduction in the composite endpoint with CABG compared to PCI at a median follow up of three years (28% v 18%, HR 1.51, 95% CI 1.13 to 2.0).

5.4.3 DIABETES MELLITUS

In patients with diabetes mellitus and multivessel coronary artery disease, CABG is associated with reduced rates of death and repeat revascularisation at the expense of an increased risk of stroke when compared with PCI.

A meta-analysis of four RCTs (n=3,052) in patients with diabetes mellitus and multivessel CAD reported lower rates of the composite endpoint of death, MI or stroke with CABG compared with PCI after four years of follow up (16.8% v 22.5%, RR 1.34, 95% CI 1.16 to 1.54, ARR 6%, number needed to treat (NNT) 18). This difference resulted from lower rates of death (9.7% v 14%, RR 1.51, 95% CI 1.09 to 2.1, ARR 4.4%, NNT 23) and repeat revascularisation (8% v 17.4%, RR 1.85, 95% CI 1.0 to 3.4, ARR 11%, NNT 11) in those receiving CABG. The rate of stroke was, however, higher with CABG than with PCI (3.8% v 2.3%, RR 0.59, 95% CI 0.39 to 0.9).

A second meta-analysis of the same four RCTs plus 10 non-randomised studies (n=7,072) confirmed these findings with lower mortality (7.3% v 10.4%, OR 0.6, 95% CI 0.55 to 0.77) and target vessel revascularisation (5.2% v 15.7%, OR 0.3, 95% CI 0.25 to 0.36) and higher risk of stroke (3.2% v 1.4%, OR 2.34, 95% CI 1.63 to 3.35) in patients treated with CABG compared with PCI.

The largest RCT (n=1,900), included in both meta-analyses, reported that although short-term outcomes (less than 30 days) favoured PCI and medium-term outcomes (6–24 months) favoured CABG, no significant difference in health status or quality of life was found between the two groups beyond two years following intervention.
5.4.4 CHRONIC KIDNEY DISEASE

Most RCTs of coronary revascularisation have excluded patients with chronic kidney disease (CKD) and evidence for treatment options in this group of patients is largely derived from retrospective observational studies. Accepting these limitations, short-term outcomes following revascularisation in patients with CKD appear to favour PCI while longer-term outcomes may favour CABG.

A meta-analysis of 31 studies (half recruiting before 2000) of patients with CKD (defined as glomerular filtration rate (eGFR) less than 60 ml/min/1.73²) (n=55,383 PCI, 43,671 CABG) showed that, compared with CABG, PCI was associated with lower short-term (less than 30 days) mortality (OR 0.51, 95% CI 0.42 to 0.62) but a higher risk of death (OR 1.12, 95% CI 1.01 to 1.24), MI (OR 1.77, 95% CI 1.44 to 2.17) and repeat revascularisation (OR 4.87, 95% CI 3.53 to 6.74) beyond one year. However, pooled studies showed high heterogeneity and only around half of the studies reported each outcome.

Broadly consistent with this, a recent RCT comparing PCI with everolimus-eluting stents and CABG (n=5,920) in patients with CKD (defined as eGFR less than 60 ml/min/1.73²) and multivessel disease reported a lower risk of death (1.0% v 1.7%, HR 0.55, 95% CI 0.35 to 0.87) and stroke (0.4% v 1.7%, HR 0.22, 95% CI 0.12 to 0.42) at 30 days with PCI compared with CABG, but no difference in MI. At follow up (mean 2.9 years), mortality was similar in both groups, but PCI was associated with a higher risk of MI (10.7% v 7.0%, HR 1.76, 95% CI 1.40 to 2.23) and repeat revascularisation (26.1% v 13.1%, HR 2.42, 95% CI 1.5 to 3.96) but a lower risk of stroke (HR 0.56, 95% CI 0.41 to 0.76) compared with CABG. In patients on dialysis (n=486), PCI was associated with a significantly greater risk of death (54.3% v 39.1%, HR 2.02, 95% CI 1.40 to 2.93) and repeat revascularisation (48.3% v 25%, HR 2.44, 95% CI 1.5 to 3.96) compared with CABG.

5.4.5 AGE

Elderly patients with stable angina tend to have more extensive CAD, greater comorbidity and less physiological reserve, and mortality following PCI and CABG is higher in this population than in younger patients. Older patients are frequently excluded from RCTs and high-quality data to guide recommendations on revascularisation strategy are lacking.

A cohort study of patients over 75 years of age with multivessel disease (n=3,864), reported no significant differences in mortality or the composite outcome of stroke, MI and mortality between PCI with DES and CABG after 2.5 years of follow up. As with younger patients, repeat revascularisation was more common after PCI (HR 7.48, 95% CI 5.61 to 9.98).

Patients with stable angina who remain symptomatic on optimal medical therapy should be considered for revascularisation by coronary artery bypass grafting or percutaneous coronary intervention.

Patients with left main-stem stenosis and/or multivessel disease should be considered for revascularisation to improve prognosis.

A tailored approach to revascularisation is required and the approach should be decided following discussion with the patient and the multidisciplinary ‘Heart Team’. Factors influencing the choice of revascularisation should include burden and complexity of coronary artery disease, presence of diabetes mellitus, age and renal dysfunction.

5.5 POSTINTERVENTION DRUG THERAPY

With the diagnosis of CVD, secondary prevention medication is mandatory and should include cholesterol-lowering therapy usually with a statin, antiplatelet therapy and, if appropriate, antihypertensive and hypoglycaemic medications (see section 4.3 and SIGN guideline 149 on risk estimation and the prevention of cardiovascular disease).
No evidence was identified for the use of long-term beta blockers for asymptomatic patients following CABG.

In all patients with evidence of left ventricular impairment, optimal medical therapy should include use of an ACE inhibitor (or angiotensin II receptor blocker if intolerant) and consider the use of beta blockers and further renin-angiotensin-aldosterone blockade (see SIGN guideline number 147 on the management of chronic heart failure).63

5.5.1 ANTIPLATELET THERAPY FOLLOWING CORONARY ARTERY BYPASS GRAFTING

Following CABG, aspirin (75–300 mg daily) is the routinely prescribed antiplatelet medication.182 The administration of aspirin within 48 hours of CABG was associated with a 48% reduction in MI and a 50% reduction in stroke. The mortality in those receiving early aspirin was 1.3% compared to 4% amongst those who did not.183 The Society of Thoracic Surgeons has recommended that aspirin should be stopped for 3–5 days before elective CABG and then restarted early after surgery.184 In those intolerant of aspirin, clopidogrel (75 mg daily) should be considered.94

5.5.2 DUAL ANTIPLATELET THERAPY FOLLOWING PERCUTANEOUS CORONARY INTERVENTION

Patients with stable angina undergoing PCI should be treated with dual antiplatelet therapy (DAPT) following PCI.185 In contrast to patients with acute coronary syndrome (see SIGN 148 on acute coronary syndromes),10 the duration of DAPT in patients with stable angina varies according to the type of stent implanted.

In patients treated with bare-metal stents, guidelines from the American Heart Association (AHA) and the American College of Cardiology (ACC) summarising the historical evidence recommend DAPT (aspirin and clopidogrel) for a minimum of one month following bare-metal stent implantation.185

In patients treated with DES, three systematic reviews and meta-analyses of RCTs have compared different durations of DAPT (aspirin plus a P2Y12-receptor antagonist). The trials included heterogeneous populations, with a significant proportion of patients having stable IHD. The type of DES used varied between and within trials (paclitaxel, sirolimus, everolimus and zotarolimus-eluting stents were all used).186-188

One meta-analysis, including four RCTs (n=8,231) of patients (26–48% of whom had stable CAD) receiving aspirin and clopidogrel DAPT reported no difference in rates of all-cause mortality, MI, stent thrombosis or stroke but found an increase in major bleeding (0.7% v 0.2%, OR 2.64, 95% CI 1.31 to 5.30) with prolonged DAPT (median duration 16.8 months) compared with control (median duration 6.2 months).186

Two subsequent meta-analyses, both of which included the same 10 RCTs, compared short-term (3–6 months), 12 months, and extended-duration (more than 12 months) DAPT in patients (n=32,000) undergoing PCI with DES. The type of P2Y12-receptor antagonist varied between and within trials, with clopidogrel used the most frequently, prasugrel in three trials and ticagrelor in two trials. Both studies reported broadly similar findings. Firstly, compared with short-term therapy, 12-month DAPT was associated with a doubling in the risk of major bleeding with no reduction in rates of MI, stent thrombosis or death. Secondly, compared with 12-month DAPT, extended therapy reduced rates of recurrent MI and stent thrombosis but increased major bleeding and overall mortality. This increase in mortality reflected an increase in non-cardiac mortality that was not offset by a reduction in cardiac mortality. Both analyses consistently demonstrated that shorter durations of DAPT are not associated with worse clinical outcomes.187, 188 Subgroup analysis did not identify any differences in outcomes between patients undergoing PCI for stable angina compared to those undergoing PCI for ACS, despite the former having a lower baseline ischaemic risk.187

Clopidogrel was the most frequently used P2Y12-receptor antagonist in the meta-analyses, however, a subgroup analysis comparing clopidogrel, prasugrel and ticagrelor demonstrated no difference in outcomes according to the type of P2Y12-receptor antagonist used.187 These results suggest that, although not licensed for use in patients with stable angina, prasugrel or ticagrelor may be appropriate alternatives in patients allergic to clopidogrel.
Following cessation of DAPT, aspirin monotherapy should be continued (see section 4.3.1).

R Following bare-metal stents implantation patients with stable angina should receive aspirin and clopidogrel for at least one month.

R Following drug-eluting stent implantation, patients with stable angina should receive aspirin and clopidogrel for 6 months.

✓ Following drug-eluting stent implantation longer courses of dual antiplatelet therapy may be considered for patients at high risk of ischaemic events. Use should be carefully weighted against the increased risk of bleeding.

5.6 POSTINTERVENTION REHABILITATION

SIGN guideline 150, on cardiac rehabilitation, recommends that patients who have undergone coronary revascularisation should receive comprehensive rehabilitation.189

5.7 MANAGING RESTENOSIS

Restenosis rates following stenting have been reduced, but not eliminated, by the use of coated stents.190 A network meta-analysis following PCI in-stent restenosis reported comparable clinical outcomes in patients receiving treatment with drug-eluting balloons or DES, with both being superior to alternative treatments (angioplasty with plain or cutting balloons, rotational atherectomy, brachytherapy).191 In patients with multivessel CAD and in-stent restenosis (ISR), CABG should be considered.

R In patients with stable angina requiring percutaneous coronary intervention for in-stent restenosis a drug-eluting balloon or a second- or third-generation drug-eluting stent should be considered.

5.8 MANAGING REFRACTORY ANGINA

Refractory angina can be defined as persisting unsatisfactory control of anginal symptoms despite maximal tolerated medical therapies and without further revascularisation options.

Options for management of angina symptoms in this group of patients include both behavioural and invasive interventions. Behavioural interventions have been shown to have positive effects on symptom control in some patients (see section 7.2). Evidence to support invasive interventions is limited, effects are mixed and the possibility of adverse events must be taken into account. It is important that the limitations and risks of treatment are clearly discussed with patients before treatment decisions are taken.

Patients presenting with refractory angina have often not received a comprehensive rehabilitation programme, which may improve management of symptoms. The initial treatment of these patients should follow an educational and rehabilitative approach, progressing to a cognitive behaviourally-informed approach where appropriate (see section 7.2). The latter has demonstrated positive outcomes for both angina and chronic pain.192, 193 Behavioural interventions should be considered in patients with stable angina before invasive interventions such as spinal cord stimulation (see section 5.8.1), surgical transmyocardial revascularization (see section 5.8.2), and enhanced external counterpulsation (see section 5.8.3) are considered.

5.8.1 SPINAL CORD STIMULATION

Spinal cord stimulation consists of inserting a stimulating electrode into the thoracic epidural space under local anaesthetic with the final position of the electrode being determined by the patient’s sensation of paraesthesia in the area where the angina pain is usually felt.
A systematic review of nine RCTs comparing spinal cord stimulation with optimal medical care, or inactive mode or low stimulation spinal cord stimulation, or alternative therapeutic interventions, suggested a small short-term treatment benefit from spinal cord stimulation, although the most recent trial (n=68) showed no difference between treatment and control groups.194 All nine trials were small, (n=12 to 104; six had 25 or fewer participants) and most were rated as low to intermediate quality. This coupled with heterogeneity in the trial designs makes interpretation of the results difficult. It is therefore not possible to make a recommendation.

5.8.2 SURGICAL TRANSMYOCARDIAL LASER REVASCULARISATION

This procedure consists of using a laser to create between 20–40 one millimetre transmural channels in the exposed left ventricle. Suggested effects are the promotion of angiogenesis, restoring blood supply to the myocardium or destroying its innervation.

A systematic review of 20 reports covering seven studies and including 1,137 participants with refractory angina and contraindications for PCI or CABG found that, compared with optimal medical treatment, the risks associated with transmyocardial laser revascularisation (TMLR) outweigh the possible benefits.195 Although improvements in angina scores were reported, particularly in the treatment group, 30-day mortality was substantially higher in the treatment group (6.8% TMLR v 0.8% controls, pooled OR 3.76, 95% CI 1.63 to 8.66). Improvements in subjective measures, such as angina scores, are associated with a high risk of bias due to the absence of blinding. Other outcomes were inconsistently reported in the trials and were not considered by the review. No new trial data has been published since 2004.

R Transmyocardial laser revascularisation is not recommended for the treatment of stable angina.

5.8.3 ENHANCED EXTERNAL COUNTERPULSATION

Enhanced external counterpulsation (EECP) involves the use of compressed air applied via cuffs to the patient’s lower extremities in synchrony with the cardiac cycle. In early diastole, pressure is applied sequentially from the lower legs to the lower and upper thighs to propel blood back to the heart. This results in an increase of arterial blood pressure and retrograde aortic blood flow during diastole (diastolic augmentation). At end-diastole, air is released instantaneously from all the cuffs to remove the externally applied pressure, allowing the compressed vessels to reconform, thereby reducing vascular impedance.

Evidence to support the use of EECP in patients with stable angina is very limited. Two systematic reviews identified one RCT with methodological limitations (n=139), dating from 1999,196,197 and one identified an additional three non-randomised studies, two of them very small (n=25 and n=40), none recent, and all assessed as having a high risk of selection bias.197

5.8.4 OTHER APPROACHES

Insufficient evidence was found to support use of the following approaches for pain relief in stable angina:

- stellate ganglion block
- nerve block
- transcutaneous electrical nerve stimulation
- thoracic sympathectomy
- analgesics
- acupuncture
- coronary sinus reducer stent.
6 Stable angina and non-cardiac surgery

Patients with coronary heart disease undergoing non-cardiac surgery are at increased risk of adverse cardiac events. The incidence of myocardial injury after non-cardiac surgery depends on definition but in one study of patients over 50 years of age undergoing inpatient non-cardiac surgery was as high as 11.6%. The physiological stress associated with surgery can include tachycardia, hypovolaemia, hypotension, hypertension, anaemia, hypothermia, acute pain, inflammation and hypercoagulable state. All of these can affect myocardial oxygen supply and demand, and precipitate events such as myocardial infarction, myocardial ischaemia or significant arrhythmias. Cardiac complications are associated with increased mortality and morbidity, length of stay and consequent higher costs and it is likely perioperative myocardial injury is underdiagnosed.

More recently, the clinical entity of "myocardial injury after non-cardiac surgery" has been described as prognostically relevant cardiac injury occurring within 30 days of surgery and which carries increased mortality. Patients who have postoperative cardiac injury are at increased risk of death and the excess hazard appears to be proportional to the magnitude of troponin release.

Thus, prevention of perioperative cardiac complications is a research priority and the subject of international practice guidelines.

6.1 ASSESSMENT PRIOR TO SURGERY

An assessment of the risk of cardiac complications in the perioperative period in patients at high risk should include early involvement of surgeons, anaesthetists, perioperative physicians and cardiologists. Specific preoperative clinics may be useful in this setting. Assessment for surgery should consider the inherent procedural risk (see Table 1), patient-specific factors and functional capacity. Increasingly, cardiopulmonary exercise testing (CPET) is being used to formally assess functional capacity prior to surgery. As myocardial ischaemia is an important predictor of major adverse cardiac events after non-cardiac surgery, a full clinical history and examination and resting electrocardiogram should be assessed. Patients at increased risk may undergo additional risk stratification usually by exercise tolerance test. Where this is impractical other non-invasive tests such as stress echocardiography or MPS could be considered. Coronary angiography may be indicated where a high risk is identified and is the investigation of choice to define the coronary anatomy.

Table 1: Surgical risk estimate according to type of surgery or intervention

<table>
<thead>
<tr>
<th>Low-risk: &lt;1%</th>
<th>Intermediate-risk: 1–5%</th>
<th>High-risk: &gt;5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Superficial surgery</td>
<td>• Intrapерitoneal: splenectomy, hiatal hernia repair, cholecystectomy</td>
<td>• Aortic and major vascular surgery</td>
</tr>
<tr>
<td>• Breast</td>
<td>• Carotid symptomatic (CEA or CAS)</td>
<td>• Open lower limb revascularisation or amputation or thromboembolectomy</td>
</tr>
<tr>
<td>• Dental</td>
<td>• Peripheral arterial angioplasty</td>
<td>• Duodeno-pancreatic surgery</td>
</tr>
<tr>
<td>• Endocrine: thyroid</td>
<td>• Endovascular aneurysm repair</td>
<td>• Liver resection, bile duct surgery</td>
</tr>
<tr>
<td>• Eye</td>
<td>• Head and neck surgery</td>
<td>• Oesophagectomy</td>
</tr>
<tr>
<td>• Reconstructive</td>
<td>• Neurological or orthopaedic: major (hip and spine surgery)</td>
<td>• Repair of perforated bowel</td>
</tr>
<tr>
<td>• Carotid asymptomatic (CEA or CAS)</td>
<td>• Urological or gynaecological: major</td>
<td>• Adrenal resection</td>
</tr>
<tr>
<td>• Gynaecology: minor</td>
<td>• Renal transplant</td>
<td>• Total cystectomy</td>
</tr>
<tr>
<td>• Orthopaedic: minor (meniscectomy)</td>
<td>• Intra-thoracic: non-major</td>
<td>• Pneumonectomy</td>
</tr>
<tr>
<td>• Urological: minor (transurethral resection of the prostate)</td>
<td></td>
<td>• Pulmonary or liver transplant</td>
</tr>
</tbody>
</table>

CAS = carotid artery stenting; CEA = carotid endarterectomy.

Surgical risk estimate is a broad approximation of 30-day risk of cardiovascular death and myocardial infarction that takes into account only the specific surgical intervention, without considering the patient’s comorbidities.

Society of Cardiology (ESC)/European Society of Anaesthesiology (ESA) Guidelines on non-cardiac surgery: cardiovascular assessment and management.
Patient-specific factors are listed in Table 2. The ACC/AHA guidelines on perioperative cardiovascular evaluation for non-cardiac surgery include a full discussion of preoperative assessment.\textsuperscript{201}

### Table 2: Risk factors for perioperative cardiac complications \textsuperscript{201}

- Coronary artery disease
- Heart failure
- Arrhythmias and conduction disorders
- Valvular heart disease
- Congenital heart disease
- Cardiomyopathy

Adapted from American Heart Association/American College of Cardiology guidelines.\textsuperscript{201}

#### 6.1.1 RISK SCORING SYSTEMS

The discovery of major risk factors before non-cardiac surgery will usually result in postponement of surgery and the investigation and treatment of that problem. Procedural risk should also be quantified (see Table 1), to help select patients who may benefit from further evaluation or investigation.

The Revised Cardiac Risk Index (RCRI) is a simple risk-stratification tool that combines patient risk and procedural risk and can aid clinical decision making (see Table 3).\textsuperscript{198} In this report of the risk of major cardiac complications with major non-emergency non-cardiac surgery, six factors with approximately equal prognostic importance were identified.\textsuperscript{198}

### Table 3: Revised Cardiac Risk Index

<table>
<thead>
<tr>
<th>Clinical factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>- High-risk surgery</td>
</tr>
<tr>
<td>- History of ischaemic heart disease (IHD)</td>
</tr>
<tr>
<td>- History of congestive heart failure</td>
</tr>
<tr>
<td>- History of cerebrovascular disease</td>
</tr>
<tr>
<td>- Preoperative insulin treatment</td>
</tr>
<tr>
<td>- Preoperative creatinine &gt;180 micromol/l.</td>
</tr>
</tbody>
</table>

High-risk surgery is defined as intraperitoneal, intrathoracic, or suprainguinal vascular procedures. A history of IHD is defined as any of the following: a history of MI, positive exercise tolerance test, current complaint of chest pain of ischaemic origin, use of nitrate therapy or pathological Q waves on ECG. Patients with prior revascularisation are only classified as having IHD if they have one of the above criteria.\textsuperscript{198}

The rates of major cardiac complications postoperatively with 0, 1, 2, 3 or more risk factors were 0.5%, 1.3%, 4% and 9%, respectively.\textsuperscript{198}

Patients identified at high risk of cardiac complications using the RCRI may undergo further risk-stratification with non-invasive testing or other risk-reduction management strategies. These risk-reduction strategies may involve preoperative revascularisation or medical therapy.\textsuperscript{203} Those identified as low risk may proceed to surgery. The RCRI has been modified for patients having vascular surgery.\textsuperscript{204}

The urgency of the surgical procedure and the presence of recent cardiac investigations will influence the decision on whether further cardiac investigations are appropriate. Clinical circumstances will determine whether a delay for investigation and preoperative optimisation can be justified.
Additional information can be derived from the functional capacity of patients and non-invasive tests such as exercise ECG tolerance testing, stress echocardiography and MPS. In general, indications for preoperative coronary angiography are similar to the non-operative setting. These are patients with known or suspected CAD and:

- evidence of high risk of adverse outcome based on non-invasive test results, or
- unstable angina facing intermediate or major types of non-cardiac surgery, or
- equivocal non-invasive test results and with high clinical risk undergoing high-risk non-cardiac surgery.\(^{201}\)

The risk of cardiac complications is significant (4% or greater) in patients undergoing high-risk surgery and who have at least one CAD risk factor (see Table 3). These individuals should generally be considered for further investigation. Some combinations of risk factors may not predispose the individual to equal levels of risk of cardiac complications and clinical judgement should be used to stratify patients accordingly.

### R As part of the routine assessment of fitness for non-cardiac surgery, a risk-assessment tool should be used to quantify the risk of serious cardiac events in patients with coronary heart disease.

### R Patients undergoing high-risk surgery who have a history of coronary artery disease, stroke, diabetes, heart failure or renal dysfunction should have further investigation either by exercise tolerance testing or other non-invasive testing or coronary angiography, if appropriate.

✔ Where high perioperative risk is identified, a strategy for risk reduction should be agreed. This will require teamwork and good communication between surgeon, anaesthetist, perioperative physician and cardiologist.

#### 6.1.2 FUNCTIONAL CAPACITY

Functional capacity has been shown to predict perioperative and long-term cardiac events and should be part of the preoperative assessment of patients with CAD undergoing major surgery.\(^{205, 206}\)

Functional capacity can be expressed in metabolic equivalents of task (METs). One MET is the oxygen consumption of a 40 year old 70 kg man at rest and is equal to 3.5 ml/min/kg. Patients who are unable to meet a four MET demand during most normal daily activities are at increased risk of perioperative and long-term cardiac events.\(^{207}\)

Different scoring systems are available to measure functional capacity objectively such as the New York Heart Association Score,\(^{208}\) Karnofsky Performance Scale\(^{209}\) or the Duke Activity Score which is a self-completed questionnaire using a set of common daily living items.\(^{210}\) Simple exercise testing may further refine risk assessment. The failure to climb two flights of stairs, which is the equivalent of more than four METs, is a good predictor of mortality associated with thoracic surgery and complications after major non-cardiac surgery.\(^{211}\)

Cardiopulmonary exercise testing has been used to identify high-risk groups for major non-cardiac surgery. The measurement of anaerobic threshold may be a better predictor than the maximum oxygen consumption (VO\(_2\) max) as it is more independent of patient motivation.\(^{205, 206}\) In elderly patients undergoing major abdominal surgery, a group of patients with an anaerobic threshold of less than 11 ml/kg/min (three METs) had a higher mortality rate when compared to the group with an anaerobic threshold of greater than 11 ml/kg/min. The anaerobic threshold is a better measure of the ability to meet the demands of prolonged stress associated with major surgery than VO\(_2\) max. The anaerobic threshold may vary in any individual between 50% to 100% of the VO\(_2\) max.
Further studies are necessary to evaluate the cost effectiveness and clinical utility of cardiopulmonary exercise testing as a means of risk assessment before major surgery. Simple assessment of functional capacity by patient questionnaires and simple exercise testing such as stair climbing prior to thoracic surgery are valuable.\textsuperscript{210, 211}

**R** An objective assessment of the functional capacity should be made as part of the preoperative assessment of all patients with coronary heart disease before major surgery.

### 6.2 PERIOPERATIVE REVASCULARISATION

Data from the Coronary Artery Surgery Study registry confirmed that clinically stable patients (n=1,297) undergoing low-risk surgery (urology, orthopaedic, breast, and skin surgery) had a low mortality (less than 1%) regardless of prior coronary treatment.\textsuperscript{212} Those (n=1,961) undergoing high-risk surgery (abdominal, vascular, thoracic and head and neck surgery) had a combined MI/death rate among patients with non-revascularised CAD of greater than 4%. Among these, prior CABG was associated with fewer deaths (1.7% v 3.3%) and myocardial infarctions (0.8% v 2.7%) compared to medically managed coronary disease. These patients were enrolled between 1974 and 1979 and the results may not be applicable to contemporary practice.

The Coronary Artery Revascularisation Trial randomly assigned patients at risk for perioperative cardiac complications and clinically significant coronary heart disease to undergo either revascularisation or no revascularisation before elective major non-cardiac vascular surgery.\textsuperscript{213} At 2.7 years after randomisation, mortality was 22% in the revascularisation group and 23% in the no revascularisation group. These results conflict with the Coronary Artery Surgery Study and may reflect the differences in the mode of revascularisation in the observational studies or advances in medical therapy over the intervening period. After coronary catheterisation patients with significant left main-stem stenosis (54 patients), poor left ventricular function (11 patients) and severe aortic stenosis (8 patients) were excluded from this study. Only 31% of the no revascularisation group had triple-vessel disease.

Preoperative CABG will be appropriate for only a minority of patients as the procedure carries a significant risk of mortality (around 3%) and morbidity, and these risks must be added to those of the coronary angiography and the non-cardiac surgery itself. Compared to case-matched controls, patients who underwent non-cardiac vascular surgery within a month of CABG suffered significantly greater mortality (20.6% v 3.9%, p<0.005).\textsuperscript{214} A significantly higher risk of cardiac complications (27%) was found in patients undergoing non-cardiac procedures in the first month after CABG.\textsuperscript{215} This remained higher (17%) until the sixth month following CABG.

Although definitive evidence for a safe period to delay non-cardiac surgery after CABG is lacking, it seems prudent to avoid elective non-cardiac surgery for at least one month and possibly up to six months. The timing of surgery will depend on the balance of risks and benefits which, in an individual patient, will depend on the severity of the CAD and the nature and urgency of the non-cardiac surgery.

Overall survival benefit is seen only in patients who would warrant CABG surgery independently of their major non-cardiac surgery. These indications are significant left main-stem stenosis, triple-vessel disease in conjunction with left ventricular dysfunction, two-vessel disease including proximal LAD, and unstable symptomatic CAD despite full medical therapy.\textsuperscript{108} When time allows these patients may be offered preoperative CABG.

There is no evidence for the use of prophylactic PCI before non-cardiac surgery in patients with stable angina. In the absence of any other data, indications for PCI are essentially identical to the non-operative setting, which are for the relief of anginal symptoms resistant to medical therapy. Patients who have had PCI and stent insertion are at risk of stent thrombosis if their dual antiplatelet therapy is discontinued prematurely.\textsuperscript{216} The risk of cardiac complications after non-cardiac surgery is greater if a coronary artery stent has been inserted recently (less than 35 days ago) compared to less recently (more than 90 days ago).\textsuperscript{217}
There is limited evidence regarding the optimal time delay after PCI before proceeding to non-cardiac surgery. Following balloon angioplasty, at least one week should be left to allow healing of the traumatised vessel wall. Following bare-metal stent insertion, four weeks of dual antiplatelet therapy are required, thus a delay of six weeks before non-cardiac surgery has been recommended by which time bare-metal stents are generally re-endothelised and clopidogrel can be discontinued. Where a drug-eluting stent is implanted, current guidance suggests that elective surgery should be delayed by at least three months (but preferably six), with the greatest risk occurring when surgery is performed early.

If surgery cannot be delayed, dual antiplatelet therapy should be continued if possible. Premature discontinuation of antiplatelet therapy is associated with a high risk of stent thrombosis which is often fatal. The bleeding risk of the proposed emergency surgical procedure must be extremely high and the disease requiring surgery must be life threatening to justify stopping antiplatelet agents prematurely.

**R** Coronary revascularisation is not recommended before major- or intermediate-risk non-cardiac surgery unless cardiac symptoms are unstable and/or coronary artery bypass grafting would be justified on the basis of long term outcome.

**R** If emergency or urgent non-cardiac surgery is required early after percutaneous coronary intervention (<6 weeks following bare-metal stent implantation; <3 months following drug-eluting stent implantation), dual antiplatelet therapy should be continued whenever possible. If the bleeding risk is unacceptable and antiplatelet therapy is to be withdrawn prematurely, it should be reintroduced as soon as possible after surgery.

✓ The indications used for revascularisation prior to non-cardiac surgery should be those used in the non-operative setting.

✓ Where possible, non-cardiac surgery should be delayed for at least one month after coronary artery grafting. When deciding when to operate, the balance of risks and benefits in an individual patient will depend on the severity of the CAD and the nature and urgency of the non-cardiac surgery.

### 6.3 DRUG THERAPY IN PATIENTS UNDERGOING NON-CARDIAC SURGERY

Medical therapy for patients with stable angina in general is discussed in section 4. The risk from non-cardiac surgery in patients with CAD may be minimised by optimising medical therapy in the perioperative period. It should be noted, however, that studies of medical therapy in the perioperative period included patients with known CAD as well as those without.

#### 6.3.1 BETA BLOCKERS

Beta blockers are an effective treatment for angina and are known to reduce mortality after MI and in patients with stable heart failure. Beta blockers prolong coronary filling time, reduce myocardial oxygen demand and may prevent arrhythmias and atheromatous plaque rupture in the presence of high sympathetic nervous system drive or other stressors in the perioperative period. There has been significant interest in the perioperative use of beta blockade to prevent cardiac complications following non-cardiac surgery in patients with and without known CAD.

Routine initiation of beta-blocker therapy with the intention of reducing cardiac complications in patients not previously treated with beta blockers but at high risk of developing cardiac complications has been extensively investigated. Three systematic reviews of perioperative initiation of beta-blocker therapy in patients with and without CAD undergoing non-cardiac surgery reported a reduction in the risk of perioperative MI but an increased risk of all-cause mortality, stroke and hypotension. A retrospective review of 782,969 patients suggested that beta-blocker treatment was associated with significant reductions in mortality in the highest risk patients (RCRI score of three or greater) but was of no benefit among the lowest risk categories (those with a score of zero or one).
The ACC/AHA guideline on perioperative beta-blocker therapy recommends continuation of established beta-blockade in patients undergoing surgery. Acute withdrawal of beta blockers in the postoperative period may increase the risk of postoperative cardiac complications and is not recommended.

**Routine initiation of perioperative beta-blocker therapy to reduce perioperative myocardial infarction in patients undergoing non-cardiac surgery is not recommended.**

**Acute withdrawal of beta blockers in the postoperative period is not recommended.**

If beta blockers are started perioperatively in patients with myocardial ischaemia a period of dose titration (weeks to months) is recommended if time permits before undergoing non-cardiac surgery. There is an increased risk of adverse effects in the perioperative period, particularly hypotension and stroke. Measures to address this such as withholding antihypertensive therapy should be considered and blood pressure should be carefully monitored after surgery with appropriate protocols to address hypotension as required.

### 6.3.2 ALPHA-2 ADRENERGIC RECEPTOR AGONISTS

Alpha-2 adrenergic receptor agonists (clonidine and dexmedetomidine are currently available in the UK) inhibit the sympathetic nerve outflow, reduce peripheral noradrenaline release and dilate post stenotic coronary arteries.

Early data suggested a potential benefit however, a meta-analysis of 20 studies of dexmedetomidine use compared with placebo or usual treatment in patients undergoing non-cardiac surgery (n=840) found no significant improvement in all-cause mortality, non-fatal MI or myocardial ischaemia with dexmedetomidine, but found significant increases in perioperative hypotension and bradycardia. The authors highlight methodological concerns about the included studies that may limit the usefulness of the findings.

More recently, a large RCT (n=10,010) of perioperative clonidine use in patients undergoing non-cardiac surgery (6% were undergoing vascular surgery), 23% of whom had a history of CAD, showed no significant effect of clonidine on the primary composite outcome of death or non-fatal myocardial infarction but found a significant increase in clinically important hypotension (47.6% clonidine v 37.1% placebo; HR 1.32, 95% CI 1.24 to 1.40) and non-fatal cardiac arrest (0.3% v 0.1%, HR 3.2, 95% CI 1.17 to 8.73) with clonidine.

**Alpha-2 adrenergic receptor agonists are not recommended for perioperative risk reduction in patients undergoing non-cardiac surgery.**

### 6.3.3 CALCIUM CHANNEL BLOCKERS

There is some evidence that CCBs may reduce the cardiac risk of non-cardiac surgery. The evidence base is weak, consisting of small, often unblinded studies. One meta-analysis included 11 studies of 1,007 patients in which diltiazem, verapamil or nifedipine were assessed in patients undergoing major non-cardiac surgery. Calcium channel blockers reduced by half perioperative ischaemia (RR 0.49, 95% CI 0.30 to 0.80) and supraventricular tachyarrhythmia (RR 0.52, 95% CI 0.37 to 0.72). There was no effect on heart failure. Trends toward a reduction in MI (RR 0.25, CI 0.05 to 1.18) and mortality (RR 0.4, 95% CI 0.14 to 1.16) were seen. Post hoc analyses showed a significant reduction in death and MI (RR 0.35, 95% CI 0.15 to 0.86). The majority of these effects were attributable to diltiazem. Further large well-designed studies are required to confirm any benefit. There are no comparative studies with other drugs.

A meta-analysis of RCTs for the prevention of cardiovascular complications of non-cardiac surgery found no benefit for the use of perioperative CCB on cardiac death.
6.3.4 ANTIPLATELET THERAPY

Aspirin has both antiplatelet and anti-inflammatory effects and is known to reduce mortality in patients with unstable angina and after MI and stroke. Most patients with stable angina will be prescribed low-dose aspirin therapy for secondary cardiovascular prevention (see section 4.3.1).

In five RCTs, preoperative administration of aspirin resulted in increased blood loss, blood transfusion and reoperation after cardiac surgery.\(^{231-235}\)

One large RCT (n=10,010) of perioperative aspirin use in patients undergoing non-cardiac surgery, around a third of whom had a history of coronary artery disease, showed no significant effect of aspirin on the primary composite outcome of death or non-fatal myocardial infarction but found a small increased risk of major bleeding (4.6% aspirin v 3.8% placebo; HR 1.23, 95% CI 1.01 to 1.49).\(^{236}\) There was no difference in outcome between patients who were already taking aspirin prior to the study and those in whom aspirin was initiated prior to surgery. In the former group, existing aspirin use was stopped at least three days before surgery and then recommenced prior to surgery and continued for seven days after surgery. In the latter group, aspirin was begun just before surgery and continued for 30 days after surgery. Similarly, there was no difference in outcome between patients with known stable CAD and those without.

Consistent with this RCT, a recent meta-analysis including both randomised and observational studies (n=46 studies; 11,592 patients) reported an increased risk of transfusion during the perioperative period with aspirin alone (RR 1.14, 1.03 to 1.26) as well as dual antiplatelet therapy (RR 1.33, 1.15 to 1.55) but no differences in rates of reintervention for bleeding.\(^{237}\) Perioperative antiplatelet use had no effect on mortality or ischaemic outcomes (MI and stroke).

There is evidence that low-dose aspirin reduces the risk of stroke associated with carotid endarterectomy and should be continued preoperatively.\(^{238}\) The American Association of Colleges of Pharmacy recommends aspirin in patients receiving prosthetic femoropopliteal grafts with therapy starting preoperatively.\(^{239}\)

The routine use of aspirin to reduce perioperative cardiac events in patients undergoing non-cardiac surgery, including those with known stable CAD, is not recommended.

Perioperative aspirin should be only continued in patients at high thrombotic risk, for example in patients with a recent acute coronary syndrome, coronary artery stents or an ischaemic stroke.

Where aspirin is to be discontinued this should be performed at least three days prior to non-cardiac surgery.

6.3.5 STATINS

In the operative setting statins may influence plaque instability and rupture and subsequent thrombosis and coronary artery occlusion.

One RCT of 100 patients undergoing vascular surgery showed that 20 mg of simvastatin administered daily for 45 days reduced the incidence of cardiac events (RR 0.31, ARR 18%).\(^{240}\) A further RCT of 497 patients undergoing vascular surgery showed that 80 mg of fluvastatin was associated with a reduction in postoperative myocardial ischaemia compared with placebo (10.8% v 19% in the fluvastatin and placebo groups, respectively; HR 0.55, 95% CI 0.34 to 0.88).\(^{241}\) Observational studies have shown associations between statin use and reduced cardiac events after non-cardiac surgery.\(^{242, 243}\)

Early concerns about the use and safety of statins during hospitalisation for major surgery have not been confirmed.\(^{244}\) In a study of 981 patients undergoing non-cardiac surgery, perioperative statin use was not associated with an increased risk of myopathy (ie creatine phosphokinase elevation with or without muscle complaints after major vascular surgery).\(^{245}\)
Long-term statin therapy is recommended for all patients with stable angina due to atherosclerotic disease (see section 4.3.2) and this should be continued in patients undergoing non-cardiac surgery. Patients with stable angina who are not on statin therapy and who are undergoing major non-cardiac vascular surgery should be considered for long term statin therapy prior to undergoing surgery.98 Evidence from two small RCTs examining reloading with atorvastatin or rosuvastatin in patients with stable CAD undergoing non-cardiac emergency surgery reported improvement in some cardiac outcomes although there is insufficient evidence on which to base a recommendation.246, 247

R Patients presenting for non-cardiac surgery who are already on statin therapy should have the statin continued through the perioperative period.
Psychological health

The impact of a diagnosis of CAD on psychological well-being has been well documented and people with stable angina may experience similar difficulties to patients with other types of CAD, including depression, anxiety and impaired quality of life. Research has tended to focus on patients with CAD as a whole, rather than on specific groups, and a review of issues relating to psychological health, including models of care, therapies and interventions, in patients with CAD is included in SIGN guideline 150 on cardiac rehabilitation.189

Evidence specific to patients with stable angina is more limited but includes the effect of stable angina on psychological health (see section 7.1), the use of psychological therapies to reduce angina symptoms (see section 7.2) and the effect of health beliefs on symptoms (see section 7.3).

7.1 HOW DOES ANGINA AFFECT QUALITY OF LIFE?

The impact of angina on psychological health and function can be measured by assessing mood and quality of life (QoL) using validated measures such as the Hospital Anxiety and Depression Scale. The evidence reviewed indicates a considerable impact of angina on QoL status. Depression was associated with poorer function.248-252

Two large Scandinavian surveys of quality of life using the questionnaires SF-36 and Swed-Qual found that patients with mild and moderate angina have significantly lower quality of life ratings compared with the general population and those with diabetes, epilepsy, and asthma.248, 253 The same study group also demonstrated reduced and impaired sexual functioning in angina patients compared with normal population.254

Two studies of patients with angina who were awaiting revascularisation found limitations in quality of life compared with the general Swedish population on all domains of Swed-Qual, and SF-36. Persistence of angina after intervention (four year follow up) was associated with reduced QoL.255, 256 A large-scale well-conducted study of 1,025 patients with CAD and angina, looked at the association between depression, physical limitations and QoL over a three-month period. Twenty eight per cent of patients were depressed, which was significantly associated with poorer scores on the Seattle Angina Questionnaire (p<0.001). At three-month follow up, depression was associated with deterioration of functional status.248

A small, well-conducted study based in Scotland followed up patients from a chest pain service for six months. Standardised measures demonstrated the presence of significant symptoms of angina (58%) and breathlessness, (72%), with more than half affected by tiredness, mobility problems and a restricted social and domestic life. More than 75% of patients had anxiety and depression above the normal range, with risk factors poorly controlled.9

R Patients with angina should be assessed by appropriately trained staff for the impact of angina on mood, quality of life and function, to monitor progress and inform treatment decisions.

✓ Mood, quality of life and function in patients with angina can be assessed using validated measures such as:
  - Short-Form Survey (SF-36)
  - Hospital Anxiety and Depression Scale (generic),
  - The Dartmouth Primary Care Co-operative Information Project Functional Health Assessment Chart
  - Seattle Angina Questionnaire – UK version
  - Cardiovascular Limitations and Symptoms profile (CAD specific)
  - Patient Health Questionnaire (PHQ-9)
  - Generalised Anxiety Disorder Assessment (GAD-7)
In primary care, assessment for depression in patients with CAD should be undertaken using validated screening instruments. For example, the NICE guideline for depression in adults with a chronic physical health problem recommends that a ‘yes answer’ to at least one of the following two screening questions can help to determine if further exploration or onward referral is warranted.257

“During the last month, have you often been bothered by feeling down, depressed or hopeless?”

“During the last month, have you often been bothered by having little interest or pleasure in doing things?”

7.2 IMPROVING SYMPTOM CONTROL WITH BEHAVIOURAL INTERVENTIONS

In patients with refractory angina and continuing anginal symptoms despite optimal medical management, and in whom revascularisation or further revascularisation is not an option, behavioral interventions offer an alternative, non-invasive, approach to symptom management.

7.2.1 SELF-MANAGEMENT INTERVENTIONS AND APPROACHES BASED ON COGNITIVE BEHAVIOUR THERAPY

An audit of the effectiveness of a psychological intervention including cognitive behavioral elements (Angina Management Programme) in reducing angina symptoms in people with chronic refractory angina (n=135) reported significant improvements in angina frequency and duration and reduced GTN use, but no change in angina severity. Compared with the two years prior to the intervention, in the two years following the intervention, the mean number of admissions fell from 1.6 to 0.5, the number of outpatient appointments fell from 0.5 to 0.3 and return outpatient appointments from 1.9 to 1.3. All participants showed reductions in resource use.258 The intervention involved nine three-hour per week sessions delivered jointly by a clinical psychologist trained in CBT and a physiotherapist.

A meta-analysis of nine RCTs (n=1,282, range 29–452) looking at the effectiveness of self-management interventions (typically including a range of cognitive, behavioural, stress management, and relaxation techniques) on angina symptoms, health-related quality of life (HRQL) and psychological well-being in patients with stable angina reported mixed results.259 For angina symptoms, seven trials reported reductions in angina frequency (standardised mean difference, SMD, 0.30, 95% CI 0.14 to 0.47) and two reported reductions in use of sublingual nitrates (SMD -0.49, 95% CI -0.77 to -0.20). There was no effect on angina stability (three trials). Physical limitation was reduced in four trials (SMD 0.38, 95% CI 0.20 to 0.55) and depression in three trials (SMD -1.38, 95% CI -2.46 to -0.30). It is unclear what aspects of the interventions were beneficial as there was a wide variation between trials, in terms of content, how they were delivered (eg to individuals or groups), duration, and who delivered the intervention.

An RCT evaluating the use of the Angina Plan (patient held workbook and relaxation programme) delivered by a nurse in primary care to patients who had begun treatment for angina within the preceding 12 months, showed a significant reduction in the mean number of self-reported angina attacks and physical limitation with reduction in anxiety (p<0.05) and depression.260

In a systematic review of 27 trials of relaxation therapy (24 of them randomised) for rehabilitation and secondary prevention of further cardiovascular events in patients with IHD, three studies in patients with angina reported reduced frequency of resting angina (-0.34, 95% CI -0.53 to -0.15).261 Two of the studies were very small (n= 29 and 58), with an intermediate risk of bias, and none were recent (1994, 1996, and 1998).

Further information can be found in SIGN guideline 150 on cardiac rehabilitation.189

Any psychoeducational treatments which are shown to reduce distress should be considered alongside conventional surgical and medical therapy.

Further research is needed to identify the key components of an effective intervention and to determine the optimum duration and characteristics of successful interventions, for example by comparing the relative efficacy of cognitive, behavioural and relaxation components.
7.2.2 OTHER APPROACHES

Psychological distress can bring on angina symptoms but no evidence was found that antidepressants prescribed to stabilise mood are effective in the treatment of angina symptoms. A systematic review of 16 RCTs in patients with CAD and depression including eight RCTs looking at pharmacological management, three of which considered the effect of antidepressants on recurrent angina pectoris, showed no reduction in recurrent angina with sertraline, mirtazepine or citalopram.262

7.3 THE EFFECT OF HEALTH BELIEFS ON SYMPTOMS AND FUNCTIONAL STATUS

Individuals’ beliefs about their condition are derived from many sources in addition to medical ones (eg, family, cultural group, media).263-265 Information from healthcare professionals may be adapted to fit existing beliefs or ignored, thereby influencing behaviour.266 Peers, including partners, have greater misconceptions than patients, which may reinforce the network of misconceptions held by patients with angina.264

Causal attributions in patients with angina appear similar to those in patients with MI. In two qualitative studies, most patients thought stress was the cause of their angina, women were more likely than men to attribute angina to stress or uncontrollable causes than to their own previous behaviour, and many do not cite risk factors they are known to have. Such beliefs were also likely to lead to avoidance of activity.267, 268

The York Angina Beliefs questionnaire is a reliable and valid tool to measure misconceptions and beliefs in angina patients, which may lead to disability, anxiety and avoidance of activity.265
8 Provision of information

This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by health professionals when discussing stable angina with patients and carers and in guiding the production of locally-produced information materials.

8.1 INFORMATION AND EDUCATION ABOUT SURGERY AND OTHER INTERVENTIONS

Preparing patients for surgery by provision of information and addressing concerns, reduces distress, length of stay and the need for analgesia.269

The educational interventions described in the evidence were not standard or delivered at the same point in time in relation to interventions. Outcomes also varied between studies.

One RCT providing educational intervention for patients with angina awaiting angiography showed no effect on measures of anxiety or well-being after the procedure.270 One observational study showed the waiting period prior to elective catheterisation is associated with a negative impact on patients' anxiety, and reduction in functioning and quality of life.271

Two RCTs provided differing educational-type interventions prior to CABG, a (pain management booklet, and an educational session early in the long wait for CABG). There was no effect on pain scores, pain-related interference with activities or on postoperative analgesia in the first study, nor on anxiety, depression, pain score, general well-being and length of stay. Patients in both studies received other educational input as part of standard care. All patients received inadequate analgesia, women had higher pain scores and longer length of stay.272, 273

One RCT of a protocol-delivered telephone educational intervention after CABG did not show any effect on the level of anxiety of the patient or partner at eight weeks.274

Motivational interviewing is a structured approach to helping people change behaviour, using patient-centred but directed strategies (see SIGN guideline number 149 on risk estimation and the prevention of cardiovascular disease and SIGN guideline 150 on cardiac rehabilitation).18, 189

One RCT delivering education using a motivational interviewing approach by a specialist cardiac nurse, shared with community nurses and the support of medical practitioners, was shown to provide effective reduction in risk factors, anxiety and depression and improved perception of general health status during the period of wait prior to CABG. The health of patients not assigned to the treatment intervention deteriorated as assessed by outcome measures.275

One RCT provided audio-taped information on strategies to deal with expected physical sensations and their management following CABG. This tape was listened to in the ward on the fourth or fifth postoperative day and was taken home by the patient. This study found benefit in terms of physical functioning in women and psychological distress, vigour and fatigue in men compared to usual care.276

Educational programmes delivered pre- and postcoronary artery bypass grafting should consider the use of strategies based on psychological principles to improve management of risk factors, psychological distress and physical functioning.

Patients newly diagnosed with angina and those who are immediately pre- and postinterventions and revascularisation, should be given appropriate information to help them understand their condition and how to manage it, and any procedure being undertaken.

Health beliefs and misconceptions should be addressed when delivering information.
8.2 CARDIAC WAITING TIMES

Long waiting times for coronary artery bypass grafting have been shown to have an adverse effect on physical and social functioning before and after surgery with an increase in postoperative adverse effects. In a cohort study of 360 Dutch patients, the median waiting time for patients placed on the elective surgical waiting list (186 patients) was 100 days. The primary outcome measures of death, myocardial infarction or unstable angina requiring hospital admission occurred in around 5% of this group of patients. The majority of events occurred within 30 days of being listed for surgery.277

One RCT of 228 patients, which measured a variety of health-related quality of life parameters revealed that a waiting period prior to elective cardiac catheterisation has a negative impact on patients' anxiety, with reduction in functioning and quality of life.270

In an American cohort patients waiting for coronary angiography were followed up for an average of eight months following the procedure and significant adverse events were classified. Compared with the event-free group, patients with adverse events more frequently had a history of known CAD (55% v 35%; p=0.03), CCS angina class III or IVa (42% v 22%; p=0.01), and positive stress test results (69% v 46%; p=0.001).278

Adverse effects in terms of morbidity and mortality occurring in patients waiting for investigative or revascularisation procedures may be preventable if waiting times are minimised.

In 2011 the waiting time target for GP consultation to treatment was 18 weeks, replacing the four cardiac targets.279 In parallel to this, the Scottish Government set a national target that patients with heart disease should wait no longer than 16 weeks for treatment from the time they are referred to a rapid access chest pain clinic, or after they have been seen in an outpatient clinic by a heart specialist who has recommended treatment.279

R Early access to angiography and coronary artery bypass surgery may reduce the risk of adverse cardiac events and impaired quality of life.

8.3 FOLLOW UP IN PATIENTS WITH ANGINA

Patients presenting with angina to their general practitioners have often been managed without appropriate assessment and referral for possible intervention.280

A meta-analysis of programmes to prevent secondary cardiac events (secondary prevention programmes) with or without an exercise programme indicated that such programmes can have a positive effect on the process of care, quality of life as well as reducing reinfarction and mortality rates.281

Multidisciplinary disease management programmes for patients with CAD have been shown in a systematic review to have a beneficial impact on the uptake of secondary prevention drugs and addressing risk-factor profiles.282 Three trials address follow up in patients with angina.

In the Southampton Heart Integrated Care Project trial, a cardiac liaison nurse co-ordinated care, with general practitioners, for patients discharged from hospital with newly diagnosed angina.283 Although this approach encouraged follow up it did not improve objective measures of risk except in relation to blood pressure in the patients with angina (p<0.05).

Health promotion provided by health visitors in Belfast to patients with angina showed improved physical activity and diet with less anginal symptoms and social isolation after two years. At follow up, five years after recruitment, and three years after the end of the intervention, most of the benefits were lost. Benefits in respect of exercise and adherence to prophylactic drugs, although less, were still evident (p<0.001 to p<0.05 for both categories).284 This would suggest that to be effective health promotion advice needs to be provided on a long-term basis.
In the third trial, patients with a diagnosis of CAD were recruited to Grampian nurse-led secondary prevention clinics versus routine care with the aim of promoting lifestyle change and secondary prevention. After attending the clinics for one year there was an improvement in the quality of life of patients and secondary prevention components except smoking. Except for exercise, these improvements were sustained after four years. There were also fewer total deaths and coronary events in those attending the clinics.285 After adjusting for age, sex and baseline secondary prevention, the proportional hazard ratios were 0.75 for all deaths (95% CI 0.58 to 0.98) and 0.76 for coronary events (95% CI 0.58 to 1.00).

Two further studies consisting of nurse or GP follow up with audit feedback286 and postal prompts287 did not lead to significant benefits in secondary prevention. Provision of the Angina Plan to patients with angina did lead to a significant improvement in reported diet and daily walking.260

Patients presenting with angina and with a diagnosis of coronary heart disease should receive long-term structured follow up in primary care.

8.4 INFORMATION NEEDS OF PATIENTS

8.4.1 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. In developing the checklist, consideration was given to what patients and carers valued. The checklist is neither exhaustive nor exclusive.

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey.

<table>
<thead>
<tr>
<th>Initial presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Offer a reassuring approach to the patients and their families/carers who may be worried or anxious and answer any questions they may have.</td>
</tr>
<tr>
<td>• Explain to the patient it is often difficult to distinguish between indigestion and angina, until all tests are completed a definite diagnosis cannot be made.</td>
</tr>
<tr>
<td>• Listen carefully to the needs and priorities of patients and their families.</td>
</tr>
<tr>
<td>• Explain the need to carry out tests to provide a diagnosis and answer any questions patients and their families have.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Assessment and investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ensure patients are kept informed about which tests will be performed, when they are likely to be carried out and what the results mean.</td>
</tr>
<tr>
<td>• Explain that symptoms of angina are often brought on by physical activity, emotional upset, cold weather or after a meal.</td>
</tr>
<tr>
<td>• Advise patients of the need to check existing medication and ensure they understand the possible side effects.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Provide time to explain the diagnosis. The patient should be reassured and given clear advice on when to seek help in the future.</td>
</tr>
<tr>
<td>• Address any anxieties/worries patients and their families may have and allow time for them to ask questions.</td>
</tr>
<tr>
<td>• Explain to patients how to distinguish between angina and a heart attack and advise them to call 999 if they suspect they are having a heart attack.</td>
</tr>
<tr>
<td>• Give written information to patients and their families, for example, BHF or CHSS patient information booklets or SIGN patient information.</td>
</tr>
</tbody>
</table>
### Treatment

- Explain different types of treatment including the risks and benefits of recommended medications and treatment and provide written information as appropriate.
- Encourage patients and their families to discuss their questions and concerns.
- Ensure consistent and appropriate information is given to patients and carers.

### Follow up

- Explain to patients that referral to a cardiac rehabilitation programme will be arranged and what this means.
- Inform patients of the importance of an annual health check.
- Offer advice to patients on ways to improve their lifestyle to prevent their angina from getting worse.
- Ensure patients and their families have all the relevant information about angina.
- Emphasise the importance of carrying their GTN spray/tablets at all times.

### 8.5 PUBLICATIONS FROM SIGN

SIGN patient versions of guidelines are documents that ‘translate’ guideline recommendations and their rationales, originally developed for healthcare professionals, into a form that is more easily understood and used by patients and the public. They are intended to:

- help patients and carers understand what the latest evidence supports around diagnosis, treatment and self care
- empower patients to participate fully in decisions around management of their condition in discussion with healthcare professionals
- highlight for patients where there are areas of uncertainty.

Cardiac rehabilitation: a booklet for patients, their families and carers. SIGN (2017)

http://www.sign.ac.uk/pat150-cardiac-rehab.html

Chronic heart failure: a booklet for patients, their families and carers. SIGN (2016)

http://www.sign.ac.uk/pat147-chronic-heart-failure.html

### 8.6 SOURCES OF FURTHER INFORMATION

**British Cardiac Patients Association**

BCPA Head Office, 15 Abbey Road, Bingham, Nottingham, NG13 8EE

Tel: 01949 837 070

www.bcpa.eu | E-mail: Admin@BPCA.eu

The British Cardiac Patients Association is a charitable organisation run by volunteers providing support, advice and information to cardiac patients and their carers.

**British Heart Foundation (Scotland)**

43a Leith Street, Edinburgh, EH1 3AT

Tel: 0131 555 5891

Heart Information line: 08450 70 80 70 (available Mon-Fri 9am-5pm)

www.bhf.org.uk | E-mail: scotland@bhf.org.uk

The British Heart Foundation provides a free telephone information service for those seeking information on heart health issues. It also provides a range of written materials offering advice and information to CAD patients and carers. Topics include physical activity, smoking and diabetes.
Chest Heart and Stroke Scotland
3rd Floor, Rosebery House, 9 Haymarket Terrace, Edinburgh, EH12 5EZ
Tel: 0131 225 6963
Advice line: 0808 801 0899 (available Mon-Fri 9.30am-4pm)
www.chss.org.uk | E-mail: webmaster@chss.org.uk

Chest Heart and Stroke Scotland provides an advice line offering confidential, independent advice on all aspects of chest, heart and stroke illness. A series of information booklets, factsheets and videos is available free of charge to patients and carers. There are over 30 cardiac support groups in Scotland which are affiliated to CHSS. Patients can contact CHSS for details of their nearest local support group.

Depression Alliance Scotland
11 Alva Street, Edinburgh, EH2 4PH
Tel: 0845 123 23 20 or 0131 467 3050 (available 10am-2pm Mon, Tues, Thurs, Fri)
www.dascot.org | Email: info@dascot.org

Depression Alliance Scotland provides information and support for people in Scotland who have depression.

NHS 24
Tel: 111
www.nhs24.com

NHS 24 is a nurse-led service for members of the public. It is a helpline offering health information, advice and help over the phone.

NHS Inform
Tel: 0800 22 44 88
www.nhsinform.scot

This is the national health and care information service for Scotland. It includes a section on heart conditions with information and links to resources to support patients with heart disease:

www.nhsinform.scot/illnesses-and-conditions/heart-and-blood-vessels

There is also a section providing advice on healthy living for physical and mental wellbeing:

www.nhsinform.scot/healthy-living
9 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

9.1 IMPLEMENTATION STRATEGY

Implementation of national clinical guidelines is the responsibility of each NHS board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

Implementation of this guideline will be encouraged and supported by SIGN. The implementation strategy for this guideline encompasses the following tools and activities.

9.2 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

The NICE guideline on chest pain of recent onset summarised the evidence for the accuracy, clinical utility and cost effectiveness of non-invasive diagnostic tests, invasive diagnostic tests and calcium scoring in patients with stable chest pain of suspected cardiac origin. The GDG considered four previous economic evaluations and a de novo cost-effectiveness analysis of the comparative cost per correct diagnosis and concluded that CT-coronary angiography as a routine investigation for patients with suspected angina was cost effective and so recommended offering 64-slice (or above) CT coronary-angiography if clinical assessment indicates typical or atypical angina, or clinical assessment indicates non-anginal chest pain but 12-lead resting ECG has been done and indicates ST-T changes or Q waves.

The financial implications of implementing a recommendation to consider CT-coronary angiography for the investigation of patients with chest pain in whom the diagnosis of stable angina is suspected, but not clear from history alone, in Scotland are currently unclear, but we will work with NHS boards to clarify this and assist them in planning for implementation. Although the majority of boards already support a CT-coronary angiography service, additional resources would likely be required, although a number of CT scanners are coming to the end of their life and could be replaced with new machines with the technological capabilities to provide the service, which could mitigate some of the potential cost impact.

9.3 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

The guideline development group has identified the following as key points to audit to assist with the implementation of this guideline:

- The number of patients in Scotland with a diagnosis of stable angina.
- The proportion of patients with a diagnosis of stable angina managed within specialist cardiology services.
- The proportion of patients with a diagnosis of stable angina receiving treatment with an oral antiplatelet agent, statin, beta blocker, ACE inhibitor.
9.4 HEALTH TECHNOLOGY ASSESSMENT ADVICE FOR NHSSCOTLAND

On 9 February 2007, the Scottish Medicines Consortium (SMC) advised that:

ivabradine (Procoralan®) is accepted for restricted use within NHS Scotland for the symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm for whom heart rate control is desirable and who have a contra-indication or intolerance for beta-blockers and rate-limiting calcium-channel blockers. (SMC 319/06)

Indication under review: symptomatic treatment of chronic stable angina pectoris in adults with CAD and normal sinus rhythm, in combination with beta blockers, in patients inadequately controlled with an optimal beta blocker dose and whose heart rate is >60 beats per minute.

The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHS Scotland. (SMC 689/11)

On 12 November 2012, the Scottish Medicines Consortium (SMC) advised that, following an Independent Review Panel Assessment:

ranolazine (Ranexa®) is not recommended for use within NHS Scotland.

Indication under review: as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies (such as beta blockers and/or calcium antagonists).

The submitting company did not present a sufficiently robust clinical and economic case to gain acceptance by the Independent Review Panel (IRP). (SMC 565/09)
10 The evidence base

10.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2005–2015. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.

The search strategies are available on the SIGN website, www.sign.ac.uk

10.1.1 LITERATURE SEARCH FOR PATIENT ISSUES

At the start of the guideline development process, a SIGN Evidence and Information Scientist conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to stable angina. Databases searched include Medline, Embase, Cinahl and PsycINFO, and the results were summarised by the SIGN Patient Involvement Advisor and presented to the guideline development group.

10.1.2 LITERATURE SEARCH FOR COST-EFFECTIVENESS EVIDENCE

The guideline development group identified key questions with potential cost-effectiveness implications, based on the following criteria, where it was judged particularly important to gain an understanding of the additional costs and benefits of different treatment strategies:

- treatments which may have a significant resource impact
- opportunities for significant disinvestment or resource release
- the potential need for significant service redesign
- cost-effectiveness evidence could aid implementation of a recommendation.

A systematic literature search for economic evidence for these questions was carried out by a SIGN Evidence and Information Scientist covering the years 2009–2015. Databases searched include Medline, Embase, NHS Economic Evaluation Database (NHS EED). Each of the selected papers was evaluated by a Health Economist, and considered for clinical relevance by guideline group members.

Interventions are considered to be cost effective if they fall below the commonly-accepted UK threshold of £20,000 per Quality-Adjusted Life Year (QALY).

10.2 RECOMMENDATIONS FOR RESEARCH

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline (see Annex 1). The following areas for further research have been identified:

- How effective are beta blockers in the management of patients with stable angina undergoing non-cardiac surgery?
- How effective is statin reload in patients with stable angina undergoing non-cardiac surgery?
- How effective are antiplatelets in the management of patients with stable angina undergoing non-cardiac surgery and what is the optimum antiplatelet regimen in different patient groups?
• In patients with stable angina who are taking warfarin and are scheduled to undergo PCI with DES, should the warfarin be stopped, be combined with DAPT or be used as an alternative to aspirin or clopidogrel?

• What aspects of psychological therapy (for example cognitive, behavioural and relaxation components) are effective in relieving symptoms in patients with stable angina and what is the optimal duration of treatment?

• Is interpersonal therapy delivered by therapists with formal training in this therapy more effective than clinical management in relieving symptoms in patients with stable angina?

• Do psychological interventions reduce levels of distress, cardiac events or cardiac mortality in patients with stable angina in the long term? Which patient groups benefit most from such interventions (age, sex, ethnicity, deprivation, education, comorbidities)?

• Which types of relaxation therapy provide most benefit to patients with stable angina and can shorter courses (<9 hours) be designed that deliver equivalent psychological and physical benefits as longer courses?

• What self-management interventions are effective at improving outcomes in patients with stable angina?

• Which aspects of stress-management interventions are effective at improving outcomes in patients with stable angina?

• What strategies are effective, in primary and secondary care, at improving medication adherence in patients with stable angina?

• What are the implications and cost effectiveness of CT-CA in investigation of patients with stable angina?

• What is the benefit (if any) of screening for depression/mood disorders in patients with stable angina versus those who are not screened?

10.3 REVIEW AND UPDATING

This guideline was issued in 2018 and will be considered for review in three years. The review history, and any updates to the guideline in the interim period, will be noted in the review report, which is available in the supporting material section for this guideline on the SIGN website: www.sign.ac.uk

Comments on new evidence that would update this guideline are welcome and should be sent to the SIGN Executive, Gyle Square, 1 South Gyle Crescent, Edinburgh, EH12 9EB (email: sign@sign.ac.uk).
11 Development of the guideline

11.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising healthcare professionals using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in ‘SIGN 50: A Guideline Developer’s Handbook’, available at www.sign.ac.uk

This guideline was developed according to the 2015 edition of SIGN 50.

11.2 THE GUIDELINE DEVELOPMENT GROUP

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Dr John Stout  General Practitioner, Peterhead
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The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest. A register of interests is available in the supporting material section for this guideline at www.sign.ac.uk
Guideline development and literature review expertise, support and facilitation were provided by SIGN Executive and Healthcare Improvement Scotland staff. All members of the SIGN Executive make yearly declarations of interest. A register of interests is available on the contacts page of the SIGN website www.sign.ac.uk

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Karen Graham Patient Involvement Advisor
Jenny Harbour Evidence and Information Scientist, Healthcare Improvement Scotland
Nicola Nelson Distribution and Office Co-ordinator
Stuart Neville Publications Designer
Domenico Romano Publications Designer
Gaynor Rattray Guideline Co-ordinator

11.2.1 ACKNOWLEDGEMENTS

SIGN would like to acknowledge the guideline development group responsible for the development of SIGN 96: Management of stable angina, on which this guideline is based.

SIGN would also like to acknowledge the following individuals who contributed during the early stages of guideline development.

Mr Stephen Heller-Murphy Programme Manager, SIGN
Mr Robert Jeffrey Consultant Cardiothoracic Surgeon, retired
Mrs Margaret Moncrieff Lay representative, South Lanarkshire

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11.4 CONSULTATION AND PEER REVIEW

11.4.1 PUBLIC CONSULTATION
The draft guideline was available on the SIGN website for three weeks to allow all interested parties to comment. All contributors made declarations of interest and further details of these are available on request from the SIGN Executive.

11.4.2 SPECIALIST REVIEW
This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments. All expert referees made declarations of interest and further details of these are available on request from the SIGN Executive. SIGN is very grateful to all of these experts for their contribution to the guideline.

11.4.3 SIGN EDITORIAL GROUP
As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers’ comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows. All members of SIGN Council make yearly declarations of interest. A register of interests is available on the SIGN Council Membership page of the SIGN website www.sign.ac.uk

Dr Roberta James SIGN Programme Lead; Co-Editor
Professor John Kinsella Chair of SIGN; Co-Editor
Dr Jenny Bennison Vice Chair; SIGN and Royal College of General Practitioners
Mr Andrew de Beaux Royal College of Surgeons, Edinburgh
Dr David Stephens Royal College of General Practitioners
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACC</td>
<td>American College of Cardiology</td>
</tr>
<tr>
<td>ACE</td>
<td>angiotensin converting enzyme</td>
</tr>
<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
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<tr>
<td>AMI</td>
<td>acute myocardial infarction</td>
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<tr>
<td>ARR</td>
<td>absolute risk reduction</td>
</tr>
<tr>
<td>BMS</td>
<td>bare-metal stent</td>
</tr>
<tr>
<td>BNF</td>
<td>British National Formulary</td>
</tr>
<tr>
<td>CABG</td>
<td>coronary artery bypass grafting</td>
</tr>
<tr>
<td>CARDia</td>
<td>Coronary Artery Risk Development in young adults</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>CBT</td>
<td>cognitive behaviour therapy</td>
</tr>
<tr>
<td>CCB</td>
<td>calcium channel blocker</td>
</tr>
<tr>
<td>CCS</td>
<td>Canadian Cardiovascular Society</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CKD</td>
<td>chronic kidney disease</td>
</tr>
<tr>
<td>CORONARY</td>
<td>CABG off or on-pump revascularisation study</td>
</tr>
<tr>
<td>CMR</td>
<td>cardiac magnetic resonance imaging</td>
</tr>
<tr>
<td>CPET</td>
<td>cardiopulmonary exercise testing</td>
</tr>
<tr>
<td>CT-CA</td>
<td>CT-coronary angiography</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
</tr>
<tr>
<td>DAPT</td>
<td>dual antiplatelet therapy</td>
</tr>
<tr>
<td>DES</td>
<td>drug-eluting stent</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>EECP</td>
<td>enhanced external counterpulsation</td>
</tr>
<tr>
<td>eGFR</td>
<td>glomerular filtration rate</td>
</tr>
<tr>
<td>ESA</td>
<td>European Society of Anaesthesiology</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>ETT</td>
<td>exercise tolerance test</td>
</tr>
<tr>
<td>EUROPA</td>
<td>the EURopean trial On reduction of cardiac events with Perindopril in stable CAD trial</td>
</tr>
<tr>
<td>FFR</td>
<td>fractional flow reserve</td>
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</tbody>
</table>
Management of stable angina

GAD-7  Generalised Anxiety Disorder Assessment
GMC  General Medical Council
GP  general practitioner
GTN  glyceryl trinitrate
HOPE  the Heart Outcomes Prevention Evaluation trial
HR  hazard ratio
HRQL  health-related quality of life
I  pacemaker current in the sinoatrial node
IHD  ischaemic heart disease
ISR  in-stent restenosis
IABP  intra-aortic balloon pump
HR  hazard ratio
IMA  internal mammary artery
LAD  left anterior descending
LV  left ventricular
MA  marketing authorisation
MASS II  Medicine, Angioplasty or Surgery Study
MD  mean difference
MET  metabolic equivalent of task
MI  myocardial infarction
MPS  myocardial perfusion scintigraphy
MRI  magnetic resonance imaging
MTA  multiple technology assessment
NICE  National Institute for Health and Care Excellence
NNT  number needed to treat
OR  odds ratio
PEACE  Prevention of Events with Angiotensin Converting Enzyme inhibition trial
PCI  percutaneous coronary intervention
PHQ-9  Patient Health Questionnaire
PTCA  percutaneous transluminal coronary angioplasty
QoL  quality of life
QUIET  the QUinapril Ischemic Event Trial

http://guide.medlive.cn/
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCRI</td>
<td>revised cardiac risk index</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised controlled trial</td>
</tr>
<tr>
<td>ROOBY</td>
<td>Randomised On/Off BY-pass trial</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
<tr>
<td>SIGN</td>
<td>Scottish Intercollegiate Guidelines Network</td>
</tr>
<tr>
<td>SF-36</td>
<td>A 36-item health survey using a set of generic quality of life measures and relying on patient self reporting</td>
</tr>
<tr>
<td>SMC</td>
<td>Scottish Medicines Consortium</td>
</tr>
<tr>
<td>SMD</td>
<td>standardised mean difference</td>
</tr>
<tr>
<td>SPECT</td>
<td>single-proton emission computed tomography</td>
</tr>
<tr>
<td>SYNTAX</td>
<td>SYNergy between PCI with TAXus and cardiac surgery</td>
</tr>
<tr>
<td>SVG</td>
<td>saphenous vein grafts</td>
</tr>
<tr>
<td>TMLR</td>
<td>transmyocardial laser revascularisation</td>
</tr>
<tr>
<td>VO₂ max</td>
<td>maximum oxygen consumption</td>
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</tbody>
</table>
Annex 1

Key questions addressed in this update

This guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search.

<table>
<thead>
<tr>
<th>Guideline section</th>
<th>Key question</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1, 3.2</td>
<td>1. What evidence is there or the clinical and cost effectiveness of the following as diagnostic and/or prognostic tests?</td>
</tr>
<tr>
<td></td>
<td>a. Clinical history, risk factors, physical examination</td>
</tr>
<tr>
<td></td>
<td>b. Resting 12-lead electrocardiogram (ECG)</td>
</tr>
<tr>
<td></td>
<td>c. Cardiac magnetic resonance imaging</td>
</tr>
<tr>
<td></td>
<td>d. Coronary angiography, including CT, coronary angiography, fractional flow reserve (pressure wire assessment) or coronary artery calcium scoring</td>
</tr>
<tr>
<td></td>
<td>e. MPS (including magnetic resonance perfusion imaging)</td>
</tr>
<tr>
<td></td>
<td>f. Echocardiogram/stress echocardiogram</td>
</tr>
<tr>
<td></td>
<td>g. Exercise ECG (stress ECG/ETT)</td>
</tr>
<tr>
<td>3.2</td>
<td>2. What evidence exists for using functional or anatomical tests in addition to risk assessment tools for preoperative assessment for patients with angina undergoing non-cardiac surgery?</td>
</tr>
<tr>
<td></td>
<td>Consider: exercise ECG/ETT/exercise stress test/stress ECG; stress echocardiography/exercise dobutamin, dipyridamole, adenosine-stress echocardiography; stress myocardial perfusion imaging/MPS/exercise thallium MPS; MPS using single photon emission CT (SPECT), stress magnetic resonance imaging/stress perfusion imaging/stress induced motion wall abnormalities; computed tomography CT/CT coronary angiography/multislice CT/coronary artery calcium score; CPET/CPEX cardio pulmonary exercise test.</td>
</tr>
<tr>
<td>4.1, 4.2</td>
<td>3. What is the most clinically and cost-effective medical intervention for the management of adults with a diagnosis of stable angina?</td>
</tr>
<tr>
<td></td>
<td>Consider: nicorandil (potassium channel blocker), ivabradine (If inhibitor), ranolazine, triple therapy, allopurinol.</td>
</tr>
<tr>
<td>4.3.1</td>
<td>4. For patients with stable angina taking warfarin, does adding aspirin give any additional benefit?</td>
</tr>
<tr>
<td>5.5.2</td>
<td>5. What is the optimal duration for antiplatelet therapy following PCI?</td>
</tr>
<tr>
<td>6.3</td>
<td>6. What is the optimum pharmacological/therapeutic management for patients with stable angina going for non-cardiac surgery?</td>
</tr>
<tr>
<td></td>
<td>Consider: beta blockers, statins, antiplatelets (clopidogrel and aspirin), alpha-2 adrenergic agonists (clonidine), calcium channel blockers, goal-directed therapy.</td>
</tr>
<tr>
<td>5.2.1, 5.2.2, 5.3, 5.4</td>
<td>7. What is the most clinically and cost-effective intervention for the alleviation of short-term angina symptoms?</td>
</tr>
<tr>
<td></td>
<td>Consider: PCI, CABG</td>
</tr>
<tr>
<td>5.2.1, 5.2.2, 5.3, 5.4</td>
<td>8. What is the most clinically and cost-effective therapeutic intervention for the long-term improvement in CHD prognosis?</td>
</tr>
<tr>
<td>Section</td>
<td>Question</td>
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<tr>
<td>---------</td>
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</tr>
<tr>
<td>5.2.2</td>
<td>In patients undergoing PCI, what is the clinical and cost effectiveness of DES compared with bare-metal stents?</td>
</tr>
<tr>
<td>5.4</td>
<td>Does a heart team/multidisciplinary team assessment improve outcomes following revascularisation?</td>
</tr>
<tr>
<td>5.3.2, 5.3.3</td>
<td>For patients with stable angina which is the most effective heart bypass surgery technique? Consider: off-pump, multiple arterial grafts (eg mammary and radial, bilateral mammary).</td>
</tr>
<tr>
<td>5.8</td>
<td>What evidence is there for the clinical and cost effectiveness of angina pain relief in patients who do not respond to traditional antianginal treatment? Consider: stellate ganglion block, nerve/neural block/phenol ablation, transcutaneous electric nerve stimulation, spinal cord stimulation (dorsal column stimulator), psychological therapies (eg CBT), temporary or destructive sympathectomy, analgesics (including oral, transdermal, epidural and transthecal opioids), myocardial laser (percutaneous or transmyocardial), EECP, acupuncture, coronary sinus reducer stent.</td>
</tr>
<tr>
<td>7.2</td>
<td>What evidence is there for interventions based on psychological principles for improving symptom control? Consider: psychological therapies (eg CBT), relaxation therapy, pacing of activity, psychological self-management, behavioural interventions, and stress management.</td>
</tr>
<tr>
<td>4.4</td>
<td>What is the effect of intervention on medication adherence?</td>
</tr>
</tbody>
</table>
Annex 2
Management options in patients with suspected angina

Suspected angina (ie where there is diagnostic uncertainty from the history)

CT-coronary angiogram (eg anatomical investigation) to determine the presence of obstructive CAD

No CAD
Discharge
No further cardiac investigations required

Non-obstructive CAD
Commence secondary prevention medication
No further cardiac investigations required
(see sections 4 and 5.5 of full guideline)

Obstructive CAD
Left main-stem or Severe 3-vessel disease

Commence secondary prevention and antianginal medication
(see sections 4 and 5.5 of full guideline)

Ongoing symptoms despite optimal medication?

Invasive coronary angiography* (*taking into consideration renal function, age, comorbidities)

Suitable for revascularisation?

Optimise medical therapy

Ongoing symptoms?

Continue medical treatment

Consider treatments for refractory angina

PCI or CABG

Abbreviations  CT – computerised tomography  CAD – coronary artery disease  PCI – percutaneous coronary intervention  CABG – coronary artery bypass grafting
Annex 3
Management options in patients with a definite diagnosis of stable angina

- **Definite diagnosis of stable angina** (e.g., known obstructive CAD, clear history)
  - Introduce or increase antianginal therapy
  - Review secondary prevention (see sections 4 and 5.5 of full guideline)

- Suitable for risk stratification with functional assessment? (e.g., exercise tolerance test, myocardial perfusion scintigraphy, stress echocardiogram, perfusion CMR imaging)
  - No
  - Yes

  - **Optimise medical therapy**

- **Ongoing symptoms despite optimal medication?**
  - Yes
    - Invasive coronary angiography* (*taking into consideration renal function, age, comorbidities)
  - No

  - **Suitable for revascularisation?**
  - Yes
    - PCI or CABG
  - No
    - **Optimise medical therapy**

- **Continue medical treatment**
- **Consider treatments for refractory angina**

Abbreviations: CAD – coronary artery disease    CMR – cardiac magnetic resonance imaging    PCI – percutaneous coronary intervention    CABG – coronary artery bypass grafting
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References


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171. Li Q, Zhang Z, Yin RX. Drug-eluting stents or coronary artery bypass grafting for unprotected left main coronary artery disease: a meta-analysis of four randomized trials and seventeen observational studies. Trials 2013;14:133.


Management of stable angina


The Healthcare Environment Inspectorate, the Scottish Health Council, the Scottish Health Technologies Group, the Scottish Intercollegiate Guidelines Network (SIGN) and the Scottish Medicines Consortium are key components of our organisation.