FINAL

STABLE ANGINA

METHODS, EVIDENCE & GUIDANCE

Produced by the National Clinical Guidelines Centre

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Glossary and abbreviations

GLOSSARY

<table>
<tr><th>Term</th><th>Description</th></tr>
<tr><td>Acute coronary syndrome</td><td>A condition in which there is an event in a coronary artery with plaque rupture or erosion, or coronary dissection, with the formation of intra-coronary thrombus. A single term which includes both unstable angina and myocardial infarction.</td></tr>
<tr><td>Acute myocardial infarction</td><td>When there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia, any one of the following criteria meets the diagnosis for myocardial infarction in people presenting with acute chest pain or discomfort:

Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:

• Symptoms of ischaemia
• ECG changes indicative of new ischaemia (new ST-T changes or new left bundle branch block (LBBB)
• Development of pathological Q waves in the ECG
• Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

The guideline accepts the definition used in the studies included in the evidence review.</td></tr>
<tr><td>Anatomical tests</td><td>Non – invasive tests that allow visualization of coronary anatomy e.g. CT angiography</td></tr>
<tr><td>Annual risk reduction</td><td>The difference between the percentage annual incidence of an adverse outcome in a treatment group</td></tr>
</table>

	compared with that in a control group.
Beta blockers (BBs)	A class of drugs that block beta-adrenergic substances such as adrenaline (epinephrine) in the "sympathetic" portion of the autonomic (involuntary) nervous system.
Biomarker	An objective measure of an indicator of a normal biologic process, a pathogenic process, or pharmacologic response to a therapeutic intervention.
Calcium channel blockers (CCBs)	Calcium channel blockers are medicines that slow the movement of calcium into the cells of the heart and blood vessels. This, in turn, relaxes blood vessels, increases the supply of oxygen-rich blood to the heart, and reduces the heart's workload.
Canadian Cardiovascular Society (CSS) Functional Classification of Angina	Class I - Ordinary activity (e.g. walking, climbing stairs at own pace) does not bring on angina. Angina occurs only with strenuous, rapid, or prolonged exertion at work or during recreation. Class II - Slight limitation of ordinary activity. Symptoms occur when walking or climbing stairs rapidly, walking up a hill, walking up stairs after a meal, in cold weather, in wind, or when under emotional stress, or only a few hours after waking, and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions. Class III - Marked limitation of ordinary activity. Symptoms occur after walking 50–100 yards on the level, or climbing more than one flight of ordinary stairs in normal conditions. Class IV - Inability to carry on any physical activity without discomfort. Angina may be present at rest.
Cardiac rehabilitation	Cardiac rehabilitation is the process by which people with cardiac disease, in partnership with a multidisciplinary team of health professionals, are encouraged and supported to achieve and maintain optimal physical and psychosocial health. The definition used by the Department of Health is Cardiac rehabilitation is a professionally supervised programme consisting of: • a medical assessment to determine risk factors, patient needs and limitations • a menu-based programme covering six components, namely: lifestyle, risk factor management, cardio-protective drug therapy and implantable devices,

	psychosocial status and quality of life , education and long-term management. (Department of Health 2010)
Cardiac syndrome X	Presence of exertional angina and angiographically normal epicardial arteries/coronary arteries.
Cardiovascular event	An acute coronary, cerebrovascular or peripheral arterial event.
Cardiovascular risk	The risk of a cardiovascular event occurring.
Clinical classification	A method of allocating patients into different groups based on clinical characteristics.
Clinical risk stratification	A method of allocating patients to different levels of risk of them suffering an adverse event, based on their clinical characteristics.
Coronary angiography	An invasive diagnostic test which provides anatomical information about the degree of stenosis (narrowing) in a coronary artery. It involves manipulation of cardiac catheters from an artery in the arm or top of the leg. A contrast medium is injected into the coronary arteries, and the flow of contrast in the artery is monitored by taking a rapid series of X-rays. It is considered the 'gold standard' for providing anatomical information and defining the site and severity of coronary artery lesions (narrowings).
Coronary artery	An artery which supplies the myocardium.
Coronary artery bypass surgery (CABG)	Open-heart surgery in which the rib cage is opened and a section of a blood vessel is grafted to the coronary artery to bypass the blocked section of the coronary artery and improve the blood supply to the heart
Coronary artery disease	Coronary artery disease is a condition in which atheromatous plaque builds up inside the coronary artery. This leads to narrowing of the arteries which may be sufficient to restrict blood flow and cause myocardial ischaemia.
Cost-consequences analysis	A type of economic evaluation where various health outcomes are reported in addition to the costs for each intervention under consideration. There is however no formal synthesis of the costs and health effects.
Cost-effectiveness analysis	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of incremental costs per unit of

	effectiveness.
Cost-utility analysis	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).
Discounting	Discounting is the process by which economists make allowances for society's time preference for costs and benefits. All else being equal, society places a higher value on the same unit of cost and benefit today than it does for the same unit in the future. For example, society prefers to receive £100 today as opposed to £100 in n years time. The differential is expressed in terms of the discount factor DF, where $DF = 1/(1+r)^n$ and where *r* is the discount rate, and *n* is the number of years forward from the current year.
Dominance	A heath intervention is said to be dominant if it is both more effective and less costly than an alternative intervention.
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Equivocal	Where a diagnostic test result is indeterminate because it can be interpreted in one of 2 or more ways.
Evidence statements	A summary of the evidence distilled from a review of the available clinical literature.
Exercise ECG (sometimes known as an exercise test or stress ECG)	An investigation which measures the electrical activity from the heart during exercise, usually used to look for signs of myocardial ischaemia.
Functional tests	Tests which stress the heart to see if evidence of ischaemia can be shown. Stress can be by exercise or by use of pharmacological agents.
Gastrointestinal therapeutic system (GITS)	A novel release system that according to Bayer, the manufacturer, provides 24-hour continuous release through an osmotic push system.
Health economic model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporates evidence from a variety of sources in order to estimate costs and health outcomes.

Health economics	The branch of economics concerned with the allocation of society's scarce health resources, between alternative healthcare treatments/programmes, in an attempt to improve the health of the population.
Health related quality of life	An attempt to summarise an individual's or the population's quality of life resulting from the combined effect of their physical, mental, and social well-being.
Incremental cost-effectiveness ratio (ICER)	The difference in the costs of two alternative treatment strategies/programmes, divided by the difference in the effectiveness outcomes of the treatment strategies/programmes for a defined population of interest. That is: <u>Cost treatment B – Cost treatment A</u> Effectiveness treatment B - Effectiveness treatment B
Intention-to-treat (ITT)	A strategy for analysing data from a randomised controlled trial. All participants are included in the arm to which they were allocated, whether or not they received (or completed) the intervention given to that arm.
Individual patient data (IPD) meta analysis	IPD meta analysis involve the central collection, validation and re-analysis of "raw" data, from all clinical trials that have addressed a common research question; obtained from those responsible for the original trials.
Life years	The number of years lived by an individual or a population. For example, if a population of 50 patients live for an average addition 2 years each as the result of receiving a healthcare intervention, then the intervention has provided 100 life years gained.
Minimal important difference (MID)	The MIDs are the threshold for appreciable benefits and harms.
Myocardial infarction	See Acute Myocardial Infarction.
Myocardial perfusion scintigraphy with SPECT (MPS)	MPS involves injecting small amounts of radioactive tracer to evaluate perfusion of the myocardium via the coronary arteries at stress and at rest. The distribution of the radioactive tracer is imaged using a gamma camera. In SPECT the camera rotates round the patient and the raw data processed to obtain tomographic images of the myocardium. Cardiovascular stress may be induced by either pharmacological agents or exercise.
Opioid	An opioid is a chemical that works by binding to opioid receptors, and has pain killing properties. The term opiate is sometimes used as synonym, but this is natural opium alkaloids occurring in the resin of the opium

	poppy and the semi-synthetic opioids derived from them, and should be restricted to this.
Opportunity cost	The cost in terms of health benefits foregone by allocating resources to one intervention over an alternative intervention. The definition implicitly acknowledges the concept of scarcity of healthcare resources.
Other anti anginal drugs	Nicorandil, ivabradine and ranolazine are the other anti-anginal drugs that are licensed for use in the treatment of stable angina. They are distinguished in this way in the BNF from BBs, CCBs and nitrates.
Percutaneous coronary intervention (PCI).	The management of coronary artery occlusion by any of various catheter-based techniques, such as percutaneous transluminal coronary angioplasty, atherectomy, angioplasty using the excimer laser, and implantation of coronary stents and related devices
Probabilistic sensitivity analysis (PSA)	The process of measuring the degree of uncertainty around outcomes in an economic evaluation by assigning probability distributions to all of the key parameters in the evaluation, and then simultaneously generating values from each of these distributions using techniques of random number generation such as Monte Carlo methods.
Quality-adjusted life-year (QALY)	An index of survival weighted to account for quality of life. The year of life is weighted by a utility value U (where $0 \leq U \leq 1$). U reflects the health related quality of life, such that a U of zero represents the worst possible quality of life (equivalent to being dead), and a U of 1 represents perfect health. For example, 1 QALY is achieved if one patient lives in perfect health for one year, or alternatively if 2 people live in perfect health for 6 months each. Alternatively, a person living with a quality of life represented by a U value of 0.5 for 2 years is also representative of 1 QALY value. QALYs have the advantage of incorporating changes in both quantity (longevity/survival) and quality of life (morbidity as represented by psychological, physical and social functioning for example). QALYs are core to cost-utility analysis where the QALY is used as the measure of effectiveness in the economic evaluation.
Refractory angina	The European Cardiology Society definition of refractory angina is angina that cannot be controlled with optimal medical therapy and where revascularisation is unfeasible.
Rehabilitation	See cardiac rehabiliation
Relative risk reduction	The ratio of the probability of an event occurring in the

	treatment group compared to the control group.
Sensitivity	Sensitivity is the proportion of people with the disease who have a positive test. Sensitivity reflects how good the test is at identifying people with the disease. A measure of the diagnostic accuracy in including individuals with the condition. Number of True Positives divided by (Number of True Positives + Number of False Negatives) True positive: People correctly diagnosed with the condition False positive: Healthy people wrongly diagnosed with the condition True negative: Healthy people correctly identified as healthy False negative: People wrongly identified as healthy
Sensitivity analysis	A means of exploring the uncertainty in the results of an economic evaluation/model by varying the parameter values of the included variables one at a time (univariate sensitivity analysis) or simultaneously (multi-variate sensitivity analysis).
Specialist	A healthcare professional that has expert knowledge of and skills in a particular clinical area, especially one who is certified by a higher medical educational organization.
Specificity	Specificity is the proportion of people free of disease who have a negative test. Specificity reflects how good the test is at identifying people without the disease. A measure of the diagnostic accuracy in excluding individuals without the condition. Number of True Negatives divided by (Number of True Negatives + Number of False Positives) True positive: People correctly diagnosed with the condition False positive: Healthy people wrongly diagnosed with the condition True negative: Healthy people correctly identified as healthy False negative: People wrongly identified as healthy
Stable angina	Angina is a symptom of myocardial ischaemia that is recognized clinically by its character, its location and its relation to provocative stimuli. Angina is stable when

	it is not a new symptom and when there is no deterioration in frequency, severity or duration of episodes.
Stress ECG	See exercise ECG above.
Stress echocardiograph	Echocardiography is an ultrasound examination of the heart. Exercise or pharmacological stress may be used to look for reversible systolic regional wall motion abnormalities consistent with the development of myocardial ischaemia.
Stress magnetic resonance imaging (stress MRI)	MRI is a diagnostic procedure that uses radio waves in a strong magnetic field. The pattern of electromagnetic energy released is detected and analysed by a computer to generate detailed images of the heart. Stress MRI is a specific application in which a contrast agent is used to detect myocardial blood flow at stress and at rest. Pharmacological stress is used to induce cardiovascular stress.
Syndrome X	See cardiac syndrome X
Technology appraisal	Formal ascertainment and review of the evidence surrounding a health technology, which in this publication refers to technology appraisals undertaken by NICE only.
Technology appraisal guidance (TAG)	Technology Appraisal Guidance (see Technology Appraisal)
Unstable angina	New (within 24 hours) onset angina or abrupt deterioration in previously stable angina, often with prolonged episodes of rest pain.
Utility	A variable usually taking a value between zero (death) and unity (perfect health) which reflects health related quality of life, and which is used in the calculation of QALYs.
Willingness to pay (WTP)	The amount of money that an individual or society is willing to pay in order to achieve a specified level of health benefit. For example, it is generally recognised that the current willingness to pay for an incremental QALY gain in the NHS is somewhere between £20,000 and £30,000.

Abbreviations

Abbreviation	Description
2VD	Two-vessel disease
3VD	Three-vessel disease
AC	Attenuation-corrected
ACE inhibitors	Angiotensin-converting enzyme inhibitors
ACER	Average cost-effectiveness ratio
AMI	Acute myocardial infarction
ARB	Angiotensin II receptor blocker
BB	Beta blocker
BMJ	British Medical Journal
BNF	British National Formulary
CA	Coronary angiography
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CAD	Coronary artery disease
CCB	Calcium channel blocker
CCS	Canadian Cardiovascular Society (CCS) Functional Classification of Angina
CFR	Coronary flow reserve
CHD	Coronary heart disease
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CVD	Cardiovascular disease
DTM	Decision tree model
EBCT	Electron beam computed tomography
ECG	Electrocardiography

ECHO	Echocardiography
FN	False negative
FP	False positive
GDG	Guideline development group
GITS	Gastrointestinal therapeutic system
GTN	Glyceryl trinitrate
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
ISMN	Isosorbide mononitrate
ITT	Intention-to-treat
IPD	Individual patient data
LAD	Left anterior descending
LBBB	Left bundle branch block
LDL	Low-density lipoprotein
LMS	Left main stem
LR	Likelihood ratio
MBF	Myocardial blood flow
MD	Mean difference
MI	Myocardial infarction
MID	Minimal Important difference
MPI	Myocardial perfusion imaging
MPI	Myocardial perfusion imaging
MPS	Myocardial perfusion scintigraphy
MRI	Magnetic resonance imaging
MVD	Multi-vessel disease
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence

NIDDM	Non-insulin dependent diabetes mellitus
NSF	National Service Framework
OR	Odds ratio
PCI	Percutaneous coronary intervention
PCT	Primary care trust
PET	Positron-emission tomography
PET	Positron emission tomography
PTCA	Percutaneous transluminal coronary angioplasty
QALY	Quality-adjusted life-year
QoL	Quality of life
QUADAS	Quality assessment of diagnostic accuracy studies
RCT	Randomised controlled trial
ROC	Receiver operating characteristic
RR	Relative risk
SA	Sensitivity analysis
SD	Standrad deviation
SPECT	Single photon emission computed tomography
SRS	Summed rest score
SVD	Single-vessel disease
TN	True negative
TP	True positive

1 Introduction

Angina is pain or constricting discomfort that typically occurs in the front of the chest (but may radiate to the neck, shoulders, jaw or arms) and is brought on by physical exertion or emotional stress. It is the main symptomatic manifestation of myocardial ischaemia and is usually caused by obstructive coronary artery disease restricting oxygen delivery to the cardiac myocytes. Other factors may exacerbate angina either by further restricting oxygen delivery (for example severe anaemia) or by increasing oxygen demand (for example left ventricular hypertrophy). Angina symptoms are associated with other cardiac disease such as aortic stenosis but the management of angina associated with non-coronary artery disease is outside the scope of this guideline.

Epidemiology: Unlike other manifestations of coronary artery disease, angina does not appear to be declining in incidence[1]. The Health Survey for England (2006)[2] found that about 8% of men and 3% of women aged between 55 and 64 years have, or have had angina. For people aged between 65 and 74 years the figures are about 14% of men and 8% of women. It is estimated that almost 2 million people in England have or have had angina. Prevalence is higher in men than in women, and increases sharply with age. Being diagnosed with angina can have a significant impact on a person's quality of life, which deteriorates progressively in proportion to the severity of symptoms[3]. Large randomised clinical trials suggest that patients with stable coronary artery disease have a good prognosis and in the ACTION trial all cause mortality was 1.5% per annum. By contrast, studies in primary care and in rapid access chest pain clinics have reported that a diagnosis of angina is associated with annual cardiovascular death rate of 1.4-6.5%[4] and 3.1%[5] respectively. These studies suggest that stable angina is not a benign condition, but prediction of cardiovascular risk in individual patients with angina is difficult because of clinical heterogeneity.

Current practice: Stable angina is a chronic medical condition. The aim of management is to abolish or minimise symptoms, and to improve quality of life and long-term morbidity and mortality. Medical management includes pharmacological strategies or a combination of pharmacological and revascularisation strategies and lifestyle interventions. Revascularisation may be performed using percutaneous techniques or by surgery.

Variation in practice: Completed in 2003, the Euro Heart Survey on Stable Angina Pectoris included 3,779 ambulatory patients from 36 countries, presenting to a cardiologist as an outpatient, with new-onset stable angina[6]. The survey revealed considerable variation between participating countries in the use of non-invasive and invasive investigations, the prescription of anti-anginal drugs and rates of revascularisation. Guideline compliant therapy was associated with reduced rates of myocardial infarction and death.

Current controversy: The variation in practice documented within the Euro Heart Survey likely reflects continuing uncertainty about appropriate management strategies in key clinical areas where the evidence base is incomplete or contradictory. This applies particularly to the role of revascularisation, for which some consensus has emerged around symptomatic indications, but prognostic indications are less well defined. Indeed, the only trials to report prognostic benefit for revascularisation were randomised comparisons of bypass surgery and medical treatment that are now more than 25 years old. It is noteworthy that these trials antedated introduction of statins and other secondary prevention treatments and the relevance of their findings to contemporary practice is unclear. More recent trials of percutaneous and surgical revascularisation strategies (COURAGE, BARI-2D, MASS II) have not demonstrated prognostic benefit, but these trials generally excluded patients with high risk coronary anatomy for whom bypass surgery might be expected to improve outcome.

Uncertainty about the effectiveness of revascularisation for delivering prognostic benefit in people with stable coronary artery disease is heightened by some recent analyses that have reported excessive incremental cost-effectiveness ratios for percutaneous revascularisation strategies compared with medical therapy. These areas of uncertainty surrounding the relative roles of medical therapy and revascularisation in managing people with stable angina have received special attention from the guideline group in making its recommendations.

Relationship between this guideline and NICE Clinical Guideline CG95 'Chest pain of recent onset'.

The National Institute for Health and Clinical Excellence (NICE) Clinical Guideline CG95 makes recommendations on the diagnosis of stable angina. That guideline covers the history, physical examination and investigations required to make a diagnosis of stable angina. This guideline presumes that a diagnosis of stable angina has already been made in accordance with NICE Clinical Guideline CG95 which recommends that angina can be diagnosed on the basis of history alone or on the basis of history and the results of functional or anatomical tests.

Typical angina is 3 out of 3 of the following: (a) constricting discomfort in anterior chest, neck, shoulder, jaw or arms; (b) precipitated by physical exertion or psychological stress and (c) relieved by rest or nitroglycerin within minutes. The requirement for functional or anatomical tests is dependent on the likelihood of coronary artery disease. That likelihood is dependent on how typical the history of angina is, the patient's age and gender and the presence of risk factors.

2 Development of the guideline

2.1 What is a guideline?

Our clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the National Health Service (NHS) – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of health care. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

Clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- guideline topic is referred to NICE from the Department of Health
- stakeholders register an interest in the guideline and are consulted throughout the development process
- the scope is prepared by the National Clinical Guidelines Centre (NCGC)
- the NCGC recruits a guideline development group
- a draft guideline is produced after the group assesses the available evidence and makes recommendations

- there is a consultation on the draft guideline
- the final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- the **full guideline** contains all the recommendations, plus details of the methods used and the underpinning evidence
- the **NICE guideline** presents the recommendations from the full version in a format suited to implementation by health professionals and NHS bodies
- the **quick reference guide** presents recommendations in a suitable format for health professionals
- information for the public (‘**understanding NICE guidance**’) is written using suitable language for people without specialist medical knowledge.

This version is the full version. The other versions can be downloaded from NICE www.NICE.org.uk.

2.2 Remit

On 19 October 2007 the Department of Health formally requested NICE to prepare a clinical guideline as described in the box below (17th Wave Work Programme).

Remit: To prepare a clinical guideline on the management of stable angina.

NICE commissioned the National Collaborating Centre for Primary Care (NCCPC) to develop this guideline. NCCPC merged in 2009 with the National Collaborating Centre for Chronic Condtion, the National Collaborating Centre for Nursing and Supportive Care and the National Collaborating Centre for Acute Care to form the NCGC.

2.3 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see section on Guideline Development Group Membership and acknowledgements).

The GDG was convened by the NCCPC/NCGC and chaired by Professor Adam Timmis in accordance with guidance from NICE.

The group met approximately every 6 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest, which were also recorded.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix J

Staff from the NCGC provided methodological support and guidance for the development process. They undertook systematic searches, retrieval and appraisal of the evidence and drafted the guideline.

2.4 What the guideline covers

2.4.1 Key clinical issues that are covered

a) Non-invasive and invasive assessments to assess functional status, underlying disease, prognosis and plan management

b) Education programmes for people with angina (and carers and families as appropriate) that aim to help patients understand and manage their condition. They include self care, symptom management, medication management and lifestyle interventions

c) Psychological interventions for symptom relief and to improve long-term outcomes

d) Pharmacological interventions for symptom relief and to improve long-term outcomes

e) Revascularisation strategies for symptom relief and to improve long-term outcomes

f) Specialised interventions for symptom relief, for example transcutaneous electrical nerve stimulation (TENS), temporary or destructive sympathectomy, and enhanced external counter pulsation (EECP)

g) Rehabilitation programmes

h) Cardiac syndrome X

2.4.2 Economic aspects

Developers took into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence was conducted and analyses were carried out as appropriate. The unit of effectiveness was the quality-adjusted life year (QALY), and the costs considered were from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see ‘Further information’).

2.4.3 Groups that are covered

a) Adults (18 years and older) who have been diagnosed with stable angina due to atherosclerotic disease

b) The following subgroups, were included:

- people of South Asian origin
- people older than 85 years
- people with chronic refractory angina
- people with diabetes
- people with normal or minimally diseased coronary arteries
- women.

For further details please refer to the scope in Appendix A.

2.4.4 Healthcare settings that are covered

a) All NHS primary, secondary and tertiary healthcare settings managing people with stable angina.

2.5 What the guideline does not cover

a) People with recent-onset chest pain or discomfort of suspected cardiac origin

b) People with acute coronary syndrome

c) People with chest pain or discomfort of unknown cause

d) People with angina-type pain that is likely to be due to non-cardiac disease, such as anaemia

e) People with angina-type pain associated with other types of heart disease, such as valvular heart disease (for example, aortic stenosis) or cardiomyopathy (for example, hypertrophic cardiomyopathy).

2.6 Relationships between the guideline and other national guidance

2.6.1 Related NICE guidance

- Off-pump coronary artery bypass grafting. NICE interventional procedure guidance 377 (2011). Available from www.nice.org.uk/guidance/IPG377

- Chronic heart failure (partial update). NICE clinical guideline 108 (2010). Available from www.nice.org.uk/guidance/CG108
- Chest pain of recent onset. NICE clinical guideline 95 (2010). Available from www.nice.org.uk/guidance/CG95
- Unstable angina and NSTEMI. NICE clinical guideline 94 (2010). Available from www.nice.org.uk/guidance/CG94
- Endoscopic saphenous vein harvest for coronary artery bypass grafting. NICE interventional procedure guidance 348 (2010). Available from www.nice.org.uk/guidance/IPG348
- Depression in chronic health problems. NICE clinical guideline 91 (2009). Available from www.nice.org.uk/guidance/CG91
- Medicines adherence. NICE clinical guideline 76 (2009). Available from www.nice.org.uk/guidance/CG76
- Percutaneous laser revascularisation for refractory angina pectoris. NICE interventional procedures guidance 302 (2009). Available from www.nice.org.uk/guidance/IPG302
- Transmyocardial laser revascularisation for refractory angina pectoris. NICE interventional procedures guidance 301 (2009). Available from www.nice.org.uk/guidance/IPG301
- Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. NICE technology appraisal guidance 159 (2008). Available from www.nice.org.uk/guidance/TA159
- Drug-eluting stents for the treatment of coronary artery disease (part review of NICE technology appraisal guidance 71). NICE technology appraisal guidance 152 (2008). Available from www.nice.org.uk/guidance/TA152
- Lipid modification. NICE clinical guideline 67 (2008). Available from www.nice.org.uk/guidance/CG67
- Smoking cessation services (2008). NICE public health guidance 10. Available from www.nice.org.uk/guidance/PH10
- Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. NICE technology appraisal guidance 132 (2007). Available from www.nice.org.uk/guidance/TA132
- Myocardial infarction: secondary prevention. NICE clinical guideline 48 (2007). Available from www.nice.org.uk/guidance/CG48
- Varenicline for smoking cessation. NICE technology appraisal guidance 123 (2007). Available from www.nice.org.uk/guidance/TA123

- Hypertension. NICE clinical guideline 34 (2006). Available from www.nice.org.uk/guidance/CG34 – currently being updated (estimated publication date August 2011)

- Statins for the prevention of cardiovascular events. NICE technology appraisal guidance 94 (2006). Available from www.nice.org.uk/guidance/TA94

- Intraoperative fluorescence angiography in coronary artery bypass grafting. NICE interventional procedure guidance 98 (2004). Available from www.nice.org.uk/guidance/IPG98

- Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction. NICE technology appraisal guidance 73 (2003). Available from www.nice.org.uk/TA73

- Guidance on the use of coronary artery stents. NICE technology appraisal guidance 71 (2003). Available from www.nice.org.uk/guidance/TA71

- Prevention of cardiovascular disease at population level. NICE public health guidance PH25 (2010). Available from www.nice.org.uk/guidance/PH25

3 Methods

This guidance was developed in accordance with the methods outlined in the NICE Guidelines Manual[7].

3.1 Developing the review questions and outcomes

Review questions were developed based on the scope (Appendix A). They were drafted by the review team and refined and validated by the GDG. Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews, risk scores and prognostic reviews. This was to guide the literature searching process and to facilitate the development of recommendations by the GDG.

3.2 Searching for evidence

3.2.1 Clinical literature search

Systematic literature searches were undertaken to identify evidence within published literature in order to answer the review questions as per The NICE Guidelines Manual[7]. Clinical databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Non-English studies were not reviewed and were therefore excluded from searches. All searches were conducted on core databases, Medline, Embase, Cinahl and The Cochrane Library. Additional subject specific databases were used for some questions. All searches were updated on the 22nd of October 2010. No papers after this date were considered.

Search strategies were checked by looking at reference lists of relevant key papers, checking search strategies in other systematic reviews and asking the GDG for known studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix D.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below and on organisations relevant to the topic. Searching for grey literature or unpublished literature was not systematically performed. All references sent by stakeholders were considered.

- Constituent websites of the Guidelines International Network (www.g-i-n.net)
- National Guideline Clearing House (www.guideline.gov/)
- National Institute for Health and Clinical Excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (consensus.nih.gov/)
- National Library for Health (www.library.nhs.uk/)

3.2.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to the stable angina population in the NHS economic evaluation database (NHS EED), the Health Economic Evaluations Database (HEED) and health technology assessment (HTA) databases with no date restrictions up to 13/9/10. Additionally, the search was run on Medline (years 1950–2007) and Embase (1996–2007), with a specific economic filter, to ensure recent publications that had not yet been indexed by these databases were identified. This was supplemented by additional searches from (1990–13/9/10) that looked for economic papers specifically relating to revascularisation, rehabilitation, nicorandil, long-acting nitrates on Medline, Embase, Cochrane (TAs and EEs, as it became apparent that some papers in this area were not being identified through the first search.

The search strategies for health economics are included in Appendix D. All searches were updated on the 13th Sept 2010. No papers after this date were considered.

3.3 Reviewing the evidence

The Research Fellow and Health Economist:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts – full papers were then obtained
- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify studies that addressed the review question in the appropriate population and reported on outcomes of interest (research protocols are included in Appendix C)
- Critically appraised relevant studies using the appropriate checklist as specified in The Guidelines Manual[7]
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix E2)

- Generated summaries of the evidence by outcome (included in the relevant chapter write-ups):
  - Randomised studies: meta-analysed, where appropriate and reported in GRADE profiles (for clinical studies) – see below for details
  - Observational studies: each study summarised in a table and narrative developed
  - Qualitative studies: each study summarised in a table and narrative developed
  - Economic studies: summarised in NICE economic evidence profiles – see below for details.

3.3.1 Inclusion/exclusion

See the review protocols in Appendix C for full details.

Population

The remit of the guideline was to make recommendations for people with stable angina. Studies were required to have at least 60% of people with stable angina to be included. The interventions (e.g. drugs and revascularisation procedures) used in stable angina are also used commonly in people who are found to have coronary artery disease or who present with other coronary artery diseases such as unstable angina or myocardial infarction (MI). Hence many of the trials for these interventions include a mixed group of patients including stable angina, unstable angina and/or MI. For this reason the GDG decided to consider studies with at least 60% stable angina population as this would be more relevant to the population specified in this guideline.

In this guideline we have also looked separately at people with cardiac syndrome X.

Intervention

The following classes of drugs have been considered in this guideline for:

The management of stable angina

- Short-acting nitrates
- Beta blockers (BBs)
- Calcium channel blockers (CCBs)
- Long-acting nitrates
- Nicorandil
- Ivabradine

- Ranolazine

Secondary prevention

- Angiotensin-converting enzyme (ACE) inhibitors
- Angiotensin receptor blockers (ARBs)
- Aspirin
- Statins

The following prognostic tests have been considered in this guideline:

- Exercise electrocardiography (ECG) / exercise tolerance test / exercise stress test / stress ECG
- Stress ECG/exercise, dobutamine, dipyridamole, adenosine-stress ECG
- Stress myocardial perfusion imaging/ myocardial perfusion scintigraphy (MPS)/ exercise thallium MPS/ MPS using single photon emission CT (SPECT)
- Stress magnetic resonance imaging / stress CMR / adenosine, dipyridamole-stress perfusion imaging / dobutamine-stress induced motion wall abnormalities
- Computed tomography (CT) / CT coronary angiography / multi slice CT, multidetector CT / CT coronary angiography / CAT
- Calcium scoring , coronary calcium scoring
- Electron beam CT (EBCT)
- Coronary angiography.

The following revascularisation procedures have been considered in this guideline:

- Percutaneous coronary intervention (PCI) (includes coronary balloon angioplasty and coronary stent implantation),
- Coronary artery bypass surgery (CABG).

The details of the interventions can be found in the relevant review sections.

Outcomes

The following outcomes are reported in this guideline:

- *Outcomes in intervention studies*

- Exercise tolerance
- Nitroglycerin consumption
- Angina frequency/severity
- MI/Non-fatal MI
- Revascularisation
- Hospitalisation
- Stroke/cerebrovascular accident
- Death
- Cardiac/cardiovascular death
- Quality of life
- Adverse events.

- *Outcomes in Prognostic studies*

  The main outcomes considered in prognostic studies were:

  - Death
  - Cardiac death/cardiovascular death
  - MI/Nonfatal MI
  - Revascularisation.

3.3.2 Health economic inclusion/exclusion criteria

Full economic evaluations (cost-effectiveness, cost-utility, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered to have the potential for inclusion as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Abstracts, posters, reviews, letters/editorials, foreign language publications and unpublished studies were excluded. Studies judged to have an applicability rating of 'not applicable' were excluded (this included studies that took the perspective of a non-OECD country).

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, other less relevant studies were not included.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (The Guidelines Manual[7], Appendix H and the health economics research protocol in Appendix C .

When no relevant economic analysis was found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the possible economic implication of the recommendation to make.

Quality assessment for inclusion of studies

All studies are quality assessed before being included as part of the systematic review. The criteria for assessment for different types of studies are listed below.

For systematic reviews and meta-analysis, the main criteria considered were:

- An appropriate and clearly focused question was addressed
- Methodology was well described
- The literature search was sufficiently robust to identify all the relevant studies
- The individual study quality included in the review was assessed and taken into account
- The studies were sufficiently similar to make combining them reasonable.

Intervention studies

The quality assessment criteria as listed in the NICE Guidelines Manual 2009 were used to assess systematic reviews, meta-analysis, and randomised controlled trials.

For randomised controlled trials, the main criteria considered were:

- An appropriate and clearly focused question was addressed
- Appropriate randomisation allocation and concealment methods were used
- Subjects, investigators and outcomes assessors were masked about treatment allocation
- The intervention and control groups are similar at baseline
- The only difference between group is the type of intervention received
- All outcomes are measured in a standard and reliable method
- Drop out rates reported and are acceptable, and all participants are analysed in the groups to which they were randomly allocated the treatment
- For multi-centred trials, results are comparable between sites.

Only studies which fulfilled some to all of the criteria included were included in the evidence review.

Prognostic studies

Prospective cohort studies were included for the prognostic questions. The prospective cohort studies' quality was assessed using the quality checklist in the NICE Guidelines Manual April 2009. The main criteria considered in assessing study quality were:

- An appropriate and clearly focused question was addressed
- The cohort(s) being studied are selected from source populations that are comparable in all respects other than the factor under investigation
- The inclusion or participation rate was reported
- The likelihood that some eligible subjects might have the outcome at the time of enrolment assessed had been taken into account in the analysis
- The drop out rate was reported and acceptable
- Comparison by the prognostic status is made between participants who completed the study and those lost to follow up
- The outcomes were clearly defined
- The assessment of outcome was blind to exposure status or acknowledged where this was not possible
- The methods of assessment used for the prognostic factor and the outcomes were valid and reliable
- The main potential confounders are identified and taken into account adequately in the design and analysis
- Confidence intervals or standard deviation were provided.

3.3.3 Methods of combining clinical studies

Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes: [death, cardiac death, MI/non-fatal MI, revascularisation, stroke, number patients free of angina, adverse events]. The continuous outcome(s) [exercise tolerance, angina frequency, nitroglycerin consumption)] was (were) analysed using an inverse variance method for pooling weighted mean differences and where the studies had different scales, standardised mean differences were used. Statistical heterogeneity was assessed by considering the chi-squared test for significance at $p<0.05$ or an I-squared inconsistency statistic of $>50\%$ to indicate significant heterogeneity. When there were a high number of studies, a p-value of 0.1 was taken as a threshold for heterogeneity. We carried out predefined subgroup analyses as defined in the protocol for each question (see Appendix B).

The standard deviations of continuous outcomes were required for imputation for meta-analysis. However, in cases where this was not reported, calculation based on methods outlined in section 7.7.3 of the Cochrane Handbook[8]: 'Data extraction for continuous outcomes' were applied to estimate the standard deviations if p values of the difference between two means, 95% confidence intervals or standard error of the mean (SEM) had been reported'. Where p values were reported as 'less than', a conservative approach was undertaken. For example, if p value was reported as '$p \leq 0.001$', the calculations for standard deviations will be based on a p value of 0.001. If these statistical measures were not available then the methods described in section 16.1.3 of the Cochrane Handbook (February 2008) 'Missing standard deviations' were applied as the last resort.

For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

In the evidence reviews in this guideline we have presented additional data from studies along with the GRADE tables. These have been referred to as 'Additional data' and refer to data which was not analysed due to lack of sufficient reported information and/or outcomes.

Data synthesis for prognostic review

Odds ratio, relative or hazard risks, with their 95% confidence intervals, from multivariate analyses were extracted from the papers. Studies were not combined in a meta-analysis for observational studies.

3.4 GRADE (Grading of Recommendations Assessment, Development and Evaluation)

The evidence for outcomes from studies which passed the quality assessment were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working group was used to assess pooled outcome data using individual study quality assessments and results from meta-analysis.

The summary of findings was presented as two separate tables in this guideline. The 'Clinical Study Characteristics' table includes details of the quality assessment while the 'Clinical Summary of Findings' table includes pooled outcome data, where appropriate, an absolute measure of intervention effect calculated and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate pooled sample size for continuous outcomes. For binary outcomes such as number of patients with an adverse event, the event rates (n/N) are shown with percentages. Reporting or publication bias was only taken into consideration in the quality assessment and included in the Clinical Study Characteristics table if it was apparent.

Each outcome was examined separately for the quality elements listed and defined in Table 3.1and each graded using the quality levels listed in Table 3.2. The main criteria considered in the rating of these elements are discussed in the literature reviewing process (see section 3.4.1 Grading of Evidence). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. Then, an overall quality of evidence for each outcome was applied by selecting from the options listed in Table 3.3. The GRADE toolbox is currently designed only for randomised controlled trials and observational studies but we adapted the quality assessment elements and outcome presentation for diagnostic accuracy studies.

Table 3.1: Descriptions of quality elements in GRADE for intervention studies

Quality element	*Description*
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect relative to the minimal important difference.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 3.2: Levels for quality elements in GRADE

Level	***Description***
None	There are no serious issues with the evidence.
Serious	The issues are serious enough to downgrade the outcome evidence by one level.
Very serious	The issues are serious enough to downgrade the outcome evidence by two levels.

Table 3.3: Overall quality of outcome evidence in GRADE

Level	***Description***
High	Further research is *very unlikely* to change our confidence in the *estimate of effect*.
Moderate	Further research is *likely* to have an important impact on our confidence in the *estimate of effect* and may change the estimate.
Low	Further research is *very likely* to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	*Any estimate of effect is very uncertain.*

3.4.1 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start HIGH and observations studies as LOW.
2. The rating was then downgraded for the specified criteria: study limitations, inconsistency, indirectness, imprecision and reporting bias. These criteria are detailed below. Observation studies were upgraded if there was: a large magnitude of effect, dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered as having ‘serious' or ‘very serious' risk of bias was rated down 1 or 2 points respectively.
3. The downgraded/upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if 1, 2 or 3 points were deducted respectively.

4. The reasons or criteria used for downgrading were specified in the footnotes.

The details of criteria used for each of the main quality element are discussed further in the following sections 3.4.2–3.4.5.

3.4.2 Study limitations

The main limitations for randomised controlled trials are listed in Table 3.4.

Table 3.4: Study limitations of randomised controlled trials

Limitation	***Explanation***
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (major problem in 'pseudo' or 'quasi' randomised trials with allocation by day of week, birth date, chart number etc.).
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated.
Incomplete accounting of patients and outcome events	Loss to follow-up not accounted and failure to adhere to the intention-to-treat principle when indicated.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results.
Other limitations	For example: • stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • use of unvalidated patient-reported outcomes • carry-over effects in cross-over trials • recruitment bias in cluster-randomised trials.

3.4.3 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (i.e. heterogeneity or variability in results), this suggests true differences in underlying treatment effect. When heterogeneity exists (Chi square $p<0.05$ [$p<0.1$ for high number of studies] or I-squared inconsistency statistic of >50%), but no plausible explanation can be found, the quality of evidence was downgraded by one or two levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. On top of the I-square and Chi square values, the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

If inconsistency could be explained based on subgroup analysis, the GDG took this into account and considered whether to make separate recommendations based on the identified explanatory factors, i.e. population and intervention. In this situation, the quality of evidence would not be downgraded.

3.4.4 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

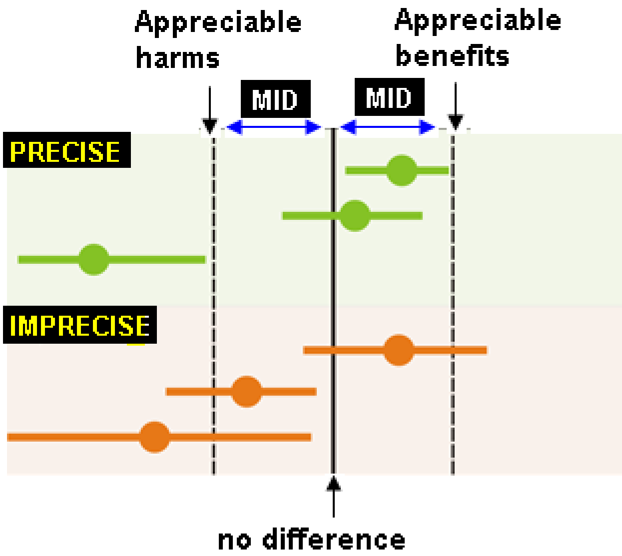
3.4.5 Imprecision

The sample size, event rates and the resulting width of confidence intervals were the main criteria considered. Where the minimal important difference (MID) of an outcome is known, the optimal information size (OIS), i.e. the sample size required to detect the difference with 80% power and $p \leq 0.05$ was calculated and used as the criteria. The criteria applied for imprecision are based on the confidence intervals for pooled or the best estimate of effect, as illustrated in Figure 3.1, and outlined in Table 3.5.

Table 3.5: Criteria applied to determine precision - criteria for downgrading an outcome for imprecision

Dichotomous and continous outcomes
1. 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect: a) Does not cross the threshold for appreciable benefit or harm defined as precise. Rating for precision: 'no serious imprecision'.
2. 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect: a) If the 95% confidence interval crosses either minimal important difference (MID) threshold, defined as imprecise. Rating for precision: 'serious'.
3. 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect: a) Crosses both the line of appreciable benefit and harm, defined as imprecise. Rating for precision: 'very serious'.

Figure 3.1: Illustration of precise and imprecise outcomes based on the confidence interval of outcomes



MID = minimal important difference determined for each outcome. The MIDs are the threshold for appreciable benefits and harms. The confidence intervals of the top three points of the diagram were considered precise because the upper and lower limits did not cross the MID. Conversely, the bottom three points of the diagram were considered imprecise because all of them crossed the MID and reduced our certainty of the results. Figure adapted from GRADEPro software.

The following are the MID for the outcomes and the methods used to calculate the OIS in this guideline.

For continuous outcomes:

- Anginal attacks per week: -3 to +3 attacks/week
- Exercise time (min): +30 to 30 sec (-0.50 to +50 min)

For all dichotomous outcomes

- The default confidence intervals in GRADE of 0.75 and 1.25.

The MIDs for the outcomes were based on the advice from the clinical advisor and chair for the guideline.

3.5 NICE economic evidence profiles

The NICE economic profile has been used to summarise cost and cost-effectiveness estimates from published studies and analyses conducted for the guideline. The economic evidence profile shows, for each economic study, an assessment of applicability and methodological quality, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from The NICE Guidelines Manual, Appendix H (2009). It also shows incremental costs, incremental outcomes (e.g. quality-adjusted life-years [QALYs]) and the incremental cost-effectiveness ratio from the primary analysis, as well as information about the assessment of uncertainty in the analysis. See Table 3.6 for more details.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity[9].

Table 3.6: Content of NICE economic profile

Item	*Description*
Study	First author name, reference, date of study publication and country perspective.
Limitations	An assessment of methodological quality of the study*: • **Minor limitations** – the study meets all quality criteria, or the study fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness • **Potentially serious limitations** – the study fails to meet one or more quality criteria, and this could change the conclusion about cost effectiveness • **Very serious limitations** – the study fails to meet one or more quality criteria and this is very likely to change the conclusions about cost effectiveness. Studies with very serious limitations would usually be excluded from the economic profile table.
Applicability	An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making*: • **Directly applicable** – the applicability criteria are met, or one or more criteria are not met but this is not likely to change the conclusions about cost effectiveness. • **Partially applicable** – one or more of the applicability criteria are not met, and this might possibly change the conclusions about cost effectiveness. • **Not applicable** – one or more of the applicability criteria are not met, and this is likely to change the conclusions about cost effectiveness.
Other comments	Particular issues that should be considered when interpreting the study.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
ICER	Incremental cost-effectiveness ratio (ICER): the incremental cost divided by the respective QALYs gained.
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

*Limitations and applicability were assessed using the economic evaluation checklist from The Guidelines Manual[7], Appendix H

Where economic studies compare multiple strategies, results are presented in the economic evidence profiles for the pair-wise comparison specified in the review question, irrespective of whether or not that comparison was 'appropriate' within the analysis being reviewed. A comparison is 'appropriate' where an intervention is compared with the next most expensive non-dominated option – a clinical strategy is said to 'dominate' the alternatives when it is both more effective and less costly. Footnotes indicate if a comparison was 'inappropriate' in the analysis.

3.5.1 Cost-effectiveness criteria

The NICE Guidelines Manual[7] sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

a) The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), **or**

b) The intervention cost less than £20,000 per QALY gained compared with the next best strategy.

3.6 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the Health Economist in priority areas. Priority areas for new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

Additional data for the analysis was identified as required through additional literature searches undertaken by the Health Economist, and discussion with the GDG. Model structure, inputs and assumptions were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

See Appendix H for details of the health economic analysis undertaken for the guideline.

3.7 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendix E2

- Summary of clinical and economic evidence and quality (as presented in chapters 5–19

- Forest plots (Appendix F)
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (Appendices G and H).

Recommendations were drafted on the basis of this evidence whenever it was available.

When clinical and economic evidence was absent, of poor quality or conflicting, the GDG drafted recommendations based on their expert opinion. This was done through discussions in the GDG. The considerations for making these consensus based recommendations included the balance between potential harms and benefits, economic or implications compared to the benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The GDG also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation.

The main considerations specific to each recommendation are outlined in the Evidence to Recommendation section preceding the recommendation section.

3.7.1 Research recommendations

When areas were identified for which good evidence was lacking, the GDG considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

3.8 Validation process

The guidance is subject to an eight-week public consultation, and feedback is used to quality assure the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website when the pre-publication check of the full guideline occurs.

3.9 Updating the guideline

Following publication, and in accordance with the NICE technical manual, NICE will conduct an evidence review and consult with stakeholders to assess whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

3.10 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

NCGC disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

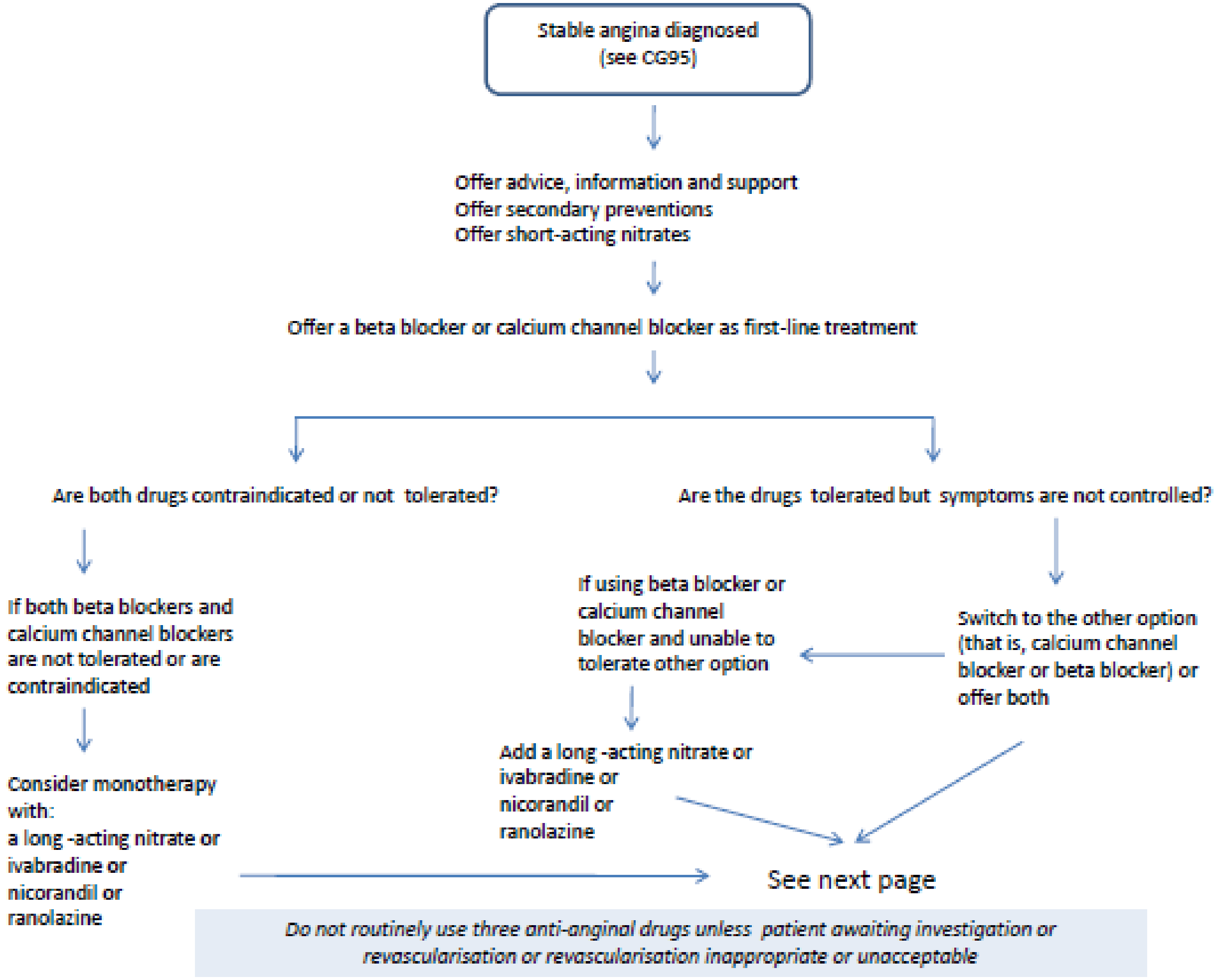
3.11 Funding

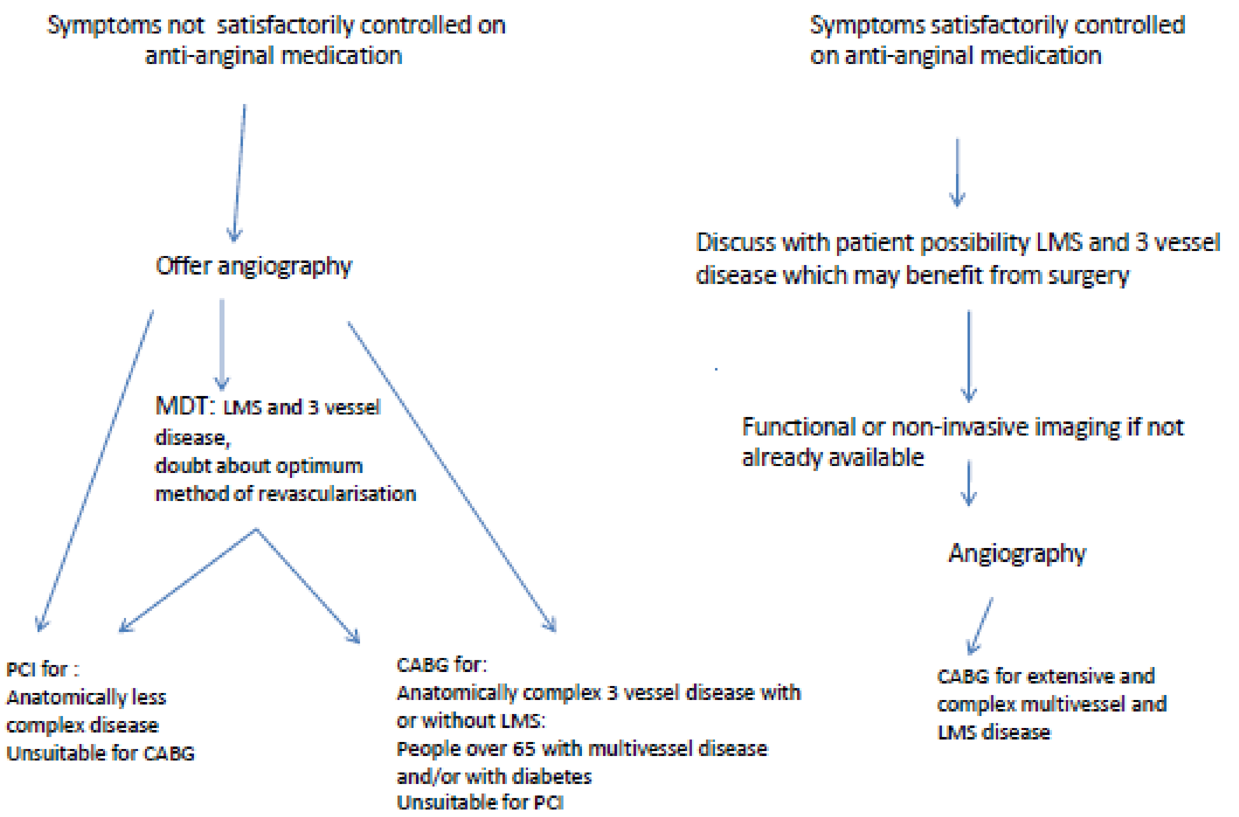
NCGC was commissioned by NICE to undertake the work on this guideline.

4 Guideline summary

4.1 Algorithms

The care pathway is summarised in the following pages. For a more detailed version, please refer to the quick reference guide for stable angina, which is available from www.nice.org.uk/guidance/CG126/QuickRefGuide


Stable angina diagnosed
(see CG95)
Offer advice, information and support
Offer secondary preventions
Offer short-acting nitrates
Offer a beta blocker or calcium channel blocker as first-line treatment
Are both drugs contraindicated or not tolerated?
Are the drugs tolerated but symptoms are not controlled?
If both beta blockers and calcium channel blockers are not tolerated or are contraindicated
If using beta blocker or calcium channel blocker and unable to tolerate other option
Switch to the other option (that is, calcium channel blocker or beta blocker) or offer both
Consider monotherapy with:
a long -acting nitrate or
ivabradine or
nicorandil or
ranolazine
Add a long -acting nitrate or
ivabradine or
nicorandil or
ranolazine
See next page
Do not routinely use three anti-anginal drugs unless patient awaiting investigation or revascularisation or revascularisation inappropriate or unacceptable



If stable angina does not respond to drug treatment or revascularisation, or revascularisation is unacceptable or inappropriate offer comprehensive re-evaluation and advice which may include: exploring understanding of the condition and the impact of symptoms, considering non-ischaemic causes of pain, reviewing treatment, explaining how the person can manage the pain, attention to the role of psychological factors in pain, development of skills to modify cognitions and behaviours associated with pain.

4.2 Key priorities for implementation

From the full set of recommendations, the GDG selected key priorities for implementation. The criteria used for selecting these recommendations are listed in detail in The Guidelines Manual[7]. The reasons that each of these recommendations were chosen are shown in the table in Appendix I.

The following recommendations have been identified as priorities for implementation.

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

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

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

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

- When either procedure would be appropriate, take into account the potential survival advantage of CABG over PCI for people with multivessel disease whose symptoms are not satisfactorily controlled with optimal medical treatment and who:
  - have diabetes or
  - are over 65 years or
  - have anatomically complex three-vessel disease, with or without involvement of the left main stem.

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

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

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

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

- Discuss the following with people whose symptoms are satisfactorily controlled with optimal medical treatment:
  - their prognosis without further investigation
  - the likelihood of having left main stem disease or proximal three-vessel disease
  - the availability of CABG to improve the prognosis in a subgroup of people with left main stem or proximal three-vessel disease
  - the process and risks of investigation
  - the benefits and risks of CABG, including the potential survival gain.

4.3 Full list of recommendations

1.1 Diagnosis

1.1.1 Diagnose stable angina according to ‘Chest pain of recent onset’ (NICE clinical guideline 95). Diagnose and manage unstable angina and NSTEMI according to ‘Chest pain of recent onset’ (NICE clinical guideline 95), ‘Unstable angina and NSTEMI’ (NICE clinical guideline 94) and ‘MI: secondary prevention’ (NICE clinical guideline 48).

1.2 Information and support for people with stable angina

1.2.1 Clearly explain stable angina to the person, including factors that can provoke angina (for example, exertion, emotional stress, exposure to cold, eating a heavy meal) and its long-term course and management. When relevant, involve the person’s family or carers in the discussion.

1.2.2 Encourage the person with stable angina to ask questions about their angina and its treatment. Provide opportunities for them to voice their concerns and fears.

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

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

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

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

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

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

1.3 General principles for treating people with stable angina

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

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

Preventing and treating episodes of angina

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

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

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

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

Drugs for secondary prevention of cardiovascular disease

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

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

1.3.7 Offer statin treatment in line with 'Lipid modification' (NICE clinical guideline 67).

1.3.8 Offer treatment for high blood pressure in line with 'Hypertension' (NICE clinical guideline 34) [replaced by 'Hypertension' (NICE clinical guideline 127)].

Dietary supplements

1.3.9 Do not offer vitamin or fish oil supplements to treat stable angina. Inform people that there is no evidence that they help stable angina.

1.4 Anti-anginal drug treatment

General recommendations

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

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

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

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

- what the medicine is
- how the medicine is likely to affect their condition (that is, its benefits)
- likely or significant adverse effects and what to do if they think they are experiencing them
- how to use the medicine
- what to do if they miss a dose
- whether further courses of the medicine will be needed after the first prescription

- how to get further supplies of medicines. [This recommendation is from 'Medicines adherence' (NICE clinical guideline 76).]

1.4.5 Review the person's response to treatment, including any side effects, 2–4 weeks after starting or changing drug treatment.

1.4.6 Titrate the drug dosage against the person's symptoms up to the maximum tolerable dosage.

Drugs for treating stable angina

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

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

1.4.9 If the person's symptoms are not satisfactorily controlled on a beta blocker or a calcium channel blocker, consider either switching to the other option or using a combination of the two[1].

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

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

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

Decide which drug to use based on comorbidities, contraindications, the person's preference and drug costs[2].

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

- a long-acting nitrate or

[1] When combining a calcium channel blocker with a beta blocker, use a dihydropyridine calcium channel blocker, for example, slow release nifedipine, amlodipine or felodipine.
[2] Since this guidance was produced, the Medicines and Healthcare products Regulatory Agency (MHRA) have published new advice about safety concerns related to ivabradine (June 2014 and December 2014) and nicorandil (January 2016).

- ivabradine[3] or
- nicorandil or
- ranolazine.

Decide which drug to use based on comorbidities, contraindications, the person's preference and drug costs[4].

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

1.4.14 Consider adding a third anti-anginal drug only when:

- the person's symptoms are not satisfactorily controlled with two anti-anginal drugs and
- the person is waiting for revascularisation or revascularisation is not considered appropriate or acceptable.

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

1.5 Investigation and revascularisation

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

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

1.5.2 Offer coronary angiography to guide treatment strategy for people with stable angina whose symptoms are not satisfactorily controlled with optimal medical treatment. Additional non-invasive or invasive functional testing may be required to evaluate angiographic findings and guide treatment decisions. [This recommendation partially updates recommendation 1.2 of 'Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction' (NICE technology appraisal guidance 73).]

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

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

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

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

- revascularisation is considered appropriate and
- PCI is not appropriate.

1.5.4 Offer PCI to people with stable angina and suitable coronary anatomy when:

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

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

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

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

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

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

- people with left main stem or anatomically complex three-vessel disease
- people in whom there is doubt about the best method of revascularisation because of the complexity of the coronary anatomy, the extent of stenting required or other relevant clinical factors and comorbidities.

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

- The main purpose of revascularisation is to improve the symptoms of stable angina.
- CABG and PCI are effective in relieving symptoms.
- Repeat revascularisation may be necessary after either CABG or PCI and the rate is lower after CABG.
- Stroke is uncommon after either CABG or PCI, and the incidence is similar between the two procedures.
- There is a potential survival advantage with CABG for some people with multivessel disease.

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

- vein and/or artery harvesting
- likely length of hospital stay
- recovery time
- drug treatment after the procedure.

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

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

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

1.5.12 After discussion (see 1.5.11) with people whose symptoms are satisfactorily controlled with optimal medical treatment, consider a functional or non-invasive anatomical test to identify people who might gain a survival benefit from surgery. Functional or anatomical test results may already be available from diagnostic assessment. [This recommendation partially updates recommendation 1.2 of 'Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction' (NICE technology appraisal guidance 73).]

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

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

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

1.6 Pain interventions

1.6.1 Do not offer the following interventions to manage stable angina:

- transcutaneous electrical nerve stimulation (TENS)
- enhanced external counterpulsation (EECP)
- acupuncture.

1.7 Stable angina that has not responded to treatment

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

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

1.8 Cardiac syndrome X

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

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

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

4.4 Key research recommendations

Adding a newer anti-anginal drus to a calcium channel blocker

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

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

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

Early revascularisation strategy for people with angina and multivessel disease

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

Cardiac rehabilitation

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

Patient self-management plans

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

5 Patient Information

5.1 Introduction

Stable angina is a chronic condition which people may live with for many years. People require information to ensure they understand their condition and the available treatments. Episodes of angina are potentially frightening and it is important that people are guided as to how to adapt their lifestyle if they have continuing symptoms. It is equally important however to ensure that people do not unnecessarily limit their lifestyle because of fear about precipitating angina or myocardial infarction. The GDG were interested in studies of people with angina where patients reported their information needs both at the time of diagnosis and later in the course of the condition. The question for the evidence review was:

"What are the information needs of people with stable angina regarding their condition and its management?"

5.2 Information needs of people with stable angina

5.2.1 Clinical Evidence

The "Review Protocol" for this topic can be found in Appendix C, the "Search Strategies" in Appendix D, the "List of Included and Excluded Studies" in Appendix E1, and the "Clinical Evidence Tables" in Appendix E2.

The studies included in this review were qualitative studies or questionnaires which reported direct patient experience. Four papers were included in this review; there were 3 qualitative studies[10-12] and 1 cross-sectional questionnaire study (analysed quantitatively)[13]. Qualitative studies were critically appraised using the NICE qualitative methodology checklist. A summary of the quality of studies is included in Table 5.1. The studies and results are described in narrative format.

Table 5.1: Quality of included studies in evidence review for "Patient information"

Study	Population	Methods	Analysis	Relevance to guideline population
Pier 2008[10]	Well reported	Well reported	Well reported and credible.	Australia. Patients with MI, CABG, angioplasty or angina from GP practices.
Weetch 2003[11]	Poorly reported	Poorly reported	Poorly reported	UK. People suffering from angina who had been hospitalised in the coronary care ward.
McGillion 2004[12]	Well reported	Well reported	Well reported and credible	Canada. People with chronic stable angina living at home.
Karlik 1990[13]	Well reported	Well reported	Quantitative analysis.	USA. In-patients experiencing angina admitted to acute –care hospital for cardiac catheterisation.

Narrative report of results

Pier 2008[10] conducted a qualitative study in Melbourne, using thematic analysis of semi-structured interviews on the types of health information that people with CHD considered useful to assist with the management of their illness. Structured clinical interviews were used to assess current and prior depressive episodes in these patients. The study had 14 patients (12 men and 2 women) with a mean age of 67 years recruited from general practices. The patients had a history of MI, CABG, angioplasty or angina. Eight of these participants had a history of depression.

Five themes relating to information on how patients could manage their cardiovascular health and improve their psychosocial wellbeing were recognised: psychosocial issues; anger management; physical activity; medical information; and information for family.

The most important information needs recognised by the patients were: the need for information on how to establish social networks and access appropriate social and support groups so as to gain support and to understand their medical condition particularly from other people with CHD; information regarding how to identify precipitating symptoms of anger and anger management; information on physical activity and amount of physical activity that could be done following an event; information regarding identification and management of risk-related physical symptoms; and information for family members and spouses, such as how the patient may react to an adverse cardiac event or medical procedure.

Weetch 2003[11] conducted a study to determine the level of satisfaction with the amount and quality of information received by patients suffering from angina who had been hospitalised in the coronary care ward. The study used questionnaires. All patients discharged from the ward with a diagnosis of angina during the study were asked to participate. Thirty patients were identified as having discharged with a diagnosis of angina during a 3 month period and were issued with a questionnaire of which 16 were returned. Seven of these 16 patients had previously been hospitalised with an MI; and 8 had angina but no previous MI. The average age of the respondents was 59.7 years (range 40 to 78 years), 60% of the respondents were male and 40% were female.

The results showed a very high satisfaction with the overall standard of care. However, the results showed that 73% of the patients were dissatisfied with the amount of information that they were given. They wanted to know more about the causes of angina, its treatment, their medication, and in particular the effect it will have on their daily activities. Although the patients agreed that nurses gave them the opportunity to ask questions, many wanted more written and verbal information. Another significant finding was the lack of satisfaction with the information that patients had received from health care professionals working in primary care settings.

McGillion 2004[12] conducted a qualitative study to determine the learning needs of people with chronic stable angina living at home, in order to inform content of a chronic stable angina self management programme. Eight (n=8) chronic stable angina patients were eligible and included in the study. Eligible patients had angina symptoms for at least 6 months, were experiencing either class I,II or III angina and had a medical diagnosis of CAD confirmed by nuclear imaging or angiography. The age of the eight patients ranged from 44 to 70 years, and one had post-secondary education. There were two women and 6 men in the study and the participants had angina from 6 months to 10 years.

Four focus groups were organised: two with chronic stable angina patients (n=5, n=3) and two with clinicians. Since the views of clinicians are not relevant to the question the results for these focus groups are not reported in the review. Each audio taped session consisted of a semi-structured interview lasting approximately 1.5 hours.

The results were organised according to the antecedent constructs of Braden's Self Help model: Perceived severity of illness; Uncertainty; and Limitation.

The patients identified that education on interpreting angina symptoms was a high priority and felt that they had great difficulty knowing when they were experiencing angina versus some other type of pain. The patients felt that they had difficulty deciding to seek professional/emergency help because they doubted their own judgment, the ER was seen as a burden and also because there had some confusion about how ambulance services and tertiary care centres were organised. Patients stated that they were concerned about medication schedules, dose, side effects; and exercise frequency and acceptable duration. The patients felt that for patients dealing with angina related symptoms needed a forum in which to discuss the difficulties of identifying safe activity limits;. Patients expressed a need for help in dealing with their anxiety and also suggested that education on stress management would be helpful. Patients also gave several suggestions on how to deal with emotional responses and triggers; the most popular were teaching guided imagery and progressive muscle relaxation as means to alleviate anxiety, stress and general tension. Also, a majority of the patients expressed a need for a programme wherein they could learn to develop their chronic stable angina self-management skills.

Karlik 1990[13] conducted a questionnaire study to compare the learning needs of angina patients rated by patients themselves and the nurses who care for them. The results of learning needs identified by nurses are not included here.

The study included 15 patients (11 men, 4 women) aged 26-70 years. The sample consisted of patients experiencing angina who were selected from inpatients admitted to an acute care hospital for cardiac catheterisation. The Cardiac Patient Learning Need Inventory (CPLNI), a 43 item instrument originally designed to measure learning needs of post MI patients, and the Educator Preference Tool were used to assess the learning needs and educator preference of the patients.

The following 8 informational categories assessed: introduction to hospital unit; anatomy and physiology; psychologic; risk factors; medications; diet; activity; and miscellaneous.

In the CPLNI assessment, when the information categories were ranked by inpatient ratings, the categories of risk factors and medications emerged as the most important to learn and the categories of introduction to the hospital unit and diet emerged as the least important to learn. The category of risk factors emerged as the most important to learn and the category of medications emerged as the second most important to learn, and the psychologic category emerged as the least important to learn when ranked by the post discharge patients.

For the Educator Preference Tool, a greater percentage of patients expressed a preference for physicians alone, rather than for nurses alone, to teach them all 8 informational categories. Nurses received the highest percentage by patients in the category of introduction to the hospital unit and the lowest percentage in the categories of risk factors and activity. No patients believed the nurse alone could teach them dietary information. Physicians received the highest percentage by patients in the category of activity and the lowest percentage in the category of diet. Combining the percentages of nurses alone and nurses with others, patients still preferred physicians to teach them all informational categories except introduction to hospital unit.

5.2.2 Economic evidence

No economic studies were found on this question.

5.2.3 Evidence statements

The following themes have been identified on requirements for information:

- on causes of angina
- treatment of angina
- Purpose of each medication
- Medication schedules distinguishing angina from other types of pain
- identification and management of risk factors
- organisation of medical services
- re-introduction of physical activity and exercise options after cardiac event
- Information for family members

Patients requested help with coping with anxiety, depression and stress management and a need for forum to discuss their condition. Patients expressed a need for learning how to manage their condition.

Economic

No economic evidence was found on this question.

5.2.4 Recommendations and link to evidence

Recommendation	**Clearly explain stable angina to the person, including factors that can provoke angina (for example, exertion, emotional stress, exposure to cold, eating a heavy meal) and its long-term course and management. Where relevant, involve the person's family or carers in the discussion.** **Encourage the person with stable angina to ask questions about their angina and its treatment. Provide opportunities for them to voice their concerns and fears.** **Discuss the person's, and if appropriate, their family or carer's ideas, concerns and expectations about their condition, prognosis and treatment. Explore and address any misconceptions about stable angina and its implications for daily activities, heart attack risk and life expectancy.** **Advise the person with stable angina to seek professional help if there is a sudden worsening in the frequency or severity of their angina.** **Discuss with the person the purpose and any risks and benefits of their treatment.** **Explore and address issues according to the person's needs, which may include:** • **self-management skills such as pacing their activities and goal setting** • **concerns about the impact of stress, anxiety or depression on angina** • **advice about physical exertion including sexual activity.** **Advise people that the aim of anti-anginal drug treatment is to prevent episodes of angina and the aim of secondary prevention treatment is to prevent cardiovascular events such as heart attack and stroke.**
Relative values of different outcomes	This review was conducted to eleicit the information needs of patients. As such the outcomes could not be pre—determined. The GDG did consider patient neds might include information on: the condition, the symptoms, prognosis, treatment (choice of treatment and side effects), need and type of rehabilitation, prevention, activities for daily living, QoL.

	Evidence based on qualitative studies confirmed that the following information themes are considered important by stable angina patients: causes of angina and management, identification and management of risk factors, organisation of medical services, physical activity, information to family members, education on stress management, forum/groups for discussion of the condition, self-management programmes, management of anger and depression, preference for educator for delivery of information.
Trade off between clinical benefits and harms	The studies reviewed do not report on harms arising from patient information. The GDG considered that patients had a right to information about their condition and did not believe there were harms that would outweigh benefits.
Economic considerations	No economic evidence was found. There is a negligible cost of staff time associated with providing information to the patient. However the benefits are likely to offset the minimal costs.
Quality of evidence	Evidence from 4 moderate quality studies. One UK study. No specific evidence on needs of subgroups was found.
Other considerations	The GDG used evidence from the studies, and their own experiences as professionals and patients to develop the recommendations about information required for patients. The GDG considered that information should be individualised to each patient and that exploring a patient’s concerns and ideas about their condition and its treatment is pivotal in addressing their information needs. The GDG were also aware of resources such as those developed by the British Heart Foundation, which provide information on the heart and heart conditions that will be useful to patients. The GDG noted that people interviewed were concerned about stress and anger and that these concerns underlie common perceptions about angina and heart disease. The GDG considered that information and advice on stress, anxiety, and depression is not necessarily required by all patients but healthcare professionals may need to address these areas with many patients. The GDG considered it particularly important that patients be advised about appropriate physical activity including sexual activity. The GDG considered it important that patients were given information about risks and benefits of treatments. The GDG considered it important that patients were informed what different drugs and revascularisation strategies would achieve e.g. improve symptoms and this recommendation was

informed by the evidence reviews of interventions.

5.2.5 Research recommendation

The GDG recommended the following research question:

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

6 Treatment & prevention of episodes of angina

6.1 Introduction

In people with stable angina short-acting drugs may be used to relieve episodes of angina and can be taken prophylactically before activities that are likely to bring on an episode. Short-acting drugs include organic nitrates (e.g. glyceryl trinitrate) and nifedipine administered via the buccal mucosa. Glyceryl trinitrate (GTN) is available as a tablet or as a metered dose aerosol spray and has a rapid onset of effect. Glyceryl trinitrate tablets deteriorate when exposed to air and should be discarded after eight weeks in use (BNF). Modified release buccal glyceryl trinitrate tablets can be used for rapid relief of an episode of angina but have a slower onset and longer duration of effect (BNF). Nifedipine capsules can be used for rapid relief of an episode of angina by releasing the fluid within the capsule into the oral cavity.

Organic nitrates act mainly by venodilatation, but coronary vasodilatation may contribute to the therapeutic effect. Nitrates may cause headache and flushing, and repeated use may cause hypotension. Short-acting formulations of nifedipine may cause reflex tachycardia and hypotension.

The GDG were interested in whether there was evidence to support use of nifedipine and evidence about mode of delivery of GTN.

6.2 Short-acting nitrates

6.2.1 Clinical question

What is the clinical /cost effectiveness of short-acting drugs for the management of anginal symptoms?

6.2.2 Clinical evidence

The "Review Protocol" for this topic can be found in Appendix C, the "Search Strategies" in Appendix D, the "List of Included and Excluded Studies" in Appendix E1, the "Clinical Evidence Tables" in Appendix E2, and the "Forest Plots" in Appendix F.

Table 6.1: Sublingual nifedipine versus placebo

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sublingual nifedipine	Placebo	Relative (95% CI)	Absolute	
Mean total work time for stepped increase in load (mins) (follow-up mean 1 hour (a); measured with: minutes; better indicated by higher values)											
Atterhog 1975[14]	randomised trials	serious (b)	no serious inconsistency	no serious indirectness	serious imprecision(d)	None	10	10 (c)	-	MD 5.2 higher (0.81 to 9.59 higher)	⊕OOO VERY LOW
Estimated workload at breakpoint for stepped increase in load (kpm/min) (follow-up mean 1 hour; measured with: kpm/min; better indicated by higher values)											
Atterhog 1975[14]	randomised trials	serious (b)	no serious inconsistency	no serious indirectness	serious imprecision(d)	None	10 (c)	10 (c)	-	MD 146 higher (257.72 to 34.28 higher)	⊕OOO VERY LOW
Total work for stepped increase in load (kpm) (follow-up mean 1 hour (a); measured with: kpm; better indicated by higher values)											
Atterhog 1975[14]	randomised trials	serious (b)	no serious inconsistency	no serious indirectness	serious imprecision(d)	None	10 (c)	10 (c)	-	MD 3685 higher (6489.71 to 880.29 higher)	⊕OOO VERY LOW
Mean total work time for continuous increase in load (mins) (follow-up mean 1 hour; measured with: minutes; better indicated by higher values)											
Atterhog 1975[14]	randomised trials	serious (b)	no serious inconsistency	no serious indirectness	serious imprecision(d)	None	10 (c)	10 (c)	-	MD 1.1 higher (2.2 to 0 higher)	⊕OOO VERY LOW
Estimated workload at breakpoint for continuous increase in load (kpm/min) (follow-up mean 1 hour (a); measured with: kpm/min; better indicated by higher values)											

Atterhog 1975[14]	randomised trials	serious (b)	no serious inconsistency	no serious indirectness	serious imprecision(d)	None	10 (c)	10 (c)	-	MD 112 higher (223.91 to 0.09 higher)	⊕OOO VERY LOW
Total work for continuous increase in load (kpm) (follow-up mean 1 hour (a); measured with: kpm; better indicated by higher values)											
Atterhog 1975[14]	randomised trials	serious (b)	no serious inconsistency	no serious indirectness	serious imprecision(d)	None	10 (c)	10 (c)	-	MD 1146 higher (1888.83 to 403.17 higher)	⊕OOO VERY LOW
Mean work capacity at angina threshold (minutes of exercise) (measured with: minutes; better indicated by higher values)											
Atterhog 1975[14]	randomised trials	serious (b)	no serious inconsistency	no serious indirectness	serious imprecision(d)	None	10	10	-	MD 2.1 higher (3.35 to 0.85 higher)	⊕OOO VERY LOW
Maximal work capacity at maximal exercise level (minutes of exercise) (measured with: minutes; better indicated by higher values)											
Atterhog 1975[14]	randomised trials	serious (b)	no serious inconsistency	no serious indirectness	serious imprecision(d)	None	10 (c)	10 (c)	-	MD 2.3 higher (3.67 to 0.93 higher)	⊕OOO VERY LOW

(a) *There were 4 tests (approx 1hr) in 2 wks after entering the study. Each test was administered within 30 mins of treatment*
(b) *Atterhog 1975[13]: Very small (n=10) sample size.The randomisation process is not reported. Allocation concealment reported. Double blindingreported. ITT not reported.*
(c) *This was a crossover trial*
(d) *very small sample size. The upper and lower confidence limit crosses the minimal important difference (MID).*

Additional data:

Adverse events: No safety issues are reported in the trial. Patients spontaneously reported a feeling of "heat in the face" at an average 14 minutes after 11 of 20 administrations of nifedipine.

Table 6.2: Sublingual nifedipine versus no treatment

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sublingual nifedipine	no treatment	Relative (95% CI)	Absolute	
Mean exercise time to 1mm ST segment depression (secs) (measured with: seconds; better indicated by higher values)											
Pupita 1993[15]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (c)	none	10 (b)	10 (b)	-	MD 146 higher (257.13 to 34.87 higher)	⊕OOO VERYLOW

(a) Pupita 1993[14]: very small sample size. Randomisation details and allocation concealment are not reported. This comparison was not blinded. No patients lost to follow-up.

(b) This was a crossover trial

(c) very small sample size. The upper and lower confidence limit crosses the minimal important difference (MID).

Table 6.3: Sublingual GTN versus sublingual nifedipine

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sublingual GTN	sublingual nifedipine	Relative (95% CI)	Absolute	
Mean exercise time to 1mm ST segment depression (secs) (follow-up 4-6 mins (a); better indicated by higher values)											
Pupita 1993[15]	randomised trials	serious (b)	no serious inconsistency	no serious indirectness	serious imprecision (h)	none	10 (c)	10 (c)	-	MD 90 higher (14.07 lower to 194.07 higher)	⊕OOO VERYLOW
Mean pain severity at 2 minutes post treatment (f) (follow-up 4-6 minutes post drug administration (a); better indicated by lower values)											
Mooss 1989[16]	randomised trials	serious (d)	no serious inconsistency	no serious indirectness	serious imprecision (h)	none	7	6	-	MD 6.3 lower (8.4 to 4.2 lower)	⊕OOO VERYLOW
Mean pain severity at 4 minutes post treatment (better indicated by lower values)											
Mooss 1989[16]	randomised trials	serious (d)	no serious inconsistency	no serious indirectness	serious imprecision(h)	none	7	6	-	MD 5.6 lower (7.08 to 4.12 lower)	⊕OOO VERYLOW
No. of participants with complete pain resolution at 2 minutes post treatment (follow-up 4 to 6 minutes post drug administration (e))											
Mooss 1989[16]	randomised trials	serious (d)	no serious inconsistency	no serious indirectness	Serious imprecision (h)	none	5/7 (71.4%)	0/6 (0%)	RR 9.63 (0.64 to 144.88)	710 more per 1000 (from 340 more to 1090 more)	⊕OOO VERYLOW
No. of participants with complete pain resolution at 4 minutes post treatment (patient pain intensity scoring)											
Mooss	randomised	serious (d)	no serious	no serious	Serious	none	5/7 (71.4%)	0/6 (0%)	RR 9.63 (0.64 to	710 more per 1000 (from 340	⊕OOO

1989[16](g)	trials		inconsistency	indirectness	imprecision (h)				144.88)	more to 1090 more)	VERYLOW

(a) Patients were involved in the study for a duration of approximately 24 days. Assessments from exercise tests were made at the start and end of this period ("off therapy") and three times directly following administration of drugs

(b) Pupita 1993[14]: Randomisation details and allocation concealment are not reported. It is unclear to what extent this comparison was blinded.

(c) This was a crossover trial

(d) Mooss 1989[15]: Randomisation details are not reported.Allocation concealment not reported. It is unclear to what extent this comparison was blinded. The trial is small - with very few participants in each arm of the parallel phase of the trial and only 4 in one arm of the crossover phase.

(e) Patients were followed for four minutes after receiving their randomised drug. Those who had <50% reduction in pain intensity were crossed over to the alternate therapy and followed for another 2 minutes.

(f) Patients were asked to rate the intensity of their chest pain using a 10 cm visual pain intensity rating scale (0= no pain, 10=most sever pain).

(g) Adverse events - Mooss 1989[15]: Adverse reactions attributable to nifedipine and nitroglycerin were negligible. No patients complained of side effects following nifedipine alone. Two of the nifedipine patients complained of flushing following GTN administration and one of these patients developed a headache. One of the seven patients who received GTN alone complained of headache.

(h) Very small sample size. The upper and lower confidence limit crosses the minimal important difference (MID).

Additional data from two studies:

A. **Sublingual GTN versus Buccal GTN: Ryden 1987[17]**
N=126 [n=113 completed the study]. Open RCT with cross over design

Population: All patients had at least a 6 month history of stable angina with a minimum of 5 attacks/week

Mean age 61+/-8 years (range 38-82)

Intervention: 2.5mg or 5mg buccal GTN tablet for the treatment or prophylaxis of angina (tablet held in the cheek for 15 minutes 1) after the relief of angina, 2) after stopping an activity inducing pain or 3) following cessation of activity, when taken prophylactically prior to activity starting)

Comparison: Sublingual GTN

Results: During the study background medications were kept constant. Outcomes recorded in patient diaries and from 2 questionnaires administered at weeks 4 and 6.

- Treatment of anginal attacks: The total number of treated anginal attacks was 31% less during the buccal (n=1381) compared to the sublingual nitroglycerin (n=1978) period ($p<0.001$).

- Prophylactic use: Prophylactic nitroglycerin was altogether utilised on 806 occasions during the sublingual period and on 929 occasions during the buccal period respectively ($p<0.05$). The expected attack of angina pectoris was prevented in 66% of the attempts with sublingual and 74% of the attempts with buccal nitroglycerin ($p<0.05$). When angina pectoris developed despite prophylactic nitroglycerin, the distribution of mild, moderate and severe attacks did not differ significantly between the two formulations.

- Adverse events: Four patients withdrew from a cross over RCT due to side effects of buccal GTN (headache 3 patients, flushing 1 patient). Significantly more patients receiving buccal GTN reported a smarting sensation in mouth than those receiving sublingual GTN ($p <0.05$). There were no significant differences between patients receiving buccal and sublingual GTN for occurrence of headache, dizziness or flushing, as reported following active enquiry.

- General preference for drug: Given the opportunity to select only one of the two nitroglycerin formulations for future use 65% ($p<0.05$) would have preferred the buccal and 19% the sublingual, while 16% did not have any particular preference. When patients were asked to give their preference for one of the two formulations considering solely the prophylactic use, 81% preferred buccal and 4% sublingual nitroglycerin, while 15% did not express any preference ($p<0.05$).

B. Sublingual GTN versus Spray GTN: Sandler 1967[18]

Quasi RCT with crossover design (n=23)

Population: People with stable angina of duration range 3–72 months with attacks occurring 3 to 40 times weekly.

Previous MI = 4/23 participants

Age range 39–69 years

Male = 20/23 participants

Intervention: Glyceryl trinitrate aerosol delivering 0.13 mg of the drug per inhalation

Comparisons: 1) Placebo aerosol 2) Standard tablets of 0.5 mg of glyceryl trinitrate

Results: SD (standard deviation) not reported for results. Results reported as narrative.

Exercise tests (using a modification of the Master two-step test) were carried out at the same time each day, in the same environment, and with the same technical staff.

No information about concurrent therapy is reported.

Mean change in exercise undertaken (no. of circuits over the steps)

Sublingual GTN tablet before exercise = 80.9

Sublingual GTN tablet after exercise = 80.0

Mean change = +0.9 circuits

GTN spray before exercise = 83.5

GTN spray after exercise = 81.5

Mean change = +2.0

Placebo aerosol before exercise: 83.0

Placebo after exercise: 80.9

Mean change: +2.1

p = non significant (reported by author)

Time taken to develop angina (sec)

Sublingual GTN tablet – Time taken for angina to develop (sec): mean change =+68.2 sec

GTN spray- Time taken for angina to develop (sec): Mean change = +14.5 sec

Placebo aerosol time taken for angina to develop (sec):+64.9 sec

p = non significant (reported by author)

Duration of angina: (sec)

Sublingual GTN tablet: 158.9 sec

GTN spray: 158.9 sec

Placebo aerosol: 218. 0 sec

p = non significant (reported by author)

Patient assessment: Outpatient assessment showed that 10 patients regarded the active aerosol as more effective in relieving anginal pain, 11 chose the placebo aerosol, while two regarded active and placebo aerosols as equally effective. Only 2 patients thought that tablets were better than aerosol. The only side effect encountered with the active aerosols was headache, which occurred in 6 patients.

6.2.3 Economic evidence

No economic studies were identified on this question. We calculated the range of cost per dose based on the unit cost reported in the BNF59[19].

Table 6.4 Drug cost – short-acting drugs

	Specific drugs and doses	Cost per dose* (£)
Short-acting nitrate tablets	Low = glyceryl trinitrate 300 micrograms	0.05
	High = glyceryl trinitrate 600 micrograms	0.28
Short-acting nitrate spray	Glyceryl trinitrate 400 micrograms	0.03
Short-acting nifedipine capsules	Low = nifedipine 5mg	0.07
	High = nifedipine 10mg	0.09

* dose = 2 tablets or 2 sprays

Overall the drug cost of short-acting nitrate spray is lower than the drug cost of sublingual nitrate tablets or nifedipine capsules.

6.2.4 Evidence statements

Clinical

Sublingual nifedipine versus placebo

Atterhog 1975[14]: Evidence from one cross over RCT shows that compared to placebo, prophylactic sublingual nifedipine was associated with significantly higher mean total work time for stepped increase in load (mins) [MD 5.20 [0.81 to 9.59]]; estimated workload at breakpoint for stepped increase in load (kpm/min) (MD 146.00 [34.28 to 257.72]; total work for stepped increase in load (kpm) (MD 3685.00 [880.29 to, 6489.71]); mean total work time for continuous increase in load (mins) (MD 1.10 [0.00 to 2.20]); estimated workload at breakpoint for continuous increase in load (kpm/min) (MD 112.00 [0.09 to 223.91]); total work for continuous increase in load (kpm) (MD 1146.00 [403.17 to 1888.83]); mean work capacity at angina threshold (mins of exercise): (MD 2.10 [0.85 to 3.35]) and maximal work capacity at maximal exercise level (mins of exercise): MD 2.30 [0.93 to 3.67].

Sublingual nifedipine versus no treatment

Pupita 1993[15]: Evidence from one cross over RCT shows that compared to no treatment, sublingual nifedipine significantly increased the mean exercise time to 1mm ST depression (sec): MD 146.00 [34.87 to 257.13].

Sublingual GTN versus sublingual nifedipine

Mooss 1989[16]: Evidence from one parallel RCT shows that sublingual GTN was significantly more effective than sublingual nifedipine in reducing pain severity (mean pain intensity rating) at 2 minutes post treatment: MD -6.30 [-8.40 to -4.20] and at reducing pain severity (mean pain intensity rating) 4 minutes post treatment: MD -5.60 [-7.08 to -4.12]. By four minutes only 2 of 6 participants in the sublingual nifedipine group had >50% reduction in mean pain intensity.

Mooss 1989[16]: sublingual GTN was significantly more effective than sublingual nifedipine in providing complete pain resolution at 2 minutes post treatment: RR 9.63 [0.64 to 144.88] and complete pain resolution at 4 minutes post treatment: RR 9.63 [0.64 to 144.88].

Pupita 1993[15]: There was no statistically significant difference between sublingual GTN and sublingual nifedipine in the mean exercise time to 1mm ST depression (sec): MD 90.00 [-14.07 to 194.07].

Economic

No economic evidence was found on this question. A simple cost analysis showed a small difference in drug costs between short-acting nitrates and nifedipine and between spray and sublingual short-acting nitrates; spray nitrates are the least costly.

6.2.5 Recommendations and link to evidence

Recommendation	**Offer a short-acting nitrate for preventing and treating episodes of angina. Advise people with stable angina:** • **how to administer the short-acting nitrate** • **to use it immediately before any planned exercise or exertion** • **that side effects such as flushing, headache and light-headedness may occur** • **to sit down or find something to hold on to if feeling light-headed.** **When a short-acting nitrate is being used to treat episodes of angina, advise people:** • **to repeat the dose after 5 minutes if the pain has not gone** • **to call an emergency ambulance if the pain has not gone 5 minutes after taking a second dose.**
Relative values of different outcomes	The outcome of interest was relief and prevention of episodes of angina.
Trade off between clinical benefits and harms	Evidence from two small randomised trials suggests that sublingual nifedipine increases measures of exercise capacity on a treadmill relative to placebo or to no treatment. Evidence from one very small trial showed that sublingual glyceryl trinitrate was more effective than sublingual nifedipine at reducing pain severity and providing complete symptom relief at two and four minutes after treatment. One trial reported that buccal glyceryl trinitrate tablet (held in cheek for 15 minutes) is more effective than sublingual glyceryl trinitrate tablet at reducing the number of angina episodes requiring treatment and at preventing expected angina attacks. One trial compared sublingual glyceryl trinitrate tablets with glyceryl trinitrate spray during daily exercise tests for six days and reported no significant differences in the amount of exercise or in the time to onset of anginal symptoms between the two treatment groups. The GDG concluded that people with stable angina should be

	offered a short-acting drug to relieve episodes of angina. Weak evidence suggests that glyceryl trinitrate relieves episodes of angina more effectively than nifedipine.
Economic considerations	No economic evidence on the use of short-acting drugs was available for review. As glyceryl trinitrate is more effective at relieving episodes of angina and it does not increase costs compared to nifedipine, this drug is likely to be more cost-effective.
Quality of evidence	The trials in this review were very small and of poor quality. No economic evidence was available.
Other considerations	The GDG noted that glyceryl trinitrate spray is easy to use and can be stored over long periods without loss of effect. After exposure to air glyceryl trinitrate tablets loose efficacy and should be discarded after eight weeks in use[19]. An advantage of glyceryl trinitrate tablets is that they can be discarded as soon as the angina episode is relieved to avoid the onset of adverse effects (including headache). The GDG did not however consider they could recommend one formulation of GTN over another and formulation should be chosen according to patient preferences and needs. The GDG considered it important that patients are given adequate information regarding use of short-acting nitrates and made a consensus recommendation about instructions for patients. The GDG considered that people whose episodes of angina had not resolved within 10 mintues should seek medical help. These were informed by the current advice from the British Heart Foundation. (http://www.bhf.org.uk/living_with_a_heart_condition/understanding_heart_conditions/types_of_heart_conditions/angina.aspx)

7 Beta blockers vs. calcium channel blockers

7.1 Introduction

Anti-anginal drugs prevent attacks of angina by decreasing myocardial oxygen consumption (by lowering heart rate, blood pressure, myocardial loading, or myocardial contractility) and/or by increasing myocardial oxygen supply (by increasing coronary blood flow).

Evidence that monotherapy with single anti-anginal agents prevents attacks of angina has been reviewed previously. The quantity and quality of this evidence is limited but there is consensus that BBs and CCBs are effective in the treatment of people with stable angina [20-23].

The aim of this review was to determine whether BBs or CCBs offer advantages as first-line treatment for people with stable angina. The review includes evidence from nine trials of monotherapy with BBs versus monotherapy with CCBs.

Beta blockers

Beta blockers reduce myocardial oxygen consumption by competitive inhibition of beta-adrenoceptors, which lowers heart rate, blood pressure, and myocardial contractility. The bradycardia prolongs diastole, thereby increasing the period of maximal coronary blood flow. Relative contra-indications to beta-blockade include obstructive airways disease, acute heart failure, and impaired atrioventricular conduction. Side effects of BBs include fatigue, altered carbohydrate metabolism, peripheral vasoconstriction, sexual dysfunction, and bronchoconstriction. Some BBs (e.g. atenolol, metoprolol, bisoprolol) are relatively cardioselective with greater inhibition of the cardiac beta1 receptors than the beta2 (bronchial) receptors and therefore have less effect on airways resistance. Atenolol, bisoprolol, and nadolol have a relatively long duration of action and are given once daily. Other BBs with shorter half-lives may be given in slow-release formulations.

In the United Kingdom the most frequently prescribed BBs are atenolol, bisoprolol, and propranolol. The cost of a BB for four weeks is low (e.g. £0.99 for atenolol 50mg daily, £1.33 for bisoprolol 10mg daily)[24].

Calcium channel blockers

Calcium channel blockers inhibit movement of calcium through slow calcium channels of cell membranes in the myocardium, cardiac conduction tissues, and vascular smooth muscle. Calcium channel blockers dilate peripheral and coronary arteries, and to a varying degree depress myocardial contractility and intra-cardiac conduction. Calcium channel blockers include dihydropyridines (e.g. amlodipine), benzothiapines (e.g. diltiazem), and phenylalkylamines (e.g. verapamil). Dihydropyridines may cause reflex tachycardia, flushing, headache, and ankle swelling. Diltiazem and verapamil depress cardiac conduction and cause bradycardia, and should not be given to people with heart block or treated with a BB. Verapamil may cause constipation.

In the United Kingdom the most frequently prescribed CCBs are amlodipine, nifedipine, felodipine, diltiazem, and verapamil. The costs of CCBs for four weeks are higher than the costs of atenolol (e.g. amlodipine 10mg daily £1.43; diltiazem MR 60mg tds £2.93; verapamil 80mg tds £2.07)[24]. Slow release formulations of CCBs are more expensive.

Generic beta blockers, calcium channel blockers included in evidence reviews

A large number of BBs and CCBs are available for clinical use in the UK and different BBs and CCBs have been used in different trials.

We looked at the prescription cost analysis table in the NHS Information Centre. We extracted the number of prescriptions in 2005 and 2008 for BB and CCB dispensed in the community. The GDG reviewed the lists and made a judgement about which drugs were currently used in stable angina and were known to be included in studies.

In this guideline we have considered evidence for the use of the following drugs:

- BB: atenolol, propranolol, bisoprolol, metoprolol, nadolol,
- CCB: amlodipine, diltiazem, felodipine, nifedipine, verapamil

In this review we have assumed that the clinical effects are consistent within a class of drug (e.g. BB or CCB), across a range of doses, and in all trial participants.

7.2 Beta blocker vs. calcium channel blocker

7.2.1 Clinical question

What is the comparative clinical /cost effectiveness of standard antianginal drugs (BBs/CCBs) for the management of angina?

7.2.2 Clinical evidence

The “Review Protocol” for this topic can be found in Appendix C, the “Search Strategies” in Appendix D, the “List of Included and Excluded Studies” in Appendix E1, the “Clinical Evidence Tables” in Appendix E2, and the “Forest Plots” in Appendix F.

Table 7.1: BB vs. CCB for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	BB	CCB	Relative (95% CI)	Absolute	
Exercise duration (min) (metoprolol vs. diltiazem; propranolol vs. diltiazem; propranolol vs. nifedipine) (follow-up 6 weeks-6 months; better indicated by higher values)											
van Dijk 1988[25]; O'Hara 1987[26]; Kawanishi 1992[27]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	88	83	-	MD 0.05 higher (0.82 lower to 0.92 higher)	⊕⊕OO LOW
Time to 1mm ST depression (sec) - metoprolol vs. nifedipine (follow-up 10 weeks; better indicated by higher values)											
Savonitto 1996[28] (IMAGE)	randomised trials	serious (c)	no serious inconsistency	no serious indirectness	serious (b)	none	65	62	-	MD 12 higher (35.06 lower to 59.06 higher)	⊕⊕OO LOW
Time to onset of angina (min) (metoprolol vs. dilitazem; propranolol vs. nifedipine) (follow-up 6 weeks-6 months; better indicated by lower values)											
van Dijk 1988[25]; Kawanishi 1992[27]	randomised trials	serious (d)	no serious inconsistency	no serious indirectness	serious (b)	none	54	49	-	MD 0.63 higher (0.27 lower to 1.53 higher)	⊕⊕OO LOW
Total mortality (atenolol vs. verapamil; metoprolol vs. verapamil; metoprolol vs. verapamil) (follow-up 2.7- 3.4 years)											
Pepine 2003[29] (INVEST); Rehnqvist 1996[30] (APSIS);	randomised trials	serious (e)	no serious inconsistency	no serious indirectness	no serious imprecision	none	915/11715 (7.8%)	898/11670 (7.7%)	RR 1.02 (0.93 to 1.11)	2 more per 1000 (from 5 fewer to 8 more)	⊕⊕⊕O MODERATE
Cardiovascular death (atenolol vs. verapamil; atenolol vs. nifedipine; metoprolol vs. verapamil) (follow-up 2-3.4 years)											
Pepine 2003[29] (INVEST); Dargie 1996[31] (TIBET); Rehnqvist 1996[30]	randomised	serious (f)	no serious	no serious	no serious	none	453/11941	456/11902	RR 0.99 (0.87 to	0 fewer per 1000 (from	⊕⊕⊕O

(APSIS)	trials		inconsistency	indirectness	imprecision		(3.8%)	(3.8%)	1.12)	5 fewer to 4 more)	MODERATE
Non fatal MI (atenolol vs. verapamil; atenolol vs. nifedipine; metoprolol vs. verapamil) (follow-up 2-3.4 years)											
Pepine 2003[29] (INVEST); Dargie 1996[31] (TIBET); Hjemdahl 2006[32] (APSIS)	randomised trials	serious (g)	no serious inconsistency	no serious indirectness	no serious imprecision	none	184/11941 (1.5%)	185/11902 (1.6%)	RR 0.99 (0.81 to 1.22)	0 fewer per 1000 (from 3 fewer to 3 more)	⊕⊕⊕O MODERATE
CV related hospitalisation – (atenolol vs. verapamil) (follow-up mean 2.7 years)											
Pepine 2003[29] (INVEST)	randomised trials	no serious limitations (h)	no serious inconsistency	no serious indirectness	no serious imprecision	none	709/11309 (6.3%)	726/11267 (6.4%)	OR 0.97 (0.88 to 1.08)	2 fewer per 1000 (from 7 fewer to 5 more)	⊕⊕⊕⊕ HIGH
Non fatal CV events (combined) – (metoprolol vs. verapamil)(follow-up median 3.4 years)											
Rehnqvist 1996[30] (APSIS)	randomised trials	serious (i)	no serious inconsistency	no serious indirectness	serious (j)	none	106/406 (26.1%)	98/403 (24.3%)	RR 1.07 (0.85 to 1.36)	17 more per 1000 (from 36 fewer to 88 more)	⊕⊕OO LOW
Angina episodes/week (atenolol vs. verapamil; metoprolol vs. diltiazem; propranolol vs. nifedipine; metoprolol vs. nifedipine) (follow-up 6 weeks-2.7 years; better indicated by lower values)											
Pepine 2003[29] (INVEST); van Dijk 1988[25]; Kawanishi 1992[27]; Savonitto 1996[28] (IMAGE) (s)	randomised trials	serious (k)	no serious inconsistency	no serious indirectness	no serious imprecision	none	11424	11377	-	MD 0.11 higher (0.07 to 0.15 higher)	⊕⊕⊕O MODERATE
Prevalence of angina – (atenolol vs. verapamil) (follow-up mean 2.7 years)											
Pepine 2003[29] (INVEST)	randomised trials	no serious limitations (h)	no serious inconsistency	no serious indirectness	serious (j)	none	228/11309 (2%)	261/11267 (2.3%)	RR 0.87 (0.73 to 1.04)	3 fewer per 1000 (from 6 fewer to 1 more)	⊕⊕⊕O MODERATE
Severity of angina assessed by investigator (moderate/markedly improved) – (nadolol vs. amlodipine) (follow-up 6 months)											

Singh 1993[33]	randomised trials	serious (l)	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/39 (53.8%)	29/39 (74.4%)	RR 0.72 (0.51 to 1.02)	208 fewer per 1000 (from 364 fewer to 15 more)	⊕⊕⊕O MODERATE
Severity of angina assessed by patients (moderate/severe) – (nadolol vs. amlodipine) (follow-up 6 months)											
Singh 1993[33]	randomised trials	serious (l)	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/40 (40%)	12/40 (30%)	RR 1.33 (0.73 to 2.45)	99 more per 1000 (from 81 fewer to 435 more)	⊕⊕⊕O MODERATE
Nitroglycerin use – (propranolol vs. nifedipine) (follow-up 6 months; better indicated by lower values)											
Kawanishi 1992[27]	randomised trials	serious (m)	no serious inconsistency	no serious indirectness	no serious imprecision	none	21	16	-	MD 0 higher (0.94 lower to 0.94 higher)	⊕⊕⊕O MODERATE
Adverse effects (head ache) – (metoprolol vs. verapamil) (follow-up median 3.4 years)											
Rehnqvist 1996[30] (APSIS)	randomised trials	serious (i)	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/406 (0.7%)	4/403 (1%)	RR 0.74 (0.17 to 3.31)	3 fewer per 1000 (from 8 fewer to 23 more)	⊕⊕⊕O MODERATE
Adverse effects (GI events) – (metoprolol vs. verapamil) (follow-up median 3.4 years)											
Rehnqvist 1996[30] (APSIS)	randomised trials	serious (i)	no serious inconsistency	no serious indirectness	serious (n)	none	10/406 (2.5%)	22/403 (5.5%)	OR 0.45 (0.22 to 0.94)	29 fewer per 1000 (from 3 fewer to 42 fewer)	⊕⊕OO LOW
Adverse effects (dizziness) – (atenolol vs. verapamil) (follow-up mean 2.7 years)											
Pepine 2003[29] (INVEST)	randomised trials	no serious limitations (h)	no serious inconsistency	no serious indirectness	no serious imprecision	none	151/11309 (1.3%)	154/11267 (1.4%)	RR 0.98 (0.78 to 1.22)	0 fewer per 1000 (from 3 fewer to 3 more)	⊕⊕⊕⊕ HIGH
Adverse effects (lightheadedness) – (atenolol vs. verapamil) (follow-up mean 2.7 years)											

Pepine 2003[29] (INVEST)	randomised trials	no serious limitations (h)	no serious inconsistency	no serious indirectness	no serious imprecision	none	70/11309 (0.6%)	48/11267 (0.4%)	RR 1.45 (1.01 to 2.1)	2 more per 1000 (from 0 more to 5 more)	⊕⊕⊕⊕ HIGH
Adverse effects (overall) (atenolol vs. amlodipine; metoprolol vs. verapamil; nadolol vs. amlodipine) (follow-up 10 weeks-3.4years)											
Pehrsson 2000[34]; Rehnqvist 1996[30] (APSIS); Singh 1993[33] (q)	randomised trials	serious (o)	no serious inconsistency	no serious indirectness	no serious imprecision	none	139/562 (24.7%)	146/559 (26.1%)	RR 0.95 (0.79 to 1.14)	13 fewer per 1000 (from 55 fewer to 37 more)	⊕⊕⊕O MODERATE
Adverse effects (constipation) – (atenolol vs. verapamil) (follow-up mean 2.7 years)											
Pepine 2003[29] (INVEST)	randomised trials	no serious limitations (h)	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/11309 (0.1%)	195/11267 (1.7%)	RR 0.08 (0.05 to 0.13)	16 fewer per 1000 (from 15 fewer to 16 fewer)	⊕⊕⊕⊕ HIGH
Withdrawals due to adverse effects – (atenolol vs. nifedipine) (follow-up mean 2 years)											
Dargie 1996[31] (TIBET) (r)	randomised trials	serious (p)	no serious inconsistency	no serious indirectness	serious (n)	none	60/226 (26.5%)	93/232 (40.1%)	RR 0.66 (0.51 to 0.87)	136 fewer per 1000 (from 52 fewer to 196 fewer)	⊕⊕OO LOW
Combined outcome (death, non fatal MI, non fatal stroke) (diabetes) - atenolol vs. verapamil (follow-up mean 2.7 years)											
Pepine 2003[29] (INVEST)	randomised trials	no serious limitations (h)	no serious inconsistency	no serious indirectness	no serious imprecision	none	450/3231 (13.9%)	463/3169 (14.6%)	RR 0.95 (0.85 to 1.07)	7 fewer per 1000 (from 22 fewer to 10 more)	⊕⊕⊕⊕ HIGH
Combined outcomes (death, non fatal MI, non fatal stroke) (females) - atenolol vs. verapamil (follow-up mean 2.7 years)											
Pepine 2003[29] (INVEST)	randomised trials	no serious limitations (h)	no serious inconsistency	no serious indirectness	no serious imprecision	none	540/5920 (9.1%)	524/5850 (9%)	RR 1.02 (0.91 to 1.14)	2 more per 1000 (from 8 fewer to 13 more)	⊕⊕⊕⊕ HIGH

Combined (death, non fatal MI, non fatal stroke) - subgroup age >70 - atenolol vs. verapamil (follow-up mean 2.7 years)											
Pepine 2003[29] (INVEST)	randomised trials	no serious limitations (h)	no serious inconsistency	no serious indirectness	no serious imprecision	none	664/3829 (17.3%)	596/3694 (16.1%)	RR 1.07 (0.97 to 1.19)	11 more per 1000 (from 5 fewer to 31 more)	⊕⊕⊕⊕ HIGH
Quality of life (sleep disturbance) – (metoprolol vs. verapamil) (follow-up median 3.4 years; better indicated by lower values)											
Rehnqvist 1996[30] (APSIS)	randomised trials	serious (i)	no serious inconsistency	no serious indirectness	serious (b)	none	270	275	-	MD 0.4 lower (1.3 lower to 0.5 higher)	⊕⊕OO LOW
Quality of life (overall life satisfaction) –(metoprolol vs. verapamil) (follow-up median 3.4 years; better indicated by lower values)											
Rehnqvist 1996[30] (APSIS)	randomised trials	serious (i)	no serious inconsistency	no serious indirectness	serious (b)	none	268	275	-	MD 0.7 lower (5.07 lower to 3.67 higher)	⊕⊕OO LOW
Quality of life (psychosomatic symptoms) – (metoprolol vs. verapamil) (follow-up median 3.4 years; better indicated by lower values)											
Rehnqvist 1996[30] (APSIS)	randomised trials	serious (i)	no serious inconsistency	no serious indirectness	serious (b)	none	275	282	-	MD 1.3 lower (3.89 lower to 1.29 higher)	⊕⊕OO LOW

(a) van Dijk 1988[25]; O'Hara 1987[26]; Kawanishi 1992[27]: All 3 studies randomised. Allocation concealment not reported in all 3 studies. All 3 studies double blind. ITT not reported in all 3 studies.

(b) 95% CI includes no effect and the upper and lower CI crosses the MID.

(c) Randomised. Double blind. Allocation concealment not reported. Baseline comparison made. Drop out <20% (11%). Intention to treat analysis not reported.

(d) van Dijk 1988[25]; Kawanishi 1992[27]: Both studies randomised. Allocation concealment not reported in both studies. ITT not reported in both studies. Both studies double blind.

(e) Pepine 2003[29]; Hjemdahl 2006[32] (APSIS); Rehnqvist 1996[30] (APSIS); All 3 randomised. Allocation concealment not reported in all 3 studies and ITT used in all 3 the studies. All 3 studies double blind.

(f) Pepine 2003[29]; Rehnqvist 1996[30] (APSIS); Dargie 1996[31] (TIBET): All 3 studies randomised. Allocation concealment reported in 1 of the 3 studies. ITT reported in all 3 studies. All 3 studies double blind.

(g) Dargie 1996 (TIBET); Pepine 2003[29]; Hjemdahl 2006[32] (APSIS): All 3 studies randomised. Allocation concealment reported in 1 of 3 studies. ITT reported in all 3 studies. All 3 studies double blind.

(h) Randomised. Allocation concealment reported. Double blind. Power calculation reported. Drop-out rate <20% (2.5%). Baseline comparisons made. Intention to treat analysis used.

- (i) *Double blind. Randomised. Allocation concealment not reported. Baseline comparisons made. Power calculation reported. Drop out <20%. Intention to treat analysis reported.*
- (j) *95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.*
- (k) *Pepine 2003[29]; van Dijk 1988[25]; Kawanishi 1992[27]; Savonitto 1996[28]: All 4 studies randomised. Allocation concealment not reported in 3 of the 4 studies. ITT not reported in 3 of the 4 studies. All 4 studies double blind.*
- (l) *Double blind. Randomised. Allocation concealment not reported. Baseline comparisons made. Drop out >20% 23% [(19/80) drop out; 20% (8/40) in the amlodipine group and 27% (11/40) in the nadolol group]. Intention to treat analysis not reported.*
- (m) *Randomised. Double blind. Allocation concealment not reported. Baseline comparisons made. Drop out < 20% (2.8% in nifedipine group and 2.6% in propronolol group). Intention to treat analysis not reported.*
- (n) *95% CI around the pooled estimate of effect includes appreciable benefit or appreciable harm.*
- (o) *Pehrsson 2000[34]; Rehnqvist 1996[30] (APSIS); Singh 1993[33]: Randomised all 3 studies. Allocation concealment not reported in all 3 of the studies. ITT not reported in 2 of the 3 studies. All 3 studies double blind.*
- (p) *Randomised. Double blind. Allocation concealment not reported. Baseline comparisons made. Drop-out >20% [60(27%) for atenolol, 93 (40%) for nifedipine, 64 (29%) for their combination]. Intention to treat analysis reported.*
- (q) *Most commonly reported side effects with nadolol were bradycardia, dizziness, headache, nausea, dyspnoea, palpitations, and fatigue. Most frequently reported side effects with amlodipine were headache, oedema, palpitations, hypoesthesia, and flushing.*
- (r) *Not reported what were the side effects.*
- (s) *The comparisons here are metoprolol +placebo vs. nifedipine +placebo.*

Additional data:

Vliegen 1991[35]

Population: n=56 (n=26 metoprolol, n=30 diltiazem).

People with stable effort induced angina pectoris for at least 3 months. The mean age in the diltiazem group was 58±9 yrs and in the metoprolol group was 64±9 yrs ($p<0.05$);

Intervention: metoprolol 100 mg b.i.d.

The treatment was preceded by a 2 week run-in period. If the patients were already taking antianginal medication (other than short-acting nitrates) this was gradually discontinued. In the second week of the run-in period, only short-acting nitrates were used by all patients. If the patients were not taking antianginal medication, the single blind run-in period was 1 week.

Comparison: diltiazem 120 mg b.i.d.

Follow-up: Follow-up 8 weeks, 20 weeks and 32 weeks.

Results:

- Exercise test (32 weeks): during treatment, mean changes in duration of exercise, time to angina pectoris, time to 1 mm ST segment depression, maximal ST segment depression were not significantly different between the patients on diltiazem and those on metoprolol. However at 20 weeks, exercise duration was longer in patients on diltiazem than in patients on metoprolol.

- Frequency of angina (8 weeks): the mean frequency of anginal attacks/ week decreased in diltiazem group from 5.9 at baseline to 3.5 during treatment ($p<0.05$) and in the metoprolol group from 7.4 at baseline to 4.7 during treatment ($p<0.01$). No differences were observed between the two treatment groups.

Side effects: no significant differences were found in incidence and severity of side effects between the 2 groups.

Drug dosages in each study:

1. Dargie 1996[31] (TIBET) - atenolol 50 mg twice daily, nifedipine (slow release) 20-40 mg twice daily

2. Pepine 2003[29] (INVEST) - Group 1: atenolol 50 mg twice daily + hydrochlorothiazide 25 mg twice daily + trandolapril 2mg/d ; Group 2: verapamil sustained release, 180 mg twice daily + hydrochlorothiazide, 25 mg/d + trandolapril, 2 mg twice daily

3. Pehrsson 2000[34] - amlodipine 10 mg once daily, atenolol 100 mg once daily.

4. van Dijk 1988[25] - diltiazem 240 mg (60 mg four times daily), metoprolol 200 mg (100 mg twice daily)

5. Savonitto 1996[28] (IMAGE)- metoprolol (controlled release, 200 mg once daily), nifedipine (retard, 20 mg tablets twice daily)

6. Rehnqvist 1996[30] (APSIS), Hjemdahl 2006[32] (APSIS)- metoprolol (Seloken ZOC 200 mg once daily), verapamil (Isoptin Retard 240 twice daily)

7. Singh 1993[33] - amlodipine 2.5-10 mg once daily, nadolol 40-160 mg once daily

8. O' Hara 1987[26] - diltiazem 360 mg once daily, propranolol 240 mg once daily

9. Kawanishi 1992[27] - nifedipine 10 mg four times daily vs. propranolol 20mg four times daily (not specified if it is long- or short-acting nifedipine)

7.2.3 Economic evidence

One study[36] included the relevant comparison. This is summarised in the economic evidence profile below. In this cost study from the UK, angina-related healthcare resource use over one year for angina patients who received one of the included drugs was obtained from a UK longitudinal database. Three subgroup analyses were conducted where resource use was monitored for 12 months after: a) patients commenced angina treatment for the first time b) patients were switched to a different angina treatment c) patients had received the same angina treatment for at least one year. Unit costs were obtained from published literature and NHS databases and were attached to resources. No clinical outcome was evaluated. The base case results reported are for patients without any of the following comorbidities: ischaemic heart disease (excluding angina), hypertension, congestive cardiac failure, hypercholesterolaemia and cerebrovascular disease. We report the results for patients with comorbidity as a part of sensitivity analysis. See also Economic Evidence Tables in Appendix G.

Table 7.2: BB vs. CCB – Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
Borghi 2000[36]	Potentially serious limitations (a)	Partial applicability (b)	Atenolol and diltiazem were respectively the BB and CCB evaluated. Resource use data were obtained from a database.

a) Based on a cross-sectional study; only one drug from each group was evaluated, the range of GP visits frequency used in the sensitivity analysis is not reported.

b) Not a full economic evaluation: only costs, not health effects.

Table 7.3: BB vs. CCB – Economic summary of findings

Study	Incremental cost per patient (£)	Incremental effects	ICER	Uncertainty
Patients in their first year of antianginal treatment				
Borghi 2000[36]	Saves 358 (a)	NR	NA	Subgroup analysis in patients with comorbidities: BB has an incremental cost of £580 per patient. The main cost drivers were the acquisition cost of the anti-anginal drugs, hospitalisation and GP visits and these were varied in a sensitivity analysis. The overall results do not change when: - frequency of GP visits is varied - incidence of hospitalisation is varied (from 0 to double) - the cost of generic drugs is used.
Patients in the year following a change in previous medication				
Borghi 2000[36]	97 (a)	NR	NA	Subgroup analysis in patients with comorbidities: BB has an incremental cost of £232 per patient.. The main cost drivers were the acquisition cost of the anti-anginal drugs, hospitalisation and GP visits and these were varied in a sensitivity analysis. The overall results do not change when: - frequency of GP visits is varied - incidence of hospitalisation is varied (from 0 to double) - the cost of generic drugs is used.
Patients who had received the same treatment during the previous year				
Borghi 2000[36]	Saves 16 (a)	NR	NA	Subgroup analysis in patients with comorbidities: BB saves £221 per patient. The main cost drivers were the acquisition cost of the anti-anginal drugs, hospitalisation and GP visits and these were varied in a sensitivity analysis. The overall results do not

Study	Incremental cost per patient (£)	Incremental effects	ICER	Uncertainty
				change when: - frequency of GP visits is varied - incidence of hospitalisation is varied (from 0 to double) - the cost of generic drugs is used.

(a) 1997/1998 GBP. Costs included were cost of anti-anginal drugs, additional medication, GP-initiated tests, GP and practice nurse visits, outpatient visits, elective and emergency admissions. Resource costs were obtained NHS databases and UK cost studies.

7.2.4 Evidence statements

Clinical

BB vs. CCB

Clinical efficacy:

Pepine 2003[29] (INVEST), Van Dijk 1988[25], Kawanishi 1992[27], Savonitto 1996[28] (IMAGE): Evidence from 4 RCT's shows that there were significantly fewer anginal episodes/week [MD 0.11 (0.07 to 0.15)] with CCB (verapamil, diltiazem, nifedipine) compared with BB (atenolol, metoprolol, propranolol) (follow-up 6 weeks–2.7 years).

Van Dijk 1988[25], O'Hara 1987[26], Kawanishi 1992[27]: Evidence from 3 RCTs shows that there was no significant difference between BB (metoprolol, propranolol) and CCB (diltiazem, nifedipine) for exercise duration (min) [MD 0.05 (-0.82 to 0.92)] (follow-up 6 weeks–6 months).

Savonitto 1996[28] (IMAGE): Evidence from one RCT shows that there was no significant difference between BB (metoprolol) and CCB (nifedipine) for time to 1mm ST segment depression [MD 12 (-35.06 to 59.06)] (follow-up 10 weeks).

Van Dijk 1988[25], Kawanishi 1992[27]: Evidence from 2 RCTs shows that there was no significant difference between BB (metoprolol, propranolol) and CCB (diltiazem, nifedipine) for time to onset of angina (min) [MD 0.63 (-0.27 to 1.53)] (follow-up 6 weeks–6 months).

Pepine 2003[29] (INVEST), Rehnqvist 1996[30] (APSIS): Evidence from 2 RCTs shows that there was no significant difference between BB (atenolol, metoprolol) and CCB (verapamil) for total mortality [RR 1.02 (0.93 to 1.11)]. (follow-up 2.7–3.4 years)

Pepine 2003[29] (INVEST), Dargie 1996[31] (TIBET), Rehnqvist 1996[30] (APSIS): Evidence from 3 RCTs shows that there was no significant difference between BB (atenolol, metoprolol) and CCB (verapamil, nifedipine) for cardiovascular death [RR 0.99 (0.87 to 1.12)] (follow-up

2–3.4 years).

Pepine 2003[29] (INVEST), Dargie 1996[31] (TIBET), Hjemdahl 2006[32] (APSIS): Evidence from 3 RCTs shows that there was no significant difference between BB (atenolol, metoprolol) and CCB (verapamil, nifedipine) for non fatal MI [RR 0.99 (0.81 to 1.22)] (follow-up 2–3.4 years).

Pepine 2003[29] (INVEST): Evidence from one RCT shows that there was no significant difference between BB (atenolol) and CCB (verapamil) for cardiovascular related hospitalisation [RR 0.97 (0.88 to 1.08)] (follow-up mean 2.7 years).

Rehnqvist 1996[30] (APSIS): Evidence from one RCT shows that there was no significant difference between BB (metoprolol) and CCB (verapamil) for non fatal CV events (acute MI, incapacitating or unstable angina, cerebrovascular events or peripheral vascular events). [RR 1.07 (0.85 to 1.36)] (Follow-up median 3.4 years).

Pepine 2003[29] (INVEST): Evidence from one RCT shows that there was no significant difference between BB (atenolol) and CCB (verapamil) for prevalence of angina [RR 0.87 (0.73 to 1.04)] (follow-up mean 2.7 years).

Singh 1993[33]: Evidence from one RCT shows that there was no significant difference between BB (nadolol) and CCB (amlodpine) for severity of angina (assessed by investigators as moderate/markedly improved) [RR 0.72 (0.51 to 1.02)] (follow-up 6 months).

Singh 1993[33]: Evidence from one RCT shows that there was no significant difference between BB (nadolol) and CCB (amlodipine) for severity of angina (assessed by patients as moderate/severe) [RR 1.33 (0.73 to 2.45)] (follow-up 6 months).

Kawanishi 1992[27]: Evidence from one RCT shows that there was no significant difference between BB (propranolol) and CCB (nifedipine) for use of nitroglycerin tablets/week [MD 0 (-0.94 to 0.94)] (follow-up 6 months).

Rehnqvist 1996[30] (APSIS): Evidence from one RCT shows that there was no significant difference between BB (metoprolol) and CCB (verapamil) for quality of life psychosomatic symptoms [MD -1.3 (-3.89 to 1.29)], overall life satisfaction [MD -0.7 (-5.07 to 3.67)], and sleep disturbance [MD -0.4 (-1.3 to 0.5)] [(follow-up median 3.4 years).

Pepine 2003[29] (INVEST): Evidence from one RCT shows that there was no significant difference between BB and CCB for combined outcomes (death, non fatal MI, non fatal stroke) in sub group analyses conducted for age> 70 years [RR 1.07 (0.97 to 1.19)], female gender [RR 1.02 (0.91 to 1.14)] and people with diabetes [RR 0.95 (0.85 to 1.07)] (follow-up mean 2.7 years).

Adverse effects:

Dargie 1996[31] (TIBET): Evidence from one RCT shows that there were significantly more withdrawals due to adverse effects [RR 0.66 (0.51 to 0.87)] with CCB (nifedipine) compared to BB (atenolol) (follow-up mean 2 years).

Pepine 2003[29] (INVEST): Evidence from one RCT shows that there were significantly more adverse effects (constipation) [RR 0.08 (0.05 to 0.13)] with CCB (verapamil) compared to BB (atenolol) (follow-up mean 2.7 years).

Pepine 2003[29] (INVEST): Evidence from one RCT shows that there were significantly more adverse effects (light headedness) [RR 1.45 (1.01 to 2.1)] with BB (atenolol) compared to CCB (verapamil) (follow-up mean 2.7 years).

Rehnqvist 1996[30] (APSIS): Evidence from one RCT shows that there were significantly more adverse effects (GI events) [RR 0.45 (0.22 to 0.94)] with CCB (verapamil) compared to BB (metoprolol) (median 3.4 years).

Pehrsson 2000[34], Rehnqvist 1996[30] (APSIS), Singh 1993: Evidence from 3 RCTs shows that there was no significant difference between BB (atenolol, metoprolol, nadolol) and CCB (amlodipine, verapamil) for adverse effects (overall) [RR 0.95 (0.79 to 1.14)] (follow-up 10 weeks–3.4 years).

Pepine 2003[29] (INVEST): Evidence from one RCT shows that there was no significant difference between BB (atenolol) and CCB (verapamil) in adverse effects (dizziness) [RR 0.98 (0.78 to 1.22)] (follow-up mean 2.7 years).

Rehnqvist 1996[30] (APSIS): Evidence from one RCT shows that there was no significant difference between BB (metoprolol) and CCB (verapamil) for adverse effects (head ache) [RR 0.74 (0.17 to 3.31)] (follow-up median 3.4 years).

Economic Patients with and without co-morbidities were analysed separately. In patients without comorbidities BB generate fewer costs during the first year of treatment. BB and CCB have similar costs after the first year. In patients with comorbidities BB generate more costs also during the first year. This evidence has potentially serious limitations and partial applicability.

7.2.5 Recommendations and link to evidence

Recommendation	**Offer either a beta blocker or a calcium channel blocker as first-line treatment for stable angina. Decide which drug to use based on comorbidities, contraindications and the person's preference.** **If the person cannot tolerate the beta blocker or calcium channel blocker, consider switching to the other option (calcium channel blocker or beta blocker).** **Do not routinely offer anti-anginal drugs other than beta blockers or calcium channel blockers as first-line treatment for stable angina.**
Relative values of different outcomes	The outcomes of most interest were long-term mortality (total and cardiovascular) and rates of major adverse cardiovascular events (myocardial infarction, stroke, myocardial revascularisation). Other outcomes included were measures of symptom severity (frequency of angina, exercise test outcomes).
Trade off between clinical benefits and harms	We found no evidence of a difference in total or cardiovascular mortality, or in risk of myocardial infarction or stroke, between people with stable angina treated with CCB or BB. In one large trial the effect of treatment with CCB and BB on a combined endpoint (death, non-fatal myocardial infarction, non-fatal stroke) was consistent across subgroups, including women, and people with diabetes or aged over 70 years. In one high quality trial the prevalence of angina two years after randomisation was similar amongst people treated with sustained release verapamil and amongst people treated with atenolol. On the other hand, evidence from four randomised controlled trials suggests that there are 0.11 fewer angina episodes per week amongst patients treated with CCB than amongst patients treated with BB. This difference equates to a single episode of angina every nine weeks and the GDG did not consider this to be of major clinical significance. In one trial there was no difference in quality of life assessed with the Cornell Medical Index between patients treated with CCB or with BB. There is no evidence of a consistent and clinically important difference in the rate of adverse events between patients treated with BB or CCB. In one large trial treatment with verapamil was associated with constipation but treatment with

atenolol was associated with light-headedness.

The GDG concluded that there is no evidence to discriminate between BB and CCB for the initial treatment of people with stable angina.

Evidence to guide treatment if monotherapy with a BB or a CCB is not tolerated or does not control symptoms of angina is very limited. The GDG reached a consensus that if one class of anti-anginal drug is not tolerated or is ineffective a switch to the other class of anti-anginal drug can be considered.

Economic considerations

The cost of treatments with BB and CCB and their consequences is similar after the first year. The presence of comorbidities might influence the level of resource use (e.g. admissions) during the first year.

Quality of evidence

Randomised trials of BBs and CCBs in people with stable angina have mainly studied older drugs within each drug class (e.g. propranolol, atenolol, metoprolol, nifedipine, diltiazem, verapamil). The trials selectively recruited patients who were suitable for treatment with either a BB or CCB.

Information about the long term effects of BBs and CCBs in the treatment of people with stable angina is very limited. Most trials were not designed to study the effects of treatment on mortality or other major cardiovascular outcomes, are limited by small study size, and only report short to medium term follow-up. One large trial was designed to detect a difference in the composite rate of death, non-fatal myocardial infarction, and non-fatal stroke at two years.[29]

The economic evidence has potentially serious limitations (it was based on a cross-sectional study and only one drug from each group was evaluated) and partial applicability (only costs, not health effects were measured).

Other considerations	The GDG recognised the historical consensus that monotherapy with BB or CCB is effective for the prevention of attacks of angina. The GDG was also aware that monotherapy with organic nitrates is limited by the development of tolerance, and that evidence to support monotherapy with other antianginal drugs (nicorandil, ivabradine, ranolazine) is very limited. The GDG concluded that anti-anginal drugs other than BBs or CCBs should not be used as first line treatments for stable angina. Previous guidelines[20-22] have suggested that BBs should be the first-line treatment for stable angina because of evidence that beta-blockade reduces mortality after acute myocardial infarction[37] and in people with chronic heart failure[38,39]. It has also been suggested that short-acting dihydropyridines may have deleterious effects in people with coronary artery disease[40]. We found no evidence to differentiate between the use of BB versus the use of CCB for first-line treatment of stable angina. The GDG were also aware of a consensus that BBs and CCBs have a class effect on symptoms of angina, but that the potential for a particular drug to cause adverse effects may be influenced by its pharmacological profile (for example cardioselectivity for BBs and effects on intra-cardiac conduction for CCBs). The GDG considered that the available evidence did not support a recommendation to use a specific BB or CCB. Nevertheless, clinicians should be aware that evidence for anti-anginal efficacy is mainly confined to the use of a small number of older agents (e.g. propranolol, atenolol, metoprolol, nifedipine, diltiazem, verapamil), and clinicians should consider comorbidity, contra-indications and patient preference when selecting a first-line anti-anginal agent. The difference in cost between BBs and CCBs is small and was not considered significant by the GDG. The choice of initial treatment should therefore be determined by co-morbidity, contraindications and patient preference.

8 Combination of beta blockers and calcium channel blockers

8.1 Introduction

This guideline identifies BBs and CCBs as first-line anti-anginal agents for the treatment of people with stable angina. In some people with angina monotherapy with a BB or CCB will control the symptoms but other people may continue to experience episodes of angina. In these people future treatment options include switching to an alternative anti-anginal drug, or addition of a second anti-anginal drug. The GDG were also interested to know whether there is long term benefit from using more than one drug even if symptoms are controlled.

In this section we review evidence that the addition of a BB to a CCB, or the addition of a CCB to a BB improves symptoms or clinical outcomes in people with stable angina.

8.2 Beta blocker vs. beta blocker+calcium channel blocker

8.2.1 Clinical question

What is the comparative clinical/cost effectiveness of BB vs. BB+CCB for the management of angina?

8.2.2 Clinical evidence

The “Review Protocol” for this topic can be found in Appendix C, the “Search Strategies” in Appendix D, the “List of Included and Excluded Studies” in Appendix E1, the “Clinical Evidence Tables” in Appendix E2, and the “Forest Plots” in Appendix F.

Table 8.1: BB vs. BB + CCB for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	BB	BB +CCB	Relative (95% CI)	Absolute	
Exercise time (min) (follow-up 10 weeks-6 months; better indicated by higher values) (propranolol vs. propranolol+nifedipine; propranolol vs. propranolol+dilitazem; propranolol vs. propranolol+nifedipine)											
Tweddel 1981[41]; O'Hara 1987[26]; Kawanishi 1992[27]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	73	41	-	MD 0.89 lower (1.67 to 0.11 lower)	⊕⊕OO LOW
Time to onset of angina (min) – (propranolol vs. propranolol+nifedipine) (follow-up 6 months; better indicated by highervalues)											
Kawanishi 1992[27] (k)	randomised trials	serious (c)	no serious inconsistency	no serious indirectness	serious (b)	none	21	16	-	MD 0.2 higher (1.13 lower to 1.53 higher)	⊕⊕OO LOW
Angina attacks/week (follow-up 10weeks-6 months; better indicated by lower values) (propranolol vs. propranolol+nifedipine; metoprolol vs. metoprolol+nifedipine)											
Kawanishi 1992[27]; Savonitto 1996[28] (IMAGE)	randomised trials	serious (d)	no serious inconsistency	no serious indirectness	no serious imprecision	none	82	77	-	MD 0.43 higher (0.56 lower to 1.41 higher)	⊕⊕⊕O MODERATE
Angina attacks/day –(propranolol vs. propranolol+nifedipine)(follow-up 10 weeks; better indicated by lower values)											
Tweddel 1981[41]	randomised trials	serious (e)	no serious inconsistency	no serious indirectness	serious (b)	none	18	18	-	MD 3 higher (2.49 lower to 8.49 higher)	⊕⊕OO LOW
Nitroglycerin tablets/week –(propranolol vs. propranolol+nifedipine) (follow-up 6 months; better indicated by lower values)											
Kawanishi 1992[27]	randomised trials	serious (c)	no serious inconsistency	no serious indirectness	no serious imprecision	none	21	16	-	MD 0.4 higher (0.15 lower to 0.95 higher)	⊕⊕⊕O MODERATE

Cardiac death – (atenolol vs. atenolol+nifedipine) (follow-up mean 2 years)											
Dargie 1996[31] (TIBET)	randomised trials	serious (f)	no serious inconsistency	no serious indirectness	serious (g)	none	3/226 (1.3%)	4/224 (1.8%)	RR 0.74 (0.17 to 3.28)	5 fewer per 1000 (from 15 fewer to 41 more)	⊕⊕OO LOW
Non fatal MI – (atenolol vs. atenolol+nifedipine) (follow-up mean 2 years)											
Dargie 1996[31] (TIBET)	randomised trials	serious (f)	no serious inconsistency	no serious indirectness	serious (g)	none	14/226 (6.2%)	7/224 (3.1%)	RR 1.98 (0.82 to 4.82)	31 more per 1000 (from 6 fewer to 119 more)	⊕⊕OO LOW
Withdrawals due to side effects – (atenolol vs. atenolol+nifedipine) (follow-up mean 2 years)											
Dargie 1996[31] (TIBET) (j)	randomised trials	serious (f)	no serious inconsistency	no serious indirectness	serious (g)	none	60/226 (26.5%)	64/224 (28.6%)	RR 0.93 (0.69 to 1.25)	20 fewer per 1000 (from 89 fewer to 71 more)	⊕⊕OO LOW
Adverse effects (overall) – (atenolol vs. atenolol+amlodipine) (follow-up 10 weeks)											
Pehrsson 2000[34]	randomised trials	serious (h)	no serious inconsistency	no serious indirectness	serious (g)	none	52/116 (44.8%)	59/119 (49.6%)	RR 0.9 (0.69 to 1.19)	50 fewer per 1000 (from 154 fewer to 94 more)	⊕⊕OO LOW
Time to 1mm ST depression (sec)- (metoprolol vs. metoprolol+nifedipine) (follow-up 10 weeks; better indicated by higher values)											
Savonitto 1996[28] (IMAGE)	randomised trials	serious (i)	no serious inconsistency	no serious indirectness	serious (b)	none	65	63	-	MD 59 lower (107.3 to 10.7 lower)	⊕⊕OO LOW

(a) O'Hara 1987[25]: Randomised cross over trial. Double blind. Allocation concealment not reported. Baseline characteristics not reported. Drop out >20% (32%). Intention to treat analysis not reported. Kawanishi 1992[26]: Randomised. Double blind. Allocation concealment not reported. Baseline comparisons made. Drop out < 20% (2.8% in nifedipine group and 2.6% in propronolol group). Intention to treat analysis not reported. Tweddel 1981[40]: Randomised cross over trial. Double blind. Baseline characteristics not reported. Allocation concealment not reported. Drop-out >20% (28%). Intention to treat analysis not reported.

(b) 95% CI includes no effect and the upper and lower CI crosses the MID.

(c) Kawanishi 1992[26] : Randomised. Double blind. Allocation concealment not reported. Baseline comparisons made. Drop out < 20% (2.8% in nifedipine group and 2.6% in propronolol group). Intention to treat analysis not reported.

(d) Kawanishi 1992[26]: Randomised. Double blind. Allocation concealment not reported. Baseline comparisons made. Drop out < 20% (2.8% in nifedipine group and 2.6% in propronolol group). Intention to treat analysis not reported. Savonitto 1996[27]: Randomised. Double blind. Allocation concealment not reported. Baseline comparison made. Drop out <20% (11%). Intention to treat analysis not reported.

(e) *Tweddel 1981[40]: Randomised cross over trial. Double blind. Baseline characteristics not reported. Allocation concealment not reported. Drop-out >20% (28%). Intention to treat analysis not reported.*
(f) *Dargie 1996[31] (TIBET): Randomised. Double blind. Allocation concealment not reported. Baseline comparisons made. Drop-out >20% [60(27%) for atenolol, 93 (40%) for nifedipine, 64 (29%) for their combination]. Intention to treat analysis reported.*
(g) *95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.*
(h) *Pehrsson 2000[33]: Randomised. Double blind. Allocation concealment not reported. Drop out <20% Baseline comparisons made. Intention to treat analysis not reported.*
(i) *Savonitto 1996[27] : Randomised. Double blind. Allocation concealment not reported. Baseline comparison made. Drop out <20% (11%). Intention to treat analysis not reported.*
(j) *Not reported what were the side effects*
(k) *At baseline (n= 74 participants): NYHA angina class I (4%), class II (73%), class III (23%)*

Drug dosages in each study:

1. Pehrsson 2000[34] - amlodipine 10 mg once daily, atenolol 100 mg once daily.
2. Dargie 1996[31] (TIBET) - atenolol 50 mg twice daily, nifedipine (slow release) 20-40 mg twice daily
3. O' Hara[26] - 1987 - diltiazem 360 mg once daily, propranolol 240 mg once daily,
4. Savonitto 1996[28] (IMAGE study)- metoprolol (controlled release, 200 mg once daily), nifedipine (Retard, 20 mg tablets twice daily)
5. Kawanishi 1992[27] - nifedipine 10 mg four times daily, propranolol 20 mg four times daily (not specified if it is long- or short-acting nifedipine)
6. Tweddel 1981[41] - nifedipine 10 mg three times daily, propranolol dose not reported. After an initial placebo phase patients were commenced on propranolol, with increasing doses at weekly intervals until a resting heart rate of less than 60 beats/min was obtained, and there was a 30% reduction in exercise tachycardia. Patients were then randomly allocated to the addition of placebo or nifedipine in a dose of 10mg, three times daily to their Β-blocker therapy in a double blind cross over fashion over two consecutive 3 week periods. Finally the Β-blocker dose of propranolol was gradually halved over a 2 week period. Patients continued on the 50% Β-blocker dose and nifedipine for a further 2 weeks

8.2.3 Economic evidence

No economic studies were identified on this question. We calculated the range (low and high) of daily and annual cost of using a combination of CCB and BB compared to single drugs based on the unit cost reported in the BNF59[19].

Table 8.2: Cost of single drugs vs combination of CCB and BB

	Specific drugs used for cost range	Additional cost per day (£)	Additional cost per year (£)
CCB	Low = amlodipine	0.04	15
	High = felodipine	0.15	55
BB	Low = atenolol	0.03	11
	High = acebutolol	0.67	245
BB+CCB	Atenolol + nifedipine	0.74	270

The costs of future adverse effects and events were not estimated.

8.2.4 Evidence statements

Clinical **BB vs. BB+CCB**

Clinical efficacy:

Tweddel 1981[41], O'Hara 1987[26], Kawanishi 1992[27]: Evidence from 3 RCTs shows that exercise time (min) [MD -0.89 (-1.67 to -0.11)] was significantly higher with BB+CCB (propranolol+nifedipine, propranolol+diltiazem) compared to BB (propranolol) (follow-up 10 weeks to 6 months).

Savonitto1996[28] (IMAGE): Evidence from one RCT shows that time to 1 mm ST segment depression (sec) [MD -59 (-107.3 to -10.7)] was significantly higher with BB+CCB (metoprolol+nifedipine) than with BB (metoprolol) (follow-up 10 weeks).

Kawanishi 1992[27]: Evidence from one RCT shows that there was no significant difference between BB (propranolol) and BB+CCB (propranolol+nifedipine) for time to onset of angina (min) [MD 0.2 (-1.13 to 1.53)] (follow-up 6 months).

Kawanishi 1992[27], Savonitto 1996[28] (IMAGE): Evidence from 2 RCTs shows that there was no significant difference between BB (propranolol, metoprolol) and BB+CCB (propranolol +nifedipine, metoprolol+nifedipine) for angina attacks/week. [MD 0.43 (-0.56 to 1.41)] (follow-up 10 weeks–6 months).

Tweddel 1981[41]: Evidence from one RCT shows that there was no significant difference between BB (propranolol) and BB+CCB (propranolol+nifedipine) for no. of angina attacks/day. [MD 3 (-2.49 to 8.49)] (follow-up 10 weeks).

Kawanishi 1992[27]: Evidence from one RCT shows that there was no significant difference between BB (propranolol) and BB+CCB (propranolol+nifedipine) for use of nitroglycerin tablets/week. [MD 0.4 (-0.15 to 0.95)] (follow-up 6 months)

Dargie 1996[31] (TIBET): Evidence from one RCT shows that there was no significant difference between BB (atenolol) and BB+CCB (atenolol+nifedipine) for cardiac death. [RR 0.74 (0.17 to 3.28)] (follow-up mean 2 years).

Dargie 1996[31] (TIBET): Evidence from one RCT shows that there was no significant difference between BB (atenolol) and BB+CCB (atenolol+nifedipine) for non fatal MI. [RR 1.98 (0.82 to 4.82)] (follow-up mean 2 years).

Adverse effects:

Dargie 1996[31] (TIBET): Evidence from one RCT shows that there was no

	significant difference between BB (atenolol) and BB+CCB (atenolol +nifedipine) for withdrawal due to side effects [RR 0.93 (0.69 to 1.25)] (follow-up mean 2 years). **Pehrsson 2000[34]:** Evidence from one RCT shows that there was no significant difference between BB (atenolol) and BB+CCB (atenolol +amlodipine) for adverse effects (overall) [RR 0.9 (0.69 to 1.19)] (follow-up 10 weeks).
Economic	No economic evidence was found on this question. A simple cost analysis showed a small increase in drug costs when a CCB is added to the therapy.

8.3 Calcium channel blocker vs. beta blocker + calcium channel blocker

8.3.1 Clinical question

What is the comparative clinical/cost effectiveness of CCB vs. BB+CCB for the management of angina?

8.3.2 Clinical evidence

The “Review Protocol” for this topic can be found in Appendix C, the “Search Strategies” in Appendix D, the “List of Included and Excluded Studies” in Appendix E1, the “Clinical Evidence Tables” in Appendix E2, and the “Forest Plots” in Appendix F

Table 8.3: CCB vs. BB + CCB for stable angina

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CCB	BB +CCB	Relative (95% CI)	Absolute		
Exercise time (min) (follow-up 18 weeks -6 months; better indicated by higher values) (diltiazem vs. propranolol +diltiazem; nifedipine vs. propranolol +nifedipine)												
O'Hara 1987[26]; Kawanishi 1992[27]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	50	26	-	MD 1.91 lower (2.87 to 0.95 lower)	⊕⊕⊕O MODERATE	
Cardiac death (nifedipine vs. atenolol+nifedipine) (follow-up mean 2 years)												
Dargie 1996[31] (TIBET)	randomised trials	serious (b)	no serious inconsistency	no serious indirectness	serious (c)	None	6/232 (2.6%)	4/224 (1.8%)	RR 1.45 (0.41 to 5.06)	8 more per 1000 (from 11 fewer to 72 more)	⊕⊕OO LOW	
Non fatal MI - nifedipine vs. atenolol+nifedipine (follow-up mean 2 years)												
Dargie 1996[31] (TIBET)	randomised trials	serious (b)	no serious inconsistency	no serious indirectness	serious (c)	None	15/232 (6.5%)	7/224 (3.1%)	RR 2.07 (0.86 to 4.98)	33 more per 1000 (from 4 fewer to 124 more)	⊕⊕OO LOW	
Withdrawals due to side effects - nifedipine vs. atenolol+nifedipine (follow-up mean 2 years)												
Dargie 1996[31] (TIBET (h)	randomised trials	serious (b)	no serious inconsistency	no serious indirectness	serious (d)	None	93/232 (40.1%)	64/224 (28.6%)	RR 1.4 (1.08 to 1.82)	114 more per 1000 (from 23 more to 234 more)	⊕⊕OO LOW	
Adverse effects (overall) - amlodipine vs. atenolol+amlodipine (follow-up 10 weeks)												
Pehrsson 2000[34]	randomised trials	serious (e)	no serious inconsistency	no serious indirectness	serious (c)	None	60/116 (51.7%)	59/119 (49.6%)	RR 1.04 (0.81 to 1.34)	20 more per 1000 (from 94 fewer to 169 more)	⊕⊕OO LOW	

Time to onset of angina (min) - nifedipine vs. propranolol+nifedipine (follow-up 6 months; better indicated by higher values)												
Kawanishi 1992[27] (j)	randomised trials	serious (f)	no serious inconsistency	no serious indirectness	serious (g)	None	16	19	-	MD 0.5 lower (1.93 lower to 0.93 higher)	⊕⊕OO LOW	
Angina episodes/week (follow-up 10 weeks-6 months; better indicated by lower values) (nifedipine vs. propranolol+nifedipine; nifedipine vs. metoprolol+nifedipine)												
Kawanishi 1992[27]; Savonitto 1996[28] (IMAGE) (i)	randomised trials	serious (h)	no serious inconsistency	no serious indirectness	no serious imprecision	None	77	76	-	MD 0.1 higher (1.62 lower to 1.82 higher)	⊕⊕⊕O MODERATE	
Nitroglycerin tablets/week - nifedipine vs. propranolol+nifedipine (follow-up 6 months; better indicated by lower values)												
Kawanishi 1992[27]	randomised trials	serious (i)	no serious inconsistency	no serious indirectness	no serious imprecision	None	16	19	-	MD 0.4 lower (1.66 lower to 0.86 higher)	⊕⊕⊕O MODERATE	
Time to 1 mm ST segment depression (sec) - nifedipine vs. metoprolol+nifedipine (follow-up 10 weeks; better indicated by lower values)												
Savonitto 1996[28] (IMAGE)	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	serious[7]	None	62	59	-	MD 70 lower (125.13 to 14.87 lower)	⊕⊕OO LOW	

(a) Kawanishi 1992[26]: Randomised. Double blind. Allocation concealment not reported. Baseline comparisons made. Drop out < 20% (2.8% in nifedipine group and 2.6% in propronolol group). Intention to treat analysis not reported; O'Hara 1987[25]: Randomised cross over trial. Double blind. Allocation concealment not reported. Baseline characteristics not reported. Drop out >20% (32%). Intention to treat analysis not reported.

(b) Dargie 1996[31]: Randomised. Double blind. Allocation concealment not reported. Baseline comparisons made. Drop-out >20% [60(27%) for atenolol, 93 (40%) for nifedipine, 64 (29%) for their combination]. Intention to treat analysis reported.

(c) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.

(d) 95% CI around the pooled estimate of effect includes appreciable benefit or appreciable harm.

(e) Pehrsson 2000[33]: Randomised. Double blind. Allocation concealment not reported. Drop out <20% Baseline comparisons made. Intention to treat analysis not reported.

(f) Kawanishi 1992[26]: Randomised. Double blind. Allocation concealment not reported. Baseline comparisons made. Drop out < 20% (2.8% in nifedipine group and 2.6% in propronolol group). Intention to treat analysis not reported.

(g) 95% CI includes no effect and the upper and lower CI crosses the MID.

(h) Kawanishi 1992[26]: Randomised. Double blind. Allocation concealment not reported. Baseline comparisons made. Drop out < 20% (2.8% in nifedipine group and 2.6% in propronolol group). Intention to treat analysis not reported; Savonitto 1996[27]: Randomised. Double blind. Allocation concealment not reported. Baseline comparison made. Drop out <20% (11%). Intention to treat analysis not reported.

(i) *Kawanishi 1992[26]: Randomised. Double blind. Allocation concealment not reported. Baseline comparisons made. Drop out < 20% (2.8% in nifedipine group and 2.6% in propronolol group). Intention to treat analysis not reported.*
(j) *Savonitto 1996[27]: Randomised. Double blind. Allocation concealment not reported. Baseline comparison made. Drop out <20% (11%). Intention to treat analysis not reported.*

Drug dosages in each study:

1. Pehrsson 2000[34] - amlodipine 10 mg once daily, atenolol 100 mg once daily.
2. Dargie 1996[31] (TIBET) - atenolol 50 mg twice daily, nifedipine (slow release) 20-40 mg twice daily
3. O' Hara[26] - 1987 - diltiazem 360 mg once daily, propranolol 240 mg once daily
4. Savonitto 1996[28] (IMAGE)- metoprolol (controlled release, 200 mg once daily), nifedipine (Retard, 20 mg tablets twice daily)
5. Kawanishi 1992[27] - nifedipine 10 mg four times daily, propranolol 20 mg four times daily (not specified if it is long- or short-acting nifedipine)
6. Tweddel 1981[41] - nifedipine 10 mg three times daily, propranolol dose not reported.

8.3.3 Economic evidence

No economic studies were identified on this question. For drug cost of combination of CCB and BB compared to single drugs see 8.2.3.

8.3.4 Evidence statements

Clinical	<u>**CCB vs. BB+CCB**</u> <u>**Clinical efficacy:**</u> **O'Hara 1987[26], Kawanishi 1992[27]:** Evidence from 2 RCTs shows that exercise time (min) [MD -1.91 (-2.87 to -0.95)] was significantly higher with BB+CCB (propranolol +diltiazem, propranolol+ nifedipine) compared to CCB (diltiazem, nifedipine) (follow-up 18 weeks–6 months). **Savonitto 1996[28] (IMAGE):** Evidence from one RCT shows that time to 1mm ST segment depression (sec) [MD -70 (-125.13 to -14.87)] was significantly higher in the BB+CCB (metoprolol +nifedipine) compared to CCB (nifedipine) (follow-up 10 weeks). **Dargie 1996[31] (TIBET):** Evidence from one RCT shows that there was no significant difference between CCB (nifedipine) and BB+CCB (atenolol +nifedipine) for cardiac death [RR 1.45 (0.41 to 5.06)] (follow-up mean 2 years). **Dargie 1996[31] (TIBET):** Evidence from one RCT shows that there was no significant difference between CCB (nifedipine) and BB+CCB (atenolol +nifedipine) for non fatal MI [RR 2.07 (0.86 to 4.98)] (follow-up mean 2 years). **Kawanishi 1992[27]:** Evidence from one RCT shows that there was

no significant difference between CCB (nifedipine) and BB+CCB (propranolol +nifedipine) for time to onset of angina (min) [MD -0.5 (-1.93 to 0.93)] (follow-up 6 months).

Kawanishi 1992[27], Savonitto 1996[28] (IMAGE): Evidence from 2 RCTs shows that there was no significant difference between CCB (nifedipine) and BB+CCB (propranolol +nifedipine, metoprolol +nifedipine) for angina episodes/week [MD 0.1 (-1.62 to 1.82)] (follow-up 10 weeks–6 months).

Kawanishi 1992[27]: Evidence from one RCT shows that there was no significant difference between CCB (nifedipine) and BB+CCB (propranolol +nifedipine) for no. of nitroglycerin tablets/week [MD -0.4 (-1.66 to 0.86)] (follow-up 6 months).

Adverse effects:

Dargie 1996[31] (TIBET): Evidence From one RCT shows that there were significantly more withdrawals due to side effects [RR 1.4 (1.08 to 1.82)] in CCB (nifedipine) compared to BB+CCB group (atenolol +nifedipine) (follow-up mean 2 years).

Pehrsson 2000[34]: Evidence from one RCT shows that there was no significant difference between CCB (amlodipine) and BB+CCB (atenolol +amlodipine) for adverse effects (overall) [RR 1.04 (0.81 to 1.34)] (follow-up 10 weeks).

Economic

No economic evidence was found on this question. A simple cost analysis showed a small increase in drug costs when a BB is added to the therapy.

8.4 Addition of CCB to basic (or standard) anti-anginal treatment

8.4.1 Clinical question

What is the comparative clinical /cost effectiveness of adding CCB to basic (or standard) anti-anginal treatment for the management of angina?

8.4.2 Clinical Evidence

The ACTION trial reports the effects of adding CCB nifedipine GITS (nifedipine gastrointestinal therapeutic system) to usual anti-anginal treatment. Although not designed to specifically examine the question of the addition of CCB to BB the GDG considered that the trial should be included as significant proportions of patients (80%) were on a BB and the trial provided useful information on long term safety of CCBs. The information from this trial also influenced the GDG in their consideration of the use of three anti-anginal drugs.

Table 8.4: CCB + basic regimen vs. placebo + basic regimen

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CCB +basic regimen	Placebo +basic regimen	Relative (95% CI)	Absolute	
All cause mortality (follow-up mean 4.9 patient-years)											
Poole-Wilson 2004[42] (ACTION) (b,d)	randomised trial	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	310/3825 (8.1%)	291/3840 (7.6%)	RR 1.07 (0.92 to 1.25)	5 more per 1000 (from 6 fewer to 19 more)	⊕⊕⊕⊕ HIGH
Cardiovascular or unknown death (follow-up mean 4.9 years)											
Poole-Wilson 2004[42] (ACTION)	randomised trial	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	178/3825 (4.7%)	177/3840 (4.6%)	RR 1.01 (0.82 to 1.24)	0 more per 1000 (from 8 fewer to 11 more)	⊕⊕⊕⊕ HIGH
MI (follow-up mean 4.9 years)											
Poole-Wilson 2004[42] (ACTION)	randomised trial	no serious limitations (a)	no serious inconsistency	no serious indirectness	serious imprecision (c)	none	320/3825 (8.4%)	296/3840 (7.7%)	RR 1.09 (0.93 to 1.26)	7 more per 1000 (from 5 fewer to 20 more)	⊕⊕⊕O MODERATE
Withdrawal due to adverse effects (follow-up mean 4.9 years)											
Poole-Wilson 2004[42] (ACTION)	randomised trial	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	389/3825 (10.2%)	172/3840 (4.5%)	RR 2.27 (1.91 to 2.7)	57 more per 1000 (from 41 more to 77 more)	⊕⊕⊕⊕ HIGH
Combined outcome (death from any cause, acute MI, refractory angina, new overt heart failure, debilitating stroke and peripheral revascularisation) (subgroup age >65yrs) (follow-up mean 4.9 years)											
Poole-Wilson	randomised	no serious	no serious	no serious	no serious	None	467/1772	466/1776	RR 1 (0.9 to	0 fewer per 1000 (from 26	⊕⊕⊕⊕

2004[42] (ACTION)	trial	limitations (a)	inconsistency	indirectness	imprecision		(26.4%)	(26.2%)	1.12)	fewer to 31 more)	HIGH
Combined outcome (death from any cause, acute MI, refractory angina, new overt heart failure, debilitating stroke and peripheral revascularisation) (subgroup females) (follow-up mean 4.9 years)											
Poole-Wilson 2004[42] (ACTION)	randomised trial	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	166/784 (21.2%)	147/797 (18.4%)	RR 1.15 (0.94 to 1.4)	28 more per 1000 (from 11 fewer to 74 more)	⊕⊕⊕⊕ HIGH
Combined outcome (death from any cause, acute MI, refractory angina, new overt heart failure, debilitating stroke and peripheral revascularisation) (subgroup diabetes) (follow-up mean 4.9 years)											
Poole-Wilson 2004[42] (ACTION)	randomised trial	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	164/565 (29%)	170/545 (31.2%)	RR 0.93 (0.78 to 1.11)	22 fewer per 1000 (from 69 fewer to 34 more)	⊕⊕⊕⊕ HIGH
Combined outcome (death from any cause, acute MI, refractory angina, new overt heart failure, debilitating stroke and peripheral revascularisation) (subgroup age <65 years) (follow-up mean 4.9 years)											
Poole-Wilson 2004[42] (ACTION)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	337/2053 (16.4%)	362/2064 (17.5%)	RR 0.94 (0.82 to 1.07)	11 fewer per 1000 (from 32 fewer to 12 more)	⊕⊕⊕⊕ HIGH
Combined outcome (death from any cause, acute MI, refractory angina, new overt heart failure, debilitating stroke and peripheral revascularisation) (sub group males) (follow-up mean 4.9 years)											
Poole-Wilson 2004[42] (ACTION)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	638/3041 (21%)	681/3043 (22.4%)	RR 0.94 (0.85 to 1.03)	13 fewer per 1000 (from 34 fewer to 7 more)	⊕⊕⊕⊕ HIGH
Combined outcome (death from any cause, acute MI, refractory angina, new overt heart failure, debilitating stroke and peripheral revascularisation) (sub group no diabetes) (follow-up mean 4.9 years)											
Poole-Wilson 2004[42] (ACTION)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	640/3260 (19.6%)	658/3295 (20%)	RR 0.98 (0.89 to 1.08)	4 fewer per 1000 (from 22 fewer to 16 more)	⊕⊕⊕⊕ HIGH

(a) *Poole-Wilson 2004[41] : Sample size calculation reported. Baseline comparison made. Allocation concealment reported. Blocked randomisation. Double blind. Drop-out <20% (12.8% in the nifedipine group and 12.2% in the placebo group). Intention to treat analysis reported.*
(b) *Drug dosage: nifedipine GITS 30 mg once daily, increasing to 60 mg once daily within 6 weeks if no evidence of intolerance seen.*

(c) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.

(d) Concomitant treatments at baseline:

Anti anginal drug: nifedipine +Basic regimen (n=3825): placebo +basic regimen (n=3840)
B-blocker- 3032 (79%): 3066 (80%)
Organic nitrate, as needed- 2157 (56%): 2175 (57%)
Organic nitrate, daily maintenance- 1455 (38%): 1417 (37%)
Other vasodilator- 158 (4%): 148 (4%)
Any of the above- 3775 (99%):3784 (99%)
Any two of the above- 1888 (49%): 1960 (51%)
Any three or four of the above- 563 (15%): 520 (14%)
Lipid lowering:
Statin- 2409 (63%): 2389 (62%)
Fibrate 242 (6%): 246 (6%)
Other- 45 (1%): 68 (2%)
Any of the above- 2607 (68%): 2591 (67%)
Blood pressure lowering:
ACE inhibitor – 771 (20%): 792 (21%)
Angiotensin II antagonist- 90 (2%):93 (2%)
Diuretic – 432 (1%): 447 (12%)
Other- 113 (3%): 81 (2%)
Any of the above- 1165 (30%): 1166 (30%)

Subgroup interaction:

There was no significant difference between sub group age > 65 years and > 65 years for combined outcomes [p=0.42]

There was no significant difference between sub group males and females for combined outcomes [p=0.070]

There was no significant difference between subgroup diabetes and no diabetes for combined outcomes [p=0.59]

8.4.3 Economic evidence

No economic studies were identified on this question. For drug cost of adding CCB see 8.2.3.

8.4.4 Evidence statements

Clinical	**<u>Addition of CCB to basic (or standard) anti-anginal treatment</u>** **<u>Clinical efficacy:</u>** **Poole-Wilson 2004[42] (ACTION):** Evidence from one RCT shows that there was no significant difference between CCB and placebo when added to usual anti-anginal treatment for all cause mortality [RR 1.07 (0.92 to 1.25)], cardiovascular or unknown death [RR 1.01 (0.82 to 1.24)] and MI [RR 1.09 (0.93 to 1.26)] (follow-up mean 4.9 patient-years). **Poole-Wilson 2004[42] (ACTION):** Evidence from one RCT shows that there was no significant difference between CCB and placebo when added to usual treatment for combined outcomes (death from any cause, acute MI, refractory angina, new overt heart failure, debilitating stroke and peripheral revascularisation) for subgroup of patients >65 yrs [RR 1 (0.9 to 1.12)] sub group patients <65 yrs [RR 0.94 (0.82 to 1.07)], sub group of female patients [RR 1.15 (0.94 to 1.4)], subgroup male patients [RR 0.94 (0.85 to 1.03)], and subgroup of diabetic patients [RR 0.93 (0.78 to 1.11)] and people with no diabetes [RR 0.98 (0.89 to 1.08)] (follow-up mean 4.9 patient-years). Sub group interaction: There was no significant interaction between the rate of the combined outcome in the two treatment groups and age >65 years [p=0.42], gender [p=0.070], or presence of diabetes [p=0.59]. **<u>Adverse effects:</u>** **Poole-Wilson 2004[42] (ACTION):** Evidence from one RCT shows that there was significantly more withdrawal due to adverse effects in the CCB group compared to placebo [RR 2.27 (1.91 to 2.7)] (follow-up mean 4.9 patient-years).
Economic	No economic evidence was found on this question. A simple cost analysis showed a small increase in drug costs when a CCB is added to the therapy.

8.5 Recommendations and link to evidence

Recommendation	**If the person's symptoms are not satisfactorily controlled on a beta blocker or a calcium channel blocker,* consider either switching to the other option or using a combination of the two **.** **Do not routinely offer anti-anginal drugs other than beta blockers or calcium channel blockers as first-line treatment for stable angina.** ** Evidence on the use of BBs or CCBs as monotherapy, is presented in chapter 7* ***When combining a calcium channel blocker with a beta blocker, use a dihydropyridine calcium channel blocker, for example, slow release nifedipine, amlodipine or felodipine*
Relative values of different outcomes	Outcomes of interest included long-term mortality (total and cardiovascular) and rates of major adverse cardiovascular events (myocardial infarction, stroke, myocardial revascularisation). Additional outcomes of interest included measures of symptom severity (frequency of angina, exercise test outcomes).
Trade off between clinical benefits and harms	There is no evidence of a difference in cardiac mortality or rate of non-fatal myocardial infarction between patients treated with the combination of BB and CCB compared with BB alone or CCB alone. There is evidence that during exercise testing the combination of BB and CCB increases exercise time and time to 1mm ST segment depression in the short term when compared with BB alone or CCB alone. This beneficial effect of combination treatment was not matched by evidence of improved symptom control, as assessed by the frequency of episodes of angina and the use of nitroglycerine. One trial reported more treatment withdrawals amongst patients treated with nifedipine alone versus patients treated with atenolol and nifedipine in combination. One other trial reported no difference in the rate of adverse events amongst patients treated with amlodipine versus patients treated with amlodipine and atenolol in combination. There was no evidence of a difference in the risk of adverse events amongst patients treated with combination therapy when compared with BB alone. The GDG concluded that evidence that combination therapy with a BB and a CCB is superior to a BB or CCB alone is weak,

	and mainly confined to a modest increase in exercise time during formal exercise testing.
Economic considerations	No economic evidence on the use of BBs in combination with CCBs versus CCBs or BBs alone for the first-line treatment of stable angina was available for review. A simple cost analysis showed a small increase in drug costs when either a BB or a CCB is added to the therapy.
Quality of evidence	Trials comparing the combination of BB and CCB with BB or CCB alone were relatively small with limited statistical power to detect differences in mortality or other major adverse clinical outcomes and only short-term follow-up data were available. No economic evidence was available.
Other considerations	The GDG concluded that there is no evidence to recommend addition of a BB to a CCB or CCB to a BB for patients whose symptoms are controlled on one drug alone. There is some evidence of short-term improvement in exercise tolerance with combination therapy. The GDG considered that response to the first drug was likely to vary with some patients having minimal improvement with one drug and others marked improvement with one drug. The GDG considered that patients not controlled on one drug class should be offered a change to the other drug class, or combination therapy with both drug classes. This should be decided on a case by case basis and in discussion with the patient. A dihydropyridine CCB should be used when a CCB is combined with a BB.

Recommendation	**Do not offer a third anti-anginal drug* to people whose stable angina is controlled with two anti-anginal drugs.** **Consider adding a third anti-anginal drug* only when:** • **the person's symptoms are not satisfactorily controlled with two anti-anginal drugs and** • **the person is waiting for revascularisation or revascularisation is not considered appropriate or acceptable.** **Decide which drug* to use based on comorbidities, contraindications, the person's preference and drug costs.** **These recommendations also draw on the evidence reviews of nicorandil, ranolazine and ivabradine*
Relative values of different outcomes	Outcomes of interest included long-term mortality (total and cardiovascular), rates of major adverse cardiovascular events (myocardial infarction, stroke, myocardial revascularisation), and measures of symptom severity (frequency of angina, exercise test outcomes).
Trade off between clinical benefits and harms	We found no evidence that directly addressed the use of three classes of anti-anginal drug (BB, CCB, long-acting nitrate, or a new anti-anginal drug [nicorandil, ivabradine, ranolazine]) in combination (versus one or two classes of anti-anginal drug) in people with stable angina. In one large trial (ACTION) there was no evidence that the addition of long-acting nifedipine GITS (gastrointestinal therapeutic system) to standard anti-anginal treatment (with BB and/or organic nitrate) reduces the risk of death or myocardial infarction in people with stable angina. There is no evidence of an advantage of nifedipine GITS in women, people aged over 65 years, or people with diabetes. Impact of nifedipine GITS on symptoms of angina was not reported, but nifedipine GITS was associated with a lower rate of coronary arteriography and coronary artery bypass surgery than placebo. Treatment withdrawal due to adverse effects was increased with nifedipine GITS. The GDG concluded that routine addition of nifedipine GITS to standard anti-anginal treatment (with BB and/or long-acting nitrate) does not confer any major clinical benefit.

Economic considerations	There is no clinical evidence that adding a third drug to standard antianginal treatment generates any clinical benefit. It could therefore increase costs with no additional benefit.
Quality of evidence	There was no evidence on the use of three classes of anti-anginal drug in people with stable angina. A large high quality randomised controlled trial provided evidence on the use of nifedipine GITS in addition to treatment with BB and/or long-acting nitrate.
Other considerations	The GDG concluded that there is no evidence that routine addition of a third class of antianginal drug provides benefit in people with stable angina already treated with two classes of antianginal drug. The GDG considered that patients should not have repeated trials of different antianginal drug combinations given the lack of evidence for use of more than two drugs. The GDG considered that a therapeutic trial of a third class of anti-anginal drug could be considered in people with stable angina whose symptoms are not controlled by two classes of anti-anginal drug, and when awaiting revascularisation or when revascularisation is not appropriate or desirable. The GDG considered that in clinical practice this group of people can be a considerable challenge and a recommendation was required to guide healthcare professionals. The response to the addition of a third class of antianginal drug should be reviewed after 2-4 weeks and the drug should be continued only if the person's angina is improved.

9 Long-acting nitrates

9.1 Introduction

Long-acting organic nitrates are indicated for the prophylaxis and treatment of angina. The therapeutic effects of organic nitrates are mediated through dilatation of capacitance veins and conductive coronary and peripheral arteries. These haemodynamic changes reduce ventricular preload, and to a lesser extent ventricular afterload, thereby lowering myocardial oxygen demand and improving subendocardial blood flow.

In many people with stable angina continuous use of organic nitrates induces tolerance, with reduced therapeutic effect. Tolerance can be avoided by a nitrate-free interval each day, but this may lower the threshold for episodes of angina. The pathophysiology of tolerance is incompletely understood but continuous treatment with organic nitrates causes sympathetic activation, increases oxidative stress, and induces endothelial dysfunction. Other unwanted effects of nitrates include flushing, headache, and postural hypotension. Phosphodiesterase type 5 inhibitors should not be used within 24 hours of long-acting nitrate administration because of the risk of severe hypotension.

The GDG were interested in whether there was evidence for the addition of a long-acting nitrate to treatment with a BB or CCB.

9.1.1 Clinical question

What is the clinical and cost effectiveness of adding long-acting nitrates to BB and/or CCBs?

9.1.2 Clinical evidence

The “Review Protocol” for this topic can be found in Appendix C, the “Search Strategies” in Appendix D, the “List of Included and Excluded Studies” in Appendix E1, the “Clinical Evidence Tables” in Appendix E2, and the “Forest Plots” in Appendix F.

Table 9.1: BB+nitrates vs. BB+CCB for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	BB+nitrates	BB+CCB	Relative (95% CI)	Absolute	
Exercise time (sec) (follow-up 12 weeks; better indicated by higher values)											
de Vries[43] 1994 (d)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	46	46	-	MD 10 lower (41.14 lower to 21.14 higher)	⊕⊕OO LOW
Time to onset of angina (sec) (follow-up 12 weeks; better indicated by higher values)											
de Vries[43] 1994	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	46	46	-	MD 31 lower (78.08 lower to 16.08 higher)	⊕⊕OO LOW
Time to ST segment depression (sec) (better indicated by higher values)											
de Vries[43] 1994	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	46	46	-	MD 47 lower (102.4 lower to 8.4 higher)	⊕⊕OO LOW
Adverse effects (overall) (follow-up 12 weeks) (d)											
de Vries[43] 1994	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (c)	None	22/46 (47.8%)	14/43 (32.6%)	RR 1.47 (0.87 to 2.48)	153 more per 1000 (from 42 fewer to 482 more)	⊕⊕OO LOW
Stopping treatment due to adverse events (follow-up 12 weeks)											
de Vries[43] 1994	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (c)	None	8/46 (17.4%)	2/43 (4.7%)	RR 3.74 (0.84 to 16.64)	127 more per 1000 (from 7 fewer to 727 more)	⊕⊕OO LOW
Headache (follow-up 12 weeks)											
de Vries[43] 1994	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (c)	None	10/46 (21.7%)	4/43 (9.3%)	RR 2.34 (0.79 to 6.9)	125 more per 1000 (from 20 fewer to 549 more)	⊕⊕OO LOW

(a) de Vries[42] 1994: Randomised, double blind, cross over, single centre, sample size calculation reported, 4/46 (8.6%) lost to follow-up. Allocation concealment not reported, Intention to treat analysis not reported.

(b) 95% CI includes no effect and the upper and lower CI crosses the MID.

(c) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.

(d) Drug dosages: felodipine extended release 5 mg daily, isosorbide mononitrate 10 mg or 20 mg thereafter twice daily, optimal B-blockade, fixed dose (exact dose not reported).

(e) Adverse events: headache, peripheral oedema, tiredness, cerebrovascular disorder, flushing.

Table 9.2: BB+nitrates vs. BB+CCB for stable angina (Results from one study – data reported graphically. Data reported as in the text of the paper).

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	BB+nitrates	BB+CCB	Relative (95% CI)	Absolute	
Anginal attacks (Follow-up 15 weeks)											
Morse 1985[44] (b)	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	27	27	Data reported graphically	BB+nitrates and BB+CCB resulted in significant reduction in anginal frequency. BB+CCB were superior to BB+nitrates in reducing the frequency of angina episodes. (p=0.03)	⊕⊕OO LOW
Nitroglycerin consumption (follow-up 15 weeks)											
Morse 1985[44]	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	27	27	Data reported graphically	No sig. difference for nitroglycerin consumption between BB+CCB and BB+nitrates	⊕⊕OO LOW
Total Exercise time (sec) (follow-up 15 weeks)											
Morse 1985[44]	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	27	27	Data reported graphically	BB+CCB resulted in significant increase in total exercise time compared to BB+nitrates (p<0.02)	⊕⊕OO LOW
Time to onset of pain (sec) (follow-up 15 weeks)											
Morse 1985[44]	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	27	27	Data reported graphically	Time to onset of angina was significantly prolonged in BB+CCB compared to BB+nitrates (p=0.003)	⊕⊕OO LOW

(a) *Morse 1985[43]: Randomised cross over, double blind, drop out 10%, small sample size, allocation concealment not reported, intention to treat analysis not reported, data cannot be analysed as results reported graphically.*

(b) *Drug dosages: nifedipine was 77.0 mg/day, isosorbide mononitrate 90.4 mg/day, propranolol median dose was 120 mg/day (range 60 to 240.*

9.1.3 Economic evidence

No economic studies were identified on this question. We calculated the range (low and high) of daily and annual cost of adding long-acting nitrates based on the unit cost reported in the BNF59[19].

Table 9.3: Cost of adding long-acting nitrates

	Specific drugs used for cost range	Cost per day (£)	Cost per year (£)
Long-acting nitrates	Low = isosorbide mononitrate	0.052	19
	High = isosorbide dinitrate	0.09	34

The cost of adverse effects was not estimated.

9.1.4 Evidence statements

Clinical **Addition of nitrates**

Clinical efficacy:

De Vries 1994[43]: Evidence from one RCT shows that there was no significant difference between BB+nitrates and BB+CCB for exercise time (sec) [MD -10 (-41.14 to 21.14)], time to onset of angina (sec) [MD -31 (-78.08 to 16.08)] and time to ST segment depression (Sec) [MD -47 (-102.4 to 8.4)] (follow-up 12 weeks).

Adverse effects:

De Vries 1994[43]: Evidence from one RCT shows that there was no significant difference between BB+nitrates and BB+CCB for adverse effects overall [RR 1.47 (0.87 to 2.48)], stopping due to adverse events [RR 3.74 (0.84 to 16.64)] and headache [RR 2.34 (0.79 to 6.9)] (follow-up 12 weeks).

Economic No economic evidence was found on this question. A simple cost analysis showed the annual cost of adding long-acting nitrates to range between £19 and £34.

9.1.5 Recommendations and link to evidence

<table>
<tr><td>Recommendation</td><td>If the person cannot tolerate beta blockers and calcium channel blockers or both are contraindicated, consider monotherapy with one of the following drugs:
a long-acting nitrate or
ivabradine or
nicorandil or
ranolazine.
Decide which drug to use based on comorbidities, contraindications, the person's preference and drug costs[5].

For people on beta blocker or calcium channel blocker monotherapy whose symptoms are not controlled and the other option (calcium channel blocker or beta blocker) is contraindicated or not tolerated, consider one of the following as an additional drug:
a long-acting nitrate or
ivabradine* or
nicorandil or
ranolazine.
Decide which drug to use based on comorbidities, contraindications, the person's preference and drug costs[5].

* When combining ivabradine with a calcium channel blocker, use a dihydropyridine calcium channel blocker, for example, slow release nifedipine, amlodipine, or felodipine.</td></tr>
<tr><td>Relative values of different outcomes</td><td>Outcomes of interest included long-term mortality (total and cardiovascular), rates of major adverse cardiovascular events (myocardial infarction, stroke, myocardial revascularisation), and measures of symptom severity (frequency of angina, exercise test outcomes).</td></tr>
</table>

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

Trade off between clinical benefits and harms	We found no evidence to confirm the safety or efficacy of long-term use of organic nitrate as an additional anti-anginal agent in patients already taking a BB or CCB. In patients aged over 65 years addition of either isosorbide mononitrate or felodipine to treatment with a BB had comparable short-term effects on exercise time, and time to onset of angina or ST segment depression during exercise stress testing. There was no difference in adverse effects of treatment between the two groups. In one small study of poor quality the combination of propranolol and nifedipine resulted in greater reduction in angina frequency and longer exercise times than the combination of isosorbide dinitrate and propranolol.
Economic considerations	No economic evidence on the use of long-acting organic nitrates for the treatment of stable angina was available for review. The drug cost ranges from £19 to £34 per year.
Quality of evidence	Evidence to support the use of long-acting nitrates in combination with BB in people with stable angina is of poor quality and available trials are limited by small sample size and short duration of follow-up. No trials of nitrates in combination with CCBs were identified. No economic evidence was available.
Other considerations	The GDG concluded that evidence to support the addition of long-acting nitrate to monotherapy with BB or CCB in people with stable angina is very weak. The GDG recognized that organic nitrates have been used for the relief of attacks of angina for over 100 years. In addition there is consensus that monotherapy with long-acting nitrates is effective in the treatment of stable angina in the short-term, but that the efficacy of long-acting nitrates may be limited by the development of tolerance. The GDG made a consensus recommendation that long-acting nitrates can be considered for monotherapy if BBs and CCBs are not tolerated or are contraindicated. The GDG also agreed that addition of a long-acting nitrate can be considered in people whose symptoms are not controlled by monotherapy with either BB or CCB if the combination of BB and CCB is not appropriate. The cost of long-acting nitrate varies between different

formulations but is less than the cost of newer antianginal drugs (e.g. nicorandil, ivabradine, ranolazine – see chapter 10). There is however less evidence for its use in combination than there is for newer drugs.

The GDG concluded that there was insufficient evidence to make a firm recommendation about the choice of antianginal drug as monotherapy or as an additional antianginal drug if a CCB and/or BB are not tolerated or are contraindicated.

10 Other anti anginal drugs and general drug recommendations

10.1 Introduction

Ivabradine, nicorandil, and ranolazine are anti-anginal drugs that are licensed for use in the treatment of stable angina. The GDG were interested in evidence for the use of these drugs either as monotherapy or in combination with other anti-anginal drugs, and their place in the pathway for people with stable angina.

Ivabradine is licensed for the treatment of angina in patients in sinus rhythm in combination with a BB, or when a BB is contra-indicated or not tolerated. Nicorandil has been available for longer than the other drugs considered in this chapter and although it does not have a licence to be used in combination with other antianginal drugs it is regularly used this way in practice. Ranolazine is licensed as adjunctive therapy in patients who are inadequately controlled or intolerant of first-line antianginal drugs.

The costs of drugs at standard doses are listed below and compared with the cost of long-acting nitrates.

Table 10: Cost of drugs

	Specific drugs used for range	Cost per day (£)	Cost per year (£)
Long-acting nitrates	Low = isosorbide mononitrate	0.05	19
	High = isosorbide dinitrate	0.09	34
Ivabradine, 5 mg or 7.5 mg twice daily	Low = high	1.39	507
Ranolazine, 375 mg, 500 mg or 750 mg twice daily	Low = high	1.63	595
Nicorandil	Low = 10 mg tablets twice daily	0.27	99
	High = 20 mg tablets twice daily	0.52	190

10.2 Ivabradine

Ivabradine is a heart rate-lowering agent that acts by selectively inhibiting the If current, an ionic current across the sarcolemma in cells of the sino-atrial node that is involved in pacemaker activity. Ivabradine reduces the slope of spontaneous diastolic depolarization in sino-atrial cells, and lowers heart rate at rest and during exercise. Side effects of ivabradine include bradycardia, heart block, and visual disturbances (phosphenes and blurred vision).

10.2.1 Clinical question

What is the clinical /cost effectiveness of ivabradine for the management of stable angina?

10.2.2 Clinical evidence

The “Review Protocol” for this topic can be found in Appendix C, the “Search Strategies” in Appendix D, the “List of Included and Excluded Studies” in Appendix E1, the “Clinical Evidence Tables” in Appendix E2, and the “Forest Plots” in Appendix F.

The evidence review included evidence for the use of ivabradine as monotherapy or in combination with BB to control symptoms and improve outcome in people with stable angina.

Table 10.1: Ivabradine vs. Placebo

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ivabradine	placebo	Relative (95% CI)	Absolute	
Time to angina onset (sec) (trough change from baseline) (follow-up 14 days; better indicated by higher values) (g)											
Borer 2003[45] (e)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	serious (b)	None	59	68	-	MD 14.1 higher (11.73 lower to 39.93 higher)	⊕⊕⊕O MODERATE
Time to angina onset (sec) (peak change from baseline) (follow-up 14 days; better indicated by higher values) (h)											
Borer[45] 2003	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	serious (b)	None	59	68	-	MD 43.2 higher (16.75 to 69.65 higher)	⊕⊕⊕O MODERATE
Time to 1mm ST depression (sec) (at peak of drug activity) (follow-up 14 days; better indicated by higher values)											
Borer[45] 2003	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	serious (b)	None	59	68	-	MD 52.90 higher (26.85 to 78.95 higher)	⊕⊕⊕O MODERATE
Time to 1mm ST depression (sec) (at trough) (follow-up 14 days; better indicated by higher values)											
Borer[45] 2003	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	serious (b)	None	59	68	-	MD 35.10 higher (9.68 to 60.52 higher)	⊕⊕⊕O MODERATE
Patients with limiting angina (j) - CV death or hospitalisation for MI or HF - (follow-up median 18 months)											
Fox 2009[46] (BEAUTIFUL) (f)	randomised trials	no serious limitation (c)	no serious inconsistency	no serious indirectness	serious (d)	None	88/734 (12%)	120/773 (15.5%)	RR 0.77 (0.6 to 1)	36 fewer per 1000 (from 62 fewer to 0 more)	⊕⊕⊕O MODERATE
Patients with limiting angina - all cause mortality - (follow-up median 18 months)											
Fox 2009[46] (BEAUTIFUL)(i)	randomised trials	no serious limitation (c)	no serious inconsistency	no serious indirectness	serious (d)	None	64/734 (8.7%)	77/773 (10%)	RR 0.88 (0.64 to 1.2)	12 fewer per 1000 (from 36 fewer to 20 more)	⊕⊕⊕O MODERATE
Patients with limiting angina - cardiac death - (follow-up median 18 months)											
Fox 2009[46] (BEAUTIFUL)	randomised trials	no serious limitation (c)	no serious inconsistency	no serious indirectness	serious (d)	None	11/734 (1.5%)	16/773 (2.1%)	RR 0.72 (0.34 to 1.55)	6 fewer per 1000 (from 14 fewer to 11 more)	⊕⊕⊕O MODERATE
Patients with limiting angina - hospitalisation for HF - (follow-up median 18 months)											
Fox 2009[46] (BEAUTIFUL)	randomised trials	no serious limitation (c)	no serious inconsistency	no serious indirectness	serious (d)	None	33/734 (4.5%)	41/773 (5.3%)	RR 0.85 (0.54 to 1.33)	8 fewer per 1000 (from 24 fewer to 18 more)	⊕⊕⊕O MODERATE

Patients with limiting angina - hospitalisation for MI or unstable angina - (follow-up median 18 months)											
Fox 2009[46] (BEAUTIFUL)	randomised trials	no serious limitation (c)	no serious inconsistency	no serious indirectness	serious (d)	None	56/734 (7.6%)	65/773 (8.4%)	RR 0.9 (0.64 to 1.28)	8 fewer per 1000 (from 30 fewer to 24 more)	⊕⊕⊕O MODERATE
Patients without limiting angina - CV death or hospitalisation for MI or heart failure (follow-up 18 months)											
Fox 2009[46] (BEAUTIFUL)	randomised trials	no serious limitation (c)	no serious inconsistency	no serious indirectness	no serious imprecision	None	756/4745 (15.9%)	712/4665 (15.3%)	RR 1.04 (0.95 to 1.15)	6 more per 1000 (from 8 fewer to 23 more)	⊕⊕⊕⊕ HIGH
Patients without limiting angina - all cause mortality (follow-up median 18 months)											
Fox 2009[46] (BEAUTIFUL)	randomised trials	no serious limitation (c)	no serious inconsistency	no serious indirectness	no serious imprecision	None	508/4745 (10.7%)	470/4665 (10.1%)	RR 1.06 (0.94 to 1.2)	6 more per 1000 (from 6 fewer to 20 more)	⊕⊕⊕⊕ HIGH
Patients without limiting angina - cardiac death (follow-up median 18 months)											
Fox 2009[46] (BEAUTIFUL)	randomised trials	no serious limitation (c)	no serious inconsistency	no serious indirectness	serious (d)	None	125/4745 (2.6%)	135/4665 (2.9%)	RR 0.91 (0.72 to 1.16)	3 fewer per 1000 (from 8 fewer to 5 more)	⊕⊕⊕O MODERATE
Patients without limiting angina - hospitalisation for heart failue (follow-up median 18 months)											
Fox 2009[46] (BEAUTIFUL)	randomised trials	no serious limitation (c)	no serious inconsistency	no serious indirectness	no serious imprecision	None	393/4745 (8.3%)	386/4665 (8.3%)	RR 1 (0.87 to 1.15)	0 fewer per 1000 (from 11 fewer to 12 more)	⊕⊕⊕⊕ HIGH
Patients without limiting angina - hospitalisation for MI or unstable angina (follow-up median 18 months)											
Fox 2009[46] (BEAUTIFUL)	randomised trials	no serious limitation (c)	no serious inconsistency	no serious indirectness	no serious imprecision	None	247/4745 (5.2%)	252/4665 (5.4%)	RR 0.96 (0.81 to 1.14)	2 fewer per 1000 (from 10 fewer to 8 more)	⊕⊕⊕⊕ HIGH
All serious adverse events (follow-up median 18 months)											
Fox 2009[46] (BEAUTIFUL)	randomised trials	no serious limitation (c)	no serious inconsistency	no serious indirectness	no serious imprecision	None	135/734 (18.4%)	144/773 (18.6%)	RR 0.99 (0.80 to 1.22)	2 fewer per 1000 (from 37 fewer to 41 more)	⊕⊕⊕⊕ HIGH

(a) Borer 2003[44]: Randomisation, allocation concealment, double blinding and ITT reported. Baseline comparisons made, there was no clinically relevant differences in baseline characteristics were observed between the 2 groups. In Ivabradine 2.5 mg bd 3/90 (3.3%); Ivabradine 5 mg bd 4/91 (4.4%); Ivabradine 10 mg bd 3/88 (3.4%) and; Placebo 1/91 (1.1%) were lost to follow-up.

(b) The upper and lower CI crosses the MID.

(c) Fox 2009[45] (BEAUTIFUL): Randomisation, allocation concealment, double blinding and ITT reported. This is a post hoc analysis, and therefore the results should be considered as hypothesis generating. Sample size calculation reported.

(d) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.

(e) Ivabradine 5 mg bid vs. placebo

(f) Ivabradine 7.5 mg bid vs. placebo

(g) Trough = 12 hours after administration of ivabradine

(h) Peak = 4 hours after administration of ivabradine

(i) In this post hoc analysis, the BEAUTIFUL population was divided according to the presence of limiting angina symptoms at baseline using the New York Heart Association (NYHA) functional classification. Patients were questioned at the inclusion visit regarding the presence of symptoms limiting activity, and whether they were related to anginal pain or due to presence of heart failure (fatigue, palpitations or dyspnoea).

(j) Limiting angina symptoms were identified in 13.8% of the BEAUTIFUL population at baseline (1507 out of 10917 patients). Of these, 734 were randomised to ivabradine treatment and 773 to placebo.

Table 10.2: Ivabradine vs. atenolol

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ivabradine	Atenolol	Relative (95% CI)	Absolute	
Total exercise duration (sec) (trough change from baseline) (follow-up 16 weeks; better indicated by higher values)											
Tardif 2005[47] (d) (e)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	300	286	-	MD 8 higher (13.26 lower to 29.26 higher)	⊕⊕⊕O MODERATE
Time to angina onset (sec) (trough change from baseline) (follow-up 16 weeks; better indicated by higher values)											
Tardif 2005[47]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	300	286	-	MD 10 higher (14.96 lower to 34.96 higher)	⊕⊕OO LOW
Weekly number of angina attacks (follow-up 16 weeks; better indicated by lower values)											
Tardif 2005[47]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	307	294	-	MD 0.5 higher (0.99 lower to 1.99 higher)	⊕⊕⊕O MODERATE
Short-acting nitrate consumption units/week (follow-up 16 weeks; better indicated by lower values)											
Tardif 2005[47]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	307	294	-	MD 0.4 lower (1 lower to 0.2 higher)	⊕⊕⊕O MODERATE
Withdrawal due to adverse events (follow-up 16 weeks)											
Tardif 2005[47]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (c)	None	28/315 (8.9%)	17/307 (5.5%)	RR 1.61 (0.9 to 2.87)	34 more per 1000 (from 6 fewer to 104 more)	⊕⊕OO LOW

(a) *Tardif 2005[46]: Allocation concealment not reported. Randomisation using permutation blocks. Double blinding. Capsules of ivabradine and placebo identical. Patients, investigators, central readers of ETT data were blinded to the treatment received by the patients. Calculation of sample size reported. Baseline comparisons made no difference between the study groups. ITT reported.*

(b) *95% CI includes no effect and the upper and lower CI crosses the MID.*

(c) *95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.*

(d) *Ivabradine 5 mg bid for 4 weeks and then 7.5 bid for 12 weeks or atenolol 50 mg od for 4 weeks and then 100 mg od for 12 weeks.*

(e) *The authors state that the study does not allow to strictly comparing the safety of ivabradine and atenolol, because about two-thirds of the patients had previously received BB and were known to tolerate these drugs; patients with known intolerance or contraindications to atenolol were specifically excluded. There was slightly higher number of deaths in the ivabradine groups (2 (0.6%) and 3 (1%) respectively) than in the atenolol group (1 (0.3%) that was not statistically significant.*

Table 10.3: Ivabradine + atenolol vs. atenolol+placebo

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ivabradine plus atenolol	Atenolol	Relative (95% CI)	Absolute	
Total exercise duration (sec) (follow-up 2 months; better indicated by higher values) (e)											
Tardif 2009[48] (d)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	441	434	-	MD 8.7 higher (0.98 to 16.42 higher)	⊕⊕⊕⊕ HIGH
Time to angina onset (sec) (follow-up 2 months; better indicated by higher values)											
Tardif 2009[48]	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	441	434	-	MD 13 higher (3.43 to 22.57 higher)	⊕⊕⊕⊕ HIGH
Time to 1mm ST depression (sec) (follow-up 2 months; better indicated by higher values)											
Tardif 2009[48]	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	serious (b)	None	441	434	-	MD 27.2 higher (16.15 to 38.25 higher)	⊕⊕⊕O MODERATE
Total exercise duration (sec)(follow-up 4 months; better indicated by higher values)											
Tardif 2009[48]	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	441	434	-	MD 16.6 higher (8.05 to 25.15 higher)	⊕⊕⊕⊕ HIGH
Time to onset of angina(sec) (follow-up 4 months; better indicated by higher values)											
Tardif 2009[48]	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	serious (b)	None	441	434	-	MD 26.4 higher (15.64 to 37.16 higher)	⊕⊕⊕O MODERATE
Time to 1 mm ST depression (sec) (follow-up 4 months; better indicated by higher values)											
Tardif 2009[48]	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	serious (b)	None	441	434	-	MD 30.3 higher (18.4 to 42.2 higher)	⊕⊕⊕O MODERATE
angina attacks/week (follow-up 4 months; better indicated by lower values)											
1 Tardif 2009[48]	randomised trials	no serious limitations(a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	441	434	-	MD 0.00 higher (0.30 lower to 0.30 higher)	⊕⊕⊕O HIGH
Adverse events (follow-up 4 months)											
Tardif 2009[48]	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	serious (c)	None	13/441 (2.9%)	4/434 (0.9%)	RR 3.2 (1.05 to 9.73)	20 more per 1000 (from 0 more to 80 more)	⊕⊕⊕O MODERATE

(a) *Tardif 2009[47]: Randomisation, allocation concealment, double blinding and ITT reported. The random allocation was computer generated. Sample size calculation reported. 2% of patients lost to follow-up. The full analysis included 875 (98% of those randomised).*
(b) *The upper and lower CI crosses the MID.*
(c) *95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.*
(d) *Patients receiving atenolol 50 mg/day were randomised to receive ivabradine 5 mg b.i.d for 2 months, increased to 7.5 mg b.i.d for a further 2 months.*
(e) *12 hours after last dose ivabradine, 24 hours after last dose atenolol*

Table 10.4: Ivabradine vs. amlodipine

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ivabradine	Amlodipine	Relative (95% CI)	Absolute	
Total exercise duration (sec) (follow-up 3 months; better indicated by higher values)											
Ruzyllo 2007[49] (c)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	381	398	-	MD 3.6 lower (16.5 lower to 9.3 higher)	⊕⊕⊕⊕ HIGH
Time angina onset (sec) (follow-up 3 months; better indicated by higher values)											
Ruzyllo 2007[49]	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	381	398	-	MD 1.9 lower (16.24 lower to 12.44 higher)	⊕⊕⊕⊕ HIGH
Short-acting nitrate use (units/week) (follow-up 3 months; better indicated by lower values)											
Ruzyllo 2007[49]	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	389	398	-	MD 0.8 higher (0.04 to 1.56 higher)	⊕⊕⊕⊕ HIGH
Frequency of angina attacks/week - (follow-up 3 months; better indicated by lower values)											
Ruzyllo 2007[49]	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	389	398	-	MD 0 higher (0.77 lower to 0.77 higher)	⊕⊕⊕⊕ HIGH
Adverse events (follow-up 3 months)											
Ruzyllo 2007[49]	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	serious (b)	None	181/400 (45.3%)	152/404 (37.6%)	RR 1.2 (1.02 to 1.42)	75 more per 1000 (from 8 more to 158 more)	⊕⊕⊕O MODERATE

(a) *Ruzyllo 2007[48] : Randomisation, allocation concealment, double blinding and ITT reported. N=1195 randomised (Ivabradine 7.5 n=400, Ivabradine 10 mg n=391, or amlodipine n=404). The ITT population consisted of 1155 patients (96.7%). Sample size calculation reported.*

(b) *95% CI around the pooled estimate of effect includes appreciable benefit or appreciable harm.*

(c) *Ivabradine 7.5 mg twice daily vs. amlodipine 10 mg once daily*

10.2.3 Economic evidence

No economic studies were identified on this question. We calculated the daily and annual cost of ivabradine treatment based on the unit cost reported in the BNF59[19].

Table 10.5: Drug cost of Ivabradine

	Cost per day (£)	Cost per year (£)
Ivabradine, 5 mg or 7.5mg twice daily	1.39	507

The costs adverse effects were not estimated.

10.2.4 Evidence statements

Clinical **Ivabradine versus placebo**

Borer 2003[45]: Evidence from one RCT shows that there was no significant difference between ivabradine and placebo for time to angina onset (sec) (at trough) [MD 14.1 (-11.73 to 39.93). Time to angina onset (sec) (at peak) [MD 43.2 (16.75 to 69.65)], time to 1 mm ST depression (sec) at peak [MD 52.90 (26.85 to 78.95)], time to 1mm ST depression (sec) at trough [MD 35.10 (9.68 to 60.52)] was significantly higher in the ivabradine group (5 mg) compared to placebo (follow-up 14 days).

Fox 2009[46]: Evidence from one RCT shows that there was no statistically significant difference between ivabradine (7.5 mg) and placebo in patients with limiting angina for CV death or hospitalisation for MI or HF [RR 0.77 (0.6 to 1.0)], all cause mortality [RR 0.88 (0.64 to 1.2)], cardiac death [RR 0.72 (0.34 to 1.55)], hospitalisation for heart failure [RR 0.85 (0.54 to 1.33)], hospitalisation for heart failure or unstable angina [RR 0.9 (0.64 to 1.28)].

Evidence from RCT shows that there was no statistically significant difference between ivabradine (7.5 mg) and placebo in patients without limiting angina for CV death or hospitalisation for MI or HF [RR 1.04 (0.95 to 1.15)], all cause mortality [RR 1.06 (0.94 to 1.2),] cardiac death [RR 0.91 (0.72 to 1.16)] , hospitalisation for heart failure [RR 1 (0.87 to 1.15)] and hospitalisation for heart failure or unstable angina [RR 0.96 (0.81 to 1.14)] and serious adverse events [RR 0.99 (0.80 to 1.22)] (median follow-up 18 months).

Ivabradine versus atenolol

Tardif 2005[47]: Evidence from one RCT shows that there was no statistically significant difference between ivabradine (5 mg bid for 4 weeks and then 7.5 mg bid for 12 weeks) and atenolol (50 mg) for total exercise duration at trough (sec) [MD 8.00 (-13.26 to 29.26)], time to angina onset at trough (sec) [MD 10.00 (-14.96 to 34.96)], weekly number of angina attacks [MD 0.50 (0.99 to 1.99)], short-acting nitrate consumption (units/week) [MD -0.40 (1.00 to 0.20)], and withdrawal due to adverse events [RR1.61 (0.90 to 2.87)] (follow-up 16 weeks).

Ivabradine plus atenolol versus atenolol plus placebo

Tardif 2009[48] : Evidence from one RCT shows that total exercise duration at trough (sec) [MD 8.70 (0.98 to 16.42)], time to angina onset at trough (sec) [MD 13.00 (3.43 to 22.57)] and time to 1mm ST segment depression (sec) [MD 27.2 (16.15 to 38.25)] at 2 months and total exercise duration at trough (sec) [MD 16.6 (8.05 to 25.15)], time to angina onset at trough (sec) [MD 26.4 (15.64 to 37.16)] and time to 1mm ST segment depression (sec) [MD 30.3 (18.4 to 42.2)] at 4 months was significantly higher in the ivabradine plus atenolol (ivabradine 5 mg b.i.d for 2 months, increased to 7.5 mg b.i.d for a further 2 months) group compared to atenolol. There was no significant difference between Ivabradine and atenolol for angina attacks/week at 4 months [MD 0.00 (0.30 to 0.30)].

The rate of adverse events was significantly higher [(RR3.20 (1.05 to 9.73)] in the ivabradine plus atenolol group compared to atenolol alone (follow-up 2 months and 4 months).

Ivabradine versus amlodipine

Ruzyllo 2007[49]**:** Evidence from one RCT shows that there were no statistically significant differences between ivabradine (7.5 mg bid) and amlodipine (10 mg/daily) for total exercise duration at trough (sec) [MD -3.60 (-16.5 to 9.3)], time to angina onset at trough (sec) [MD -1.90 (-16.24 to 12.44)], weekly number of angina attacks [MD 0.0 (-0.77 to 0.77)] or short-acting nitrate consumption (units/week) [MD 0.80 (0.04 to 1.56)]. There was significantly higher risk of adverse events with in the ivabradine group compared with amlodipine (RR1.20 (1.02 to 1.42) (follow-up 12 weeks).

Economic No economic evidence was found on this question. A simple cost analysis showed a significant drug cost of ivabradine.

10.2.5 Recommendations and link to evidence

Recommendation	**If the person cannot tolerate beta blockers and calcium channel blockers or both are contraindicated, consider monotherapy with one of the following drugs*:** • **a long-acting nitrate or** • **ivabradine or** • **nicorandil or** • **ranolazine.** **Decide which drug to use based on comorbidities, contraindications, the person's preference and drug costs[6].** **For people on beta blocker or calcium channel blocker monotherapy whose symptoms are not controlled and the other option (calcium channel blocker or beta blocker) is contraindicated or not tolerated, consider one of the following as an additional drug*:** • **a long-acting nitrate or** • **ivabradine** or** • **nicorandil or** • **ranolazine.** **Decide which drug to use based on comorbidities, contraindications, the person's preference and drug costs[6].** ** Evidence on long-acting nitrates is presented in chapter 9. Evidence on nicorandil and ranolazine is presented in sections 10.3 and 10.4 respectively of this chapter.* *** When combining ivabradine with a calcium channel blocker, use a dihydropyridine calcium channel blocker, for example, slow release nifedipine, amlodipine, or felodipine.*
Relative values of different outcomes	Outcomes of interest included long-term mortality (total and cardiovascular), rates of major adverse cardiovascular events

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

	(myocardial infarction, stroke, myocardial revascularisation), and measures of symptom severity (frequency of angina, exercise test outcomes).
Trade off between clinical benefits and harms	Short-term trials of monotherapy with ivabradine versus monotherapy with atenolol or amlodipine demonstrated similar increases in total exercise duration, and similar reductions in the frequency of angina episodes in both treatment groups. One short-term trial reported that addition of ivabradine to monotherapy with atenolol resulted in small increases in total exercise duration (16.6s) and time to angina on the treadmill, but did not reduce the frequency of episodes of angina. These data suggest that ivabradine is an effective anti-anginal agent with comparable short-term efficacy to atenolol and amlodipine. In addition there is a statistically significant incremental benefit of adding ivabradine to atenolol in people with angina, but this benefit is of uncertain clinical significance. There are significantly higher rates of adverse events in ivabradine treated patients, partly due to visual disturbance (phosphenes and blurred vision).
Economic considerations	No economic evidence on the use of ivabradine for the treatment of stable angina was available for review. The cost of ivabradine is substantially higher than the costs of other standard treatments (including BB, CCB, and long-acting nitrate).
Quality of evidence	The trials assessing the short-term anti-anginal efficacy of ivabradine were relatively large, well-designed studies. Evidence confirming the long-term efficacy and safety of ivabradine in people with stable angina is limited. The BEAUTIFUL trial assessed the effect of ivabradine in people with coronary artery disease and impaired left ventricular function. In a subgroup analysis of patients whose limiting baseline symptom was angina, ivabradine was associated with a reduction in the composite rate of the primary endpoint (cardiovascular death and hospitalization for myocardial infarction or heart failure) of borderline statistical significance. The rate of hospitalisation for myocardial infarction was lower in the ivabradine treated patients (RR 0.58, 95%CI 0.37–0.92, p=0.021)[46]. The subgroup was defined retrospectively, only includes 13.8% of the total trial population, and lacks statistical power for the primary endpoint. The GDG considered this analysis to be exploratory, rather than providing definitive evidence of benefit of ivabradine in people with stable angina and impaired left

ventricular systolic function.

No economic evidence was found on this question.

Other considerations	There is some evidence for the use of ivabradine as monotherapy or in combination with BB, but no evidence for use of ivabradine in combination with CCB was found. Concomitant use of ivabradine with heart rate reducing CCB such as verapamil or diltiazem is not recommended by the manufacturers. Ivabradine is a relatively new drug with limited information on efficacy in stable angina. The cost of ivabradine is comparable with the costs of nicorandil and ranolazine but more than the cost of long-acting nitrate. Nevertheless the GDG considered that there was insufficient evidence to make a firm recommendation about the choice of antianginal drug as monotherapy or as an additional antianginal drug if a CCB or BB is not tolerated or is contraindicated. The GDG concluded that monotherapy with ivabradine should not be used as an alternative to monotherapy with a BB or CCB. Monotherapy with ivabradine can be considered in people with stable angina in whom BB and CCB are contraindicated or not tolerated. The GDG concluded that ivabradine can be considered as an additional drug for people whose symptoms are not controlled by monotherapy with a BB and the addition of CCB is contraindicated or not tolerated. Ivabradine can be combined with CCB but there is less evidence for efficacy and safety. The summary of product characteristics (SPC) for ivabradine states that ivabradine should only be combined with dihydropyridine CCB. Ivabradine is metabolised by CYP3A4, and CYP3A4 inhibitors and inducers are liable to interact with ivabradine and influence its metabolism and pharmacokinetics to a clinically significant extent. Drug-drug interaction studies have established that CYP3A4 inhibitors increase ivabradine plasma concentrations. Specific interaction studies in healthy volunteers and patients have shown that the combination of ivabradine with the heart rate reducing agents diltiazem or verapamil resulted in an increase in ivabradine exposure (2 to 3 fold increase in AUC) and an additional heart rate reduction of 5 bpm.

10.3 Nicorandil

Nicorandil is a nitrate derivative of nicotinamide that is licensed for the prevention and long-term treatment of angina. Nicorandil is believed to have a dual mechanism of action. Specifically nicorandil provides a nitrate moiety that dilates epicardial coronary arteries and systemic venous capacitance vessels. In addition, nicorandil opens ATP-sensitive potassium channels (K_{ATP}) in vascular smooth muscle cells, thereby dilating arterial resistance vessels in the peripheral and coronary circulations. In humans nicorandil decreases ventricular filling pressure, coronary vascular resistance, and mean arterial pressure, and these combined effects increase coronary blood flow and reduce myocardial work.

K_{ATP} channels are an important mediator of ischaemic preconditioning. The molecular mechanisms have not been fully elucidated but activation of the K_{ATP} channel has a cardioprotective effect similar to ischaemic preconditioning, while K_{ATP} channel blockade prevents preconditioning. Experimental and clinical studies of myocardial ischaemia provide evidence that pretreatment with nicorandil reduces ischaemic myocardial injury. It has therefore been suggested that in addition to relieving symptoms of ischaemia nicorandil may have a clinically relevant cardioprotective effect.

10.3.1 Clinical question

What is the clinical /cost effectiveness of nicorandil for the management of stable angina?

10.3.2 Clinical evidence

The “Review Protocol” for this topic can be found in Appendix C, the “Search Strategies” in Appendix D, the “List of Included and Excluded Studies” in Appendix E1, the “Clinical Evidence Tables” in Appendix E2, and the “Forest Plots” in Appendix F.

Table 10.6: Nicorandil + usual treatment versus Placebo + usual treatment

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Nicorandil	Placebo	Relative (95% CI)	Absolute	
CHD death (follow-up 1.6 years)											
Dargie 2002[50] (IONA) (d)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	60/2565 (2.3%)	73/2561 (2.9%)	RR 0.82 (0.59 to 1.15)	5 fewer per 1000 (from 12 fewer to 4 more)	⊕⊕OO LOW
Non fatal MI (follow-up 1.6 years)											
Dargie 2002[50] (IONA)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	56/2565 (2.2%)	72/2561 (2.8%)	RR 0.78 (0.55 to 1.1)	6 fewer per 1000 (from 13 fewer to 3 more)	⊕⊕OO LOW
Unstable angina (follow-up 1.6 years)											
Dargie 2002[50] (IONA)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	115/2565 (4.5%)	127/2561 (5%)	RR 0.9 (0.71 to 1.16)	5 fewer per 1000 (from 14 fewer to 8 more)	⊕⊕OO LOW
All cause mortality (follow-up 1.6 years)											
Dargie 2002[50] (IONA)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	111/2565 (4.3%)	129/2561 (5%)	RR 0.86 (0.67 to 1.1)	7 fewer per 1000 (from 17 fewer to 5 more)	⊕⊕OO LOW
Worsening of angina status (follow-up 1.6 years)											
Dargie 2002[50] (IONA)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	569/2565 (22.2%)	602/2561 (23.5%)	RR 0.94 (0.85 to 1.04)	14 fewer per 1000 (from 35 fewer to 9 more)	⊕⊕⊕O MODERATE
GI disturbances (follow-up 1.6 years)											
Dargie 2002[50] (IONA)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (c)	None	194/2565 (7.6%)	132/2561 (5.2%)	RR 1.47 (1.18 to 1.82)	24 more per 1000 (from 9 more to 42 more)	⊕⊕OO LOW
Combined outcome CHD death, non-fatal MI or hospital admission for chest pain (diabetes subgroup) (follow-up 1.6 years)											
IONA Study Group 2004[51] (IONA)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	27/197 (13.7%)	40/232 (17.2%)	RR 0.79 (0.51 to 1.25)	36 fewer per 1000 (from 84 fewer to 43 more)	⊕⊕OO LOW
Combined outcomes CHD death, non-fatal MI or hospital admission for chest pain (age subgroup >70 yrs) (follow-up 1.6 years)											
IONA Study Group 2004[51] (IONA)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	131/927 (14.1%)	167/948 (17.6%)	RR 0.8 (0.65 to 0.99)	35 fewer per 1000 (from 2 fewer to 62 fewer)	⊕⊕OO LOW
Combined outcomes CHD death, non-fatal MI or hospital admission for chest pain (female subgroup) (follow-up 1.6 years)											
IONA Study Group 2004[51] (IONA)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	86/603 (14.3%)	87/613 (14.2%)	RR 1 (0.76 to 1.32)	0 fewer per 1000 (from 34 fewer to 45 more)	⊕⊕OO LOW
Composite (CHD death, non fatal MI or hospital admission. for chest pain) (follow-up 1.6 years)											

Dargie 2002[50] (IONA)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (c)	None	337/2565 (13.1%)	398/2561 (15.5%)	RR 0.85 (0.74 to 0.97)	23 fewer per 1000 (from 5 fewer to 40 fewer)	⊕⊕OO LOW
Headache (follow-up 1.6 years)											
Dargie 2002[50] (IONA)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	364/2565 (14.2%)	81/2561 (3.2%)	RR 4.49 (3.55 to 5.67)	110 more per 1000 (from 81 more to 148 more)	⊕⊕⊕O MODERATE

(a) Dargie 2002[49] : Randomisation process was reported; allocation concealment was not reported; study was double blind; Number of drop outs were reported and >20%; Intention to treat analysis was reported; the study was powered for primary outcome (CHD death, non fatal MI, or unplanned hospitalisation). In the placebo group: 2/2561 lost to follow-up, 809/2561 discontinued intervention. In the Nicorandil group: 2/2565 lost to follow-up; 1003/2565 discontinued intervention

(b) 95% CI around the pooled estimate of effect includes both 1) no effect 2) appreciable benefit or appreciable harm

(c) 95% CI around the pooled estimate of effect includes appreciable benefit or appreciable harm

(d) Canadian Cardiovascular Society Functional classification of angina at the end of the study (follow-up mean 1.6 years):

Class I - Nicorandil 985 (43%); placebo 989 (43%)
Class II- Nicorandil 1159 (50%); placebo 1124 (49%)
Class III- Nicorandil 162 (7%); placebo 163 (7%)
Class IV- Nicorandil 9 (<1%) ; placebo 15 (1%)

Table 10.7: Nicorandil versus diltiazem

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Nicorandil	Diltiazem	Relative (95% CI)	Absolute	
Exercise capacity (work to peak exercise) (KJ) (follow-up 90 days: better indicated by more)											
Guermonprez 1993[52]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	50	56	-	MD 2.4 higher (60.15 lower to 64.95 higher)	⊕⊕OO LOW
Exercise capacity (work to onset of angina) (KJ) (follow-up 90 days: better indicated by more)											
Guermonprez 1993[52]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	50	56	-	MD 3.40 higher (58.91 lower to 65.71 higher)	⊕⊕OO LOW
Adverse events (combined) (follow-up 90 days)											
Guermonprez 1993[52]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (c)	None	19/60 (31.7%)	19/63 (30.2%)	RR 1.05 (0.62 to 1.78)	15 more per 1000 (from 115 fewer to 235 more)	⊕⊕OO LOW

(a) *Guermonprez 1993[51]: Allocation concealment was not reported; study was double blind; intention to treat analysis was not reported. The two groups were comparable in terms of age, sex, history of myocardial infarction and severity of coronary lesions.Drop-out: Nicorandil: 3 (5%) drop outs due to insufficeint efficacy; 4(6.7%) drop outs due to other adverse events. Diltiazem: 4 (6.3%) drop outs due to insufficient efficacy; 1 (1.6%) drop outs due to other adverse events.*

(b) *95% CI includes no effect and the upper and the lower confidence limit crosses the MID.*

(c) *95% CI around the pooled estimate of effect includes both 1) no effect 2) appreciable benefit or appreciable harm*

Table 10.8: Nicorandil vs. diltiazem * (Data for this outcome not able to analyse. Results reported as in the paper)

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
Frequency of anginal attacks per week	1 (Guermonprez)	RCT (double blind)	Serious[1]	No serious Inconsistency	No serious indirectness	No serious imprecision

Outcome	Nicorandil	Placebo	Relative risk	Absolute effect	Quality
Follow-up 90 days					
Frequency of anginal attacks per week	0.7 (mean)[2]	-	-	SD not reported. P=0.56 (Difference between groups not significant).	MODERATE

1 Guermonprez 1993[51]: Allocation concealment was not reported; study was double blind; Number of drop-outs were reported and < 20%; Intention to treat analysis was not reported.
2 Mean value reported for both groups together. No standard deviation (SD) reported

Table 10.9: Nicorandil versus amlodipine

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Nicorandil	Amlodipine	Relative (95% CI)	Absolute	
ETT (Total exercise duration) (min) (follow-up 8 weeks; better indicated by higher values)											
Chatterjee 1999[53]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	56	62	-	MD 0.7 lower (1.69 lower to 0.29 higher)	⊕⊕OO LOW
ETT (Time to ST-segment depression) (follow-up 8 weeks; better indicated by higher values)											
Chatterjee 1999[53]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	56	62	-	MD 0.6 lower (1.45 lower to 0.25 higher)	⊕⊕OO LOW
ETT (Time to onset of anginal pain) (follow-up 8 weeks; better indicated by higher values)											
Chatterjee 1999[53]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	56	62	-	MD 0.9 lower (2 lower to 0.2 higher)	⊕⊕OO LOW
Sum of weekly anginal attacks (follow-up 8 weeks; better indicated by lower values)											
Chatterjee 1999[53]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (c)	none	56	62	-	MD 1.2 higher (0.54 to 1.86 higher)	⊕⊕OO LOW
Adverse events (combined) (follow-up 8 weeks)											
Chatterjee 1999[53]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (d)	none	20/57 (35.1%)	20/64 (31.3%)	RR 1.12 (0.68 to 1.86)	38 more per 1000 (from 100 fewer to 269 more)	⊕⊕OO LOW

(a) Chatterjee 1999[52]: Randomised, double blind, parallel group design. Allocation concealment was not reported. The study reports of 6/121 patients drop out [5 because of adverse events (nicorandil n=3 and amlodipine n=2) and one due to compliance problems (amlodipine)]. The study reports that 118 /121 were evlauted for efficacy on an ITT basis. The treatment groups were comparable for demographic and clinical characteristics within and between the two countries (Austria and Switzerland), with the exception of history of previous MI among patients recruited in Austria (nicorandil, n=2; amlodipine,n=14). The mean number of anginal attacks/week was similar in both nicorandil and amlodipine groups at baseline. However, the mean number of nitroglycerin units required for pain relief was significantly higher (p=0.04) in the nicorandil group (2.3 vs. 1.0 units/week).Baseline BP,HR and ETT variables were similar in the 2 treatment groups.

(b) 95% CI includes no effect and the upper and the lower confidence limit crosses the MID.

(c) The upper and the lower confidence limit crosses the MID.

(d) 95% CI around the pooled estimate of effect includes both 1) no effect 2) appreciable benefit or appreciable harm

Table 10.10: Nicorandil vs. nifedipine for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Nicorandil	Nifedipine	Relative (95% CI)	Absolute	
Weekly anginal attack rate (follow-up after 8 weeks of treatment; better indicated by lower values)											
Ulvenstam 1992[54]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	27	23	-	MD 5.3 lower (11.48 lower to 0.88 higher)	⊕⊕OO LOW
Exercise duration (min) (follow-up after 8 weeks of treatment; better indicated by higher values)											
Ulvenstam 1992[54]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	25	23	-	MD 1 higher (0.59 lower to 2.59 higher)	⊕⊕OO LOW
Time to onset of angina pectoris (min) (follow-up after 8 weeks of treatment; better indicated by higher values)											
Ulvenstam 1992[54]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	23	22	-	MD 1.1 higher (0.75 lower to 2.95 higher)	⊕⊕OO LOW
Time to 1mm ST-depression (min) (follow-up after 8 weeks of treatment; better indicated by higher values)											
Ulvenstam 1992[54]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	23	20	-	MD 1.6 higher (0.02 lower to 3.22 higher)	⊕⊕OO LOW
ST depression on maximal identical workload (mm) (follow-up after 8 weeks of treatment; better indicated by higher values)											
Ulvenstam 1992[54]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	24	20	-	MD 0.2 higher (0.28 lower to 0.68 higher)	⊕⊕OO LOW
Adverse events (combined) follow-up after 8 weeks of treatment; better indicated by lower values)											
Ulvenstam 1992[54]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	25/29 (86.2%)	28/29 (96.6%)	RR 0.89 (0.76 to 1.05)	106 fewer per 1000 (from 232 fewer to 48 more)	⊕⊕⊕O MODERATE

(a) *Ulvenstam 1992[53] : Double-blind, randomised, multicentre study. 55/58 completed the study. Allocation concealment not reported. ITT not reported. Baseline comparisons made-previous MI more frequent in the nicorandil group.*

(b) *95% CI includes no effect and the upper and the lower confidence limit crosses the MID.*

Table 10.11: Nicorandil versus isosorbide mononitrate

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Nicorandil	ISMN	Relative (95% CI)	Absolute	
ETT (Total exercise time) (sec) (follow-up 2 weeks; better indicated by higher values)											
Zhu 2007[55]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision(b)	None	115	117	-	MD 3.2 lower (37.26 lower to 30.86 higher)	⊕⊕OO LOW
ETT (Time to ST depression) (follow-up 2 weeks; better indicated by higher values)											
Zhu 2007[55]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (b)	None	114	116	-	MD 2.4 higher (37.98 lower to 42.78 higher)	⊕⊕OO LOW
Adverse event (Headache) (follow-up 2 weeks)											
Zhu 2007[55]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (c)	None	15/123 (12.2%)	18/123 (14.6%)	RR 0.83 (0.44 to 1.58)	25 fewer per 1000 (from 82 fewer to 85 more)	⊕⊕OO LOW

(a) Zhu 2007[54]: Randomised, allocation concealment not reported. Double blind.Power calculation used. N=232 patients completed the study (N=115 in nicorandil group and N=117 in the Isosorbide mononitrate (ISMN) group).Drop-out rate: 7% drop out (8% in the nicorandil group and 6% in the ISMN group). Intention to treat analysis was not reported. Baseline comparisons made. No significant difference between the groups.

(b) 95% CI includes no effect and the upper and the lower confidence limit crosses the MID.

(c) 95% CI around the pooled estimate of effect includes both 1) no effect 2) appreciable benefit or appreciable harm

Table 10.12: Nicorandil versus propanolol

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Nicorandil	Propanolol	Relative (95% CI)	Absolute	
Angina free in daily life (%) (follow-up 6 weeks ;better indicated by higher values)											
Meeter 1992[56]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision (b)	None	11/32 (34.4%)	13/37 (35.1%)	RR 0.98 (0.51 to 1.87)	7 fewer per 1000 (from 172 fewer to 306 more)	⊕⊕⊕O MODERATE
12 hrs after medication - change in maximal work load (follow-up 3 weeks; better indicated by higher values)											
Meeter 1992[56]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (c)	None	32	37	-	MD 6 lower (14.77 lower to 2.77 higher)[4]	⊕⊕OO LOW
12 hrs after medication - change in maximal work load (W) (follow-up 6 weeks; better indicated by higher values)											
Meeter 1992[56]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (e)	None	32	37	-	MD 5 lower (15.72 lower to 5.72 higher)	⊕⊕OO LOW
12 hrs after treatment - change in time to angina (follow-up 3 weeks; better indicated by higher values)											
Meeter 1992[56]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (c)	None	32	37	-	MD 0.10 lower (1.05 lower to 0.85 higher)	⊕⊕OO LOW
12 hrs after treatment - change in time to angina (follow-up 6 weeks; better indicated by lower values)											
Meeter 1992[56]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (c)	None	32	37	-	MD 0.40 lower (1.35 lower to 0.55 higher)	⊕⊕OO LOW
2 hrs after treatment - change in maximal work load (follow-up 3 weeks; better indicated by higher values)											
Meeter 1992[56]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	32	37	-	MD 5.00 lower (13.07 lower to 3.07 higher)	⊕⊕⊕O MODERATE
2 hrs after treatment - change in maximal work load (W) (follow-up 6 weeks; better indicated by higher values)											
Meeter 1992[56]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (c)	None	32	37	-	MD 5.00 lower (14.47 lower to 4.47 higher)	⊕⊕OO LOW
2 hrs after treatment - change in time to angina (follow-up 3 weeks; better indicated by lower values)											
Meeter 1992[56]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (c)	None	32	37	-	MD 0.20 higher (0.53 lower to 0.93 higher)	⊕⊕OO LOW
2 hrs after medication - change in time to angina (follow-up 6 weeks; better indicated by higher values)											
Meeter 1992[56]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision (c)	None	32	37	-	MD 0.60 higher (0.35 lower to 1.55 higher)	⊕⊕⊕O MODERATE

(a) Meeter 1992[55]: Allocation concealment not reported; double blind; drop-out rate reported and < 20%; Intention to treat analysis not reported. Baseline comparisons made-Nicorandil group had shorter duration of angina at baseline compared to propranolol median 12 vs 20 months. Fewer patients had a history of MI on nicorandil vs

propranolol 16/38 vs. 22/39. 5/77 were withdrawn from the trial (4 receiving nicorandil and one receiving propranolol). The patients receiving nicorandil were withdrawn because of worsening of angina complaints or headaches.

(b) 95% C around the pooled estimate of effect includes both 1) no effect 2) appreciable benefit or appreciable harm.

(c) The upper and lower limits of 95% CI crosses the MI.

10.3.3 Economic evidence

No economic evidence was found on the use of nicorandil as monotherapy. Based on the unit cost reported in the BNF59[19] the annual drug cost ranges from £99 and £190.

We found one study[57] comparing the addition of nicorandil to usual care with placebo. This is summarised in the economic evidence profile below. See also Economic Evidence Tables in Appendix G.

Table 8.13: Nicorandil+usual care vs. placebo+usual care – Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
Walker 2006[57]	Potentially serious limitations (a)	Partial applicability (b)	Intervention was nicorandil 20mg bd + usual care (57% BB, 55% CCB, 87% nitrates, 88% aspirin). Based on the IONA trial[50] included in the clinical review.

a) *Short follow-up (up to 1.6 years). Sensitivity analysis was quite limited and was applied only to the primary analysis (cost of care after discharge excluded). Morbidity associated with gastro-intestinal events is not included. Effectiveness data were reported only in the incremental analysis.*
b) *QALYs were not estimated.*

Table 8.14: Nicorandil+usual care vs. placebo+usual care – Economic summary of findings

Study	*Incremental cost per patient (£)*	*Incremental effects per patient (primary end-point averted)*	*ICER*	*Uncertainty*
Walker 2006[57]	Saves £0.12 (a)	0.024 (b)	Dominant	Nicorandil is not cost-saving when: - cost of care after discharge is included - either cost of cardiology, cardiac surgery or ICU is reduced by 20%. Results were similar when the measure of effectiveness considered was the number of event-free survivors (events were cardiac death, non-fatal MI, unstable and stable angina, stroke, hospital admission for TIA) or the number of cases of definite acute coronary syndromes (coronary heart disease death, non-fatal myocardial infarction or unstable angina).

(a) *2002 GBP. Costs included were cost of Nicorandil (including 10% dispensing fee and two additional physician visits), adverse events related to Nicorandil, hospital admissions, surgical procedures. The cost of post-discharge care was not included in the base case analysis.*

(b) Primary end-points considered in the analysis were cardiac death, non-fatal MI, hospital admission for cardiac chest pain.

10.3.4 Evidence statements

Clinical **Clinical Efficacy**

Nicorandil +usual treatment versus Placebo + usual treatment

Dargie 2002[50] and IONA Study Group 2004[51]: Evidence from one RCT shows that the composite outcomes (CHD death, non-fatal MI, or unplanned hospital admission for chest pain) for the entire group [RR 0.85 (0.74 to 0.97)] and for people aged over 70 years [RR 0.80 (0.65 to 0.99)] were significantly reduced in the nicorandil group compared to placebo (mean follow-up 1.6 years).

Dargie 2002[50] and IONA Study Group 2004[51]: Evidence from one RCT shows that there were no statistically significant differences between nicorandil and placebo for CHD death [RR 0.82 (0.59 to 1.15)], non fatal MI [RR 0.78 (0.55 to 1.10)], all cause mortality [RR (0.86 (0.67 to 1.10)], unstable angina [RR 0.90 (0.71 to 1.16)], and worsening of angina status [RR 0.94 (0.85 to 1.04)]. There were no statistically significant differences between treatment groups for a composite morbidity/mortality outcome (CHD death, non-fatal MI, or unplanned hospital admission for chest pain) in subgroup analyses of results for women [RR 1.00 [0.76 to 1.31], and people with diabetes [RR 0.79 (0.51 to 1.25)] (mean follow-up 1.6 years).

Nicorandil versus diltiazem

Guermonprez 1992[52]: Evidence from one RCT shows that there was no significant difference between nicorandil and diltiazem for exercise capacity (work to peak exercise] [MD 2.4 (-60.15 to 64.95) and exercise capacity (work required to reach onset of angina) [MD 3.40 (-58.91 to 64.95)] (follow-up 90 days).

Nicorandil versus amlodipine

Chatterjee 1999[53]: Evidence from one RCT shows that there were no significant differences between nicorandil and amlodipine for total exercise duration (min), MD -0.70 [-1.69 to 0.29] , ETT (Time to onset of anginal pain) MD -0.9 (-2 to 0.2), and ETT (Time to ST-segment depression) [MD -0.6 (-1.45 to 0.25 higher) and sum of weekly anginal attacks, [MD 1.20 [0.54 to 1.86] (follow-up 8 weeks).

Nicorandil versus nifedipine

Ulvenstam 1992[54]: Evidence from one RCT shows that there was no statistically significant differences between nicorandil and nifedipine for weekly anginal attack rate [MD -5.3 (-11.48 to 0.88)], exercise duration (min) [MD 1 higher (-0.59 to 2.59)], time to onset of angina pectoris (min) [MD 1.1 (-0.75 to 2.95)], time to 1mm ST-depression (min) [MD 1.6 (-0.02 to 3.22)], and ST depression on maximal identical workload (mm) [MD 0.2 (-0.28 to 0.68)] (follow-up after 8 weeks of treatment).

Nicorandil versus isosorbide mononitrate

Zhu 2007[55]: Evidence from one RCT shows that there was no significant difference between nicorandil and isosorbide mononitrate for total exercise time (sec) [MD -3.20 [-37.26 to 30.86] and ETT (time to ST-depression) [MD 2.4 (-37.98 to 42.78)] (follow-up 2 weeks).

Nicorandil versus propranolol
Meeter 1992[56]: Evidence from one RCT shows that there was no significant difference between nicorandil and propranalol for frequency of anginal attacks [RR 0.98 (0.51 to 1.87)] (follow-up 6 weeks).

Meeter 1992[56]: Evidence from one RCT shows that there was no significant difference between nicorandil and propanalol for change in maximal workload 12 hrs after medication at 3 weeks [MD -6 (-14.77 to 2.77)] and 6 weeks [MD -5 (-15.72 to 5.72)], change in time to angina decimal min 12 hrs after medication at 3weeks [MD -0.10 (-1.05 to -0.85)] and 6 weeks [MD -0.40 (-1.35 to 0.55)] , change in maximal workload 2 hrs after treatment at 3 weeks [MD -5.00 (-13.07 to 3.07)] and 6 weeks [MD -5.00 (-14.47 to 4.47)], change in time to angina 2 hrs after treatment at 3 weeks [MD 0.20 (-0.53 to 0.93)] and 6 weeks [MD 0.60 (-0.35 to 1.55)] (follow-up 6 weeks).

Adverse events

Nicorandil versus placebo
Dargie 2002[50] (IONA): Evidence from one RCT shows that there were significantly greater GI disturbances [RR 1.47 (1.18 to 1.82)] and headaches in the nicorandil compared to placebo [RR 4.49 (3.55 to 5.67)] (mean follow-up 1.6 years) (follow-up mean 1.6 years).

Nicorandil versus diltiazem
Guermonprez 1993[52]: Evidence from one RCT shows that there were no statistically significant differences between nicorandil and diltiazem for adverse effects (combined) [RR 1.05 (0.62 to 1.78)] (follow-up 90 days).

Nicorandil versus amlodipine
Chatterjee 1999[53]: Evidence from one RCT suggests that there were no statistically significant differences between nicorandil and amlodipine for adverse effects (combined) [RR 1.1 (0.68 to 1.86)] (follow-up 8 weeks).

Nicorandil vs. nifedipine
Ulvenstam 1992[54]: Evidence from one RCT suggests that there were no statistically significant differences between nicorandil and nifedipine for adverse events (combined) [RR 0.89 (0.76 to 1.05)] (follow-up after 8 weeks of treatment).

Nicorandil versus isosorbide mononitrate
Zhu 2007[55]: Evidence from one RCT suggests that there were no statistically significant difference between nicorandil and isosorbide mononitrate for adverse effects (headache) [RR 0.83 (0.44 to 1.58)] (follow-up 2 weeks).

Nicorandil versus propranolol

Meeter 1992[56]: Adverse effects not reported (follow-up 6 weeks).

Economic Nicorandil is cost-neutral when post discharge care is not included and over a short time (1.6 years). It could be less cost effective when post-discharge care is included. This evidence has potentially serious limitations and partial applicability.

10.3.5 Recommendations and link to evidence

Recommendation	**If the person cannot tolerate beta blockers and calcium channel blockers or both are contraindicated, consider monotherapy with one of the following drugs*:** • **a long-acting nitrate or** • **ivabradine or** • **nicorandil or** • **ranolazine.** **Decide which drug to use based on comorbidities, contraindications, the person's preference and drug costs[7].** **For people on beta blocker or calcium channel blocker monotherapy whose symptoms are not controlled and the other option (calcium channel blocker or beta blocker) is contraindicated or not tolerated, consider one of the following as an additional drug*:** • **a long-acting nitrate or** • **ivabradine** or** • **nicorandil or** • **ranolazine.** **Decide which drug to use based on comorbidities, contraindications, the person's preference and drug costs[7].** ** Evidence on long-acting nitrates is presented in chapter 9. Evidence on ivabradine and ranolazine is presented in sections 10.2 and 10.4 respectively of this chapter.* *** When combining ivabradine with a calcium channel blocker, use a dihydropyridine calcium channel blocker, for example, slow release nifedipine, amlodipine, or felodipine.*
Relative values of different outcomes	Outcomes of interest included long-term mortality (total and cardiovascular), rates of major adverse cardiovascular events (myocardial infarction, stroke, myocardial revascularisation), and measures of symptom severity (frequency of angina,

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

	exercise test outcomes).
Trade off between clinical benefits and harms	No evidence was found to assess the effects of monotherapy with nicorandil on long term mortality or rates of major adverse cardiovascular events in people with stable angina. Short-term trials of monotherapy with nicorandil versus monotherapy with other anti-anginal drugs (diltiazem, amlodipine, or propranolol) demonstrated similar reductions in the frequency of episodes of angina in both treatment groups. These trials also reported similar increases in total exercise capacity during monotherapy with nicorandil and monotherapy with diltiazem, amlodipine, propranolol, or isosorbide mononitrate. No difference in the short-term rate of adverse effects was reported between nicorandil and diltiazem, amlodipine, or isosorbide mononitrate.
Economic considerations	No economic evidence on the use of nicorandil monotherapy was found. The annual drug cost of nicorandil ranges from £99 to £190.
Quality of evidence	Low quality evidence from trials with small sample size and short duration of follow-up. In one trial [56] no intention to treat analysis was carried out. No economic evidence was found.
Other considerations	The GDG concluded that there is insufficient evidence to recommend monotherapy with nicorandil in preference to monotherapy with a BB or CCB as first line treatment for angina. Nicorandil can be considered as monotherapy for the treatment of stable angina if BB and CCB are not tolerated or contraindicated. Adverse effects of nicorandil include headache (especially on initiation of treatment), flushing, dizziness, reduction in blood pressure and/or increase in heart rate, and gastrointestinal side effects including mucosal ulceration. In the IONA trial routine treatment with nicorandil was associated with a higher risk of gastrointestinal side effects and GDG members have experience of patients who developed gastrointestinal ulceration during treatment with nicorandil.

Recommendation	**For people on beta blocker or calcium channel blocker monotherapy whose symptoms are not controlled and the other option (calcium channel blocker or beta blocker) is contraindicated or not tolerated, consider one of the following as an additional drug:** • **a long-acting nitrate or** • **ivabradine* or** • **nicorandil or** • **ranolazine.** **Decide which drug to use based on comorbidities, contraindications, the person's preference and drug costs[8].** **When combining ivabradine with a calcium channel blocker, use a dihydropyridine calcium channel blocker for example, slow release nifedipine, amlodipine, or felodipine.* *NOTE: Evidence on long-acting nitrates is presented in chapter 9. Evidence on ivabradine and ranolazine is presented in sections 10.2 and 10.4 respectively of this chapter.*
Relative values of different outcomes	Outcomes of interest included long-term mortality (total and cardiovascular), rates of major adverse cardiovascular events (myocardial infarction, stroke, myocardial revascularisation), and measures of symptom severity (frequency of angina, exercise test outcomes).
Trade off between clinical benefits and harms	In a large trial addition of nicorandil to standard antianginal treatment (BB 56%, CCB 55%, nitrate 87%) in people with stable angina reduced the composite of coronary heart disease death, myocardial infarction, and unplanned hospitalisation for chest pain. There were trends for lower rates of all events included in the composite primary endpoint in the nicorandil group, but these were not statistically significant. At the end of the study (1.6 years) the Canadian Cardiovascular Society angina class did not differ between the two groups. Headache, gastrointestinal disturbance, and treatment withdrawal because of adverse effects were more frequent in the nicorandil group. The GDG concluded that the 2.4% absolute reduction in the

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

	rate of the primary composite endpoint in IONA did not justify the routine use of nicorandil as add-on therapy to standard antianginal treatment in people with stable angina, particularly as the drug is associated with an excess risk of adverse events, including headache and gastrointestinal disturbance.
Economic considerations	An economic analysis based on IONA suggested that addition of nicorandil to standard anti-anginal treatment is cost neutral. However there is a high uncertainty over this conclusion as the cost of post-discharge care and adverse events was not considered, and the follow-up time was only 1.6 years.
Quality of evidence	Moderate quality evidence from a large multicentre trial powered to detect a 20% reduction in the primary endpoint. Allocation concealment was not reported and treatment withdrawal was >20% in both groups. The economic evidence has potentially serious limitations and partial applicability.
Other considerations	The GDG concluded that addition of nicorandil is an option for people whose symptoms of angina are not controlled by a BB or CCB. Nicorandil is slightly cheaper than ivabradine and ranolazine but more than the cost of long-acting nitrate. The GDG concluded that there was insufficient evidence to make a firm recommendation about the choice of an additional antianginal drug if a BB or CCB is not tolerated or is contraindicated.

10.4 Ranolazine

The mechanism of action of ranolazine has not been fully elucidated, but it is believed to act by selective inhibition of late sodium influx across the sarcolemma, which attenuates the abnormalities of ventricular repolarisation and contractility associated with myocardial ischaemia. Reported side-effects include dizziness, constipation, and nausea. Ranolazine has the potential to prolong the QT interval and is contraindicated in people with pre-existing QT prolongation. Ranolazine should be avoided in severe hepatic or renal impairment. Ranolazine is available in a sustained release formulation, with an elimination half-life of about seven hours.

The summary of product characteristics (SPC) for ranolazine reports that minimal decreases in mean heart rate and mean systolic blood pressure have been observed in patients treated with ranolazine either alone or in combination with other antianginal medicinal products in controlled studies. No proarrhythmic effects were observed in 3,162 patients treated with ranolazine based on 7-day Holter monitoring in the MERLIN-TIMI 36 study[58].

This section reviews evidence for the use of ranolazine as adjunctive therapy to control symptoms and improve outcome in people with stable angina.

10.4.1 Clinical question

What is the clinical/cost effectiveness of ranolazine for the management of stable angina?

10.4.2 Clinical evidence

The “Review Protocol” for this topic can be found in Appendix C, the “Search Strategies” in Appendix D, the “List of Included and Excluded Studies” in Appendix E1, the “Clinical Evidence Tables” in Appendix E2, and the “Forest Plots” in Appendix F.

Table 10.15: Ranolazine (750 mg bid) + antianginal treatment vs. placebo + antianginal treatment (follow-up 12 weeks)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ranolazine (750 mg bid) + antianginal	Placebo + antianginal	Relative (95% CI)	Absolute	
Exercise duration (sec) (trough - change from baseline) - (follow-up 12 weeks; better indicated by higher values)											
Chaitman 2004[59] (CARISA) (c)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	272	258	-	MD 23.7 higher (1.11 to 46.29 higher)	⊕⊕⊕⊕ HIGH
Time to onset of angina (sec) (trough - change from baseline) - (follow-up 12 weeks; better indicated by higher values)											
Chaitman 2004[59] (CARISA)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	272	258	-	MD 29.7 higher (4.62 to 54.78 higher)	⊕⊕⊕⊕ HIGH
Exercise duration (sec) (peak - change from baseline) - (follow-up 12 weeks; better indicated by higher values)											
Chaitman 2004[59] (CARISA)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	270	256	-	MD 34 higher (11.96 to 56.04 higher)	⊕⊕⊕⊕ HIGH
Time to onset of angina (sec) (peak - change from baseline) - (follow-up 12 weeks; better indicated by higher values)											
Chaitman 2004[59] (CARISA)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	272	256	-	MD 38 higher (13.91 to 62.09 higher)	⊕⊕⊕⊕ HIGH
Adverse events (follow-up 12 weeks)											
Chaitman 2004[59] (CARISA)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	serious (b)	none	82/279 (29.4%)	71/269 (26.4%)	RR 1.11 (0.85 to 1.46)	29 more per 1000 (from 40 fewer to 121 more)	⊕⊕⊕O MODERATE
Angina attacks per week (follow-up 12 weeks; better indicated by lower values)											
Chaitman 2004[59] (CARISA)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	272	258	-	MD 0.8 lower (1.52 to 0.08 lower)	⊕⊕⊕⊕ HIGH

(a) Chaitman 2004[57]: Stratified randomisation. Allocation concealment reported. Double blind. ITT reported. Baseline comparisons made, marginally fewer patients in the placebo group had undergone bypass surgery.

(b) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.

(c) Ranolazine 750 mg twice plus anti-anginal drugs including atenolol 50 mg (42%% patients), amlodipine 5 mg (31%) and diltiazem 180 mg (26%) vs. placebo plus antianginal drugs including atenolol 50 mg (44%), Amlodipine 5 mg (30%), Diltiazem 180 mg (26%)

Table 10.16: Ranolazine (750 mg bid) + antianginal treatment vs. placebo+antianginal treatment – Subgroup diabetes (follow-up 12 weeks)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ranolazine (750 mg bid) + antianginal treatment	Placebo+antianginal treatment - diabetic patients	Relative (95% CI)	Absolute	
Exercise duration sec (trough change from baseline) - 12 wks (follow-up 12 weeks; better indicated by higher values)											
Timmis 2006[60] (CARISA) (c)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	serious (b)	none	68	57	-	MD 28.7 higher (50.9 lower to 108.3 higher)	⊕⊕⊕O MODERATE
Time to onset of angina sec (trough change from baseline) - 12 wks (follow-up 12 weeks; better indicated by higher values)											
Timmis 2006[60] (CARISA)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	serious (b)	none	68	57	-	MD 50.8 higher (37.56 lower to 139.16 higher)	⊕⊕⊕O MODERATE
Angina episodes per week - 12 wks (follow-up 12 weeks; better indicated by lower values)											
Timmis 2006[60] (CARISA)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	serious (b)	none	68	57	-	MD 0.91 lower (3.25 lower to 1.43 higher)	⊕⊕⊕O MODERATE
Nitroglycerin consumption per week - 12 wks (follow-up 12 weeks; better indicated by lower values)											
Timmis 2006[60] (CARISA)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	serious (b)	none	68	57	-	MD 2.32 lower (7.18 lower to 2.54 higher)	⊕⊕⊕O MODERATE

(a) Timmis 2006[58]: Randomised. Allocation concealment reported. ITT reported.
(b) 95% CI includes no effect and the upper and lower CI crosses the MID.
(c) Ranolazine 750 mg twice plus anti-anginal drugs including atenolol 50 mg (42% patients), amlodipine 5 mg (31%) and diltiazem 180 mg (26%) vs. placebo plus antianginal drugs including atenolol 50 mg (44%), Amlodipine 5 mg (30%), Diltiazem 180 mg (26%)

Sub-group interaction between diabetic and non-diabetic patients: *There was no significant treatment by subgroup interaction for exercise duration (p=0.89) and time to onset of angina (p=0.54) between diabetic and non diabetic patients. Statistical tests for interaction between diabetes status and treatment effect showed no evidence that the effects of ranolazine differed between diabetic and non-diabetic patients either in the number of angina episodes per week (p=0.81) or nitroglycerin usage (p=0.063); and therefore no evidence that the treatment effect differed between diabetic and non-diabetic patients.*

Table 10.17: Ranolazine (1000 mg bid) + antianginal treatment vs. placebo +antianginal treatment – Subgroup age (follow-up 6 weeks)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ranolazine (1000 mg bid) + antianginal treatment	Placebo +antianginal treatment- age	Relative (95% CI)	Absolute	Quality
Weekly angina attacks < 70 yrs (follow-up 6 weeks; better indicated by lower values)											
Rich 2007[61] (CARISA, ERICA)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	403	409	-	MD 0.5 lower (1.1 lower to 0.1 higher)	⊕⊕⊕⊕ HIGH
Weekly angina attacks > 71 yrs (follow-up 6 weeks; better indicated by lower values)											
Rich 2007[61] (CARISA, ERICA)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	135	130	-	MD 1.13 lower (2.05 to 0.21 lower)	⊕⊕⊕⊕ HIGH
Nitroglycerin consumption < 70 yrs (follow-up 6 weeks; better indicated by lower values)											
Rich 2007[61] (CARISA, ERICA)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	403	409	-	MD 0.97 lower (1.64 to 0.3 lower)	⊕⊕⊕⊕ HIGH
Nitroglycerin consumption > 71 yrs (follow-up 6 weeks; better indicated by lower values)											
Rich 2007[61] (CARISA, ERICA)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	135	130	-	MD 0.94 lower (1.74 to 0.14 lower)	⊕⊕⊕⊕ HIGH
Adverse events <70 years (follow-up 6 weeks) (c)											
Rich 2007[61] (CARISA, ERICA)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	194/604 (32.1%)	131/420 (31.2%)	RR 1.03 [0.86, 1.24]	9 more per 1000 (from 44 fewer to 75 more)	⊕⊕⊕⊕ HIGH
Adverse events > 70 years (follow-up 6 weeks) (c)											
Rich 2007[61] (CARISA, ERICA)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	serious (b)	none	102/231 (44.2%)	43/132 (32.6%)	RR 1.36 [1.02, 1.80]	117 more per 1000 (from7 more to 261 more)	⊕⊕⊕O MODERATE

(a) Rich 2007[59]: Randomised. Allocation concealment reported. Double blind. ITT reported. Baseline comparisons made between the 2 age groups, history of MI was more common among younger patients and older patients were somewhat more likely to have diabetes. Systolic blood pressure was slightly higher and diastolic blood pressure was slightly lower in older patients and there was a trend of having more women in the older subgroup.

(b) 95% CI around the pooled estimate of effect includes appreciable benefit or appreciable harm.
(c) Adverse events- cardiac adverse events, constipation, nausea, dyspepsia, dizziness, headache, peripheral edema asthenia, serious adverse events such as MI, syncope,, transient ischemic attack. The most common events resulting in discontinuation of study drug were related to the gastrointestinal, nervous, and cardiac organ systems.

Table 10.18: Ranolazine (1000 mg bid) plus amlodipine (10 mg) vs. amlodipine (10mg) (follow-up 6 weeks)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ranolazine (1000 mg bid) plus amlodipine (10 mg)	amlodipine (10mg)	Relative (95% CI)	Absolute	Quality
Adverse events (follow-up 6 weeks)											
Stone 2006[62] (ERICA) (b) (c)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	serious (b)	none	112/281 (39.9%)	100/284 (35.2%)	RR 1.13 (0.91 to 1.4)	46 more per 1000 (from 32 fewer to 141 more)	⊕⊕⊕O MODERATE
Weekly angina frequency - (follow-up 6 weeks; better indicated by lower values)											
Stone 2006[62] (ERICA)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	277	281	-	MD 0.43 lower (1 lower to 0.14 higher)	⊕⊕⊕⊕ HIGH
Weekly nitroglycerin consumption - (follow-up 6 weeks; better indicated by lower values)											
Stone 2006[62] (ERICA)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	277	281	-	MD 0.65 lower (1.23 to 0.07 lower)	⊕⊕⊕⊕ HIGH

(a) Stone 2006[60]: Randomised. Randomisation wascentralised and not stratified by centre. Allocation concealment reported. Double blind. Blinding of outcome assessors reported. Ranolazine: 7/281 (2%); Placebo: 6/284 (2%) lost to follow-up. ITT reported. 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.

(b) Ranolazine 1000 mg twice daily plus amlodipine 10 mg/daily vs. amlodipine 10 mg/daily

(c) Per protocol, the patients in this study were not taking BB, and hence the authors state that this data may be especially applicable to the proportions of patients who cannot tolerate BB therapy.

10.4.3 Economic evidence

No economic studies were identified on this question. We calculated the daily and annual cost of ranolazine treatment based on the unit cost reported in the BNF59[19].

Table 10.19: Drug cost of Ranolazine

	Cost per day (£)	Cost per year (£)
Ranolazine, 375 mg, 500 mg or 750 mg twice daily	1.63	595

The costs of adverse effects were not estimated.

10.4.4 Evidence statements

Clinical <u>**Clinical Efficacy**</u>

<u>**Ranolazine plus antianginal treatment versus placebo plus antianginal treatment**</u>

Chaitman 2004[59] (CARISA): Evidence from one RCT shows that exercise duration at trough (sec) [MD 23.70 (1.11 to 46.29)], time to onset of angina at trough (sec) [MD 29.70 (4.62 to 54.76)], exercise duration at peak (sec) [MD 34 (11.96 to 56.04)] and time to onset of angina at peak(sec) [MD 38 (13.91 to 62.09)] were significantly higher in the ranolazine plus antianginal treatment compared with placebo plus antianginal treatment [follow-up 12 weeks]. Angina attacks per week was significantly lower in the ranolazine plus antianginal treatment compared with placebo plus antianginal treatment [MD 0.8 lower (1.52 to 0.08 lower)]. There were no statistically significant differences between ranolazine plus antianginal treatment and placebo plus antianginal treatment for the outcome of adverse events [RR 1.11 (0.85 to 1.46)] (follow up 12 weeks).

Timmis 2006[60] (CARISA): Evidence from a post-hoc sub-group analyses of one RCT shows that there were no statistically significant differences in the outcomes of exercise duration (sec) [MD 28.70 (-50.90 to 108.30)], time to onset of angina (sec) [MD 50.80 (-37.56 to 139.16)], frequency of angina attacks [MD -0.91 (-3.25 to 1.43) and nitroglycerin consumption [MD -2.32 (-7.18 to 2.54)] between ranolazine plus anti anginal treatment and placebo plus anti-anginal treatment in people with diabetes (follow-up 12 weeks).

Rich 2007[61] (CARISA): Evidence from one post-hoc sub-group analysis of a RCT shows that in patients younger than 70 years ranolazine plus anti anginal treatment resulted in a statistically significant reduction in nitroglycerine consumption [MD -0.97 (-1.64 to -0.30)] but no significant difference in weekly angina attacks [MD -0.50 (-1.10 to 0.10)] or adverse events [RR1.03 [0.86, 1.24] when compared with placebo plus anti-anginal treatment [follow-up 6 weeks]. In patients older than 70 years ranolazine plus anti anginal treatment resulted in statistically significantly reductions in weekly angina attacks [MD -1.13 (-2.05 to -0.21)] and nitroglycerin consumption [MD -0.94 (-1.74 to -0.14) but a statistically significant increase in adverse events [RR 1.36 [1.02, 1.80] when compared with placebo plus anti-anginal treatment (follow-up six weeks).

Ranolazine plus amlodipine versus amlodipine

Stone 2006[62] (ERICA): Evidence from one RCT shows that weekly nitroglycerin consumption was significantly lower with ranolazine plus amlodipine compared to amlodipine alone [MD -0.65 (-1.23 to -0.07)]. There were no statistically significant differences between ranolazine plus amlodipine and amlodipine for weekly angina frequency [MD-0.43 (1.00 to 0.14)] and adverse events (RR 1.13 (0.91 to 1.40) (follow-up 6 weeks).

Economic No economic evidence was found on this question. A simple cost analysis showed a significant drug cost of ranolazine.

10.4.5 Recommendations and link to evidence

Recommendation	**If the person cannot tolerate beta blockers and calcium channel blockers or both are contraindicated, consider monotherapy with one of the following drugs*:** • **a long-acting nitrate or** • **ivabradine or** • **nicorandil or** • **ranolazine.** **Decide which drug to use based on comorbidities, contraindications, the person's preference and drug costs[9].** **For people on beta blocker or calcium channel blocker monotherapy whose symptoms are not controlled and the other option (calcium channel blocker or beta blocker) is contraindicated or not tolerated, consider one of the following as an additional drug*:** • **a long-acting nitrate or** • **ivabradine** or** • **nicorandil or** • **ranolazine** **Decide which drug to use based on comorbidities, contraindications, the person's preference and drug costs[9].** ** Evidence on long-acting nitrates is presented in chapter 9. Evidence on ivabradine and nicorandil is presented in sections 10.2 and 10.3 respectively of this chapter.* ***When combining ivabradine with a calcium channel blocker, use a dihydropyridine calcium channel blocker, for example, slow release nifedipine, amlodipine, or felodipine.*
Relative values of different outcomes	Outcomes of interest included long-term mortality (total and cardiovascular), rates of major adverse cardiovascular events (myocardial infarction, stroke, myocardial revascularisation), and measures of symptom severity (frequency of angina,

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

	exercise test outcomes).
Trade off between clinical benefits and harms	We found no evidence on the effects of ranolazine monotherapy or ranolazine in combination with other anti-anginal drugs on long-term outcome in people with stable angina. In one randomised trial addition of ranolazine to standard anti-anginal treatment for twelve weeks increased exercise duration (by 20 to 30 seconds) and time to angina at trough (and at peak). Ranolazine reduced the frequency of angina attacks and nitroglycerine use by about one per week. These effects were consistent in people with diabetes and in people aged over 70 years. In one randomised trial addition of ranolazine to amlodipine reduced nitroglycerine consumption (by 0.65 doses per week) but not weekly angina frequency after six weeks follow-up. Addition of ranolazine to amlodipine did not increase the risk of adverse events when compared with amlodipine alone. There was also no difference in risk of adverse events between ranolazine plus antianginal treatment versus placebo plus antianginal treatment for the entire group, but addition of ranolazine to antianginal treatment was associated with an increased risk of adverse events in a sub group of patients older than 70 years of age.
Economic considerations	No economic evidence on the use of ranolazine for the treatment of stable angina was available for review. The cost of ranolazine is substantially higher than the costs of first-line anti-anginal drugs (BBs and CCBs) and long-acting nitrates.
Quality of evidence	The available evidence for ranolazine was of moderate or high quality but were not designed to assess the long-term effects of ranolazine on mortality or other major adverse cardiac events. The improvements in exercise time and symptom severity associated with short-term ranolazine treatment are modest and of uncertain clinical significance. No economic evidence was available on this question.
Other considerations	Evidence to support the long-term use of ranolazine as adjunctive anti-anginal therapy is very limited. The GDG concluded that there is insufficient evidence to recommend routine use of ranolazine, but ranolazine may have a role in people with stable angina who are inadequately controlled or intolerant of first-line anti-anginal therapies.

	The cost of ranolazine is comparable with the costs of ivabradine but more than the cost of long-acting nitrate. Ranolazine has a licence for use in combination treatment. The GDG concluded that there was insufficient evidence to make a firm recommendation about the choice of an additional anti-anginal drug if a BB and/or CCB are not tolerated or are contraindicated.

10.5 General drug recommendations

Recommendation	**Offer people optimal drug treatment for the initial management of stable angina. Optimal drug treatment consists of one or two anti-anginal drugs as necessary plus drugs for secondary prevention of cardiovascular disease.**
Other considerations	The evidence reviews indicated benefit from secondary prevention treatment and anti-anginal treatment. The GDG considered it important to emphasise the importance for patients to receive optimal medical treatment and made a consensus recommendation for this.

Recommendation	**Advise people that the aim of anti-anginal drug treatment is to prevent episodes of angina and the aim of secondary prevention treatment is to prevent cardiovascular events such as heart attack and stroke.**
Other considerations	The GDG were aware of the importance of patient adherence to secondary prevention treatment. They also considered it important that patients understand that the purpose of anti-angnal drugs is to improve symptoms. The GDG made a consensus recommendation to ensure that professionals explain these points adequately to patients.

Recommendation	**Review the person's response to treatment, including any side effects, 2–4 weeks after starting or changing drug treatment.** **Titrate the drug dosage against the person’s symptoms up to the maximum tolerable dosage.** **Discuss how side effects of drug treatment might affect the**

	person's daily activities and explain why it is important to take drug treatment regularly.
Other considerations	The GDG debated the need to review the response to treatment after starting or changing any anti-anginal medication. The GDG reached a consensus that response to treatment, including any side effects, should be reviewed 2-4 weeks after starting or changing any anti-anginal drug. If the person's angina is not controlled, the dose of the anti-anginal drug should be titrated up to the maximum tolerable dose (within the licensed dose range) with the objective of achieving control of symptoms of stable angina. The GDG also considered it important that patients do not remain on drugs that are not providing benefit to them and healthcare professionals should stop anti-anginal drugs that are not providing symptomatic benefit.

Recommendation	**Patients differ in the type and amount of information they need and want. Therefore the provision of information should be individualised and is likely to include, but not be limited to:** • **what the medicine is** • **how the medicine is likely to affect their condition (that is, its benefits)** • **likely or significant adverse effects and what to do if they think they are experiencing them** • **how to use the medicine** • **what to do if they miss a dose** • **whether further courses of the medicine will be needed after the first prescription** • **how to get further supplies of medicines. [This recommendation is from 'Medicines Adherence' (NICE clinical guideline 76).]**
Other considerations	The GDG agreed to include this recommendation from Medicine Adherence Clinical Guideline 76 to ensure people with stable angina are given adequate information about the drugs they are prescribed.

10.6 Research recommendation

The GDG recommended the following research question:

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

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

11 Medical versus revascularisation interventions

11.1 Introduction

This chapter compares the effectiveness of medical treatment to revascularisation (PCI or CABG) for treating people with stable angina.

Coronary artery bypass surgery has been used to treat people with stable angina since the 1970s. Until recently coronary surgery required extracorporeal circulation, but new techniques have facilitated 'off-pump' surgery without circulatory bypass[63]. During surgery reversed saphenous vein, and internal mammary or other arterial conduits are used to bypass areas of coronary arterial obstruction.

Percutaneous transluminal coronary (balloon) angioplasty (PTCA) was established as a routine treatment for stable angina in the 1980's. The results of coronary balloon angioplasty were limited by peri-procedural occlusion of the treated artery, and by recurrence of the arterial stenosis ('restenosis') within a few months in around one third of patients. The introduction of metallic ('bare metal') coronary artery stents in the 1990's improved the results of percutaneous coronary intervention, but was associated with the new problems of thrombotic stent occlusion ('stent thrombosis') and in-stent restenosis. In the last decade the development of drug-eluting stents has facilitated focal inhibition of the intimal proliferative response to arterial wall injury, resulting in a reduced risk of in-stent restenosis but a small but important risk of late stent thrombosis. Meta-analyses of randomised trials confirm that bare metal and drug eluting coronary stents reduce the risk of restenosis and need for repeat revascularisation procedures, but have no impact on mortality[64-66].

The role of coronary angiography and myocardial revascularisation in people with coronary artery disease has been investigated in numerous randomised trials. Nevertheless, after several decades of research there is persisting uncertainty about the indications for, and optimal timing of invasive investigation and myocardial revascularisation in people with stable angina. The trials in this review compared an initial treatment strategy of continued medical therapy versus an initial treatment strategy of continued medical therapy and myocardial revascularisation (with coronary artery bypass surgery or percutaneous coronary intervention).

Evidence review - studies included

The focus of this guideline is the management of stable angina and we only included studies that had more than 60% stable angina patients.

The evidence review includes evidence from RCTs and from individual patient data (IPD) meta-analyses of medical treatment vs. surgery [67].

The RCT evidence addressed three main comparisons:

- Medical vs. CABG
- Medical vs. PCI
- Medical vs. PCI or CABG

Some trials selectively recruited patients with single vessel coronary artery disease but other trials recruited patients with single or multi-vessel disease and/or presented subgroup analyses by the number of diseased vessels. Definitions for these subgroups are not universally agreed and results for patients with single and multi-vessel disease are not reported consistently across the trials. In the evidence reviews we have combined evidence from trials that included patients with multi-vessel disease, but results for patients with single vessel disease are considered separately. We also consider subgroups of older patients, those with two or three vessel disease, and those with involvement of the left anterior descending artery or with left main stem disease. Results are presented for three time periods, short term (1 yr), medium term (2-4 yrs), and longer term follow-up (>4yrs).

Evidence review - outcomes

The main outcomes analysed were:

- Death (all causes)
- Cardiac death
- MI/non fatal MI
- Stroke
- Non protocol revascularisation (PCI and/or CABG)
- Freedom from angina

Evidence review- presentation of results

The results of the review are presented as follows:

A. Medical vs. CABG

- Multi-vessel disease – short term follow-up (1 year)

- Multi-vessel disease - medium term follow-up (2 to 4 years)
- Multi-vessel disease - long term follow-up (>4 years)
- Single vessel disease - medium term follow-up (2 to 4 years)
- Single vessel disease - long term follow-up (>4 years)
- Left main stem disease - medium term follow-up (2 to 4 years)
- Left main stem disease - long term follow-up (>4 years)
- Left anterior descending artery - long term follow-up (>4 years)

B. Medical vs. PCI

- Multi-vessel disease - short term follow-up (1 year)
- Multi-vessel disease - medium term follow-up (2 to 4 years)
- Multi-vessel disease - long term follow-up (> 4 years follow-up)
- Single vessel disease - medium term follow-up (2 -4 years)
- Single vessel disease - long term follow-up (>4 years)

C. Medical vs. PCI or CABG

- Multi-vessel disease - short term follow-up (1 year)
- Multi-vessel disease - medium term follow-up (2 to 4 years)
- Multi-vessel disease - long term follow-up (>4 years)

The narrative summary of the outcome 'Quality of life' is presented separately for each of the above comparisons (as data was not analysed for this outcome).

11.2 Medical interventions versus CABG

11.2.1 Clinical question

What is the clinical and cost effectiveness of medical interventions versus CABG in people with stable angina?

11.2.2 Clinical evidence

The "Review Protocol" for this topic can be found in Appendix C, the "Search Strategies" in Appendix D, the "List of Included and Excluded Studies" in Appendix E1, the "Clinical Evidence Tables" in Appendix E2, and the "Forest Plots" in Appendix F.

Table 11.1: Medical vs. CABG – Multi-vessel disease – Short term follow-up (1 year) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Medical	CABG	Relative (95% CI)	Absolute	
Death (follow-up 1 year)											
Hueb 2004[68] (MASS-II)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	3/203 (1.5%)	8/203 (3.9%)	RR 0.38 (0.1 to 1.39)	24 fewer per 1000 (from 35 fewer to 15 more)	⊕⊕OO LOW
Q wave MI (follow-up 1 year)											
Hueb 2004[68] (MASS-II)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	10/203 (4.9%)	4/203 (2%)	RR 2.5 (0.8 to 7.84)	30 more per 1000 (from 4 fewer to 135 more)	⊕⊕OO LOW
Stroke (follow-up 1 year)											
Hueb 2004[68] (MASS-II)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	3/203 (1.5%)	3/203 (1.5%)	RR 1 (0.2 to 4.9)	0 fewer per 1000 (from 12 fewer to 58 more)	⊕⊕OO LOW
Non protocol revascularisation (follow-up 1 year)											
Hueb 2004[68] (MASS-II)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	16/203 (7.9%)	1/203 (0.5%)	RR 16 (2.14 to 119.52)	74 more per 1000 (from 6 more to 584 more)	⊕⊕⊕O MODERATE
Free of angina (follow-up 1 year)											
Hueb 2004[68] (MASS-II)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (c)	None	74/203 (36.5%)	120/203 (59.1%)	RR 0.62 (0.5 to 0.76)	225 fewer per 1000 (from 142 fewer to 296 fewer)	⊕⊕OO LOW
Death- subgroup diabetes (follow-up 1 year)											
Soares 2006[69] (MASS-II)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	2/75 (2.7%)	4/59 (6.8%)	RR 0.39 (0.07 to 2.07)	41 fewer per 1000 (from 63 fewer to 73 more)	⊕⊕OO LOW
Death- subgroup no diabetes (follow-up 1 year)											
Soares 2006[69] (MASS-II)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	2/128 (1.6%)	7/144 (4.9%)	RR 0.32 (0.07 to 1.52)	33 fewer per 1000 (from 45 fewer to 25 more)	⊕⊕OO LOW

(a) Hueb 2004[66]: Randomised. ITT reported. Allocation concealment unclear.
(b) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.
(c) 95% CI around the pooled estimate of effect includes appreciable benefit or appreciable harm.

Table 11.2: Medical vs. CABG – Multi-vessel disease – Medium term follow-up (2 to 4 years) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Medical	CABG	Relative (95% CI)	Absolute	
Death (follow-up 2-4 years)											
Read 1978[70] (VA); Varnauskas 1980[71] (ECSS)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	89/727 (12.2%)	67/726 (9.2%)	RR 1.29 (0.96 to 1.74)	27 more per 1000 (from 4 fewer to 68 more)	⊕⊕OO LOW
Cardiac death (follow-up 2 years)											
Varnauskas 1980[71] (ECSS)	randomised trials	serious (c)	no serious inconsistency	no serious indirectness	no serious imprecision	none	27/373 (7.2%)	10/394 (2.5%)	RR 2.85 (1.4 to 5.81)	47 more per 1000 (from 10 more to 122 more)	⊕⊕⊕O MODERATE
MI (follow-up 2-2.8 years)											
Guinn 1976[72]	randomised trials	serious (d)	no serious inconsistency	no serious indirectness	serious (b)	none	11/60 (18.3%)	5/56 (8.9%)	RR 2.05 (0.76 to 5.54)	94 more per 1000 (from 21 fewer to 405 more)	⊕⊕OO LOW
Free of angina (follow-up 2-2.8 years)											
Guinn 1976[72]; Varnauskas 1980[71] (ECSS)	randomised trials	serious (e)	serious (f)	no serious indirectness	no serious imprecision	none	180/433 (41.6%)	353/450 (78.4%)	RR 0.53 (0.47 to 0.60)	369 fewer per 1000 (from 314 fewer to 416 fewer)	⊕⊕OO LOW
Death - sub group 2 vessel disease (follow-up 2 years)											
Varnauskas 1980[71] (ECSS)	randomised trials	serious (c)	no serious inconsistency	no serious indirectness	serious (b)	none	6/154 (3.9%)	10/147 (6.8%)	RR 0.57 (0.21 to 1.54)	29 fewer per 1000 (from 54 fewer to 37 more)	⊕⊕OO LOW
Death - sub group 3 vessel disease (follow-up 2-4 years)											
Detre 1977[73] (VA); Varnauskas 1980[71] (ECSS)	randomised trials	serious (g)	no serious inconsistency	no serious indirectness	serious (b)	none	46/346 (13.3%)	28/354 (7.9%)	RR 1.57 (1.02 to 2.44)	45 more per 1000 (from 2 more to 114 more)	⊕⊕OO LOW
Non protocol revascularisation (follow-up 2.8 years)											
Guinn 1976[72]	randomised trials	serious (h)	no serious inconsistency	no serious indirectness	serious (b)	none	4/60 (6.7%)	1/56 (1.8%)	RR 3.73 (0.43 to 32.4)	49 more per 1000 (from 10 fewer to 561 more)	⊕⊕OO LOW

(a) Read 1978[68]; Varnauskas 1980[69]: Randomised, ITT reported in all studies. Allocation not reported in all studies. No heterogeneity I^2=0%

(b) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.

(c) Varnauskas 1980[69]: randomised. Low attrition bias. Intention to treat analysis used. Reporting of outcome is not always very clear; crossover 26/394 (6.5%) of patients assigned to surgery did not complete treatment; medical group 50/373 (13%) had surgery; unclear allocation concealment

(d) *Guinn 1976[70]: Randomised. No loss to follow-up. Baseline comparisons made. Intention to treat analysis reported. Allocation concealment not reported. No heterogeneity I^2=0%*
(e) *Guinn 1976[70]; Varnauskas 1980[69]: Randomised, ITT reported in all. Allocation concealment not reported in both studies.*
(f) *High heterogeneity - I^2=93%*
(g) *Detre 1977[71] (VA); Varnauskas 1980[69]: Randomised, ITT used in both the studies. Allocation concealment not reported in both.*
(h) *Strengths: Randomised. No loss to follow-up. Baseline comparisons made. Intention to treat analysis reported. Limitations: allocation concealment not reported.*

Sub group interaction
There was no significant difference between sub group of patients with 2 vessel or 3 vessel disease for death (p=0.07) at medium term follow-up (2- to 4 years).

Table 11.3: Medical vs. CABG – Multi-vessel disease – Long term follow-up (>4 years) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Medical	CABG	Relative (95% CI)	Absolute	
Death (follow-up 5-22 years)											
Alderman 1990[74] (CASS); Frick 1985[75]; Kloster 1979[76]; Peduzzi 1998[77] (VA); Varnauskas 1988[78] (ECSS); Hueb 2010[79] (MASS-II)	randomised trials	serious (a)	serious (b)	no serious indirectness	no serious imprecision	none	533/1419 (37.6%)	484/1415 (34.2%)	RR 1.08 (0.99 to 1.17)	27 more per 1000 (from 3 fewer to 58 more)	⊕⊕OO LOW
Cardiac death (follow-up 12 years)											
Bhayana 1980[80] (VA); Varnauskas 1988[78] (ECSS)	randomised trials	serious (c)	serious (d)	no serious indirectness	serious (e)	none	112/448 (25%)	79/465 (17%)	RR 1.44 (1.12 to 1.84)	75 more per 1000 (from 20 more to 143 more)	⊕OOO VERY LOW
MI (follow-up 5-22 years)											
Fisher 1985[81] (CASS); Kloster 1979[76]; Peduzzi 1998[77] (VA); Hueb 2010[79] (MASS-II)	randomised trials	serious (f)	serious (g)	no serious indirectness	no serious imprecision	none	216/996 (21.7%)	221/976 (22.6%)	RR 0.94 (0.80 to 1.10)	14 fewer per 1000 (from 45 fewer to 23 more)	⊕⊕OO LOW
Free of angina (follow-up 5-15 years)											
Peduzzi 1992[82] (VA); Rogers 1990[83] (CASS); Varnauskas 1982[84] (ECSS); Hueb 2010[79] (MASS-II)	randomised trials	serious (h)	serious (i)	no serious indirectness	serious (j)	none	365/1320 (27.7%)	507/1319 (38.4%)	RR 0.73 (0.66 to 0.81)	104 fewer per 1000 (from 73 fewer to 131 fewer)	⊕OOO VERY LOW
Stroke (follow-up 10 years)											
Hueb 2010[79] (MASS-II)	randomised trials	serious (k)	no serious inconsistency	no serious indirectness	serious (e)	none	14/203 (6.9%)	17/203 (8.4%)	RR 0.82 (0.42 to 1.63)	15 fewer per 1000 (from 49 fewer to 53 more)	⊕⊕OO LOW
Non protocol revascularisation (follow-up 10-22 years)											
Peduzzi 1998[77] (VA); Rogers 1990[83] (CASS); Hueb 2010[79] (MASS-II)	randomised trials	serious (l)	serious (m)	no serious indirectness	no serious imprecision	none	442/947 (46.7%)	142/925 (15.4%)	RR 3.02 (2.56 to 3.55)	310 more per 1000 (from 239 more to 391 more)	⊕⊕OO LOW
Death- sub group 2 vessel disease (follow-up 5-12 years)											

Alderman 1990[74] (CASS); Kloster 1979[76]; Varnauskas 1982[84] (ECSS)	randomised trials	serious (n)	no serious inconsistency	no serious indirectness	serious (j)	none	53/321 (16.5%)	33/324 (10.2%)	RR 1.64 (1.1 to 2.45)	65 more per 1000 (from 10 more to 148 more)	⊕⊕OO LOW
Death- sub group 3 vessel disease (follow-up 5-12 years)											
Alderman 1990[74] (CASS); Kloster 1979[76]; Varnauskas 1982[84] (ECSS)	randomised trials	serious (n)	serious (o)	no serious indirectness	serious (j)	none	71/343 (20.7%)	49/368 (13.3%)	RR 1.48 (1.07 to 2.06)	64 more per 1000 (from 9 more to 141 more)	⊕OOO VERY LOW
Death age >53 yrs (follow-up 10 years)											
Alderman 1990[74] (CASS)	randomised trials	serious (p)	no serious inconsistency	no serious indirectness	serious (e)	none	46/163 (28.2%)	39/163 (23.9%)	RR 1.18 (0.82 to 1.7)	43 more per 1000 (from 43 fewer to 167 more)	⊕⊕OO LOW
Death - age <47 years (follow-up 10 years)											
Alderman 1990[74] (CASS)	randomised trials	serious (p)	no serious inconsistency	no serious indirectness	serious (e)	none	16/101 (15.8%)	17/92 (18.5%)	RR 0.86 (0.46 to 1.6)	26 fewer per 1000 (from 100 fewer to 111 more)	⊕⊕OO LOW
Death - age 47-53 years (follow-up 10 years)											
Alderman 1990[74] (CASS)	randomised trials	serious (p)	no serious inconsistency	no serious indirectness	serious (e)	none	23/126 (18.3%)	16/135 (11.9%)	RR 1.54 (0.85 to 2.78)	64 more per 1000 (from 18 fewer to 211 more)	⊕⊕OO LOW

(a) *Alderman 1990[72] (CASS); Frick 1985[73]; Kloster 1979[74]; Peduzzi 1998[75] (VA); Varnauskas 1988[76] (ECSS); Hueb 2010[77] (MASS-II): Randomised, ITT used in all studies. Allocation concealment not reported in all studies.*
(b) *Considerable heterogeneity I^2=71%*
(c) *Bhayana 1980[78] (VA); Varnauskas 1988[76] (ECSS): Both studies randomised, unclear allocation concealment in both the studies. ECSS- ITT used. Loss to follow-up not reported (Bhayana 1980)[78].*
(d) *Substantial heterogeneity -I^2=79%*
(e) *95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.*
(f) *Fisher 1985[79] (CASS); Kloster 1979[74]; Peduzzi 1998[75] (VA); Hueb 2010[77] (MASS-II): Randomised, ITT reported in all 4 studies. Allocation concealment not reported in all 4 studies. Loss to follow-up not reported (Kloster 1979)[74].*
(g) *I^2=73%*
(h) *Peduzzi 1992[80] (VA); Rogers 1990[81] (CASS); Varnauskas 1982[82] (ECSS); Hueb 2010[77] (MASS-II): Randomised, ITT used in all 4 studies. Allocation concealment not reported in all 4 studies.*
(i) *Substantial heterogeneity -I^2=70%*
(j) *95% CI around the pooled estimate of effect includes appreciable benefit or appreciable harm.*
(k) *Hueb 2010[77] (MASS-II): Randomised. ITT reported. Allocation concealment unclear.*
(l) *Peduzzi 1998[75] (VA); Rogers 1990[81] (CASS); Hueb 2010[77] (MASS-II): Randomised, ITT used in both studies. Allocation concealment not reported in both studies.*
(m) *Substantial heterogeneity -I^2=82%*

(n) Alderman 1990[72] (CASS); Kloster 1979[74]; Varnauskas 1982[82] (ECSS): Randomised in all studies. Loss to follow-up and ITT not reported in one study (Kloster 1979)[74]. Allocation concealment not reported in all 3 studies.
(o) Substantial heterogeneity -I^2=75%
(p) Alderman 1990[72] (CASS): randomised (stratified randomisation). Baseline comparisons made. Intention to treat analysis reported. Limitations: Allocation concealment not reported.

Sub group interaction:

There was no significant difference between sub groups 2 vessel and 3 vessel disease for death (p=0.70) at long term follow-up (5–12 years).

There was no significant difference between sub groups age<47 years, 47-53 years and >53 years for death (p= 0.41) at long term follow-up (10 years)

Table 11.4: Medical vs. CABG – Single vessel disease – Medium term follow-up (2–4 years) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Medical	CABG	Relative (95% CI)	Absolute	
Death (follow-up 3 years)											
Hueb 1995[85] (MASS- I)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	0/72 (0%)	1/70 (1.4%)	RR 0.32 (0.01 to 7.83)	10 fewer per 1000 (from 14 fewer to 98 more)	⊕⊕OO LOW
Stroke (follow-up 3 years)											
Hueb 1995[85] (MASS- I)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	0/72 (0%)	0/70 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE
MI (follow-up 3 years)											
Hueb 1995[85] (MASS- I)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	2/72 (2.8%)	1/70 (1.4%)	RR 1.94 (0.18 to 20.96)	13 more per 1000 (from 12 fewer to 285 more)	⊕⊕OO LOW
Non protocol revascularisation (follow-up 3 years)											
Hueb 1995[85] (MASS- I)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	7/72 (9.7%)	0/70 (0%)	RR 14.59 (0.85 to 250.71)	100 more per 1000 (from 20 more to 170 more)	⊕⊕OO LOW
Free of angina (follow-up 3 years)											
Hueb 1995[85] (MASS- I)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	23/72 (31.9%)	68/70 (97.1%)	RR 0.33 (0.23 to 0.46)	651 fewer per 1000 (from 525 fewer to 748 fewer)	⊕⊕⊕O MODERATE

(a) Hueb 1995[83] (MASS- I): Randomised. Baseline comparisons made. Number of patients lost to follow-up not reported. ITT reported. Allocation concealment not reported. Blinding of outcome assessors not reported.

(b) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm

Table 11.5: Medical vs. CABG – Single vessel disease – Long term follow-up (>4 years) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Medical	CABG	Relative (95% CI)	Absolute	
Death (follow-up 5-10 years)											
Alderman 1990[74] (CASS); Kloster 1979[76]; Hueb 1999[86] (MASS-I)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	26/189 (13.8%)	18/185 (9.7%)	RR 1.41 (0.81 to 2.46)	40 more per 1000 (from 18 fewer to 142 more)	⊕⊕OO LOW
Cardiac death (follow-up 5 years)											
Hueb 1999[86] (MASS-I)	randomised trials	serious (c)	no serious inconsistency	no serious indirectness	serious (b)	None	2/72 (2.8%)	2/70 (2.9%)	RR 0.97 (0.14 to 6.71)	1 fewer per 1000 (from 25 fewer to 163 more)	⊕⊕OO LOW
MI (follow-up 5 years)											
Hueb 1999[86] (MASS-I)	randomised trials	serious (c)	no serious inconsistency	no serious indirectness	serious (b)	None	3/72 (4.2%)	3/70 (1.4%)	RR 0.97 (0.20 to 4.66)	27 more per 1000 (from 10 fewer to 377 more)	⊕⊕OO LOW
Stroke (follow-up 5 years)											
Hueb 1999[86] (MASS-I)	randomised trials	serious (c)	no serious inconsistency	no serious indirectness	serious (b)	None	1/72 (1.4%)	1/70 (1.4%)	RR 0.97 (0.06 to 15.24)	0 fewer per 1000 (from 13 fewer to 203 more)	⊕⊕OO LOW
Non protocol revascularisation (follow-up 5 years)											
Hueb 1999[86] (MASS-I)	randomised trials	serious (c)	no serious inconsistency	no serious indirectness	no serious imprecision	None	12/72 (16.7%)	0/70 (0%)	RR 24.32 (1.47 to 402.97)	170 more per 1000 (from 80 more to 260 more).	⊕⊕⊕O MODERATE
Free of angina (follow-up 5 years)											
Hueb 1999[86] (MASS-I)	randomised trials	serious (c)	no serious inconsistency	no serious indirectness	no serious imprecision	None	17/72 (23.6%)	48/70 (68.6%)	RR 0.34 (0.22 to 0.54)	453 fewer per 1000 (from 315 fewer to 535 fewer)	⊕⊕⊕O MODERATE

(a) *Alderman 1990[72] (CASS); Kloster 1979[74]; Hueb 1999[84] (MASS-I): All 3 Randomised. ITT not reported in Kloster 1979[74]. Allocation concealment not reported in all 3 papers.*
(b) *95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.*
(c) *Hueb 1999[84] (MASS-I): Randomised, Baseline comparisons made. Number of patients lost to follow-up not reported. ITT reported. Limitations: allocation concealment not reported. Blinding of outcome assessors not reported.*

Table 11.6: Medical vs. CABG – Left main stem disease – Medium term follow-up (2 to 4 years) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Medical	CABG	Relative (95% CI)	Absolute	
Death (follow-up 2-4 years)											
Detre 1977[73] (VA); Varnauskas 1980[71] (ECSS)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	20/75 (26.7%)	5/74 (6.8%)	RR 4 (1.6 to 10.03)	203 more per 1000 (from 41 more to 610 more)	⊕⊕⊕O MODERATE

(a) Detre 1977[71] (VA); Varnauskas 1980[69] (ECSS): Both studies randomised. ITT used in both studies. Allocation concealment not reported in both studies. Low heterogeneity I^2=19%

Table 11.7: Medical vs. CABG – Left main stem disease – Long term follow-up (>4 years) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Medical	CABG	Relative (95% CI)	Absolute	
Death (follow-up 10-22 years)											
Alderman 1990[74] (CASS); Peduzzi 1998[77] (VA); Varnauskas 1982[84] (ECSS)	randomised trials	serious (a)	serious (b)	no serious indirectness	serious (c)	None	51/80 (63.8%)	47/84 (56%)	RR 1.18 (0.97 to 1.43)	101 more per 1000 (from 17 fewer to 241 more)	⊕OOO VERY LOW
MI (follow-up 22 years)											
Peduzzi 1998[77] (VA)	randomised trials	serious (d)	no serious inconsistency	no serious indirectness	serious (c)	None	16/43 (37.2%)	21/48 (43.8%)	RR 0.85 (0.51 to 1.41)	66 fewer per 1000 (from 214 fewer to 179 more)	⊕⊕OO LOW

(a) Alderman 1990[72] (CASS); Peduzzi 1998[75] (VA); Varnauskas 1982[82] (ECSS): Randomised, ITT reported in all 3 studies. Allocation concealment not reported all 3 studies.
(b) Substantial heterogeneity I^2=79%
(c) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.
(d) Peduzzi 1998[75]: Randomised, baseline comparisons made. Intention to treat analysis reported. Allocation concealment not reported

Table 11.8: Medical vs. CABG – Left anterior descending artery – Long term follow-up (>4 years) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Medical	CABG	Relative (95% CI)	Absolute	
Death (follow-up 10-12 years)											
Alderman 1990[74] (CASS); Varnauskas 1988[78] (ECSS)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	144/515 (28%)	113/539 (21%)	RR 1.34 (1.09 to 1.66)	71 more per 1000 (from 19 more to 138 more)	⊕⊕OO LOW

(a) *Alderman 1990[72] (CASS); Varnauskas 1988[76] (ECSS): Randomised, ITT used in both studies. Allocation concealment not reported in both studies. No heterogeneity I^2=0%*

(b) *95% CI around the pooled estimate of effect includes appreciable benefit or appreciable harm.*

Table 11.9: IPD meta-analyses – Medical vs. CABG – Multivessel disease – Long term follow-up

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Medical	CABG	Odds ratio (95% CI)	Absolute	
Total mortality (follow-up 10 years)											
Yusuf 1994[67] (c)	randomised trial	serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	404/1325 (30.5%)	350/1324 (26.4%)	OR 0.83 (0.70 to 0.98)	38 fewer per 1000 (from 4 fewer to 69 fewer)	⊕⊕⊕O MODERATE
Mortality - sub group one vessel disease (follow-up 5 years)											
Yusuf 1994[67]	randomised trial	serious limitations (b)	no serious inconsistency	no serious indirectness	no serious imprecision	None	Not reported	Not reported	OR 0.54 (0.22 to 1.33)	Cannot be calculated	⊕⊕⊕O MODERATE
Mortality - subgroup 2 vessels (follow-up 5 years)											
Yusuf 1994[67]	randomised trial	serious limitations (b)	no serious inconsistency	no serious indirectness	no serious imprecision	None	Not reported	Not reported	OR 0.84 (0.54 to 1.32)	Cannot be calculated	⊕⊕⊕O MODERATE
Mortality- sub group 3 vessels											
Yusuf 1994[67]	randomised trial	serious limitations (b)	no serious inconsistency	no serious indirectness	no serious imprecision	None	Not reported	Not reported	OR 0.58 (0.42 to 0.80)	Cannot be calculated	⊕⊕⊕O MODERATE
Mortality- sub group Left main artery (follow-up 5 years)											
Yusuf 1994[67]	randomised trial	no serious limitations (b)	no serious inconsistency	no serious indirectness	no serious imprecision	None	Not reported	Not reported	OR 0.32 (0.15 to 0.70)	Cannot be calculated	⊕⊕⊕O MODERATE
Mortality- LAD disease present											
Yusuf 1994[67]	randomised trial	serious limitations (b)	no serious inconsistency	no serious indirectness	no serious imprecision	None	Not reported	Not reported	OR 0.50 (0.43 to 0.77	Cannot be calculated	⊕⊕⊕O MODERATE
Mortality- sub group normal LV function (follow-up 5 years)											
Yusuf 1994[67]	randomised trial	serious limitations (b)	no serious inconsistency	no serious indirectness	no serious imprecision	None	Not reported	Not reported	OR 0.61 (0.46 to 0.81)	Cannot be calculated	⊕⊕⊕O MODERATE
Mortality- sub group abnormal LV function (follow-up 5 years)											
Yusuf 1994[67]	randomised trial	serious limitations (b)	no serious inconsistency	no serious indirectness	no serious imprecision	None	Not reported	Not reported	OR 0.59 (0.39 to 0.91)	Cannot be calculated	⊕⊕⊕O MODERATE

Mortality- subgroup class 0,I,II (follow-up 5 years)											
Yusuf 1994[67]	randomised trial	serious limitations (b)	no serious inconsistency	no serious indirectness	no serious imprecision	None	Not reported	Not reported	OR 0.63 (0.46 to 0.87)	Cannot be calculated	⊕⊕⊕O MODERATE
Mortality- sub group class III,IV (follow-up 5 years)											
Yusuf 1994[67]	randomised trial	serious limitations (b)	no serious inconsistency	no serious indirectness	no serious imprecision	None	Not reported	Not reported	OR 0.57 (0.40 to 0.81)	Cannot be calculated	⊕⊕⊕O MODERATE

(a) Yusuf 1994[65]: *This is an IPD (Individual patient data) meta analyses. This review addresses an appropriate and clearly focused question. The review included only RCTs which was relevant to the review question. There was adequate description of the methodology used in the meta analyses. The mortality analysis was an ITT (irrespective of crossover between treatments or failure of CABG patients to receive surgery). The paper does not report the search strategy used. The IPD meta analyses did not look at the longest follow-up of the VA trial comparing medical treatment to surgery in stable angina patients (22 years for VA study). Quality assessment of individual studies not reported*. This meta analyses did not include all studies relevant to the question. We have separately assessed the quality of individual studies in the evidence review. Additional studies have been included in the study level meta analyses conducted by us. Note: One study (Norris 1981)[87] from this meta analyses was not included in our evidence review as the study did not meet our inclusion criteria (study population was recurrent MI).*

(b) *None of the included studies reported of allocation concealment. Sub group analyses conducted for selected sub groups. If a study had no event in a given subgroup, it was omitted from the analysis for that sub group.*

(c) *Studies included in this IPD - Norris 1981[87], Mathur 1977[88] (ECSS), Kloster 1979[76] (CASS).*

Extension of survival (Yusuf IPD[67] meta-analyses)

Analysis of overall survival during the first 10 years after randomisation showed an improvement in survival with CABG surgery over medical treatment of 4.26 months with a 1.96 SE of 2.35 months. The benefit seemed to increase with disease severity. The improvement in survival was greatest for patients with left main artery disease, intermediate for those with three vessel disease, and least for those with one vessel or two vessel disease (p=0.02 for trend) . Greater survival prolongation was also found among patients with abnormal exercise tests (p for interaction 0.71) and abnormal LV function (p<0.01) than in patients without these characteristics.

Quality of Life data from studies:

Alderman 1993[89] (CASS) – 5 year follow-up:

In this RCT, Quality of Life was derived from a composite of subjective (questionnaire) and objective (exercise test) measures. Patients reported symptoms such as chest pain status, heart failure, activity limitation employment and recreational status, drug therapy, hospitalisation, smoking and supervised exercise program (i.e. whether the patient participated in such activities during the 2 months before follow-up). In addition blood pressure, cholesterol and weight was measure and patients took part in an exercise test.

Results: n=780 (n=390 in surgery and n=390 in CABG). At a mean of 5.5 years follow-up patients in the surgical group had significantly less chest pain, fewer activity limitations and required less therapy with nitrates and beta-blockers. There was no significant difference in self reported symptoms of heart failure, employment and recreational status. The number of days in hospital was higher in the surgical compared to the medical group. All these results are graphically presented in the paper, but individual mean results are not given in the text. Treadmill exercise test results were significantly better for the surgical compared to the medical group (time to induced angina and ST segment depression). There were no significant differences in cholesterol levels, blood pressure, body weight and levels of smoking between the two groups. From these results the researchers deduced that CABG improves the quality of life as manifest by relief of chest pain, improvement in both subjective and objective measurements of functional status, and a diminished requirement for drug therapy.

Rogers 1990[83] (CASS) – 10 year follow-up:

Same measures as described above.

Results: N=654 remaining at 10 year follow-up (CABG (n=333); Medical (n=324)). *Chest pain.* At 10 years the proportion of surgical patients who were asymptomatic had declined from medium term follow-up (to 47%) and the proportion of medical patients who were asymptomatic had increased (42%), which remains nonetheless a significant difference in favour of the surgical group. *Heart failure.* Absence of heart failure symptoms was reported by 72% in the medical and 75% in the surgical group (p=ns). *Activity limitations.* Proportion of patients without activity limitations at 10 year follow-up was not significant (34% vs. 28%). *Employment status.* 34% of the surgical group and 32% of the medical treatment group were employed after 10 years (p=ns). *Recreational status* did not differ after 10 years (proportion of patients who participate in moderate-strenuous exercise: 25% medical group and 26% surgical group. The authors concluded from this that the advantage reported in their Quality of Life assessment at short to medium follow-up length were much less apparent after a 10 year interval.

11.2.3 Economic evidence

One study[90] was found that included the relevant comparison. This is summarised in the economic evidence profile below. See also Economics Evidence Tables in Appendix G.

Table 11.10: CABG vs. medical treatment – Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
Griffin 2007[90]	Potentially serious limitations (a)	Partial applicability (b)	Patients included in the analysis were those who had coronary angiography between April 1996 and April 1997 at three hospitals of one NHS trust in London and who were suitable for both CABG and PCI. Their suitability was assessed using the RAND appropriateness method. A third arm with PCI was included in this study but it was less cost-effective than CABG.

a) *Not a randomised study; EQ-5D data were not collected at baseline and at one year and scores were only predicted at these time points from other variables.*
b) *Criteria for assessment of the suitability for revascularisation could have changed since time of study. PCI procedure could have been without stents.*

Table 11.11: CABG vs. medical treatment – Economic summary of findings

Study	*Incremental cost per patient over 6 years (£)*	*Incremental QALYs per patient over 6 years*	*ICER (£/QALY)*	*Uncertainty*
Griffin 2007[90]	7,169 (a, b)	0.3 (b, c)	18,603	For patients deemed appropriate for CABG only, ICER=£14,675/QALY At a threshold of £20,000/QALY all the strategies including PCI have a similar probability of being cost-effective.

(a) *2004 GBP. Costs included were cost of intervention, angiography, hospital stay, drugs, admissions for chest pain, GP and outpatient visits, visits to the emergency department. Occurrence of admissions and LOS obtained from the NHS-wide clearing service; data on drugs from hospital case notes, GP and patients' questionnaires; unit costs from published studies and pricing lists for the UK.*
(b) *Discounted by 3.5%*
(c) *Based on EQ-5D data from participants in the study.*

11.2.4 Evidence statements

Clinical

<u>Medical vs. CABG – Multi-vessel disease – short term follow-up (1 year)</u>

Soares 2006[69] **(MASS-II):** Evidence from one RCT shows that there were significantly higher patients free of angina [RR 0.62 (0.5 to 0.76)] in CABG group compared to medical treatment group. There were significantly higher repeat revascularisations [RR 16 (2.14 to 119.52)] in the medical treatment group compared to CABG. There was no significant difference between medical treatment group and PCI for death [RR 0.38 (0.1 to 1.39)], MI [RR 2.5 (0.8 to 7.84)], stroke [RR 1 (0.2 to 4.9)]. There was no significant difference between medical treatment and CABG for death in a sub group of patients with diabetes [RR 0.39 (0.07 to 2.07)] and no diabetes [RR 0.32 (0.07 to 1.52]. [Follow-up 1 year]

Medical vs. CABG – Multi -vessel disease – Medium term follow-up (2 to 4 years)

Read 1977[70] (VA); Varnauskas 1980[71] (ECSS): Evidence from 2 RCTS's shows that there was no significant difference between medical treatment and CABG for deaths [RR 1.29 (0.96 to 1.74)]. [Follow-up 2 to 4 years]

Varnauskas 1980[71] (ECSS): Evidence from one RCT shows that there was significantly fewer cardiac death in the CABG compared to medical treatment. RR 2.85 (1.4 to 5.81) [follow-up 2 years]

Guinn 1976[72] (VA): Evidence from one RCTs to show that there was no significant difference between medical treatment and CABG for MI in the CABG [RR 2.05(0.76 to 5.54). [Follow-up 2.8 years]

Guinn 1976[72] (VA); Varnauskas 1979[71] (ECSS): Evidence from 2 RCTs shows that there were significantly more patients free of angina in the CABG group compared to medical treatment group. [RR 0.53 (0.47 to 0.60). [Follow-up 2 to 2.8 years]

Varnauskas 1980[71] (ECSS): Evidence from one RCT shows that there was no significant difference between medical treatment and CABG group for death in sub group 2 vessel disease [RR 0.57 (0.21 to 1.54)] .[Follow-up 2 years]

Detre 1977[73] (VA); Varnauskas 1980[71] (ECSS): Evidence from 2 RCTs shows that there were significantly fewer deaths in the CABG group compared to medical treatment [RR 1.57 (1.02 to 2.44)] in patients with sub group 3 vessel disease. [follow-up 2-4 years]]. But there was no significant difference between sub group of patients with 2 vessel or 3 vessel disease for death (p=0.07) at medium term follow-up (2- to 4 years).

Guinn 1976[72]: Evidence from one RCT shows that there was no significant difference between medical treatment and CABG for non protocol revascularisation. [RR 3.73 (0.43 to 32.4)]. [follow-up 2.8 years]

Medical vs. CABG – Multi -vessel disease – Long term follow-up (>4 years)

Alderman 1990[74] (CASS); Frick 1985[75]; Kloster 1979[76]; Peduzzi 1998[77] (VA); Varnauskas 1988[78] (ECSS); Hueb 2010[79] (MASS – II): Evidence from 6 RCTs shows that there was no significant difference between medical treatment and CABG for death [RR

1.08 (0.99 to 1.17))]. [Follow-up 5 to 22 years]

Bhayana 1978[80] (VA); Varnauskas 1988[78] (ECSS): Evidence from 2 RCTs shows that there was significantly fewer cardiac death in CABG compared to medical treatment [RR 1.44 (1.12 to 1.84)] [Follow-up 12 years]

Fisher 1984[81] (CASS); Kloster 1979[76]; Peduzzi 1998[77] (VA); Hueb 2010[79] (MASS –II): Evidence from 4 RCTs shows that there was no significant difference between medical treatment and CABG for MI [RR 0.94 (0.80 to 1.10)]. [Follow-up 5–22 years]

Peduzzi 1992[82] (VA); Rogers 1990[83] (CASS); Varnauskas 1982[84] (ECSS); Hueb 2010[79] (MASS –II): Evidence from 4 RCTs show that there were significantly more patients free of angina in the CABG group compared to medical treatment. [RR 0.73 (0.66 to 0.81)]. [Follow-up 5–15years]

Peduzzi 1998[77] (VA); Rogers 1990[83] (CASS); Hueb 2010[79] (MASS –II): Evidence from 3 RCTs shows that there were significantly more patients with non protocol revascularisation in the medical treatment group compared to CABG [RR 3.02 (2.56 to 3.55)]. [Follow-up 10–22 years]

Hueb 2010[79] (MASS –II): Evidence from 1 RCT shows that there was no significant difference between medical treatment and CABG for stroke [RR 0.82 (0.42 to 1.63) [Follow-up 10 years]

Alderman 1990[74] (CASS); Kloster 1979[76]; Varnauskas 1982[84] (ECSS): Evidence from 3 RCTs' shows that there was significantly fewer deaths in the CABG group compared to medical treatment in a sub group of people with 2 vessel disease RR 1.64 (1.1 to 2.45) and 3 vessel disease RR 1.48 (1.07 to 2.06). [Follow-up 5-12 years] But there was no significant difference between sub groups 2 vessel and 3 vessel disease for death (p=0.70) at long term follow-up (5–12 years).

Alderman 1990[74] (CASS): Evidence from one RCT shows that there was no significant difference between medical treatment and CABG for death in a sub group of people age >53 years [RR 1.18 (0.82 to 1.7)]. [Follow-up 10 years]

Alderman 1990[74] (CASS): Evidence from one RCT shows that there was no significant difference between medical treatment and CABG for death in a sub group of people age <47 years [RR 0.86 (0.46 to 1.60)]. [Follow-up 10 years]

Alderman 1990[74] (CASS): Evidence from one RCT shows that there was no significant difference between medical treatment and CABG for death in a sub group of people age 47-53 years [RR 1.54 (0.85 to 2.78)]. [Follow-up 10 years] But there was no significant difference between sub groups age<47 years, 47-53 years and >53 years for death (p= 0.41) at long term follow-up (10 years)

Medical vs. CABG – Single vessel disease – Medium term follow-up (2–4 years)

Hueb 1995[85] (MASS- I): Evidence from one RCT shows that there were statistically significant higher no. of patients free of angina in the CABG group compared to medical treatment [RR 0.33 (0.23 to 0.46)]. There was no statistically significant difference medical and CABG for death [RR 0.32 (0.01 to 7.83)], stroke [0/72 in medical and 0/70 in CABG], MI [RR 1.94 (0.18 to 20.96)], and non protocol revascularisation [RR 14.59 (0.85 to 250.71)] [Follow-up 3 years]

Medical vs. CABG – Single vessel disease – Long term follow-up (>4 years)

Alderman 1990[74] (CASS); Kloster 1979[76]; Hueb 1999[86] (MASS-I): Evidence from 3 RCTs shows that there was no statistically significant difference between medical treatment and CABG for death [RR 1.41 (0.81 to 2.46) [Follow-up 5–10 years]

Hueb 1999[86] (MASS-I): Evidence from one RCT shows that significantly higher no. of patients free of angina in the CABG group compared to medical treatment [RR 0.34 (0.22 to 0.54)]. There was significantly higher non protocol revascularisation in the medical treatment group compared to CABG group [RR 24.32 (1.47 to 402.97)]. There was no significant difference between medical treatment and CABG group for cardiac death [RR 0.97 (0.14 to 6.71)], MI [RR 0.97 (0.20 to 4.66)], stroke [RR 0.97 (0.06 to 15.24)] [Follow-up 5 years]

Medical vs. CABG – Left main stem disease – Medium term follow-up (2 to 4 years)

Detre 1977[73] (VA); Varnauskas 1980[71] (ECSS): Evidence from 2 RCTs shows that there was significantly fewer deaths in the CABG compared to medical treatment in patients with left main stem disease [RR 4 (1.6 to 10.03)].[follow-up 2–4 years]

Medical vs. CABG – Left main stem disease – Long term follow-up (>4 years)

Alderman 1990[74] (CASS); Peduzzi 1998[77] (VA); Varnauskas 1982[84] (ECSS) : Evidence from 3 RCTs shows that there was no significant difference between CABG and medical treatment for death in patients with left main stem disease [RR 1.18 (0.97 to 1.43)].[follow-up 10–22 years]

Peduzzi 1998[77] (VA): Evidence from one RCT shows that there was no significant difference medical treatment and CABG for MI [RR 0.85 (0.51 to 1.41]. [follow-up 22 years]

Medical vs. CABG – Left anterior descending artery – Long term follow-up (>4 years)

Alderman 1990[74] (CASS); Varnauskas 1988[78] (ECSS): Evidence from 2 RCTs shows that there was significantly fewer deaths in the CABG group compared to medical treatment in patients with involvement of left anterior descending artery [RR 1.34 (1.09 to 1.66)].[follow-up 10–12 years]

IPD meta-analyses – Medical vs. CABG – Multivessel disease – Long term follow-up

Yusuf 1994[67]: Evidence from one IPD meta analyses shows that there were significantly fewer deaths in the CABG group compared to medical treatment [OR 0.83 (0.70 to 0.98)].[follow-up 10 years]

Yusuf 1994[67]: Evidence from one IPD meta analyses shows that there was no significant difference between medical treatment and CABG for death in sub group one vessel [OR 0.54 (0.22 to 1.33)] and 2 vessel [OR 0.84 (0.54 to 1.32)], significantly fewer deaths in CABG in patients with 3 vessel disease [OR 0.58 (0.42 to 0.80)], left main artery [OR 0.32 (0.15 to 0.70)] LAD disease [OR 0.50 (0.43 to 0.77)]. The benefits of surgery were similar among people with normal [OR 0.61 (0.46 to 0.81)] and abnormal LV function [OR 0.59 (0.39 to 0.91)] and all severity of angina classes [subgroup class 0, I, II-OR 0.63 (0.46 to 0.87)][sub group class III,IV - OR 0.57 (0.40 to 0.81)]. [Follow-up 5 years]

Economic

Medical treatment and CABG have the same probability of being cost-effective for patients suitable for both.

This evidence has potentially serious limitations and partial applicability.

11.3 Medical interventions versus PCI

11.3.1 Clinical question

What is the clinical and cost effectiveness of medical interventions versus PCI in people with stable angina?

11.3.2 Clinical evidence

The "Review Protocol" for this topic can be found in Appendix C, the "Search Strategies" in Appendix D, the "List of Included and Excluded Studies" in Appendix E1, the "Clinical Evidence Tables" in Appendix E2, and the "Forest Plots" in Appendix F.

Table 11.12: Medical vs. PCI – Multi-vessel disease – Short term follow-up (1 year) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Medical	PCI	Relative (95% CI)	Absolute	
Death (follow-up 1 years)											
Hueb 2004[68] (MASS-II)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	3/203 (1.5%)	9/205 (4.4%)	RR 0.34 (0.09 to 1.23)	29 fewer per 1000 (from 40 fewer to 10 more)	⊕⊕OO LOW
Q wave MI (follow-up 1 years)											
Hueb 2004[68] (MASS-II)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	10/203 (4.9%)	16/205 (7.8%)	RR 0.63 (0.29 to 1.36)	29 fewer per 1000 (from 55 fewer to 28 more)	⊕⊕OO LOW
Stroke (follow-up 1 years)											
Hueb 2004[68] (MASS-II)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	3/203 (1.5%)	2/205 (1%)	RR 1.51 (0.26 to 8.97)	5 more per 1000 (from 7 fewer to 78 more)	⊕⊕OO LOW
Non protocol revascularisation (follow-up 1 years) (d)											
Hueb 2004[68] (MASS-II)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	16/203 (7.9%)	25/205 (12.2%)	RR 0.65 (0.36 to 1.17)	43 fewer per 1000 (from 78 fewer to 21 more)	⊕⊕OO LOW
Free of angina (follow-up 1 years)											
Hueb 2004[68] (MASS-II)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (c)	none	74/203 (36.5%)	107/205 (52.2%)	RR 0.7 (0.56 to 0.87)	157 fewer per 1000 (from 68 fewer to 230 fewer)	⊕⊕OO LOW
Death- Sub group diabetes (follow-up 1 years)											
Soares 2006[69] (MASS-II)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	2/75 (2.7%)	3/56 (5.4%)	RR 0.5 (0.09 to 2.88)	27 fewer per 1000 (from 49 fewer to 101 more)	⊕⊕OO LOW
Death- Subgroup no diabetes (follow-up 1 years)											
Soares 2006[69] (MASS-II)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	2/128 (1.6%)	8/149 (5.4%)	RR 0.29 (0.06 to 1.35)	38 fewer per 1000 (from 50 fewer to 19 more)	⊕⊕OO LOW

(a) *MASS-II: Randomised. Allocation concealment unclear. More patients in PCI group had MI and fewer were current or past smokers; other characteristics similar at baseline; could indicate these patients had worse disease. In CABG group, 4/203 declined surgery and received medical therapy. In PCI group, 6/205 had CABG instead, 3 declined PCI and received medical therapy and 2 died before treatment.*

(b) *95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.*

(c) *95% CI around the pooled estimate of effect includes appreciable benefit or appreciable harm.*

(d) *Medical treatment group – 12 non protocol CABG and 4 non protocol PCI; PCI group- 7 non protocol CABG and 18 non protocol PCI; CABG group-1 non protocol PCI.*

Table 11.13: Medical vs. PCI – Multi-vessel disease – medium term follow-up (2 to 4 years) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Medical	PCI	Relative (95% CI)	Absolute	
Death (follow-up 2.7 years)											
Chamberlain 1997[91] (RITA-2)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	7/514 (1.4%)	11/504 (2.2%)	RR 0.62 (0.24 to 1.6)	8 fewer per 1000 (from 17 fewer to 13 more)	⊕⊕OO LOW
Cardiac death (follow-up 1.5-2.7 years)											
Chamberlain 1997[91] (RITA-2); Pitt 1999[92] (AVERT)	randomised trials	serious (c)	no serious inconsistency	no serious indirectness	serious (b)	none	4/678 (0.6%)	6/681 (0.9%)	RR 0.67 (0.19 to 2.35)	3 fewer per 1000 (from 7 fewer to 12 more)	⊕⊕OO LOW
Non fatal MI (follow-up 1.5-2.7 years)											
Chamberlain 1997[91] (RITA-2); Pitt 1999 (AVERT)	randomised trials	serious (c)	no serious inconsistency	no serious indirectness	serious (b)	none	14/678 (2.1%)	26/681 (3.8%)	RR 0.54 (0.28 to 1.02)	18 fewer per 1000 (from 27 fewer to 1 more)	⊕⊕OO LOW
Stroke (follow-up 1.5-2.7 years)											
Chamberlain 1997[91] (RITA-2); Pitt 1999[92] (AVERT)	randomised trials	serious (c)	no serious inconsistency	no serious indirectness	serious (b)	none	6/678 (0.9%)	1/668 (0.1%)	RR 5.88 (0.71 to 48.69)	7 more per 1000 (from 0 fewer to 71 more)	⊕⊕OO LOW
Hospitalisation (for worsening of angina) no. of patients (follow-up 18 months)											
Pitt 1999[92] (AVERT)	randomised trials	serious (d)	no serious inconsistency	no serious indirectness	serious (e)	none	11/164 (6.7%)	25/177 (14.1%)	RR 0.47 (0.24 to 0.93)	75 fewer per 1000 (from 10 fewer to 107 fewer)	⊕⊕OO LOW
Non protocol Revascularisation (follow-up 1.5-2.7 years)											
Chamberlain 1997[91] (RITA-2); Pitt 1999[92] (AVERT)	randomised trials	serious (c)	serious (f)	no serious indirectness	serious (b)	none	151/678 (22.3%)	132/681 (19.4%)	RR 1.14 (0.93 to 1.4)	27 more per 1000 (from 14 fewer to 78 more)	⊕OOO VERY LOW

(a) Chamberlain 1997[89] (RITA-2): multicentre (20 centres in UK and Ireland), stratified blocked randomisation. Sample size calculation reported. Intention to treat analysis reported. Loss to follow-up - 5.1% in PTCA and 3.3% in medical group (N=478 PTCA an n=497 at 2.7 yrs) Blind outcome assignment. Allocation concealment not reported.

(b) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.

(c) Chamberlain 1997[89] (RITA-2); Pitt 1999 (AVERT): Blind outcome assignment in both studies. Both studies allocation concealment not reported. RITA-2 -stratified blocked randomisation. Sample size calculation reported. Intention to treat analysis reported. AVERT- No loss to follow-up.

(d) Pitt 1999[90] (AVERT): open label randomised, multi centre, sample size calculation reported. Blind outcome assessment. No loss to follow-up. ITT reported. Allocation concealment not reported. This study is a 18 month follow-up of the AVERT trial.

(e) 95% CI around the pooled estimate of effect includes appreciable benefit or appreciable harm.

(f) I^2= 73%

Table 11.14: Medical vs. PCI – Multi-vessel disease – long term follow-up (> 4 years follow-up) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Medical	PCI	Relative (95% CI)	Absolute	
Death (follow-up 2.7-10 years)											
Boden 2007[93] (COURAGE) (l); Henderson 2003[94] (RITA-2); Hueb 2010[79] (MASS-II)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	201/1855 (10.8%)	177/188 (94.1%)	RR 1.14 (0.94 to 1.37)	132 more per 1000 (from 56 fewer to 348 more)	⊕⊕OO LOW
Cardiac death (follow-up 2.7-4.6 years)											
Boden 2007[93] (COURAGE); Henderson 2003[94] (RITA-2)	randomised trials	serious (c)	serious (d)	no serious indirectness	serious (b)	none	47/1652 (2.8%)	36/1653 (2.2%)	RR 1.30 (0.85 to 2)	7 more per 1000 (from 3 fewer to 22 more)	⊕OOO VERY LOW
Non fatal MI (follow-up 2.7-10 years)											
Boden 2007[93] (COURAGE) (l); Henderson 2003[94] (RITA-2); Hueb 2010[79] (MASS-II)	randomised trials	serious (a)	serious (e)	no serious indirectness	serious	none	193/1855 (10.4%)	202/1858 (10.9%)	RR 0.96 (0.80 to 1.16)	4 fewer per 1000 (from 22 fewer to 17 more)	⊕OOO VERY LOW
Non protocol Revascularisation (follow-up 2.7-10 years)											
Boden 2007[93] (COURAGE) (l) Henderson 2003[94] (RITA-2) Hueb 2010[79] (MASS-II)	randomised trials	serious (a)	serious (f)	no serious indirectness	no serious imprecision	none	630/1855 (34%)	463/1858 (24.9%)	RR 1.36 (1.23 to 1.51)	90 more per 1000 (from 57 more to 127 more)	⊕⊕OO LOW
Stroke (follow-up 4.6-10 years)											
Boden 2007[93] (COURAGE); Hueb 2010[79] (MASS-II)	randomised trials	serious (g)	no serious inconsistency	no serious indirectness	serious (b)	none	28/1341 (2.1%)	33/1354 (2.4%)	RR 0.86 (0.52 to 1.41)	3 fewer per 1000 (from 12 fewer to 10 more)	⊕⊕OO LOW
Free of angina (follow-up 4.6-10 years)											
Boden 2007[93] (COURAGE); Folland 1997[95] (ACME); Hueb 2010[79] (MASS-II)	randomised trials	serious (a)	serious (h)	no serious indirectness	no serious imprecision	none	402/1391 (28.9%)	463/1405 (33%)	RR 0.88 (0.79 to 0.98)	40 fewer per 1000 (from 7 fewer to 69 fewer)	⊕⊕OO LOW
Death- sub group age <65 yrs (follow-up 4.6 years)											
Teo 2009[96] (COURAGE)	randomised trials	serious (i)	no serious inconsistency	no serious indirectness	serious (b)	none	41/693 (5.9%)	25/688 (3.6%)	RR 1.63 (1 to 2.65)	23 more per 1000 (from 0 more to 60 more)	⊕⊕OO LOW
MI - sub group age <65 yrs (follow-up 4.6 years)											
Teo 2009[96] (COURAGE)	randomised trials	serious (i)	no serious inconsistency	no serious indirectness	serious (b)	none	76/693 (11%)	83/688 (12.1%)	RR 0.91 (0.68 to	11 fewer per 1000 (from 39 fewer to	⊕⊕OO LOW

									1.22)	27 more)	
Free of angina- sub group age<65 years (follow-up 4.6 years)											
Teo 2009[96] (COURAGE)	randomised trials	serious (i)	no serious inconsistency	no serious indirectness	no serious imprecision	none	485/693 (70%)	481/688 (69.9%)	RR 1 (0.93 to 1.07)	0 fewer per 1000 (from 49 fewer to 49 more)	⊕⊕⊕O MODERATE
Death- sub group age >65 yrs (follow-up 4.6 years)											
Teo 2009[96] (COURAGE)	randomised trials	serious (j)	no serious inconsistency	no serious indirectness	serious (b)	none	54/444 (12.2%)	57/460 (12.4%)	RR 0.98 (0.69 to 1.39)	2 fewer per 1000 (from 38 fewer to 48 more)	⊕⊕OO LOW
MI- sub group age >65 yrs (follow-up 4.6 years)											
Teo 2009[96] (COURAGE)	randomised trials	serious (j)	no serious inconsistency	no serious indirectness	serious (b)	none	52/444 (11.7%)	60/460 (13%)	RR 0.9 (0.63 to 1.27)	13 fewer per 1000 (from 48 fewer to 35 more)	⊕⊕OO LOW
Free of angina- sub group age >65 yrs (follow-up 4.6 years)											
Teo 2009[96] (COURAGE)	randomised trials	serious (j)	no serious inconsistency	no serious indirectness	no serious imprecision	none	324/444 (73%)	368/460 (80%)	RR 0.91 (0.85 to 0.98)	72 fewer per 1000 (from 16 fewer to 120 fewer)	⊕⊕⊕O MODERATE
Death- sub group 2 vessel disease (follow-up 6 years)											
Folland 1997[95] (ACME)	randomised trials	serious (k)	no serious inconsistency	no serious indirectness	serious (b)	none	10/50 (20%)	9/51 (17.6%)	RR 1.13 (0.5 to 2.55)	23 more per 1000 (from 88 fewer to 274 more)	⊕⊕OO LOW
Non fatal MI- sub group 2 vesel disease (follow-up 6 years)											
Folland 1997[95] (ACME)	randomised trials	serious (k)	no serious inconsistency	no serious indirectness	serious (b)	none	7/50 (14%)	7/51 (13.7%)	RR 1.02 (0.39 to 2.7)	3 more per 1000 (from 84 fewer to 233 more)	⊕⊕OO LOW

(a) Boden 2007[91] (COURAGE) (I); Henderson 2003[92] (RITA-2); Hueb 2010[77] (MASS-II): Randomisation, sample size calculation, blind outcome assessment and, ITT reported in all 3 studies. Allocation concealment not reported in 3 studies.

(b) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.

(c) Boden 2007[91] (COURAGE); Henderson 2003[92] (RITA-2): Randomisation, sample size calculation, blind outcome assessment and ITT reported in both the studies. Allocation concealment not reported in both the studies.

(d) I^2=62%

(e) I^2=69%

(f) I^2=83%

(g) Boden 2007[93] (COURAGE); Hueb 2010[79] (MASS-II): Randomisation reported in both the studies. Allocation concealment unclear in both studies, ITT reported in both studies.

(h) I^2=62%

(i) *Teo 2009[94] (COURAGE): Randomisation method reported (permuted block design within strata -prior CABG/no prior CABG and by medical centre), sample size calculation reported, Blind outcome assessment (clinical outcome adjudicated by an independent committee whose members were unaware of treatment assignments). 9% of patients were lost to follow-up in the two groups (107 in the PCI group and 97 in the medical therapy group, p=0.51). Intention to treat analysis reported.*

(j) *Teo 2009[94] (COURAGE): Randomisation method reported, sample size calculation reported, Blind outcome assessment . Intention to treat analysis reported. Loss to follow-up not reported separately for subgroup age >65 years*

(k) *Folland 1997[93] (ACME): Strengths: Randomised, baseline comparison made, intention to treat analysis used. Weakness: Randomisation method not clearly described. Allocation concealment not reported.*

(l) *Medical therapy in COURAGE trial - All patients received aspirin, and those who were undergoing PCI also received clopidogrel in accordance with treatment guidelines. Ant ischemic therapy included long-acting metoprolol, amlodipine, and isosorbide mononitrate, alone or in combination, together with simvastatin and either lisinopril or losartan for secondary prevention.*

Additional data:

(Multi vessel disease – Long term follow-up – RITA-2)

Henderson 2003[94] (RITA-2): The prevalence of angina declined in both treatment groups during the first five years of follow-up, but this symptomatic improvement was much more rapid in the PTCA group. At 3 months after randomisation, 19.4% and 35.9% of the PTCA and medical groups, respectively, had angina grade 2 or worse (difference 16.5%, 95% CI 11.0% to 21.9%). By 5 years follow-up, the prevalence of angina grade 2 or worse in the PTCA group remained steady at 15%, whereas in the medical group the prevalence of angina was reduced to 21.4%. The 5 year treatment difference was thus much smaller, 6.4% in favour of PTCA (95% CI 1.5% to 11.3%, p=0.011). During the next 3 years, the prevalence of angina began to increase slightly in both treatment groups.

Sub group interaction- age <65 years and >65 years

There was no significant difference between sub groups age <65 years and >65 years for death (p=0.10), MI (p=0.96) and free of angina (p=0.06).

(Multi vessel disease – Long term follow-up (5 year follow-up) – MASS-II)

Lopes 2008[97] (MASS-II): n=825 (n=214 single vessel disease, n=253 two vessel disease, n=358 three vessel disease)

Overall mortality was significantly higher in 3 vessel disease (17.8%) compared to 2 vessel disease (12.2%) and single vessel disease (n=6%) [p=0.001]. Multivariate Cox regression model (including variables such as age, hypertension, gender, hyperlipidemia, no. of coronary disease and treatment allocation) for mortality revealed a 3-fold increased risk of mortality in 3 vessel disease comparing to single vessel disease [p=0.005, HR 3.14, 95% CI 1.4 to 97.0]. There was no significant difference between 2 vessel disease and single vessel disease for mortality [p=0.15, HR 1.89, 95% CI 0.75 to 4.56].

Table 11.15: Medical vs. PCI – Single vessel disease – medium term follow-up (2–4 years) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Medical	PCI	Relative (95% CI)	Absolute	
Death (follow-up 2–3 years)											
Hartigan 1998[98] (ACME); Hueb 1995[85] (MASS-I)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	7/179 (3.9%)	6/177 (3.4%)	RR 1.14 (0.41 to 3.17)	5 more per 1000 (from 20 fewer to 74 more)	⊕⊕OO LOW
MI (follow-up 2–3 years)											
Hartigan 1998[98] (ACME); Hueb 1995[85] (MASS-I)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/179 (5%)	12/177 (6.8%)	RR 0.74 (0.32 to 1.7)	18 fewer per 1000 (from 46 fewer to 47 more)	⊕⊕⊕O MODERATE
Hospitalisation (no. of patients) (follow-up 2–3 years)											
Hartigan 1998[98] (ACME)	randomised trials	serious (c)	no serious inconsistency	no serious indirectness	serious[2]	none	69/107 (64.5%)	64/105 (61%)	RR 1.06 (0.86 to 1.3)	37 more per 1000 (from 85 fewer to 183 more)	⊕⊕OO LOW
Free of angina (follow-up 2–3 years)											
Hartigan 1998[98] (ACME); Hueb 1995[85] (MASS-I)	randomised trials	serious (a)	serious (d)	no serious indirectness	no serious imprecision	none	73/179 (40.8%)	123/177 (69.5%)	RR 0.59 (0.48 to 0.72)	285 fewer per 1000 (from 195 fewer to 361 fewer)	⊕⊕OO LOW
Non protocol revascularisation (follow-up 2–3 years)											
Hartigan 1998[98] (ACME); Hueb 1995[85] (MASS-I)	randomised trials	serious (a)	serious (e)	no serious indirectness	serious (f)	none	54/179 (30.2%)	76/177 (42.9%)	RR 0.7 (0.53 to 0.93)	129 fewer per 1000 (from 30 fewer to 202 fewer)	⊕OOO VERY LOW
Stroke (follow-up 3 years)											
Hueb 1995[85] (MASS-I)	randomised trials	serious (g)	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/72 (0%)	0/72 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE

(a) Hartigan 1998[96] (ACME): - Randomised, baseline comparison made, intention to treat analysis used. Randomisation method not clearly described. Allocation concealment not reported. Hueb 1995[83] MASS-I: Randomised, Baseline comparisons made. Number of patients lost to follow-up not reported. ITT reported. Allocation concealment not reported. Blinding of outcome assessors not reported.

(b) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.

(c) Hartigan 1998[96] (ACME): Randomised, baseline comparison made, intention to treat analysis used. Randomisation method not clearly described. Allocation concealment not reported.

(d) I^2 =88%

(e) I^2 =92%

(f) 95% CI around the pooled estimate of effect includes appreciable benefit or appreciable harm.

(g) Hueb 1995[83] (MASS-I): Randomised, Baseline comparisons made. Number of patients lost to follow-up not reported. ITT reported. Allocation concealment not reported. Blinding of outcome assessors not reported.

Table 11.16: Medical vs. PCI – Single vessel disease – long term follow-up (>4 years) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Medical	PCI	Relative (95% CI)	Absolute	
Death (follow-up 4.6-6 years)											
Folland 1997[95] (ACME); Hueb 1995[85] (MASS-I)	randomised trials	serious (a)	no serious inconsistency (b)	no serious indirectness	serious (c)	none	22/184 (12%)	23/187 (12.3%)	RR 0.98 (0.57 to 1.68)	2 fewer per 1000 (from 53 fewer to 84 more)	⊕OOO LOW
Non fatal MI (follow-up 4.6-6 years)											
Folland 1997[95] (ACME); Hueb 1995[85] (MASS-I)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (c)	none	11/184 (6%)	22/187 (11.8%)	RR 0.51 (0.26 to 1.02)	58 fewer per 1000 (from 87 fewer to 2 more)	⊕⊕OO LOW
Non protocol Revascularisation (follow-up 4.6-6 years)											
Hueb 1995[85] (MASS-I)	randomised trials	serious (d)	no serious inconsistency	no serious indirectness	serious (c)	none	12/72 (16.7%)	29/72 (40.3%)	RR 0.41 (0.23 to 0.75)	238 fewer per 1000 (from 101 fewer to 310 fewer)	⊕OOO VERY LOW
cardiac death (follow-up 4.6-6 years)											
Hueb 1995[85] (MASS-I)	randomised trials	serious (e)	no serious inconsistency	no serious indirectness	serious (c)	none	2/72 (2.8%)	4/72 (5.6%)	RR 0.5 (0.09 to 2.64)	28 fewer per 1000 (from 51 fewer to 91 more)	⊕⊕OO LOW
stroke (follow-up 5 years)											
Hueb 1995[85] (MASS-I)	randomised trials	serious (e)	no serious inconsistency	no serious indirectness	serious (c)	none	1/72 (1.4%)	1/72 (1.4%)	RR 1 (0.06 to 15.68)	0 fewer per 1000 (from 13 fewer to 204 more)	⊕⊕OO LOW
Free of angina (follow-up 5 years)											
Hueb 1995[85] (MASS-I)	randomised trials	serious (e)	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/72 (23.6%)	44/72 (61.1%)	RR 0.39 (0.25 to 0.61)	373 fewer per 1000 (from 238 fewer to 458 fewer)	⊕⊕⊕O MODERATE

(a) Folland 1997[93] (ACME): Randomised, baseline comparison made, intention to treat analysis used, no patients lost to follow up. Randomisation method not clearly described. Allocation concealment not reported. Hueb 1995[83] (MASS-I): Randomised, Baseline comparisons made. Number of patients lost to follow-up not reported. ITT reported. Allocation concealment not reported. Blinding of outcome assessors not reported.

(b) $I^2 = 0\%$

(c) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.

(d) Strengths: Randomised, Baseline comparisons made. Number of patients lost to follow-up not reported. ITT reported. Weaknesses: allocation concealment not reported. Blinding of outcome assessors not reported.

(e) Hueb 1995[83] (MASS-I): Randomised, Baseline comparisons made. Number of patients lost to follow-up not reported. ITT reported. Allocation concealment not reported. Blinding of outcome assessors not reported.

Sub group interaction – single vessel and 2 vessel – Long term follow-up:

There was no significant difference between sub groups single and 2 vessel for death (p=0.61) and MI (p=0.54).

Quality of Life data from studies:

Strauss 1995[99] (ACME):

In ACME Quality of Life was assessed with the Psychologic General Well-Being Index (PGWB) developed to measure an individual's subjective sense of well-being or distress. It measures the patient's perception of his or her well-being in the month preceding assessment. Six categories of psychological well-being were assessed: anxiety, depressed mood, positive well-being, self-control, general health and vitality. The test consists of 22 questions, the responses to which are graded from 0 (most negative) to 5 (most positive). There are three to five non-overlapping items or responses that form the subscales with which to measure the six states. The answers to the 22 questions are summed to yield an overall psychological well-being QOL score (maximum, 110).

Results: n=170 (n for each group not separately specified) with paired baseline and follow-up (6 months) data. At 6 month follow-up the mean change in Quality of Life score was significantly higher in the PCI group (+1.98±14.7 Medical vs. +7.36 ±15.6; p<.02). Within the subscales there was also a significant difference in perceived General Health which was significantly higher for the PCI group and all other subcomponents of the questionnaire showed the same trend (subscale mean change scores given in Figure, but not text).

Folland 1997[95] (ACME) – single vessel vs. double vessel disease:

See above for details of measure.

Results: n=267 (n=35 PCI double-vessel, n=37 Medical double-vessel, n=95 PCI single-vessel; and n=100 Medical single-vessel). At 6 mean QOL scores improved for both treatment groups with double-vessel disease, but the difference between treatment groups was not significant (+4.4 Medical vs. +1.3 PCI, p=.32). For patients with single-vessel disease there was significantly greater improvement in the PCI compared to the Medical group (+1.5 Medical vs. +7.1 PCI, p=.01).

Pitt 1999[92] (AVERT trial):

Quality of Life was assessed using the 36-item Medical Outcomes Study Short-Form General Health Survey (see below for details) at baseline, 6 and 18 months after randomisation.

Results: n=341 (n=177 in PTCA and n=164 in medical treatment). Both treatment groups had a mean increase in the summary scores for physical and mental health at both 6-month and 18-month assessments, denoting an improvement in the quality of life from baseline. Mean increases in scores ranged from 2.9 to 6.3; the increases were slightly, but not significantly, larger in the angioplasty group. No further details were provided.

Pocock 2000[100] (RITA-2):

Patients assessed their Quality of Life using the SF-36 health survey, at baseline, 3 months, 1 year and 3 years. The SF-36 comprises 36 items that can be combined into the following eight multi-item summary scores: physical functioning (10 items), vitality

(4 items), bodily pain (2 items), mental health (5 items), social functioning (2 items) role limitation due to physical health (4 items) and due to emotional problems (3 items) and general health perceptions (5 items), plus one item assessing a change in health over the past year. Each summary score is obtained by simple unweighted summation of item scores and is then scaled from 0 to 100, with 0 and 100 indicating 'worst' and 'best' possible health respectively.

Results: n=1018 (n=504 in PTCA and n=514 in medical treatment). Quality of life by SF-36 values (mean; SEM) reported in figures. Reported in text - The PTCA group showed highly significant superiority over the medical group in terms of physical functioning, vitality and general health at both 3 months and 1 year after randomisation. Mental health was also significantly better in the PTCA group at 3 months and 1 year, although the magnitude of this difference was quite small. The slight superiority of the PTCA group in pain, social functioning and physical and emotional role functioning did not achieve such marked levels of statistical significance. None of the 8 SF-36 scores showed a significant treatment difference at 3 years.

Weintraub 2008[101] (COURAGE)

Measurement of health status: Health status related to angina was assessed directly from patients at baseline; at 1, 3, 6 and 12 months; and at annual evaluations there after. Each assessment was performed with the use of the Seattle Angina Questionnaire, a 19 item questionnaire that quantifies physical limitations due to angina, any recent change in the severity of angina, the frequency of angina, satisfaction with treatment, and quality of life. Scores range from 0 to 100; higher scores indicate better health status.

Measurement of general health status: General health status was measured with the use of the RAND-36 health survey, which includes the following domains: physical functioning, role limitation due to physical problems, role limitation due to emotional problems, vitality, emotional well being social functioning, pain, and general health. Scores for each domain range from 0 to 100, with higher scores reflecting better health status. The RAND-36 health survey contains the same items as the Medical Outcomes Study 36-item Short Form General Health Survey (SF-36).

Results: N=2287 (n=1149 PCI and n=1138 in OMT). Patients were followed for a minimum of 30 months.

Health status: Baseline mean (± SD) Seattle Angina Questionnaire scores (which range from 0 to 100, with higher scores indicating better health status) were 66± 25 for physical limitations, 54±32 for angina stability, 69±26 for angina frequency, 87±16 for treatment satisfaction, and 51±25 for quality of life. By 3 months, these scores had increased in the PCI group, as compared with medical therapy group, to 76±24 versus 72±23 for physical limitation (p=0.004), 77±28 versus 73±27 for angina stability (p=0.002), 85±22 versus 80±23 for angina frequency (p<0.001), 92±12 versus 90±14 for treatment satisfaction (p<0.001), and 73±22 versus 68±23 for quality of life (p<0.001). In general, patients had an incremental benefit from PCI for 6 months to 24 months; people with more severe angina had a greater benefit from PCI.

General Health status: There were no significant differences at baseline between the groups for any RAND-36 domain. There was improvement in all domains in both groups between randomisation and follow-up at 1 to 3 months ($p<0.001$ for all comparisons).There was also an incremental advantage of PCI over medical therapy at 3 months for the scores in five domains: physical functioning (69±27vs. 65±26,$p<0.001$), role limitation-physical (60±42 vs. 52±43,$p<0.001$), vitality (56±23 vs. 53±23,$p=0.008$), pain (72±25 vs. 68±26,$p=0.006$), and general health (61±21 vs. 58±21,$p<0.001$).The benefit across domains was less consistent than seen in the results for the Seattle Angina Questionnaire, with an advantage of PCI that was noted in most but not all domains and that had a shorter duration. At 6 months, the PCI group was more likely than the medical therapy group to have a clinically significant improvement in physical functioning (50% vs. 43%)and role limitation-physical (48% vs. 43%), but no advantage was observed at 12 months. There were no significant subgroup interactions in the RAND-36 results.

11.3.3 Economic evidence

Three studies[90,102,103] were found that included the relevant comparison. One of them[90] was excluded from this comparison because it had potentially serious limitations (not a randomised study; PCI procedure could have been without stents. EQ-5D data were not collected at baseline and at one year; scores were only predicted at these time points from other variables); therefore the other two studies[102,103] were deemed more reliable. These are summarised in the economic evidence profile below. See also Economics Evidence Tables in Appendix G.

Table 8.17: PCI vs. medical treatment – Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
Sculpher 2002[102]	Minor limitations (a)	Partial applicability (b)	Based on the RITA-2 study[91] included in the clinical review. Patients had arteriographically proven coronary artery disease and were recruited from 20 centres in the UK and Ireland.
Weintraub 2008[103]	Minor limitations (c)	Partial applicability (d)	Based on the COURAGE trial[93]. Patients had stable coronary artery disease with >70% stenosis in at least one major epicardial coronary artery with objective evidence of myocardial ischemia or at least one coronary stenosis >80% and classic angina without provocative testing.

(a) No incremental analysis was conducted.
(b) Utility values were not estimated. Stents and other coronary interventional techniques were only used if initial revascularisation with balloon angioplasty was unsatisfactory.
(c) Valuation of utilities not obtained from public but from patients. Effectiveness was estimated for the total duration of the trial (4.6 years) while costs only for 3 years. These results were combined.
(d) Patients in the study were low risk. PCI group included angioplasty too. USA study.

Table 8.18: PCI vs. medical treatment – Economic summary of findings

Study	Incremental cost per patient over three years (£)	Incremental effectiveness	ICER (£/QALY)	Uncertainty
Sculpher 2002[102]	2,686 (a, b)	(c)	NA	Similar results when patients were stratified by CCS score, breathlessness, exercise time, and overall score. Similar results when no discount rate is applied, cost of visits for non-cardiac reasons is excluded, or when unit costs from the 5 hospitals are used separately.
Weintraub 2008[103]	6,174 (d, e)	0.05 QALYs (e, f)	125,759	Extrapolating beyond RCT follow-up: PCI is still significantly more costly and more effective (not sig). Use of drug-eluting stents: no revascularisation after PCI was assumed, additional cost of $600 and clopidogrel for one year, PCI would not be cost-effective. At a $50k/QALY threshold PCI has a 25% probability of being cost-effective.

(a) 1999 GBP. Cost of cardiac procedures, in-hospital stay, subsequent procedures, GP and outpatient visits, antianginal and cardiac drugs.
(b) Discounted by 6%
(c) Number of deaths was higher in PTCA group (not statistically significant); number of deaths and MI was higher in PTCA group (statistically significant). More patients with grade 2 or worse angina in medical treatment group (statistically significant at 1 year, not statistically significant at 3 years).
(d) 2008 GBP obtained by using the purchasing power parities and GDP deflator indexes (http://eppi.ioe.ac.uk/costconversion/default.aspx). Costs included were hospitalisation, PCI, medication, outpatient services.
(e) Discounted by 3%
(f) Utility values estimated with the standard gamble method from participants of the trial.

11.3.4 Evidence statements

Clinical

Medical vs. PCI – Multi-vessel disease – short term follow-up (1 year) for stable angina

Hueb 2004[68] (MASS-II): Evidence from one RCT shows that significantly higher number of patients were free of angina [RR 0.7 (0.56 to 0.87)] in the PCI group compared to medical treatment. There was no significant difference between medical treatment and PCI for death [RR 0.34 (0.09 to 1.23)], Q wave MI [RR 0.63 (0.29 to 1.36)], stroke [RR 1.51 (0.26 to 8.97)], non protocol revascularisation [RR 0.65 (0.36 to 1.17)].

Soares 2006[69] (MASS-II): Evidence from one RCT shows there was no significant difference between medical treatment and PCI for and death in a sub group of patients with diabetes [RR 0.5 (0.09 to 2.88)] and no diabetes [RR 0.29 (0.06 to 1.35)]. [Follow-up 1 year].

Medical vs. PCI – Multi-vessel disease – medium term follow-up (2 to 4 years) for stable angina

Chamberlain 1997[91] (RITA-2): Evidence from one RCT shows that there was no significant difference between medical treatment and PCI for death [RR 0.62 (0.24 to 1.6)]. [Follow-up 2.7 years]

Chamberlain 1997[91] (RITA-2); Pitt 1999[92] (AVERT): Evidence from 2 RCTs shows that there was no significant difference between medical treatment and PCI for cardiac death [RR 0.67 (0.19 to 2.35)], non fatal MI [RR 0.54 (0.28 to 1.02)], and stroke [RR 5.88 (0.71 to 48.69)]. [follow-up 1.5–2.7 years]

Pitt 1999[92] (AVERT): Evidence from one RCT shows that there were significantly fewer hospitalisations for worsening of angina in medical treatment compared to PCI [RR 0.47 (0.24 to 0.93)] [follow-up 18 months]

Chamberlain 1997[91] (RITA-2); Pitt 1999[92] (AVERT): Evidence from 2 RCTs shows that there was no significant difference medical treatment and PCI for non protocol revascularisation [RR 1.14 (0.93 to 1.4)]. [Follow-up 1.5–2.7 years]

Medical vs. PCI – Multi vessel disease – long term follow-up (> 4 years follow-up) for stable angina

Boden 2007[93] (COURAGE); Henderson 2003[94] (RITA-2); Hueb 2010[79] (MASS-II): Evidence from 3 RCTs shows that significantly higher number of patients were free of angina in the PCI compared to medical treatment [RR 0.88 (0.79 to 0.98)]. There was significantly higher non protocol revascularisation in medical treatment compared to PCI [RR 1.36 (1.23 to 1.51)]. There was no significant difference between medical treatment and PCI for death [RR 1.14 (0.94 to 1.37)], non fatal MI [RR 0.96 (0.80 to 1.16] [follow-up 4.6–10 years]

Boden 2007[93] (COURAGE); Henderson 2003[94] (RITA-2): Evidence from 2 RCTs shows that there was no significant difference between medical treatment and PCI for cardiac death [RR 1.30 (0.85 to 2.00)]. [follow-up 4.6–7 years]

Boden 2007[93] (COURAGE); Hueb 2010[79] (MASS-II): Evidence from 2 RCT shows that there was no significant difference medical treatment and PCI for stroke [RR 0.86 (0.52 to 1.41))] [follow-up

4.6–10 years]

Teo 2009[96] (COURAGE): Evidence from one RCT shows that there was no significant difference medical treatment and PCI for death [RR 0.98 (0.69 to 1.39)], MI [RR 0.9 (0.63 to 1.27)] in subgroup of patients aged >65 years. There were significantly more patients free of angina [RR 0.91 (0.85 to 0.98)] in PCI compared to medical treatment in patients aged >65 years. [Follow-up 4.6 years]

Teo 2009[96] (COURAGE): Evidence from one RCT shows that there was significantly higher death [RR 1.63 (1.00 to 2.65)] in medical treatment compared to PCI in patients aged <65 years. There was no significant difference medical treatment and PCI for MI [RR 0.91 (0.68 to 1.22)] and free of angina [RR 1.00 (0.93 to 1.07)], in patients aged >65 years. [Follow-up 4.6 years] . But there was no significant difference between sub groups age <65 years and >65 years for death (p=0.10), MI (p=0.96) and free of angina (p=0.06).

Folland 1997[95] (ACME): Evidence from one RCT shows that there was no significant difference between medical treatment and PCI for death [RR 1.13 (0.5 to 2.55)], non fatal MI [RR 1.02 (0.39 to 2.7)] in sub group of patients with 2 vessel disease. [Follow-up 6 years]

<u>Medical vs. PCI – Single vessel disease – medium term follow-up (2–4 years) for stable angina</u>

Hartigan 1998[98] (ACME); Hueb 1995[85] (MASS-I): Evidence from 2 RCTs shows that there was statistically significant higher no. of patients free of angina [RR 0.59 (0.48 to 0.72]) in PCI compared to medical treatment; there was statistically significant higher non - protocol revascularisation the PCI group compared to medical treatment [RR 0.7 (0.53 to 0.93)]. There was no significant difference between medical treatment and PCI for death [RR 1.14 (0.41 to 3.17]), MI [RR 0.74 (0.32 to 1.7]), hospitalisation [RR 1.06 (0.86 to 1.3)] and stroke [PCI-0/72 and CABG-0/72]. [Follow-up 2-4 years]

<u>Medical vs. PCI – Single vessel disease – long term follow-up (>4 years) for stable angina</u>

Folland 1997[95] (ACME); Hueb 1995[85] (MASS-I): Evidence from 2 RCTs shows that there was no statistically significant difference between medical treatment and PCI for death [RR 0.98 (0.57 to 1.68)] , non fatal MI [RR 0.51 (0.26 to 1.02)][Follow-up 4.6 to 6 years]

Hueb 1995[85] (MASS-I): Evidence from one RCT shows that there was statistically significant higher no. of patients free of angina in

	the PCI group compared to medical treatment [RR 0.39 (0.25 to 0.61)]. There was no statistically significant difference between medical treatment and PCI for cardiac death [RR 0.5 (0.09 to 2.64)], non –protocol revascularisation [RR 0.41 (0.23 to 0.75)] and stroke [RR 1 (0.06 to 15.68)]. [Follow-up 5 years]
Economic	Medical treatment is more cost-effective than early revascularisation with PCI in people with stable coronary artery disease. This evidence has minor limitations and partial applicability.

11.4 Medical interventions versus PCI or CABG

11.4.1 Clinical question

What is the clinical and cost effectiveness of medical interventions versus PCI or CABG in people with stable angina?

11.4.2 Clinical evidence

The “Review Protocol” for this topic can be found in Appendix C, the “Search Strategies” in Appendix D, the “List of Included and Excluded Studies” in Appendix E1, the “Clinical Evidence Tables” in Appendix E2, and the “Forest Plots” in Appendix F.

Table 11.19: Medical vs. PCI or CABG – Multi-vessel disease – short term follow-up (1 year) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Medical	PCI or CABG	Relative (95% CI)	Absolute	
Death (follow-up 1 years)											
Pfisterer 2003[104] (TIME)	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/148 (8.1%)	17/153 (11.1%)	RR 0.73 (0.36 to 1.47)	30 fewer per 1000 (from 71 fewer to 52 more)	⊕⊕⊕O MODERATE
MI (follow-up 1 years)											
Pfisterer 2003[104] (TIME)	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/148 (13.5%)	14/153 (9.2%)	RR 1.48 (0.78 to 2.81)	44 more per 1000 (from 20 fewer to 167 more)	⊕⊕⊕O MODERATE
Non protocol revascularisation (follow-up 1 years)											
Pfisterer 2003[104] (TIME)	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	71/148 (48%)	16/153 (10.5%)	RR 4.59 (2.8 to 7.51)	377 more per 1000 (from 189 more to 684 more)	⊕⊕⊕O MODERATE

(a) Pfisterer 2003[102] (TIME): Randomised, low attrition bias (on-treatment analysis so no loss to follow up). The potential for bias is substantial because both treatment groups contain failures of the other treatment. In addition the patient number is relatively low. No allocation concealment /No intention to treat analysis as it is an on treatment analysis.

Table 11.20: Medical vs. PCI or CABG – Multi-vessel disease – medium term follow-up (2 to 4 years) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Medical	PCI or CABG	Relative (95% CI)	Absolute	
Death (follow-up 4 years)											
Pfisterer 2004[105] (TIME)	randomised trial	Serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	31/139 (22.3%)	29/137 (21.2%)	RR 1.05 (0.67 to 1.65)	11 more per 1000 (from 70 fewer to 138 more)	⊕⊕⊕O MODERATE
Non protocol revascularisation (follow-up 4 years)											
Pfisterer 2004[105] (TIME)	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/139 (2.9%)	4/137 (2.9%)	RR 0.99 (0.25 to 3.86)	0 fewer per 1000 (from 22 fewer to 83 more)	⊕⊕⊕O MODERATE
Non fatal MI (follow-up 4 years)											
Pfisterer 2004[105] (TIME)	randomised trial	Serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/139 (0.7%)	6/137 (4.4%)	RR 0.16 (0.02 to 1.35)	37 fewer per 1000 (from 43 fewer to 15 more)	⊕⊕⊕O MODERATE

(a) Pfisterer 2004[103] (TIME): Randomised, low attrition bias (on-treatment analysis so no loss to follow up). The potential for bias is substantial because both treatment groups contain failures of the other treatment. In addition the patient number is relatively low. No allocation concealment /No intention to treat analysis as it is an on treatment analysis.

Table 11.21: Medical vs. PCI or CABG – Multi-vessel disease- short term follow-up (1 year) for stable angina – Angiography pre-randomisation

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Medical	PCI or CABG	Relative (95% CI)	Absolute	
Death (follow-up 1 years)											
Rogers 1995[106] (ACIP) (b)	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/183 (4.4%)	0/192 (0%)	RR 17.83 (1.04 to 306.73)	40 more per 1000 (from 10 more to 70 more)	⊕⊕⊕O MODERATE
MI (follow-up 1 years)											
Rogers 1995[106] (ACIP)	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/183 (5.5%)	5/192 (2.6%)	RR 2.1 (0.73 to 6.02)	29 more per 1000 (from 7 fewer to 131 more)	⊕⊕⊕O MODERATE
Repeat revascularisation (follow-up 1 years)											
Rogers 1995[106] (ACIP)	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	44/183 (24%)	18/192 (9.4%)	RR 2.56 (1.54 to 4.27)	147 more per 1000 (from 51 more to 307 more)	⊕⊕⊕O MODERATE

(a) Rogers 1995[104] (ACIP): Randomised, baseline characteristics reported. Intention to treat analysis reported. At 1 year after entry, follow-up was 100% complete for death and 96% complete for other clinical events. Allocation concealment not reported. This is a 1 year follow-up of the ACIP study.

(b) 3 arms to the study: 1) Pharmacologic therapy to suppress angina (angina guided therapy) 2) Pharmacologic therapy to suppress both angina and ambulatory ECG evidence of ischemia (ischemia guided strategy) 3) Revascularisation with either angioplasty or surgery. We have analysed data for only 2 arms – angina guided therapy vs. revascularisation.

Table 11.22: Medical vs. PCI or CABG – Multi-vessel disease- medium term follow-up (2–4 year) for stable angina – Angiography pre-randomisation

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Medical	PCI or CABG	Relative (95% CI)	Absolute	
Death (follow-up 2 years)											
Davies 1997[107] (ACIP)	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/183 (6.6%)	2/192 (1%)	RR 6.3 (1.43 to 27.74)	53 more per 1000 (from 4 more to 267 more)	⊕⊕⊕O MODERATE
Non protocol revascularisation (follow-up 2 years)											
Davies 1997[107] (ACIP)	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	56/183 (30.6%)	25/192 (13%)	RR 2.35 (1.54 to 3.60)	175 more per 1000 (from 70 more to 338 more)	⊕⊕⊕O MODERATE

(a) Davies 1997[105] (ACIP): Randomised, baseline characteristics reported. Intention to treat analysis reported. Allocation concealment not reported.

Table 11.23: Medical vs. PCI or CABG – Multi-vessel disease – Long term follow-up (>4 years) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Medical	PCI or CABG	Relative (95% CI)	Absolute	
Death (patients with type 2 diabetes) (follow-up 5 years)											
Frye 2009[108] (BARI-2D) (b)	randomised trial	Serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	121/991 (12.2%)	112/953 (11.8%)	RR 1.04 (0.82 to 1.32)	5 more per 1000 (from 21 fewer to 38 more)	⊕⊕⊕O MODERATE
Death (in PCI stratum in BARI-2D) (follow-up 5 years)											
Frye 2009[108] (BARI-2D) (b)	randomised trial	Serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	82/807 (10.2%)	86/798 (10.8%)	RR 0.94 (0.71 to 1.26)	6 fewer per 1000 (from 31 fewer to 28 more)	⊕⊕⊕O MODERATE
Death (in CABG stratum in BARI-2D) (follow-up 5 years)											
Frye 2009[108] (BARI-2D) (b)	randomised trial	Serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	63/385 (16.4%)	51/378 (13.5%)	RR 1.21 (0.86 to 1.71)	28 more per 1000 (from 19 fewer to 96 more)	⊕⊕⊕O MODERATE
Freedom from CV events (death, MI or stroke) - PCI stratum (BARI-2D) (follow-up 5 years)											
Frye 2009[108] (BARI-2D) (b)	randomised trial	Serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	637/807 (78.9%)	614/798 (76.9%)	RR 1.03 (0.97 to 1.08)	23 more per 1000 (from 23 fewer to 62 more)	⊕⊕⊕O MODERATE
Freedom from CV events (death, MI or stroke)- CABG stratum(BARI-2D) (follow-up 5 years)											
Frye 2009[108] (BARI-2D) (b)	randomised trial	Serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	268/385 (69.6%)	293/378 (77.5%)	RR 0.9 (0.82 to 0.98)	78 fewer per 1000 (from 15 fewer to 140 fewer)	⊕⊕⊕O MODERATE

(a) Frye 2009[106] (BARI-2D): Large scale randomised control trial (randomisation method not reported), intention to treat analysis, power calculation for 5 year follow-up reported, baseline comparisons were made . No allocation concealment reported, not all of the patients enrolled suffered from stable angina.

(b) All patients underwent clinically indicated coronary angiography before randomisation; most of them provided consent during screening before angiography but after meeting clinical eligibility requirements. Thus, the number of patients who were excluded for reasons unrelated to coronary anatomy was unavailable.

Interaction between study group assignment in to PCI and CABG stratum in the BARI-2D trial

At 5 years, the rates of death did not differ significantly between the revascularisation group and medical therapy group in either the CABG [RR 1.21 (0.86 to 1.71)] or the PCI stratum [RR 0.94 (0.71 to 1.26)]. The interaction between study group assignment and intended method of revascularisation was not significant for death (p=0.27). Patients in the CABG stratum who were assigned to the revascularisation group had significantly more patients were free from major cardiovascular events than did patients in the CABG stratum who were assigned to the medical therapy group [RR 0.90 (0.82 to 0.98)]. Freedom from major cardiovascular events among patients in the PCI stratum assigned to the revascularisation group did not differ significantly from those who were assigned to the medical therapy [RR (1.03 (0.97 to 1.08)].

The interaction between study group assignment and intended method of revascularisation was significant for freedom from major cardiovascular events (p=0.01), which indicated that the benefit associated with prompt coronary revascularisation, as compared with medical therapy, was significantly greater for patients selected for CABG than for patients selected for PCI.

Quality of life data from studies:

Medical vs. PCI or CABG

Pfisterer 2003[104] (TIME) – 6 months and 1 year follow-up

Quality of Life was measured by items from three questionnaires that and 91% of surviving patients at 4 year follow-up provided data for this. The questionnaires were the short-form SF36 the Duke Activity Status Index (DASI) and the Rose questionnaire.

Results: N=282 (CABG or PCI n=140; Medical n=142). QOL increased in both groups. The Rose Score and the General Health component of SF36 showing significantly larger improvements for the revascularisation group compared to the medical group at the time of the first follow-up (6 months). However, improvements were no longer significant between the 2 treatment groups after 1 year. Improvements in the DASI were not significantly different between groups at 6 or 12 months follow-up.

Pfisterer 2004[105] (TIME) – 4 year follow-up:

See above, instead of SF36 they reported SF12 results.

Results: N=282 (CABG or PCI n=140; Medical n=142). After 4 years cores from the Rose, SF12 physical component and DASI continued to be significantly improved compared to baseline. However, none of the group differences were significant. The SF12 mental-component summary scores did not change significantly in either treatment group (p=.29) compared to baseline and remained constant throughout the entire study period.

Medical vs. PCI vs. CABG

Favarato 2007[109] (MASS-II)

In the MASS II study Quality of Life was assessed using short form 36 (SF-36) at 1 year. The SF-36 comprises 36 items that can be combined in to the following 8 multi-item summary scores: physical functioning (10 items), vitality (four items), bodily pain (2 items), mental health (5 items), social functioning (2 items), role limitations due to physical health (4 items) and due to emotional problems (3 items) and general health perceptions (5 items), plus one item assessing a change in health over the past year. Each summary score is obtained by simple unweighted summation of item scores and is scaled from 0 to 100, with 0 and 100 indicating 'worst' and 'best' possible health, respectively (higher scores indicate better perceived health).

Results: N=522 (n=17 medical treatment, n=180 PCI, n=175 CABG). The SF-36 mean scores for CABG, PCI and Medical treatment respectively were: Role physical (48.37 vs. 50 vs. 40.26); role emotional (66.08 vs. 63.48 vs. 62.63); mental health (70.69 vs. 70.43 vs. 68.13); vitality (71.33 vs. 67.37 vs. 61.59); physical functioning (71.51 vs. 68.29 vs. 62.63); bodily pain (72.24 vs. 70.10 vs. 64.92); general health (76.59 vs. 71.32 vs. 69.58); social functioning (81.89 vs. 81.82 vs. 77.05). None of the eight SF-36 scores showed a significant treatment difference at 12 months between PCI and CABG. However, the CABG group better than the medical group in terms of vitality (p<0.001), physical functioning (p<0.001) and general health (p<0.001) at 12 months. The PCI group showed significantly superiority over the medical group just in terms of vitality and functioning at 12 months (p<0.001). All these treatment comparisons were done using the analysis of co-variance, adjusting for the patient's baseline scores.

11.4.3 Economic evidence

One study[110] was found that included the relevant comparison in people with type 2 diabetes mellitus. This is summarised in the economic evidence profile below. See also Economics Evidence Tables in Appendix G.

Table 8.24: CABG and PCI vs. medical treatment – Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
Hlatky 2009[110]	Potentially serious limitations (a)	Partial applicability (b)	Based on the BARI 2D trial. Patients had type 2 diabetes mellitus and stable, angiographically documented coronary disease.

(a) *Not clear how utility estimates were used to calculate results in the study. In the clinical paper the probability of cardiovascular events was lower in the CABG stratum and this was inconsistent with the QALYs calculation. QALYs were not adjusted by baseline values.*
(b) *USA study.*

Table 8.25: CABG and PCI vs. medical treatment – Economic summary of findings

Study	*Incremental cost per patient over 4 years*	*Incremental QALYs per patient over 4 years*	*ICER (£/QALY)*	*Uncertainty*
Hlatky 2009[110]	Medical treatment costs saving (a)	Medical treatment more effective (b)	Medical treatment dominant	Medical therapy was not dominant but still cost-effective when: - results were extrapolated to lifetime assuming costs after 4 years are the same in the 2 groups - QALYs were adjusted by baseline values - a reduced survival after MI (2 and 3 years) and after non-fatal stroke (3 years) was assumed.

(a) *Costs included were hospitalisation, outpatient visits, nursing home/rehab, medications, test and procedure. Hospital costs calculated using a ratio of cost to charges. Discounted by 3%.*
(b) *Total QALYs at 4 years were higher in the medical treatment group compared to both the PCI and CABG strata.*

11.4.4 Evidence statements

Clinical

Medical vs. PCI or CABG – Multi-vessel disease – short term follow-up (1 year) for stable angina

Pfisterer 2003[104] (TIME): Evidence from one RCT shows that there was no significant difference medical treatment or revascularisation (PCI or CABG) for death [RR 0.73 (0.36 to 1.47)], MI [RR 1.48 (0.78 to 2.81)]. There was significantly higher non protocol revascularisation [RR 4.59 (2.80 to 7.51)] in the medical treatment compared to revascularisation (PCI or CABG). [Follow-up 1 year]

Medical vs. PCI or CABG – Angiography pre-randomisation – Multi-vessel disease – short term follow-up (1 year) for stable angina

Rogers 1995[106] (ACIP): Evidence from one RCT shows that there were significantly higher deaths in medical treatment compared to revascularisation (medical or PCI), there no significant difference medical treatment or revascularisation (PCI or CABG) for MI [RR 2.10 (0.73 to 6.02)], MI [RR 1.64 (0.95 to 2.84)] .There was significantly higher non protocol revascularisation [RR 2.56 (1.54 to 4.27)] in the medical treatment group compared to revascularisation (PCI or CABG).[follow-up 1 year]

Medical vs. PCI or CABG – Multi-vessel disease – medium term follow-up (2 to 4 years) for stable angina

Pfisterer 2004[105] (TIME): Evidence from 1 RCT shows that there was no significant difference between medical treatment and revascularisation (PCI or CABG) for death [RR 1.05 (0.67 to 1.65)], non fatal MI, [RR 0.16 (0.02 to 1.35)] . There were significantly higher non protocol revascularisations [RR 0.99 (0.25 to 3.86)] in medical treatment compared to revascularisation (PCI or CABG). [Follow-up 4 years]

Medical vs. PCI or CABG – Angiography pre-randomisation – Multi-vessel disease – medium term follow-up (2 to 4 years) for stable angina

Davies 1997[107] (ACIP): Evidence from one RCT shows that there was significantly higher death in medical treatment compared to revascularisation (PCI or CABG) [RR 6.30 (1.43 to 27.74)]. There were significantly higher non protocol revascularisations [RR 2.35 (1.54 to 3.60)] in the medical treatment group compared to revascularisation (PCI or CABG). [Follow-up 2 years]

Medical vs. PCI or CABG – Multi-vessel disease – Long term

	follow-up (5 years) for stable angina
	Frye 2009[108] (BARI-2D): Evidence from one RCT in patients with type 2 diabetes shows that there was no significant difference between medical treatment and revascularisation (PCI or CABG) for death [RR 1.04 (0.82 to 1.32)] [Follow-up 5.3 years]
	Frye 2009[108] (BARI-2D): Evidence from one RCT in patients with type 2 diabetes shows that the rates of death did not differ significantly between the revascularisation group and medical treatment group in either the CABG [RR 1.21 (0.86 to 1.71)] or the PCI stratum [RR 0.94 (0.71 to 1.26)]. The interaction between study group assignment and intended method of revascularisation was not significant for death (p=0.27). [Follow-up 5.3 years]
	Frye 2009[108] (BARI-2D): Evidence from one RCT in patients with type 2 diabetes shows that patients in the CABG stratum who were assigned to the revascularisation group had significantly more patients were free from major cardiovascular events than did patients in the CABG stratum who were assigned to the medical therapy group [RR 0.90 (0.82 to 0.98)]. Freedom from major cardiovascular events among patients in the PCI stratum assigned to the revascularisation group did not differ significantly from those who were assigned to the medical therapy [RR (1.03 (0.97 to 1.08)]. The interaction between study group assignment and intended method of revascularisation significant for freedom from major cardiovascular events (p=0.01). [Follow-up 5.3 years]
Economic	Medical treatment is more cost-effective than early revascularisation with either CABG or PCI in people with type 2 diabetes mellitus and stable coronary artery disease. This evidence has potentially serious limitations and partial applicability.

11.5 Recommendations and link to evidence – patients whose symptoms are not satisfactorily controlled with optimal medical treatment

Recommendation	**Consider revascularisation (CABG or PCI) for people with stable angina whose symptoms are not satisfactorily controlled with optimal medical treatment.** **Offer coronary angiography to guide treatment strategy for people with stable angina whose symptoms are not satisfactorily controlled with optimal medical treatment. Additional non-invasive or invasive functional testing may be required to evaluate angiographic findings and guide treatment decisions. [This recommendation partially updates recommendation 1.2 of 'Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction' (NICE technology appraisal**

	guidance 73).]
Relative values of different outcomes	Outcomes of interest included long-term mortality (total and cardiovascular), rates of major adverse cardiovascular events (myocardial infarction, stroke, myocardial revascularisation), measures of symptom severity (frequency of angina, exercise test outcomes), and quality of life.
Trade off between clinical benefits and harms	**Medical treatment versus CABG** The randomised trials of initial treatment strategies of coronary artery bypass surgery versus continued medical therapy included in the evidence review were mainly conducted in the 1970's. The individual patient data meta-analysis of the trials suggests that coronary artery bypass surgery is associated with a survival advantage that translates into a mean extension of survival of around four months over ten years (95% CI 1.91-6.61). This benefit is greater for people with three-vessel or left main stem disease (mean extensions of survival of 5.7 and 19.3 months over 10 years, respectively) than for people with less extensive disease (one or two vessel disease). A risk model incorporating multiple clinical and angiographic predictor variables suggests that absolute survival benefit is greatest in patients at highest baseline risk[67]. The trials also confirm that coronary artery bypass surgery is associated with a greater improvement in symptoms of angina and quality of life than continued medical therapy, and this benefit persists for up to ten years[74,81,83]. These trials of coronary surgery have several important limitations, which restrict their relevance to current clinical practice: The trials recruited a highly selected group of patients who were considered suitable for management with either initial treatment strategy. Moreover, the individual trials have limited statistical power and the meta-analysis of the trials included only 2649 patients, of whom only 150 patients had left main stem disease. Interpretation of the trial results is confounded by relatively high rates of myocardial revascularisation among patients initially assigned to a strategy of continued medical therapy. In the individual patient data meta-analysis 25% and 41% of medical patients underwent coronary surgery by five and ten years, respectively. This high crossover rate may dilute any long term differences between the two treatment strategies and lead to an underestimation of the true treatment effect. The profile of patients undergoing coronary artery bypass surgery has changed over time. In the individual patient data

meta-analysis almost all were male (96.8%), the majority (84.2%) were aged between 40 and 60 years (mean age 50.8 years), and the mean left ventricular ejection fraction was 59%[67]. It is likely that most of the patients enrolled in the trials would therefore have been good candidates for surgical revascularisation. By contrast, in contemporary practice coronary artery bypass operations are often carried out in elderly people of either gender who have extensive coronary artery disease, impaired left ventricular function, and multiple co-morbidities.

Since the early trials of CABG were conducted there have been major advances in the surgical treatment of people with angina. For example, in the individual patient data meta-analysis internal mammary artery grafts were used in only 9.9% of patients assigned to coronary bypass surgery, but internal mammary artery grafts are associated with improved long-term outcome and are used routinely in contemporary cardiac surgical practice[111,112].

Most of the trials included in the evidence review were conducted before the widespread introduction of contemporary secondary prevention measures, which improve long-term outcome in people with coronary artery disease. In the individual patient data meta-analysis only 18.8% of the medical patients were taking antiplatelet agents, and statins, inhibitors of the renin-angiotensin system, and thienopyridines were not used. It is noteworthy that treatment with a statin alone can result in a reduction in coronary heart disease mortality similar to that associated with coronary bypass surgery[113]. In a large meta-analysis a reduction in mean LDL cholesterol of 1.09mmol/L resulted in a 12% reduction in all-cause mortality and a 19% reduction in coronary heart disease mortality[114]. In the individual patient data meta-analysis coronary artery surgery was associated with a 39% relative risk reduction in mortality at five years, and a 17% reduction at ten years. The extent to which bypass surgery confers incremental prognostic benefit in people with three vessel or left main stem disease who are also treated with contemporary secondary prevention therapies (antiplatelet agents, statins, renin-angiotensin system inhibitors) is uncertain.

Medical treatment versus PCI

The randomised trials of percutaneous coronary intervention versus continued medical therapy included in the evidence review recruited patients considered suitable for either initial treatment strategy.

We found no evidence of a beneficial effect of percutaneous coronary intervention on medium or long-term mortality, but coronary intervention was associated with better symptom relief than continued medical therapy. This treatment difference attenuated over several years, partly because many patients assigned to medical therapy subsequently underwent myocardial revascularisation, but probably also because of restenosis and disease progression among patients assigned to percutaneous intervention. Several of the trials also reported greater improvements in quality of life scores among coronary intervention patients, but this was not confirmed in all trials (AVERT[92]) or sustained long-term (RITA-2[91,94], COURAGE[93,96]). Treatment effects were consistent among people with single vessel and multi-vessel disease.

Several issues limit the relevance of these trials to contemporary practice:

The trials recruited a highly selected group of patients that may not be representative of the wider population with stable angina. Patients were considered for randomisation following coronary angiography and patients with high risk coronary anatomy for which coronary bypass surgery might confer prognostic benefit (including left main stem or proximal three vessel disease) were generally excluded. In RITA-2[91,94], participating hospitals carried out over 70 000 coronary arteriograms during the recruitment period, but only identified 2750 eligible patients of whom 1018 patients were randomised[91,94]. In COURAGE[93,96] 35,539 patients were screened of whom 3071 met the eligibility criteria and 2287 were subsequently randomised (6.4% of the screened population). COURAGE [93,96] excluded patients with severe (CCS class IV) angina, marked ischaemia on an exercise test, or impaired left ventricular function.

Several of the trials (RITA-2[91,94], ACME [95,98], AVERT [92], MASS-I[85,86]) recruited patients before coronary artery stents were available. Only two trials compared an initial treatment strategy of percutaneous coronary intervention using bare metal stents with an initial treatment strategy of continued medical therapy (MASS-II[68,69,79], COURAGE[93,96]). We found no trials of percutaneous coronary intervention with drug-eluting stents versus continued medical therapy.

In several of the trials the use of statins and ACE inhibitors was suboptimal by contemporary standards. The COURAGE[93,96] trial is the largest trial to compare percutaneous coronary intervention and 'optimal' medical therapy (including anti-platelet therapy, anti-ischaemic therapy, renin-angiotensin system inhibition, and lipid-lowering therapy) with optimal medical therapy alone, but with only 413 end point events the trial has limited statistical power for the primary endpoint (death or non-fatal myocardial infarction). Moreover, after a mean follow-up of 4.6-years vital status was unknown in 8.4% of the patients [93,96].

All of the trials reported high rates of revascularisation procedures among patients assigned to medical therapy, which may have reduced any real differences between the two treatment strategies [non-protocol revascularisation rates - 630/1855 (34%) in the medical group and 463/1858 (24.9%) in the PCI group at long term follow-up].

The spectrum of patients considered suitable for PCI has changed over time and with evolving techniques and increasing operator experience a wider range of people with a more complex pattern of coronary artery disease are now considered eligible for percutaneous treatment.

Medical treatment versus myocardial revascularisation

These trials compared initial treatment strategies of invasive management and continued medical therapy in patients considered suitable for either strategy. In ACIP and BARI-2D patients were randomised after coronary angiography to medical therapy or revascularisation, but in TIME patients were randomised to medical therapy or coronary angiography and revascularisation (CABG or PCI) if appropriate.

The ACIP [106,107] trial reported lower short- and medium-term mortality in patients assigned to a revascularisation strategy, but there was no difference in mortality between the treatment groups in TIME[104,105] or BARI-2D[108]. In BARI-2D[108], among patients prospectively stratified to revascularisation by CABG (CABG stratum) there was a significant difference in major cardiovascular events (death, myocardial infarction, or stroke) between surgical and medical treatment groups. This was driven mainly by a difference in the rate of myocardial infarction but there was no difference in five year survival between patients assigned to surgical revascularisation or medical therapy [115].

Interpretation of these trials is complicated by several limitations:

ACIP [106,107] recruited patients before the introduction of coronary artery stents and amongst 192 patients assigned to revascularisation 102 patients were selected for coronary balloon angioplasty and 90 patients for coronary bypass surgery. Aspirin was prescribed to 89% of patients but statins were not used.

The TIME [104,105] trial randomised patients to an invasive strategy (coronary angiography followed by revascularisation) or to medical therapy. Of 155 patients assigned to the invasive strategy 79 underwent percutaneous coronary intervention and 30 underwent bypass surgery. The trial did not report the use of stents and lipid-lowering therapy was used in only 23% of patients.

In BARI-2D [108] most patients were treated with statins and renin-angiotensin system inhibitors. Among 1176 patients assigned to the revascularisation group, 765 underwent PCI, of whom 34.7% received a drug-eluting stent and 56.0% received a bare metal stent (9.3% did not receive a stent). During follow-up 42.1% of patients in the medical group underwent myocardial revascularisation [108].

The GDG concluded that myocardial revascularisation by either coronary artery bypass surgery or by percutaneous coronary intervention is an effective treatment for angina. Subgroup analyses of trials of bypass surgery versus medical therapy conducted over 25 years ago indicate that myocardial revascularisation also confers prognostic benefit in people with stable angina and high risk coronary anatomy. The magnitude of any incremental prognostic benefit from coronary bypass surgery in patients with stable angina who are also treated with contemporary medical therapy (antiplatelet agents, statins, and renin-angiotensin system inhibitors) is uncertain.

All people with stable angina should be offered appropriate medical therapy, but if symptoms are not controlled they should be considered for myocardial revascularisation. Patients in whom myocardial revascularisation is an acceptable treatment strategy should be offered coronary angiography and percutaneous coronary intervention or coronary bypass surgery as appropriate.

Economic considerations

Medical treatment is more cost-effective than early revascularisation with either CABG or PCI in people with stable coronary artery disease including people with type 2 diabetes mellitus. However if symptoms are not controlled, revascularisation is effective and could be cost-effective.

Quality of evidence

See discussion under balance of benefits and harms above.

The economic evidence regarding people with stable coronary artery disease has overall minor limitations but partial applicability. The economic evidence regarding people with type 2 diabetes and stable coronary artery disease has potentially serious limitations (unclear QALY calculations) and partial applicability (USA study).

Other considerations	The GDG were aware that in some patients interpretation of coronary arteriographic findings is difficult. In such cases assessment of the significance of a coronary stenosis with an invasive functional test (pressure wire) or by non-invasive functional imaging may be helpful to determine the appropriate treatment strategy. The GDG therefore made a consensus recommendation that additional non-invasive or invasive functional testing may be required to evaluate angiographic findings and guide treatment decision.

11.6 Recommendations and link to evidence – people with stable angina whose symptoms are satisfactorily controlled with optimal medical treatment

Recommendation	**Discuss the following with people whose symptoms are satisfactorily controlled with optimal medical treatment:** • **their prognosis without further investigation** • **the likelihood of having left main stem disease or proximal three-vessel disease** • **the availability of CABG to improve the prognosis in a subgroup of people with left main stem or proximal three-vessel disease** • **the process and risks of investigation** • **the benefits and risks of CABG, including the potential survival gain.** **After discussion (see above recommendation) with people whose symptoms are satisfactorily controlled with optimal medical treatment, consider a functional or non-invasive anatomical test to identify people who might gain a survival benefit from surgery. Functional or anatomical test results may already be available from diagnostic assessment. [This recommendation partially updates recommendation 1.2 of 'Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction' (NICE technology appraisal guidance 73).]** **After discussion (see above recommendation) with people whose symptoms are satisfactorily controlled with optimal medical treatment, consider coronary angiography when:** • **functional testing indicates extensive ischaemia or non-invasive anatomical testing indicates the**

	likelihood of left main stem or proximal three-vessel disease and • **revascularisation is acceptable and appropriate.** **Consider CABG with people with stable angina and suitable coronary anatomy whose symptoms are satisfactorily controlled with optimal medical treatment, but coronary angiography indicates left main stem disease or proximal three-vessel disease.**
Relative values of different outcomes	Outcomes of interest included long-term mortality (total and cardiovascular), rates of major adverse cardiovascular events (myocardial infarction, stroke, myocardial revascularisation), measures of symptom severity (frequency of angina, exercise test outcomes), and quality of life.
Trade off between clinical benefits and harms	Evidence that myocardial revascularisation prolongs life in people with stable angina comes from subgroup analyses of trials of coronary bypass surgery conducted over 25 years ago. These trials have a number of limitations that are discussed in section 11.5. Nevertheless, the trials have been very influential in cardiovascular medicine and the established management paradigm is to offer myocardial revascularisation to patients with high risk anatomy (left main stem disease and proximal three vessel disease) to improve prognosis. The trials of coronary bypass surgery have also influenced the design of recent randomised trials in stable angina, which have systematically excluded patients with high risk anatomy. The magnitude and clinical importance of any incremental prognostic benefit from myocardial revascularisation in patients with high risk anatomy who are also treated with optimal medical therapy (including statins, rennin-angiotension system inhibitiors, and antiplatelet agents) is therefore uncertain.
Economic considerations	Medical treatment is more cost-effective than early revascularisation with either CABG or PCI in people with stable coronary artery disease including people with type 2 diabetes mellitus. Offering functional or anatomical tests to patients whose symptoms are satisfactorily controlled with medical treatment would generate additional costs. There are subgroups of patients (with left main stem disease and proximal three-vessel disease) in whom revascularisation might have prognostic benefits; offering a test to patients who are likely to have left main stem disease and proximal three-vessel disease could be cost-effective.

Quality of evidence	See Evidence to recommendations section 11.5
Other considerations	The GDG were aware that investigation for ischaemia or high risk coronary anatomy to identify patients who may gain prognostic benefit from myocardial revascularisation is part of established cardiological and cardiac surgical orthodoxy. Although this practice is not based on strong evidence, there is insufficient evidence to recommend an alternative management pathway. The GDG therefore made consensus recommendations about the management of patients with stable angina for whom investigation is not indicated on symptomatic grounds. The GDG agreed that patients whose symptoms are controlled on medical therapy can be considered for a functional imaging or non-invasive anatomical investigation to identify high risk patients who may potentially gain prognostic benefit from myocardial revascularisation. The GDG did not consider there was sufficient evidence to recommend a preferred method of investigation and the choice should be made on clinical grounds and availability grounds. Patients may already have had a relevant functional or anatomical investigation as part of diagnostic assessment and in many cases additional investigations will not be required. The GDG agreed that an investigation for ischaemia or high risk coronary anatomy is appropriate only in people who are potentially candidates for invasive investigation and myocardial revascularisation. The GDG therefore made a consensus recommendation that before any tests are carried out patients should be informed about: • their prognosis without further investigation • the availability of coronary bypass surgery to improve the prognosis in a subgroup of people with left main stem disease and proximal three-vessel disease • the likelihood of having left main stem disease or proximal three-vessel disease • the process and risks of investigation • the benefits and risks of CABG, including the potential survival gain. The following information may aid healthcare professionals when discussing non-invasive functional or anatomical investigation with patients whose symptoms are controlled by

medical treatment:

- Patients with stable angina are generally thought to have a good prognosis although published information is limited[116]. In a large randomised trial all cause mortality was 1.5% per annum[42]. Studies in primary care have reported higher annual mortality rates ranging from 2.8% to 6.6%[4].

- The composite risk of a complication during coronary angiography is 1%-2%, with a composite risk of death, myocardial infarction or stroke of around 0.1%-0.2%[117,118].

- The prevalence of left main stem disease in patients with stable angina whose symptoms are controlled by medical therapy is unknown. In the CASS registry of 20137 patients who underwent coronary angiography left main coronary disease (≥50% stenosis) was found in 1477 patients (7.3%), but only 53 (3.6%) of these patients were asymptomatic[119]. In a more recent registry of 13228 patients undergoing coronary arteriography left main stem disease (≥60% stenosis) was found in 3.6%[120].

- In the IPD meta-analysis survival was extended by CABG in patients with left main stem disease by a mean19.3 months (95%CI 5.6-33.0) over 10 years and three vessel disease by 5.7 months (95%CI 2.1-9.3) over 10 years[67]. There is no direct evidence that PCI improves survival in patients with stable angina and high risk coronary anatomy.

- In 2008 isolated, first-time elective CABG was associated with an in-hospital mortality of 1%, and rates of re-operation for bleeding, new renal support (haemofiltration or dialysis), and post-operative stroke were 2.9%, 1.8%, and 0.9% respectively. Operative mortality increases with age (2.5% over 75 years) and is higher in women and patients with left main stem disease[121].

Patients who make an informed decision to proceed with investigation should be considered for a non-invasive functional or anatomical test. Patients with extensive ischaemia on functional testing or high risk anatomy on anatomical testing should be offered coronary angiography, and those found to have LMS disease or proximal three vessel disease should be considered for CABG.

11.7 Recommendations and link to evidence (Subgroup populations)

Recommendation	**Do not exclude people with stable angina from treatment based on their age alone.** **Do not investigate or treat symptoms of stable angina differently in men and women or in different ethnic groups.**
Other considerations	Elderly people commonly present with symptoms of cardiovascular disease. The very old (> 80 or 85 years depending on definition used) and those with co-morbidity are commonly not included in trials and the GDG considered that this was an area where consensus recommendation was required. There is evidence that outcome of revascularization is influenced by age but their analysis shows difference differs between people younger than 65 and those older than 65. The GDG considered that there was no clear evidence that the very old respond differently to treatment although greater age can be associated with frailty and co-morbidity, and the absolute risk for the elderly will be greater. The GDG agreed that age alone should not preclude consideration for medical or revascularisation treatment. Review protocols included women and people belonging to South Asian ethnic group as subgroups. No evidence was found to indicate that investigation or treatment should differ for people according to gender or ethnic group.

12 Revascularisation

12.1 Introduction

People with stable angina may be considered for myocardial revascularisation with percutaneous coronary intervention or coronary artery bypass surgery. The choice between the two revascularisation procedures is influenced by the result of coronary arteriography. Some patients are not angiographically suitable for percutaneous or surgical revascularisation but many patients are technically suitable for either revascularisation technique. Over the last three decades randomised controlled trials have compared strategies of percutaneous coronary (balloon) angioplasty (1980s), percutaneous coronary intervention using bare metal stents (1990s), and percutaneous coronary intervention using drug-eluting stents (2000s) with coronary artery bypass surgery in patients who are suitable for either method of revascularisation.

The following key clinical question is addressed in this chapter: In adults with stable angina, what is the clinical/cost effectiveness of revascularisation techniques to alleviate angina symptoms and to improve long term outcomes?

The evidence review for the determination of the clinical effectiveness of PCI vs. CABG included a total of 42 papers.

Twenty seven papers included patients with multi- vessel disease, 10 papers focused on single vessel disease, two paper focused on patients with left main coronary disease , two papers included patients with left main coronary artery or three vessel disease and one included paper was an IPD meta-analysis of trials comparing PCI and CABG.

The included IPD [122] included 10 trials with data on 7812 patients with a median follow-up of 5.9 years. PCI with balloon angioplasty was used in 6 trials and bare metal stents in 4 trials. Of the 10 trials, 3 trials (BARI [123], ERACI-II[124,125] and Toulouse[126]) were not included in the study level meta-analyses as they did not meet the inclusion criteria for the minimum number of stable angina patients. The results of the IPD meta- analyses should be considered taking into account the inclusion of unstable angina population in the results.

The main outcomes analysed were:

- Death (all causes)
- Cardiac death
- Non fatal MI
- Stroke
- Repeat revascularisation (PCI and/or CABG)
- Free of angina

Outcomes were also analysed separately for the sub-groups: Diabetes (yes and no), and number of vessels.

The results of the review have been analysed based on the involvement of vessels (Multi vessel disease, single vessel disease, Left main coronary disease and Left main coronary artery or 3 vessel disease) and follow-up periods (Immediate follow-up (in-hospital), short term-follow-up (1 yr), medium term follow-up (2-4 yrs) and long term follow-up (>5 yrs).

In this guideline, the classification 'Multi-vessel disease' includes studies with patients having:

- Multi-vessel disease only (2 vessel disease, 3 vessel disease)
- Multi-vessel disease along with single vessel disease

This was because most of the studies on revascularisation for stable angina did nod not report data separately for multi vessel disease and single vessel disease separately. Sub group analysis was conducted separately for 2 vessel and 3 vessel diseases if the results were reported separately in the studies.

The main results of the review are presented as follows:

A. Multi-vessel disease

- Multi-vessel disease - Immediate follow-up for Stable angina
- Multi -vessel disease - short term follow-up (1 year) for Stable angina
- Multi-vessel disease - medium term follow-up (2 to 4 years) for Stable angina
- Multi-vessel disease - Long term follow-up (> 5 years) for Stable angina

B. Single vessel disease

- Single vessel disease - short term follow-up (1 year) for Stable angina
- Single vessel disease - medium term follow-up (2 to 4 years) for Stable angina
- Single vessel disease - Long term follow-up (>5 years) for Stable angina

C. Left main coronary disease

- Left main coronary disease - short term follow-up (1 year) for Stable angina

D. Left main coronary artery or 3 vessel disease

- Left main coronary artery or 3 vessel disease - short term follow-up (1year) for Stable angina

E. IPD meta-analyses (Multi-vessel disease- Immediate, short and Long term follow-up)

12.2 Multi-vessel disease

12.2.1 Clinical evidence

The “Review Protocol” for this topic can be found in Appendix C, the “Search Strategies” in Appendix D, the “List of Included and Excluded Studies” in Appendix E1, the “Clinical Evidence Tables” in Appendix E2, and the “Forest Plots” in Appendix F.

Table 12.1: PCI vs. CABG – Multi-vessel disease – Immediate follow-up for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	PCI	CABG	Relative (95% CI)	Absolute	
Stroke											
Eefting 2003[127] Hamm 1994[128] (GABI) Hampton 1993[129] (RITA) King 1994[130] (EAST) Zhang 2006[131] (SOS)	randomised trial	serious (a)	no serious inconsistency (b)	no serious indirectness	serious (c)	none	5/1509 (0.3%)	15/1495 (1%)	RR 0.35 (0.13 to 0.92)	6 fewer per 1000 (from 1 fewer to 9 fewer)	⊕⊕OO LOW

(a) *Eefting 2003[119]; Hamm 1994[120] (GABI); Hampton 1993[121] (RITA); King 1994[122] (EAST); Zhang 2006[123] (SOS): All studies randomised, 3 out of 5 studies reported allocation concealment, 4 out of studies blind outcome assessment, ITT reported in all studies.*

(b) *No heterogeneity.*

(c) 95% CI around the pooled estimate of effect includes appreciable benefit or appreciable harm.

Table 12.2: PCI vs. CABG – Multi-vessel disease – short term follow-up (1 year) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	PCI	CABG	Relative (95% CI)	Absolute	
Death (all causes) (follow-up 1 years)											
Eefting 2003[127]; Hamm 1994[128] (GABI);Rickards 1995 (CABRI); Serruys 2001[132] (ARTS); Sigwart 2002[133] (SoS); Hueb 2004[68] (MASS-II)	randomised trials	serious (a)	serious (b)	no serious indirectness	serious (c)	none	61/2127 (2.9%)	56/2102 (2.7%)	RR 1.06 (0.75 to 1.52)	2 more per 1000 (from 7 fewer to 14 more)	⊕OOO VERY LOW
Cardiac mortality (follow-up 1 years)											
Eefting 2003[127]	randomised trials	no serious limitations (d)	no serious inconsistency	no serious indirectness	serious (c)	none	0/138 (0%)	2/142 (1.4%)	RR 0.21 (0.01 to 4.25)	11 fewer per 1000 (from 14 fewer to 46 more)	⊕⊕⊕O MODERATE
Non fatal MI (follow-up 1 years)											
Eefting 2003[127];Hamm 1994[128] (GABI); Rickards 1995[134] (CABRI); Serruys 2001[132] (ARTS); Sigwart 2002[133] (SoS); Hueb 2004[68] (MASS-II)	randomised trials	serious (a)	serious (e)	no serious indirectness	serious (c)	None	114/2127 (5.4%)	105/2102 (5%)	RR 1.07 (0.83 to 1.39)	3 more per 1000 (from 8 fewer to 19 more)	⊕OOO VERY LOW
Repeat revascularisation (follow-up 1 years)											
Eefting 2003[127];Hamm 1994[128] (GABI);Rickards 1995[134] (CABRI); Serruys 2001[132] (ARTS);Sigwart 2002[133] (SoS); Hueb 2004[68] (MASS-II)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	538/2127 (25.3%)	93/2102 (4.4%)	RR 5.64 (4.57 to 6.97)	205 more per 1000 (from 158 more to 264 more)	⊕⊕⊕O MODERATE
Free of angina (follow-up 1 years)											
Eefting 2003[127]; Hamm 1994[128] (GABI); Rickards 1995[134] (CABRI); Serruys	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	1435/2110 (68%)	1620/2095 (77.3%)	RR 0.88 (0.85 to 0.91)	93 fewer per 1000 (from 70 fewer to 116	⊕⊕⊕O MODERATE

2001[132] (ARTS); Sigwart 2002[133] (SoS); Hueb 2004[68] (MASS-II)										fewer)	
Stroke (follow-up 1 years)											
Eefting 2003[127]; Serruys 2001[132] (ARTS); Sigwart 2002[133] (SoS); Hueb 2004[68] (MASS-II)	randomised trials	no serious limitations (f)	no serious inconsistency	no serious indirectness	serious (c)	None	19/1431 (1.3%)	24/1450 (1.7%)	RR 0.80 (0.44 to 1.45)	3 fewer per 1000 (from 9 fewer to 7 more)	⊕⊕⊕O MODERATE
Subgroup-diabetes- Death (all causes) (follow-up 1 years)											
Abizaid 2001[135] (ARTS); Kapur 2010[136] (CARDia trial); Hueb 2004[68] (MASS-II)	randomised trials	no serious limitations (g)	no serious inconsistency	no serious indirectness	serious (c)	None	18/422 (4.3%)	15/403 (3.7%)	RR 1.15 (0.58 to 2.25)	6 more per 1000 (from 16fewer to 47 more)	⊕⊕⊕O MODERATE
Subgroup diabetes-MI (follow-up 1 years)											
Abizaid 2001[135] (ARTS); Kapur 2010[136] (CARDia trial)	randomised trials	no serious limitations (g)	no serious inconsistency	no serious indirectness	serious (h)	none	32/366 (8.7%)	17/344 (4.9%)	RR 1.79 (1.01 to 3.17)	39 more per 1000 (from 0 more to 107 more)	⊕⊕⊕O MODERATE
Subgroup diabetes- Repeat revascularisation (follow-up 1 years)											
Abizaid 2001[135] (ARTS); Kapur 2010[136] (CARDia trial)	randomised trials	no serious limitations (g)	no serious inconsistency	no serious indirectness	no serious imprecision	None	55/366 (15%)	8/344 (2.3%)	RR 6.36 (3.07 to 13.16)	125 more per 1000 (from 48 more to 283 more)	⊕⊕⊕⊕ HIGH
Sub group diabetes- Non fatal stroke (follow-up 1 years)											
Kapur 2010[136] (CARDia trial)	randomised trials	no serious limitations (i)	no serious inconsistency	no serious indirectness	serious (c)	None	1/254 (0.4%)	7/248 (2.8%)	RR 0.14 (0.02 to 1.13)	24 fewer per 1000 (from 28 fewer to 4 more)	⊕⊕⊕O MODERATE
Subgroup age>65 yrs- Death (all causes) (follow-up 1 years)											
Zhang 2006[131] (SOS)	randomised trials	no serious limitations (j)	no serious inconsistency	no serious indirectness	serious (c)	None	4/190 (2.1%)	1/205 (0.5%)	RR 4.32 (0.49 to 38.27)	16 more per 1000 (from 2 fewer to 182 more)	⊕⊕⊕O MODERATE
Subgroup age>65 yrs-MI (follow-up 1 years)											
Zhang 2006[131] (SOS)	randomised	no serious	no serious	no serious	serious (c)	None	13/190	17/205	RR 0.83	14 fewer per	⊕⊕⊕O

	trials	limitations (j)	inconsistency	indirectness			(6.8%)	(8.3%)	(0.41 to 1.65)	1000 (from 49 fewer to 54 more)	MODERATE
Subgroup age>65 yrs- stroke (follow-up 1 years)											
Zhang 2006[131] (SOS)	randomised trials	no serious limitations (j)	no serious inconsistency	no serious indirectness	serious (c)	None	5/190 (2.6%)	5/205 (2.4%)	RR 1.08 (0.32 to 3.67)	2 more per 1000 (from 17 fewer to 65 more)	⊕⊕⊕O MODERATE
Subgroup age>65 yrs- repeat revascularisation (follow-up 1 years)											
Zhang 2006[131] (SOS)	randomised trials	no serious limitations (j)	no serious inconsistency	no serious indirectness	no serious imprecision	None	37/190 (19.5%)	7/205 (3.4%)	RR 5.7 (2.61 to 12.48)	160 more per 1000 (from 55 more to 392 more)	⊕⊕⊕⊕ HIGH
Sub group age <65 yrs- Death (follow-up 1 years)											
Zhang 2006[131] (SOS)	randomised trials	no serious limitations (j)	no serious inconsistency	no serious indirectness	serious (c)	None	8/298 (2.7%)	3/295 (1%)	RR 2.64 (0.71 to 9.85)	17 more per 1000 (from 3 fewer to 90 more)	⊕⊕⊕O MODERATE
Sub group age <65 yrs-MI (follow-up 1 years)											
Zhang 2006[131] (SOS)	randomised trials	no serious limitations (j)	no serious inconsistency	no serious indirectness	serious (c)	None	8/298 (2.7%)	17/295 (5.8%)	RR 0.47 (0.2 to 1.06)	31 fewer per 1000 (from 46 fewer to 3 more)	⊕⊕⊕O MODERATE
Sub group age<65 yrs- Stroke (follow-up 1 years)											
Zhang 2006[131] (SOS)	randomised trials	no serious limitations (j)	no serious inconsistency	no serious indirectness	serious (c)	None	2/298 (0.7%)	3/295 (1%)	RR 0.66 (0.11 to 3.92)	3 fewer per 1000 (from 9 fewer to 30 more)	⊕⊕⊕O MODERATE
Sub group age<65 yrs- Repeat revascularisation (follow-up 1 years)											
Zhang 2006[131] (SOS)	randomised trials	no serious limitations (j)	no serious inconsistency	no serious indirectness	no serious imprecision	None	48/298 (16.1%)	14/295 (4.7%)	RR 3.39 (1.91 to 6.02)	113 more per 1000 (from 43 more to 238 more)	⊕⊕⊕⊕ HIGH

(a) *Eefting 2003[119]; Hamm 1994[120] (GABI);Rickards 1995 (CABRI); Serruys 2001[124] (ARTS); Sigwart 2002[125] (SoS); Hueb 2004[66] (MASS-II): All studies randomised, ITT reported in all studies, 4 out of 6 studies reported allocation concealment, all studies reported of blind outcome assessment.*
(b) $I^2=47\%$.
(c) *95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.*
(d) *Eefting 2003[119]: Method of Randomisation and allocation concealment reported. No loss to follow up. Analysis was conducted on an intent-to-treat basis. An independent committee blinded to the treatment allocation evaluated all events. Risk of bias was low*
(e) $I^2=65\%$. *Considerable heterogeneity*
(f) *Eefting 2003[119]; Serruys 2001[124] (ARTS); Sigwart 2002[125] (SoS); Hueb 2004[66] (MASS-II): Randomised, allocation concealment, blind outcome assessment and ITT reported in all studies.*
(g) *Abizaid 2001[127] (ARTS); Kapur 2010[128] (CARDia trial): Randomisation and ITT reported in all studies. , allocation concealment, blind outcome assessment in 2 of 3 studies*
(h) *95% CI around the pooled estimate of effect includes appreciable benefit or appreciable harm.*
(i) *Kapur 2010[128] (CARDia trial): Randomisation undertaken either by a local secure computer-based system or telephone contact with the coordinating centre stratifying for urgency of intervention, sex, and number of diseased vessels. Allocation concealment reported. Sample size calculation reported. Blind outcome assessors. ITT used.*
(j) *Zhang 2006[123] (SOS): Multi centre, Randomisation method reported, allocation concealment reported, sample size calculation reported, baseline comparisons made, Numbers lost to follow reported (1 year- 8/488 (1.6%) in PCI and 13/500 (2.6%) in CABG) (not reported separately for >65 yrs of age), Intention to treat analysis reported. Blind outcome assessment (A clinical events committee, consisting of study interventionists and surgeons, adjudicated all outcome measures. The members of the clinical events committee did not adjudicate patients treated at their own centres and were blinded to the randomisation allocation and of the identities of patients and centres). Not reported if blind outcome assessment for quality of life. Patients aware of treatment allocation. * This study reports 1 year follow-up of the SOS trial reporting outcomes in the subgroup of people aged ≥ 65 years.*

Sub group interaction:

Age >65 yrs and Age <65 yrs: There was no significant difference between sub group of patients with age >65 yrs and age <65 yrs for death (p=0.70), MI (p=0.12), repeat revascularisation (p=0.29) at short term follow-up

Table 12.3: PCI vs. CABG – Multi-vessel disease – medium term follow-up (2 to 4 yrs) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PCI**	**CABG**	**Relative (95% CI)**	**Absolute**	
Death (all causes) (follow-up 2-4 years)											
Hampton 1993[129] (RITA); King 1994[130] (EAST); Legrand 2004[137] (ARTS); Martuscelli 2008[138] (CABRI); Sigwart 2002[133] (SOS)	randomised trials	no serious limitations (a)	serious (b)	no serious indirectness	serious (c)	none	89/1916 (4.6%)	71/1903 (3.7%)	RR 1.23 (0.91 to 1.67)	9 more per 1000 (from 3 fewer to 25 more)	⊕⊕OO LOW
Cardiac mortality (follow-up 2-4 years)											
Hampton 1993[129] (RITA); Sigwart 2002[133] (SoS)	randomised trials	no serious limitations (d)	no serious inconsistency	no serious indirectness	serious (c)	none	13/998 (1.3%)	8/1001 (0.8%)	RR 1.64 (0.68 to 3.92)	5 more per 1000 (from 3 fewer to 23 more)	⊕⊕⊕O MODERATE
Non fatal MI (follow-up 2-4 years)											
Hampton 1993[129] (RITA); King 1994[130] (EAST); Legrand 2004[137] (ARTS); Martuscelli 2008[138] (CABRI)	randomised trials	no serious limitations (e)	serious (f)	no serious indirectness	serious (c)	none	115/1428 (8.1%)	101/1403 (7.2%)	RR 1.12 (0.87 to 1.45)	9 more per 1000 (from 9 fewer to 32 more)	⊕⊕OO LOW
Repeat revascularisation (follow-up 2-4 years)											
Hampton 1993[129] (RITA); King 1994[130] (EAST); Legrand 2004[137] (ARTS); Sigwart 2002[133] (SoS)	randomised trials	no serious limitations (e)	serious (g)	no serious indirectness	no serious imprecision	none	590/1796 (32.9%)	121/1800 (6.7%)	RR 4.87 (4.06 to 5.85)	260 more per 1000 (from 206 more to 326 more)	⊕⊕⊕O MODERATE
Free of angina (follow-up 2-4 years)											
Unger 2003[139] (ARTS)	randomised trials	no serious limitations (h)	no serious inconsistency	no serious indirectness	no serious imprecision	none	478/600 (79.7%)	527/605 (87.1%)	RR 0.91 (0.87 to 0.96)	78 fewer per 1000 (from 35 fewer to 113 fewer)	⊕⊕⊕⊕ HIGH
Stroke (follow-up 2-4 years)											
Legrand 2004[137] (ARTS)	randomised trials	no serious limitations (h)	no serious inconsistency	no serious indirectness	serious (c)	none	20/600 (3.3%)	20/605 (3.3%)	RR 1.01 (0.55 to 1.85)	0 more per 1000 (from 15 fewer to 28 more)	⊕⊕⊕O MODERATE
Sub group diabetes- Mortality (follow-up 2-4 years)											
Booth 2008[140] (SoS); Kurbaan 2001[141] (CABRI); Legrand 2004[137] (ARTS)	randomised trials	no serious limitations (i)	no serious inconsistency	no serious indirectness	serious (c)	none	25/242 (10.3%)	13/233 (5.6%)	RR 1.87 (0.99 to 3.5)	49 more per 1000 (from 1 fewer to 139 more)	⊕⊕⊕O MODERATE
Sub group diabetes- MI (follow-up 3 years)											

Legrand 2004[137] (ARTS)	randomised trials	no serious limitations (j)	no serious inconsistency	no serious indirectness	serious (c)	none	11/112 (9.8%)	6/96 (6.3%)	RR 1.57 (0.6 to 4.09)	36 more per 1000 (from 25 fewer to 193 more)	⊕⊕⊕O MODERATE
Sub group diabetes- Repeat revascularisation (follow-up 2-4 years)											
Booth 2008[140] (SoS) Legrand 2004[137] (ARTS)	randomised trials	no serious limitations (k)	no serious inconsistency	no serious indirectness	no serious imprecision	none	63/180 (35%)	12/170 (7.1%)	RR 4.84 (2.71 to 8.64)	271 more per 1000 (from 121 more to 539 more)	⊕⊕⊕⊕ HIGH
Sub group- Left Anterior descending coronary artery proximally- Death (follow-up 3 years)											
Aoki 2004[142] (ARTS)	randomised trials	no serious limitations (l)	no serious inconsistency	no serious indirectness	serious (c)	none	11/246 (4.5%)	11/253 (4.3%)	RR 1.03 (0.45 to 2.33)	1 more per 1000 (from 24 fewer to 58 more)	⊕⊕⊕O MODERATE
Sub group LAD artery- Stroke (follow-up 3 years)											
Aoki 2004[142] (ARTS)	randomised trials	no serious limitations (l)	no serious inconsistency	no serious indirectness	serious (c)	none	5/246 (2%)	7/253 (2.8%)	RR 0.73 (0.24 to 2.28)	7 fewer per 1000 (from 21 fewer to 35 more)	⊕⊕⊕O MODERATE
Sub group LAD artery- MI (follow-up 3 years)											
Aoki 2004[142] (ARTS)	randomised trials	no serious limitations (l)	no serious inconsistency	no serious indirectness	serious (c)	none	17/246 (6.9%)	16/253 (6.3%)	RR 1.09 (0.56 to 2.11)	6 more per 1000 (from 28 fewer to 70 more)	⊕⊕⊕O MODERATE
Sub group LAD artery- Repeat revascularisation (follow-up 3 years)											
Aoki 2004[142] (ARTS)	randomised trials	no serious limitations (l)	no serious inconsistency	no serious indirectness	no serious imprecision	none	54/246 (22%)	12/253 (4.7%)	RR 4.63 (2.54 to 8.44)	172 more per 1000 (from 73 more to 353 more)	⊕⊕⊕⊕ HIGH

(a) *Hampton 1993[121] (RITA); King 1994[122] (EAST); Legrand 2004[129] (ARTS); Martuscelli 2008[130] (CABRI); Sigwart 2002[125] (SOS): Randomisation, allocation concealment, and ITT reported in all studies. Blind outcome assessment in 4 out of 5 studies*

(b) *I^2=60%. Substantial heterogeneity*

(c) *95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.*

(d) *Hampton 1993[121] (RITA); Sigwart 2002[125] (SoS): Randomisation, allocation concealment, blind outcome assessment and ITT reported in both studies.*

(e) *Hampton 1993[121] (RITA); King 1994[122] (EAST); Legrand 2004[129] (ARTS); Sigwart 2002[125] (SoS): Randomisation, allocation concealment, and ITT reported in all studies.*

(f) *I^2=42%. Moderate heterogeneity*

(g) *I^2=77%. High heterogeneity*

(h) *Unger 2003[131] (ARTS): Multi centre, randomised, allocation concealment reported, sample size calculation reported, baseline comparisons made. Nos. lost to follow-up reported). Intention to treat analysis reported. Clinical events adjudicated by an independent committee. No risk of bias.*

(i) *Booth 2008[132] (SoS); Kurbaan 2001[133] (CABRI); Legrand 2004[129] (ARTS): Randomisation, allocation concealment, ITT and blind outcome assessment reported in all studies.*

*(j) Legrand 2004[129] (ARTS): Multi centre, randomised, allocation concealment reported, sample size calculation reported, baseline comparisons made. Nos. lost to follow-up reported (0.4%; 6/1205**). Intention to treat analysis reported. Clinical events adjudicated by an independent committee. No risk of bias. * This study is a 3 year follow-up of the ARTS trial. ** 1 patient was lost to follow-up, 3 were alive but withdrew their consent from further participation in the trial, and 2 patients were never treated by either modality.*

(k) Booth 2008[132] (SoS); Legrand 2004[129] (ARTS): Randomisation, allocation concealment, ITT and blind outcome assessment reported in both studies.

*(l) Aoki 2004[134] (ARTS): Multi centre, randomised, allocation concealment reported, sample size calculation reported, baseline comparisons made. Nos. lost to follow-up reported (1.2%; 3/243 in stenting and 3.1%; 8/253 in CABG). Intention to treat analysis reported. Clinical events adjudicated by an independent committee. No risk of bias. * This study is a sub-analysis of the ARTS trial comparing 3 year outcomes after stenting vs. CABG in patients with multi vessel disease involving the proximal left anterior descending artery.*

Additional data for PCI vs. CABG – Multi-vessel disease – medium term follow-up (2 to 4 yrs)

Martuscelli 2008[138] (CABRI) (Follow-up 30 months)

No. of participants: n= 223 (CABG (n=103); PTCA (n=120))

At 30 months, of the patients initially randomised to PTCA, required a significantly higher second revascularisation (46.7% (n=56) vs. 5.8% (n=6); p<0.01) and a third revascularisation (10% (n=12) vs. 1 (1%); p<0.05).

Hampton 1993[129] (RITA) (2.5 Years)

No. of participants: n=1011 (n=501 in the CABG and n=510 in the PTCA)

There was striking improvement in reported angina in both the treatment groups at all follow-ups (1 month, 6 months, 1 and 2 years). However, at every point there was a significant excess of patients with angina in the PTCA group. At 6 months 11% of CABG patients had anginal symptoms compared with 31.6% of PTCA patients (RR=0.35, 95% CI 0.26-0.47; p<0.001). Two years after randomisation the prevalence of angina in the CABG group had increased to 21.5% but this was still significantly less than the 31.3% for PTCA patients (p=0.007).

Legrand 2004[137] (ARTS) (3 YEARS)

No. of participants: n=1205 (n=600 in stent and n=605 in CABG)

After 3 years patients in the surgery group had significantly less angina (12.8% in surgery vs. 18.4% in the stenting group, p=0.011)

King 1994[130] (EAST) (3 years)

No. of participants: n=392 (n=194 in the CABG group and n=198 in the PTCA group)

Angina was more prevalent in the PTCA group at 3 years, with 20% of the patients having CCS class II, III, or IV angina, as compared with 12% of patients in the CABG group (p=0.039).

Table 12.4: PCI vs. CABG – Multi-vessel disease – Long term follow-up (> 5 years) for Stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	PCI	CABG	Relative (95% CI)	Absolute	
Death (all causes) (follow-up 5-13 years)											
Buszman 2009[143] (SoS); Henderson 1998[144] (RITA); Kaehler[145] (GABI 2005); Serruys 2005[146] (ARTS); Hueb 2010[79] (MASS-11)	randomised trials	serious limitations (a)	no serious inconsistency	no serious indirectness	No serious imprecision	none	169/1296 (13%)	166/1297 (12.8%)	RR 1.01 (0.83 to 1.23)	5 more per 1000 (from 22 fewer to 29 more)	⊕⊕⊕O MODERATE
Cardiac mortality (follow-up 5-13 years)											
Booth 2008[140] (SoS); Henderson 1998[144] (RITA); Kaehler 2005[145] (GABI)	randomised trials	no serious limitations (c)	no serious inconsistency	no serious indirectness	serious (b)	none	47/929 (5.1%)	38/939 (4%)	RR 1.24 (0.82 to 1.87)	10 more per 1000 (from 7 fewer to 35 more)	⊕⊕⊕O MODERATE
Non fatal MI (follow-up 5-10 years)											
Henderson 1998[144] (RITA); Serruys 2005[146] (ARTS); Hueb 2010[79] (MASS-11)	randomised trials	serious limitations (d)	no serious inconsistency	no serious indirectness	serious (b)	none	102/1082 (9.4%)	80/1087 (7.4%)	RR 1.28 (0.97 to 1.69)	21 more per 1000 (from 2 fewer to 51 more)	⊕⊕⊕O LOW
Repeat revascularisation (follow-up 5-13 years)											
Buszman 2009[143] (SoS); Henderson 1998[144] (RITA); Kaehler 2005[145] (GABI); King 2000[147] (EAST); Serruys 2005[146] (ARTS); Hueb 2010[79] (MASS-11)	randomised trials	no serious limitations (e)	serious (f)	no serious indirectness	no serious imprecision	none	671/1494 (44.9%)	251/1491 (16.8%)	RR 2.65 (2.35 to 2.98)	278 more per 1000 (from 227 more to 333 more)	⊕⊕⊕O MODERATE
Stroke (follow-up 5-10 years)											
Serruys 2005[146] (ARTS); Hueb 2010 (MASS-11)	randomised trials	no serious limitations (g)	no serious inconsistency	no serious indirectness	serious (b)	none	34/805 (4.2%)	38/808 (4.7%)	RR 0.90 (0.57 to 1.41)	5 fewer per 1000 (from 20 fewer to 19 more)	⊕⊕⊕O MODERATE
Sub group diabetes - Death (all causes) (follow-up 05-10 years)											
Booth 2008[140] (SoS); Henderson 1998[144] (RITA); Serruys 2005[146] (ARTS)	randomised trials	no serious limitations (h)	serious (i)	no serious indirectness	serious (b)	none	29/209 (13.9%)	20/203 (9.9%)	RR 1.43 (0.83 to 2.47)	42 more per 1000 (from 17 fewer to 145 more)	⊕⊕OO LOW
Sub group diabetes- Repeat revascularisation (follow-up 5 years)											
Serruys 2005[146] (ARTS)	randomised	no serious	no serious	no serious	no serious	none	48/112	10/96	RR 4.11	324 more per	⊕⊕⊕⊕

	trials	limitations (g)	inconsistency	indirectness	imprecision		(42.9%)	(10.4%)	(2.2 to 7.68)	1000 (from 125 more to 696 more)	HIGH
Sub group diabetes- stroke (follow-up 5 years)											
Serruys 2005[146] (ARTS)	randomised trials	no serious limitations (g)	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/112 (6.3%)	7/96 (7.3%)	RR 0.86 (0.31 to 2.36)	10 fewer per 1000 (from 50 fewer to 99 more)	⊕⊕⊕⊕ HIGH
Sub group diabetes- MI (follow-up 5 years)											
Serruys 2005[146] (ARTS)	randomised trials	no serious limitations (g)	no serious inconsistency	no serious indirectness	serious (b)	none	12/112 (10.7%)	7/96 (7.3%)	RR 1.47 (0.6 to 3.58)	34 more per 1000 (from 29 fewer to 188 more)	⊕⊕⊕O MODERATE
Free of angina (follow-up 5-10 years)											
Serruys 2005[146] (ARTS); Hueb 2010 (MASS-II)	randomised trials	no serious limitations (g)	no serious inconsistency	no serious indirectness	no serious imprecision	none	587/805 (72.9%)	641/808 (79.3%)	RR 0.92 (0.87 to 0.97)	68 fewer per 1000 (from 25 fewer to 110 fewer)	⊕⊕⊕⊕ MODERATE
Sub group-no diabetes -Death (all causes) (follow-up 5-10 years)											
Booth 2008[140] (SoS); Serruys 2005[146] (ARTS)	randomised trials	no serious limitations (j)	serious (k)	no serious indirectness	serious (b)	none	74/908 (8.1%)	68/935 (7.3%)	RR 1.12 (0.82 to 1.54)	9 more per 1000 (from 13 fewer to 39 more)	⊕⊕OO LOW
Sub group 2 vessel- Death (follow-up 10 years)											
Booth 2008[140] (SoS)	randomised trials	no serious limitations (l)	no serious inconsistency	no serious indirectness	serious (b)	none	31/305 (10.2%)	16/264 (6.1%)	RR 1.68 (0.94 to 3)	41 more per 1000 (from 4 fewer to 121 more)	⊕⊕⊕O MODERATE
Sub group 3 vessel- Death (follow-up 10 years)											
Booth 2008[140] (SoS)	randomised trials	no serious limitations (l)	no serious inconsistency	no serious indirectness	serious (b)	none	22/183 (12%)	18/236 (7.6%)	RR 1.58 (0.87 to 2.85)	44 more per 1000 (from 10 fewer to 141 more)	⊕⊕⊕O MODERATE
Sub group no diabetes- stroke (follow-up 5 years)											
Serruys 2005[146] (ARTS)	randomised trials	no serious limitations (g)	no serious inconsistency	no serious indirectness	serious (b)	none	16/488 (3.3%)	14/509 (2.8%)	RR 1.19 (0.59 to 2.42)	5 more per 1000 (from 11 fewer to 39 more)	⊕⊕⊕O MODERATE
Sub group no diabetes- MI (follow-up 5 years)											
Serruys 2005[146] (ARTS)	randomised trials	no serious limitations (l)	no serious inconsistency	no serious indirectness	serious (b)	none	38/488 (7.8%)	31/509 (6.1%)	RR 1.28 (0.81 to 2.02)	17 more per 1000 (from 12 fewer to 62	⊕⊕⊕O MODERATE

										more)	
Sub group no diabetes- Repeat revascularisation (follow-up 5 years)											
Serruys 2005[146] (ARTS)	randomised trials	no serious limitations (l)	no serious inconsistency	no serious indirectness	no serious imprecision	none	134/488 (27.5%)	43/509 (8.4%)	RR 3.25 (2.36 to 4.48)	190 more per 1000 (from 115 more to 294 more)	⊕⊕⊕⊕ HIGH

(a) *Buszman 2009[135] (SoS); Henderson 1998[136] (RITA); Kaehler[137] (GABI 2005); Serruys 2005[138] (ARTS); Hueb 2010[77] (MASS-11): Randomisation reported in all studies. Allocation concealment, ITT reported in 4/5 studies. Blind outcome assessment reported in 3 out of 5 studies.*

(b) *95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.*

(c) *Booth 2008[132] (SoS); Henderson 1998[136] (RITA); Kaehler 2005[137] (GABI): Randomisation, allocation concealment, ITT and blind outcome assessment reported in 2 out of 3 studies.*

(d) *Henderson 1998[136] (RITA); Serruys 2005[138] (ARTS); Hueb 2010[77] (MASS-11): Randomisation, ITT and reported in all 3 studies. Allocation concealment and blind outcome assessment reported in 2 out of 3 studies.*

(e) *Buszman 2009[135] (SoS); Henderson 1998[136] (RITA); Kaehler 2005[137] (GABI); King 2000[139] (EAST); Serruys 2005[138] (ARTS); Hueb 2010[77] (MASS-11): Randomisation, allocation concealment, ITT and blind outcome assessment reported in 4 out of 5 studies.*

(f) *I^2=95%. High heterogeneity*

(g) *Serruys 2005[138] (ARTS); Hueb 2010 (MASS-II): Both randomised, allocation concealment reported in 1 out of 2 studies*

(h) *Booth 2008[132] (SoS); Henderson 1998[136] (RITA); Serruys 2005[138] (ARTS): Randomisation, allocation concealment, ITT and blind outcome assessment reported in 2 out of 3 studies.*

(i) *I^2=71%. High heterogeneity*

(j) *Booth 2008[132] (SoS); Serruys 2005[138] (ARTS): Randomisation, allocation concealment, ITT and blind outcome assessment reported in both studies.*

(k) *I^2=42 %. Moderate heterogeneity*

(l) *Booth 2008[132] (SoS): Multi centre, randomisation method reported, allocation concealment reported, sample size calculation reported, baseline comparisons made, Numbers lost to follow reported (5 years- (1.8%) 9/479 in PCI and (3%)15/500 in CABG), Intention to treat analysis reported. Blind outcome assessment (A clinical events committee, consisting of study interventionists and surgeons, adjudicated all outcome measures. The members of the clinical events committee did not adjudicate patients treated at their own centres and were blinded to the randomisation allocation and of the identities of patients and centres). Patients aware of treatment allocation.*

Sub group interaction:

Diabetes and no diabetes: There was no significant difference between diabetes and no diabetes sub group of patients for death (p=0.45), MI (p=0.79) and repeat revascularisation (p=0.51) at long term follow-up.

Single, vessel, 2 vessel and 3 vessel disease: There was no significant difference between single, 2 vessel and 3 vessel disease for death all causes (p=0.17) at long term follow-up.

Additional data for PCI vs. CABG – Multi-vessel disease – Long term follow-up > 5 years)

Buszman 2009[143] (SoS) (10 years)

No. of participants: N=100 (PCI (n=50); CABG (n=50)

At 10 years, there was significant improvement of anginal symptoms in both groups. Improvement in anginal symptoms was reported in 88.9% PCI patients and 84.38% CABG patients; p=ns.

Quality Of Life data for PCI vs. CABG – Multi-vessel disease:

Pocock1996[3]

One RCT[3] assessed quality of life by a Self reported health status (Nottingham Health Profile (NHP) which consisted of 2 parts. Part 1 included 38 statements describing levels of physical, social or emotional distress which are grouped in to 6 dimensions: energy (3 statements), pain (8), emotional reactions (9), sleep (5), social isolation (5), and physical mobility (8). Scores were calculated for each of the 6 dimensions by summing the number of positive (yes) responses: the higher the score, the greater the impairment of health. Part 2 of the NHP assessed whether an individual's health is causing problems with seven aspects of daily life: work, tasks around the home, social life, home relationships, sex life hobbies and interests and holidays. For both parts 1 and 2, NHP weighted mean scores were compared with population norms of the same age and sex derived from a general community survey.

Results: n=1011 (n=501 in the CABG and n=510 in the PCI). For both PCI and CABG groups there were marked improvements from baseline in all domains: energy, pain, emotional reactions, sleep, social isolation and physical mobility. There was no significant difference between the groups for individual domains. When all items were combined, the treatment difference at 2 years was 0.79 item (p=0.10) in favour of the CABG group.

Eefting 2003[127]

In one RCT[127] quality-of-life was assessed by the Short Form-36 generic instrument: scores ranged from 0 (worst) to 100 (best imaginable health status). The following domains were assessed: Physical functioning, role physical, role emotional, pain, vitality, general health perception, general mental health.

Results: n=280 (n=138 PCI and n=142 CABG). At 12 months there was no significant difference between PCI and CABG groups for any of the domains except for General Health Perception which was significantly higher in the CABG group (61.6 vs. 66.9; p=0.03).

Zhang 2003[148] (SOS)

In one RCT[148] cardiac related health status was assessed with the Seattle Angina Questionnaire (SAQ), a 19 item self-administered questionnaire that measures 5 domains of CAD related health status: physical limitation, angina stability, angina frequency, treatment satisfaction, and disease perception/quality of life. Scores range from 0 to 100 for each domain, with higher scores indicating better functioning. Each domain measures a unique dimension of CAD, and no summary score is available.

Results: At 1 year physical limitation, angina frequency, and quality of life improved from baseline within each treatment group. However, the greatest overall changes from baseline, as well as the greatest influence of CABG vs. PCI were seen for the angina frequency domain (PCI (n=476) vs. CABG (n=496) Physical limitation: 75.2±21.3 vs. 76.6±20.7, p=0.36; Angina frequency: 86.9±19.8 vs. 89.6±18.2, p=0.03; Treatment satisfaction: 91.2±13.1 vs. 90.0±16.0, p=0.73; Quality of life: 69.8±23.0 vs. 71.5±21.4, p=0.41).

Legrand 2004[137] (ARTS)

One RCT[137] assessed quality of life by EQ-5D questionnaire.

Higher scores on the EQ-5D summary indicate a good quality of life; whereas low scores on the 5 items of EQ-5D domain reflect a favourable assessment of each component. The following domains were assessed: Mobility, Self-care, Usual activity, Pain or discomfort, Anxiety or depression

Results: n=1205 (n=600 PCI and n=605 in CABG). EQ-5D was assessed at 1 and 3 years. At one year there was significant difference in scores between PCI and CABG, with benefit observed after CABG in specific domains such as 'mobility' (1.4±2.8 vs. 1.1 ±2.8; p=0.05), 'usual activity' (1.0 ±1.9 vs. 0.8±1.8; p=0.01) and 'anxiety or depression' (2.5±4.5 vs. 2.0±4.1; p=0.04). At 3 years, there were no significant differences in quality of life between PCI and CABG (EQ-5D summary: PCI vs. CABG: 85±17 vs. 86±17, p=0.74; EQ-5D domain: Mobility: 1.7±3.0 vs. 1.5±2.9, p=0.46; Self-care: 0.6±2.5 vs. 0.5±2.3, p=0.87; Usual activity: 1.0±1.9 vs. 0.8±1.7, p=0.09; Pain or discomfort: 4.9±6.9 vs. 5.2±7.7, p=0.78; Anxiety or depression: 2.4±4.8 vs. 2.2±4.4, p=0.77). More specifically the benefits from CABG seen at one year had disappeared by 3 years

12.2.2 Economic evidence

Eleven studies [90,127,131,135,137,144,149-153] were found that included the relevant comparison. These are summarised in the Economics Evidence Tables in Appendix G. However, none of the studies fully met our quality and applicability criteria. It was thus decided to build an original economic model to compare PCI and CABG, which is reported in the economic profile tables below. The model was based on the outcomes included in our clinical review (death, MI, repeat revascularisation, angina symptoms) at different time points up to 10 years from the initial procedure. Costs considered were the initial costs associated with the procedure (PCI or CABG, including the cost of four stents in the PCI strategy), the cost of further revascularisations and further investigations, anti-anginal medications, and the cost of treating myocardial infarctions. Please see cost-effectiveness analysis in Appendix H for further details.

Table 8.5: CABG vs. PCI – Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
NCGC model (Appendix H)	Minor limitations (a)	Direct applicability	Based on the systematic review (see Appendix K) including only studies where PCI was with stents. Patients had multi vessel disease and were suitable for both PCI and CABG.

(a) *Based on clinical data up to 10 years (limited time horizon).*

Table 8.6: CABG vs. PCI – Economic summary of findings

Study	*Incremental cost per patient over ten years (£)*	*Incremental effectiveness (QALYs)*	*ICER (£/QALY)*	*Uncertainty*
NCGC model (Appendix H)	2,427 (a, b, c)	0.0694 (b, c)	34,971 (c)	95% CI: CABG dominant – PCI dominant. At a willingness to pay of £20,000/QALY, PCI has 63% of probability of being cost-effective, while CABG has 37% of probability. If more than 85% of the repeat procedures are CABG, PCI is no longer cost-effective.

(a) *Cost of initial procedures, further revascularisations, further investigations, medications, treatment of myocardial infarctions.*
(b) *Discounted by 3.5%.*
(c) *Results of probabilistic analysis.*

Patients in the model had multi-vessel disease; in single vessel disease the repeat revascularisation rate is generally lower compared to multi-vessel disease and PCI is likely to be an even more cost-effective option for this group of patients.

The other studies considered for inclusion[90,127,131,135,137,144,149-153] (see economic evidence tables in Appendix G) consistently reported higher cost of CABG compared to PCI. The difference in costs tends to decrease when a longer follow-up time was considered (e.g. in the ARTS study [137], RITA trial [144]). Of the other three cost-utility analyses[90,127,153], two[127,153] showed that CABG was not cost-effective but their analysis was limited to a one-year time horizon. The other analysis[90] concluded that CABG was cost-effective in patients suitable for both procedures; however this study was based on non-randomised data and probably most of the PCI procedures were without stents.

12.2.3 Evidence statements

Clinical

PCI vs. CABG – Multi-vessel disease (Immediate follow-up)

Eefting 2003[127]; Hamm 1994[128] (GABI); Hampton 1993[129] (RITA); King 1994[130] (EAST); Zhang 2006[131] (SoS): Evidence from 5 RCTs shows that there was significantly higher stroke in CABG patients compared to PCI [RR 0.35 (0.13 to 0.92)] at immediate follow-up (in-hospital event) [Immediate follow-up].

PCI vs. CABG – Multi-vessel disease (Short term follow-up – 1 year)

Eefting 2003[127]; Hamm 1994[128] (GABI); Rickards 1995[134] (CABRI); Serruys 2001[132] (ARTS); Sigwart 2002[133] (SoS); Hueb 2004[68] (MASS-II): Evidence from 6 RCTs shows that there were significantly higher repeat revascularisations in the PCI group compared to CABG [RR 5.64 (4.57 to 6.97)] . There were significantly more patients in CABG were free of angina compared to PCI [RR 0.88 (0.85 to 0.91)]. There was no significant difference between PCI and CABG for death (all causes) [RR 1.06 (0.75 to 1.52) and non fatal MI [RR 1.07 (0.83 to 1.39)] [1 year follow-up].

Eefting 2003[127]: Evidence from one RCT shows that there was no significant difference between PCI and CABG for cardiac mortality [RR 0.21 (0.01 to 4.25)] [1 year follow-up].

Eefting 2003[127]; Serruys 2001[132] (ARTS); Sigwart 2002[133] (SoS); Hueb 2004[68] (MASS-II): Evidence from 4 RCTs shows that there was no significant difference between PCI and CABG for stroke. [RR 0.80 (0.44 to 1.45)] [1 year follow-up].

Abizaid 2001[135] (ARTS); Kapur 2010[136] (CARDia): Evidence from 2 RCT shows that there was significantly higher repeat revascularisation [RR 6.36 (3.07 to 13.16)] and there was no significant difference between PCI and CABG for MI [RR 1.79 (1.01 to 3.17)] in a sub group of people with diabetes [1 year follow-up].

Abizaid 2001 (ARTS); Kapur 2009[136] (CARDia); Hueb 2004[68] (MASS-II): Evidence from 3RCT shows that there was no significant difference between PCI and CABG for death [RR 1.15 (0.58 to 2.25)] in a sub group of people with diabetes [1 year follow-up].

Kapur 2010[136] (CARDia): Evidence from one RCT shows that there was no significant difference between PCI and CABG for stroke [RR 0.14 (0.02 to 1.13)] in a sub group of patients with diabetes [1 year follow-up]

Zhang 2006[131] (SoS): Evidence from one RCT shows that there was significantly higher repeat revascularisation [RR 5.7 (2.61 to 12.48)] in the PCI compared to CABG and there was no significant difference between PCI and CABG for death all causes [RR 4.32 (0.49 to 38.27)], MI [RR 0.83 (0.41 to 1.65)], stroke [RR 1.08 (0.32 to 3.67)], in a sub group of people aged > 65 years [1 year follow-up].

Zhang 2006[131] (SoS): Evidence from one RCT shows that there was significantly higher repeat revascularisation [RR 3.39 (1.91 to 6.02)] in the PCI compared to CABG and there was no significant difference between PCI and CABG for death all causes [RR 2.64 (0.71 to 9.85)], MI [RR 0.47 (0.20 to 1.06)], stroke [RR 0.66 (0.11 to 3.92)], in a sub group of people aged < 65 years [1 year follow-up].

Sub group interaction: There was no significant difference between sub group of patients with age >65 yrs and age <65 yrs for death (p=0.70), MI (p=0.12), repeat revascularisation (p=0.29) at short term follow-up

PCI vs. CABG – Multi-vessel disease (Medium term follow-up – >1 to 4 years)

Hampton 1993[129] (RITA); King 1994[130] (EAST); Legrand[137] 2004 (ARTS); Martuscelli 2008[138] (CABRI); Sigwart 2002[133] (SoS): Evidence from 5 RCTs shows that there was no significant difference between PCI and CABG for death (all causes) [RR 1.23 (0.91 to 1.67)] [2–4 years follow-up]

Hampton 1993[129] (RITA); Sigwart 2002[133] (SOS): Evidence from 2 RCTs shows that there was no significant difference between PCI and CABG for cardiac mortality [RR 1.64 (0.68 to 3.92)] [2–4 years follow-up].

Hampton 1993[129] (RITA); King 1994[130] (EAST); Legrand 2004 (ARTS); Sigwart 2002[133] (SOS): Evidence from 4 RCTs shows that there was no significant difference between PCI and CABG for non fatal MI [RR 1.12 (0.87 to 1.45)] [2–4 years follow-up].

Hampton 1993[129] (RITA); King 1994[130] (EAST); Legrand 2004 (ARTS); Sigwart 2002[133] (SOS): Evidence from 4 RCTs shows that there was significantly higher repeat revascularisation in the PCI group compared to CABG [RR 4.87 (4.06 to 5.85)] [2–4 years follow-up].

Unger 2003[139] (ARTS): Evidence from one RCTs shows that there was significantly higher patients free of angina in the CABG group compared to PCI [RR 0.91 (0.87 to 0.96)] [2 years follow-up].

Legrand 2004[137] (ARTS): Evidence from one RCT shows that there was no significant difference between PCI and CABG for stroke

[RR 1.01 (0.55 to 1.85)] for the entire group; and MI in a sub group of patients with diabetes [RR 1.57 (0.60 to 4.09)] [2–4 years follow-up].

Booth 2008[140] (SOS); Kurbaan 2001[141] (CABRI); Legrand 2004[137] (ARTS): Evidence from 3 RCTs shows that there was no significant difference in mortality [RR 1. 87 (0.99 to 3.50)] in the PCI group compared to CABG in a sub group of patients with diabetes [2–4 years follow-up].

Booth 2008[140] (SoS); Legrand 2004[137] (ARTS): Evidence from 2 RCTs shows that there was significantly higher repeat revascularisation in the PCI group compared to CABG [RR 4.84 (2.71 to 8.64)] in a sub group of patients with diabetes [2–4 years follow-up].

Aoki 2004[142] (ARTS): Evidence from one RCTs shows there was significantly higher repeat revascularisation in the PCI group compared to CABG [RR 4.63 (2.54 to 8.44)], there was no significant difference between PCI and CABG for death all causes [RR 1.03 (0.45 to 2.33)], stroke [RR 0.73 (0.24 to 2.28)], MI [RR 1.09 (0.56 to 2.11)], in a sub group of patients with involvement of the left Anterior descending coronary artery proximally [3 years follow-up].

PCI vs. CABG – Multi -vessel disease (Long term follow-up > 5 years)

Buszman 2009[143] (SOS); Henderson 1998[144] (RITA); Kaehler 2005[145] (GABI); Serruys 2005[146] (ARTS); Hueb 2010[79] (MASS-II): Evidence from 5 RCTs shows that there was no significant difference between PCI and CABG for death (all causes) [RR 1.01 (0.83 to 1.23)] [5–13 years follow-up].

Booth 2008[140] (SOS); Henderson 1998[144] (RITA); Kaehler 2005[145] (GABI): Evidence from 3 RCTs shows that there was no significant difference between PCI and CABG for cardiac mortality [RR 1.24 (0.82 to 1.87)] [5–13 years follow-up].

Serruys 2005[146] (ARTS); Hueb 2010[79] (MASS-II): Evidence from 2 RCTs shows that there was no significant difference between PCI and CABG for stroke [RR 0.90 (0.57 to 1.41)] [5–10 years follow-up].

Henderson 1998[144] (RITA); Serruys 2005[146] (ARTS); Hueb 2010[79] (MASS-II): Evidence from 3 RCTs shows that there was no significant difference in non fatal MI in the PCI group compared to CABG [RR 1.28 (0.97 to 1.69)] [5–10years follow-up].

Buszman 2009[143] (SoS); Henderson 1998[144] (RITA); Kaehler 2005[145] (GABI); King 2000[147] (EAST); Serruys 2005[146] (ARTS);

Hueb 2010[79] (MASS-II): Evidence from 6 RCTs shows that there was significantly higher repeat revascularisation in the PCI group compared to CABG [RR 2.65 (2.35 to 2.98) [5–13 years follow-up].

Serruys 2005[146] (ARTS); Hueb 2010[79] (MASS-II): Evidence from 2 RCTs shows that there was significantly more patients free of angina in CABG compared to PCI [RR 0.92 (0.87 to 0.97)] [5–10 yrs follow-up].

Serruys 2005[146] (ARTS): Evidence from one RCTs shows that there was no significant difference between PCI and CABG for, MI [RR 1.47 (0.6 to 3.58)], and stroke [RR 0.86 (0.31 to 2.36)] in a sub group of patients with diabetes.However there were significantly higher repeat revascularisations [RR 4.11 (2.2 to 7.68)] in the PCI group compared to CABG in a subgroup of patients with diabetes [5 years follow-up].

Booth 2008[140] (SOS); Henderson 1998[144] (RITA); Serruys 2005[146] (ARTS): Evidence from 3 RCTs shows that there was no significant difference between PCI and CABG for death [RR 1.43 (0.83 to 2.47) in a subgroup of patients with diabetes [5–10 years follow-up].

Booth 2008[140] (SoS); Serruys 2005[146] (ARTS): Evidence from 2 RCTs' shows that there was no significant difference between PCI and CABG for death [RR 1.12 (0.82 to 1.54)] in sub group of patients with no diabetes [5 years follow-up].

Serruys 2005[146] (ARTS): Evidence from one RCT shows that there was no significant difference between PCI and CABG for stroke [RR 1.19 (0.59 to 2.42)], MI [RR 1.28 (0.81 to 2.02)], and there were significantly more patients with repeat revascularisation [RR 3.25 (2.36 to 4.48)] in PCI compared to CABG in a sub group of patients with no diabetes. [5 years follow-up].

Sub group interaction: There was no significant difference between diabetes and no diabetes sub group of patients for death (p=0.45), MI (p=0.79) and repeat revascularisation (p=0.51) at long term follow-up.

Booth 2008[140] (SoS): Evidence from one RCT shows that there was no significant difference between PCI and CABG for death in sub group 2 vessel disease [RR 1.68 (0.94 to 3.00)] and sub group 3 vessel disease [RR 1.58 (0.87 to 2.85)] [5 yrs follow-up].

Sub group interaction: There was no significant difference between single, 2 vessel and 3 vessel disease for death all causes (p=0.17) at long term follow-up.

Economic	In people with multi vessel disease who are suitable for both CABG and PCI, PCI is more cost-effective. This result was not significant and a probabilistic analysis showed a high uncertainty around the cost-effectiveness of PCI vs. CABG. PCI was the preferred strategy in 63% of the simulations and results were dependent on the type of repeat procedure (if CABG was the procedure in more than 85% of the cases, PCI was not cost-effective). In people with single vessel disease PCI is likely to be even more cost-effective.

12.3 Single vessel disease

12.3.1 Clinical evidence

The “Review Protocol” for this topic can be found in Appendix C, the “Search Strategies” in Appendix D, the “List of Included and Excluded Studies” in Appendix E1, the “Clinical Evidence Tables” in Appendix E2, and the “Forest Plots” in Appendix F.

Table 12.7: PCI vs. CABG – Single vessel disease – short term follow-up (1 year) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	PCI	CABG	Relative (95% CI)	Absolute	
Death (all causes) (follow-up 1 years)											
Cisowski 2002[154]	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	serious (b)	none	1/50 (2%)	0/50 (0%)	RR 3 (0.13 to 71.92)	20 more per 1000 (from 30 fewer to 70 more)	⊕⊕⊕O MODERATE
MI (follow-up 1 years)											
Cisowski 2002[154]	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/50 (0%)	0/50 (0%)	not pooled	not pooled	⊕⊕⊕⊕ HIGH
Free of angina (follow-up 1 years)											
Cisowski 2002[154]	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	serious (b)	none	21/50 (42%)	24/50 (48%)	RR 0.88 (0.57 to 1.35)	58 fewer per 1000 (from 206 fewer to 168 more)	⊕⊕⊕O MODERATE

(a) Cisowski 2002[146]: Randomised, baseline comparisons made, blind outcome assessment. Randomisation and allocation concealment methods not reported. High attrition: at 1 yr follow-up: 44% in PCI; 52% in E-ACAB)

(b) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.

Table 12.8: PCI vs. CABG – Single vessel disease – medium term follow-up (2 to 4 years) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	PCI	CABG	Relative (95% CI)	Absolute	
Death (all causes) (follow-up 2. years)											
Drenth 2004[155]; Goy 2000[156] (SIMA); Hueb 1995[85] (MASS-1)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	2/185 (1.1%)	6/180 (3.3%)	RR 0.37 (0.09 to 1.60)	21 fewer per 1000 (from 30 fewer to 20 more)	⊕⊕OO LOW
Cardiac death (follow-up 2-2.5 years)											
Drenth 2004[155]; Goy 1994[157]; Goy 2000[156] (SIMA)	randomised trials	serious (e)	no serious inconsistency	no serious indirectness	serious (b)	none	1/181 (0.6%)	4/176 (2.3%)	RR 0.39 (0.08 to 2)	14 fewer per 1000 (from 21 fewer to 23 more)	⊕⊕OO LOW
MI (follow-up 2-2.5 years)											
Drenth 2004[155]; Goy 1994[157]; Goy 2000[156] (SIMA); Hueb 1995[85] (MASS-1)	randomised trials	serious (c)	no serious inconsistency	no serious indirectness	serious (d)	none	18/253 (7.1%)	6/246 (2.4%)	RR 2.92 (1.18 to 7.21)	47 more per 1000 (from 4 more to 151 more)	⊕⊕OO LOW
Repeat revascularisation (follow-up 2-2.5 years)											
Drenth 2004[155]; Goy 1994[157]; Goy 2000[156] (SIMA); Hueb 1995[85] (MASS-1)	randomised trials	serious (c)	no serious inconsistency	no serious indirectness	no serious imprecision	none	67/253 (26.5%)	4/246 (1.6%)	RR 13.27 (5.41 to 32.51)	200 more per 1000 (from 72 more to 512 more)	⊕⊕⊕O MODERATE
Free of angina											
Drenth 2004[155]; Goy 1994[157]; Hueb 1995[85] (MASS-1)	randomised trials	serious (e)	no serious inconsistency	no serious indirectness	serious (d)	none	144/191 (75.4%)	168/184 (91.3%)	RR 0.83 (0.75 to 0.91)	155 fewer per 1000 (from 82 fewer to 228 fewer)	⊕⊕OO LOW
Stroke (follow-up 2 years)											
Drenth 2004[155]; Goy 2000[156] (SIMA)	randomised trials	serious (f)	no serious inconsistency	no serious indirectness	serious (b)	none	2/113 (1.8%)	0/110 (0%)	RR 5 (0.25 to 101.63)	20 more per 1000 (from 20 fewer to 50 more)	⊕⊕OO LOW

(a) Drenth 2004[147]; Goy 2000[148] (SIMA); Hueb 1995[83] (MASS-1): Randomisation, ITT reported in both studies. Allocation concealment not reported in 2 out of 3 studies.
(b) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.
(c) Drenth 2004[147]; Goy 1994[149]; Goy 2000[148] (SIMA); Hueb 1995[83] (MASS-1): Randomisation, ITT reported in all 4studies. Allocation concealment not reported in all 4 studies.
(d) 95% CI around the pooled estimate of effect includes appreciable benefit or appreciable harm.
(e) Drenth 2004[147]; Goy 1994[149]; Hueb 1995[83] (MASS-1): Randomisation, ITT reported all 3 studies. Allocation concealment not reported in all 3 studies.
(f) Drenth 2004[147]; Goy 2000[148] (SIMA): Randomisation, ITT reported both studies. Allocation concealment not reported in all both studies.

Table 12.9: PCI vs. CABG – Single vessel disease – Long term follow-up (>5 years) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	PCI	CABG	Relative (95% CI)	Absolute	
Death (all causes) (follow-up 5-10 years)											
Goy 2008[158] (SIMA); Henderson 1998[144] (RITA); Hueb 1999[86] (MASS-I)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	28/367 (7.6%)	27/351 (7.7%)	RR 0.99 (0.60 to 1.65)	1 fewer per 1000 (from 31 fewer to 50 more)	⊕⊕OO LOW
Cardiac death (follow-up 10 years)											
Goy 2008[158] (SIMA); Hueb 1999[86] (MASS-I)	randomised trials	serious (c)	no serious inconsistency	no serious indirectness	serious (b)	none	6/134 (4.5%)	3/129 (2.3%)	RR 1.93 (0.49 to 7.55)	22 more per 1000 (from 12 fewer to 152 more)	⊕⊕OO LOW
MI (follow-up 5-10 years)											
Goy 2008[158] (SIMA); Henderson 1998[144] (RITA); Hueb 1999[86] (MASS-I)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	38/367 (10.4%)	23/351 (6.6%)	RR 1.58 (0.96 to 2.59)	38 more per 1000 (from 3 fewer to 104 more)	⊕⊕OO LOW
Repeat revascularisation (follow-up 5-10 years)											
Goy 2008[158] (SIMA); Henderson 1998[144] (RITA); Hueb 1999[86] (MASS-I)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	156/367 (42.5%)	32/351 (9.1%)	RR 4.60 (3.25 to 6.50)	328 more per 1000 (from 205 more to 501 more)	⊕⊕⊕O MODERATE
Free of angina (follow-up 5 years)											
Hueb 1999[86] (MASS-I);	randomised trials	serious (d)	no serious inconsistency	no serious indirectness	serious (b)	none	44/72 (61.1%)	48/70 (68.6%)	RR 0.89 (0.7 to 1.14)	75 fewer per 1000 (from 206 fewer to 96 more)	⊕⊕OO LOW

(a) Goy 2008[150] (SIMA); Henderson 1998[136] (RITA); Hueb 1999[84] (MASS-I): Allocation concealment, method of randomisation and blinding of outcome assessors reported in 1 out of 3 studies. IIT reported in all studies.

(b) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.

(c) Goy 2008[150] (SIMA); Hueb 1999[84] (MASS-I): Randomised. Intention to treat analysis reported in both, Allocation concealment and blinding of outcome assessors not reported in both the studies.

(d) Randomsied. Allocation concealment not reported. Blinding of outcome assessors not reported. ITT reported.

Additional data for PCI vs. CABG – Single vessel disease – short term follow-up (1 year)

Goy 2000[156] (SIMA) (Follow-up 1 year)

No. of participants: N=123 (CABG (n=60); Stent (n=63))

At 1 year follow-up, 56 patients (95%) in the CABG group and 56 (91%) in the stent group were in CCS class 0 or 1 (p=0.90). Only 3 patients in the CABG group were in class III or IV compared with 6 patients in the stent group (p=0.08). The functional class showed no significant differences between the 2 groups

Additional data – Hampton 1993[129] (RITA trial) – PCI vs. CABG – Medium term follow-up (2.5 years)

Sub group interaction for single vessel and multi vessel disease:

At 2.5 years the risk of death or infarction appeared unrelated to the number of treatment vessels at randomisation, there being 40 primary endpoints in the 456 single vessel disease patients (16 CABG, 24 PTCA) and 53 primary endpoints in the 555 multi vessel patients (27 CABG, 26 PTCA). The relative risk single: multi vessel is 0.91 (95% CI 0.60-1.40, p=0.66). There is no evidence that any treatment difference depends on the number of disease vessels (interaction test p=0.35).

Additional data for PCI vs. CABG – Single vessel disease – Long term follow-up – >5 years)

Goy 2008[158] (SIMA) (Follow-up 10 years)

No. of participants: n=62 in PCI and n=59 CABG

At 10 years, most of the patients in both groups were asymptomatic (93%) or suffered mild angina. Angina functional class showed no significant differences between the PTCA and CABG. (No further details reported)

Quality Of Life data for PCI vs. CABG – Single vessel disease:

Drenth 2004[155]:

In this RCT assessments of Functional Health Status (FHS) were performed with SF-36 questionnaire. SF-36 comprises 36 items covering the above 8 domains. These items were scored on a 0 to 100 range. Next, the items in the same domain were averaged together to create domain scores. For each domain, a high score indicates a more favourable health status (i.e., better physical functioning, less emotional problems, less pain and so forth).

Results: n=102 (n=51 in surgery and n=51 in PTCA). Both angioplasty and surgery resulted in good FHS in patients treated for an isolated high grade narrowing of the proximal LAD artery at 4 year follow-up. FHS did not differ between angioplasty and surgery in all domains. (Angioplasty vs. surgery: physical functioning: 77 vs. 81, p=0.48; Social functioning: 87 vs. 87, p=0.89; Role-physical: 76 vs. 78, p=0.81; Role-emotional: 87 vs. 85, p=0.98; Mental health: 82 vs. 81, p=0.86; Vitality: 70 vs.

70, p=0.96; Bodily pain: 90 vs.88, p=0.97; General health perception: 69 vs. 70, p=0.78).

Goy 2000[156] (SIMA):

In this RCT Quality of life was assessed with SF-36 and the Seattle questionnaire between 9-15 months.

Results: N=123 (CABG (n=60); PCI (n=63)). The quality of life questionnaires did not show significant differences between PCI and CABG. Only perception of the disease was more marked (but not significantly) after surgery.

12.3.2 Economic evidence

No economic studies were identified specifically on this population. However the results of our economic model (see Appendix H and section12.2.2) are likely to be applicable to people with single vessel disease.

12.3.3 Evidence statements

Clinical	<u>**PCI vs. CABG – Single vessel disease (Short term follow-up – 1 year)**</u> **Cisowski 2002[154]:** Evidence from one RCT shows that there was no significant difference between PCI and CABG for death (all causes) [RR 3 (0.13 to 71.92)], MI (not pooled- 0/50 in both groups) and free of angina [RR 0.88 (0.57 to 1.35)] [1 year follow-up]. <u>**PCI vs. CABG – Single vessel disease (Medium term follow-up – 2 to 4 years)**</u> **Drenth 2004[155]; Goy 2000[156] (SIMA); Hueb 1995[85] (MASS-I):** Evidence from 3 RCTS shows that there was no significant difference between PCI and CABG for death (all causes) [RR 0.37 (0.09 to 1.60) [2–4 years follow-up]. **Drenth 2004[155]; Goy 1994[157]; Goy 2000[156] (SIMA):** Evidence from 3 RCTs shows that there was no significant difference between PCI and CABG for cardiac death [RR 0.39 (0.08 to 2)] [2–4 years follow-up]. **Drenth 2004[155]; Goy 1994[157]; Goy 2000[156] ((SIMA); Hueb 1995[85] (MASS-I):** Evidence from 4 RCTs shows that there were significantly more patients with MI [RR 2.92 (1.18 to 7.21)] in PCI compared to CABG, significantly higher repeat revascularisation [RR 13.27 (5.41 to 32.51)] in PCI compared to CABG [2–4 years follow-up]. **Drenth 2004[155]; Goy 1994[157]; Hueb 1995[85] (MASS-I):** Evidence from 3 RCTS shows that there was significantly more patients free

of angina in the CABG group compared to PCI [RR 0.83 (0.75 to 0.91) [2–4 years follow-up].

Drenth 2004[155]; Goy 2000[156] (SIMA): Evidence from 2 RCT s shows that there was no significant difference between PCI and CABG for stroke [RR 5.00 (0.25 to 101.63)] [2–4 years follow-up].

PCI vs. CABG – Single vessel disease (Long term follow-up >5 years)

Goy 2008[156] (SIMA); Henderson 1998[144] (RITA); Hueb 1999[85] (MASS-I): Evidence from 3RCT shows that there was significantly higher repeat revascularisation [RR 4.60 (3.25 to 6.50)] in the PCI group compared to CABG, and there was no significant difference between PCI and CABG for death (all causes) [RR 0.99 (0.60 to 1.65)] and MI [RR 1.58 (0.96 to 2.59) [5–10 years follow-up].

Goy 2008[156] (SIMA); Hueb 1999[85] (MASS-I): Evidence from 2 RCT shows that there was there was no significant difference between PCI and CABG for cardiac death [RR 1.93 (0.49 to 7.55)] [10 years follow-up].

Hueb 1999[85] (MASS-I): Evidence from one RCT shows that there was there was no significant difference between PCI and CABG for free of angina [RR 0.89 (0.7 to 1.14)] [5 years follow-up].

Economic No economic studies were identified specifically on this population. The results of the economic model on people with multi-vessel disease are likely to be applicable to people with single vessel disease. Therefore PCI is more cost-effective than CABG in people eligible for both procedures. This evidence has has minor limitations and direct applicability but there is some uncertainty around this conclusion.

12.4 Left main coronary disease

12.4.1 Clinical evidence

The “Review Protocol” for this topic can be found in Appendix C, the “Search Strategies” in Appendix D, the “List of Included and Excluded Studies” in Appendix E1, the “Clinical Evidence Tables” in Appendix E2, and the “Forest Plots” in Appendix F.

Table 12.10: PCI vs. CABG – Left main coronary disease – short term follow-up (1 year) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	PCI	CABG	Relative (95% CI)	Absolute	
Death (follow-up 1 years)											
Buszman 2008[159] (LEMANS); Morice 2010[160] (SYNTAX)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	16/409 (3.9%)	19/401 (4.7%)	RR 0.83 (0.43 to 1.59)	8 fewer per 1000 (from 27 fewer to 28 more)	⊕⊕OO LOW
Non fatal MI (follow-up 1 years)											
Buszman 2008[159] (LEMANS); Morice 2010[160] (SYNTAX)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	16/409 (3.9%)	17/401 (4.2%)	RR 0.92 (0.47 to 1.8)	3 fewer per 1000 (from 22 fewer to 34 more)	⊕⊕OO LOW
Stroke (follow-up 1 years)											
Buszman 2008[159] (LEMANS); Morice 2010[160] (SYNTAX)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/409 (0.2%)	11/401 (2.7%)	RR 0.13 (0.02 to 0.7)	24 fewer per 1000 (from 8 fewer to 27 fewer)	⊕⊕⊕O MODERATE
Repeat revascularisation (follow-up 1 years)											
Buszman 2008[159] (LEMANS); Morice 2010[160] (SYNTAX)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	58/409 (14.2%)	28/401 (7%)	RR 2.04 (1.33 to 3.13)	73 more per 1000 (from 23 more to 149 more)	⊕⊕⊕O MODERATE
Cardiac death (follow-up 1 years)											
Morice 2010[160] (SYNTAX)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	14/357 (3.9%)	8/348 (2.3%)	RR 1.71 (0.72 to 4.02)	16 more per 1000 (from 6 fewer to 69 more)	⊕⊕OO LOW

(a) *Buszman 2008[151] (LEMANS): Randomised, baseline comparisons made, blind outcome assessment for some outcomes (all clinical outcomes were analysed by the Clinical Event Committee. Echocardiographic and stress test recordings were read centrally by a group of independent investigators unaware of treatment assignment). Intention to treat analysis reported. Allocation concealment not reported, nos. lost to follow-up not reported, small sample size. *This study reports 1 year follow-up results of the LEMANS (study of unprotected Left main stenting versus bypass surgery) study. Morice 20102010[152] (SYNTAX) Strengths - Randomised, allocation concealment reported. n=12 withdrew consent in CABG group (N=336, 96.6% follow-up at 12 months) and n=1 lost to follow-up and n=1 discontinued treatment in PCI group (n=355, 99.4% follow-up at 12 months). Baseline comparisons made. ITT not reported. *This study presents the outcomes in the pre-specified subgroup of patients (n=705) with LM disease in the SYNTAX trial.*

(b) *95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.*

Additional data for PCI vs. CABG – Left main coronary disease – short term follow-up 1 year

Buszman 2008[159] (LEMANS) (Follow-up 1 year)

No. of participants: (n=52 in PCI and n=53 in CABG)

Patients after PCI had more angina after 6 months (p=0.01) but had similar angina status to CABG patients after 12 months (p=0.11).

12.4.2 Economic evidence

No economic studies were identified specifically on this population.

12.4.3 Evidence statements

Clinical	**PCI vs. CABG – Left main coronary artery stenosis (Short term follow – 1 year)** **Buszman 2008[159] (LEMANS); Morice 2010[160] (SYNTAX):** Evidence from 2 RCTs shows that there was statistically significant higher stroke in the CABG group compared to PCI [RR 0.13 (0.02 to 0.7)]. There were statistically significant higher repeat revascularisations in the PCI group compared to CABG [RR 2.04 (1.33 to 3.13)]. There was no statistically significant difference between PCI and CABG for death [RR 0.83 (0.43 to 1.59)] and non fatal MI [RR 0.92 (0.47 to 1.8)] [Follow-up 1 year]. **Morice 2010[160] (SYNTAX):** Evidence from 1 RCT shows that there was no statistically significant difference between PCI and CABG for cardiac death [RR 1.71 (0.72 to 4.02)] [Follow-up 1 year].
Economic	No economic studies were identified specifically on this population.

12.5 Left main coronary artery or 3 vessel disease

12.5.1 Clinical evidence

The “Review Protocol” for this topic can be found in Appendix C, the “Search Strategies” in Appendix D, the “List of Included and Excluded Studies” in Appendix E1, the “Clinical Evidence Tables” in Appendix E2, and the “Forest Plots” in Appendix F.

Table 12.11: PCI vs. CABG – Left main coronary artery or 3 vessel disease short term follow-up (1year) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	PCI	CABG	Relative (95% CI)	Absolute	
Death (all causes) (follow-up 1 years)											
Serruys 2009[161] (SYNTAX) (d)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	serious (b)	none	39/891 (4.4%)	30/849 (3.5%)	RR 1.24 (0.78 to 1.98)	8 more per 1000 (from 8 fewer to 35 more)	⊕⊕⊕O MODERATE
cardiac mortality (follow-up 1 years)											
Serruys 2009[161] (SYNTAX)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	serious (b)	none	33/891 (3.7%)	18/849 (2.1%)	RR 1.75 (0.99 to 3.08)	16 more per 1000 (from 0 fewer to 44 more)	⊕⊕⊕O MODERATE
Stroke (follow-up 1 years)											
Serruys 2009[161] (SYNTAX)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/891 (0.6%)	19/849 (2.2%)	RR 0.25 (0.09 to 0.67)	17 fewer per 1000 (from 7 fewer to 20 fewer)	⊕⊕⊕⊕ HIGH
MI (follow-up 1 years)											
Serruys 2009[161] (SYNTAX)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	serious (b)	none	43/891 (4.8%)	28/849 (3.3%)	RR 1.46 (0.92 to 2.33)	15 more per 1000 (from 3 fewer to 44 more)	⊕⊕⊕O MODERATE
Repeat revascularisation (follow-up 1 years)											
Serruys 2009[161] (SYNTAX)	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	120/891 (13.5%)	50/849 (5.9%)	RR 2.29 (1.67 to 3.14)	76 more per 1000 (from 39 more to 126 more)	⊕⊕⊕⊕ HIGH
Sub group diabetes (Death) (follow-up 1 years)											
Banning 2010[162] (SYNTAX)	randomised trials	no serious limitations (c)	no serious inconsistency	no serious indirectness	serious (b)	none	19/227 (8.4%)	13/204 (6.4%)	RR 1.31 (0.67 to 2.59)	20 more per 1000 (from 21 fewer to 101 more)	⊕⊕⊕O MODERATE
Sub group diabetes (cardiac death) (follow-up 1 years)											
Banning 2010[162] (SYNTAX)	randomised trials	no serious limitations (c)	no serious inconsistency	no serious indirectness	serious (b)	none	16/227 (7%)	8/204 (3.9%)	RR 1.8 (0.79 to 4.11)	31 more per 1000 (from 8 fewer to 122 more)	⊕⊕⊕O MODERATE
Sub group diabetes (stroke) (follow-up 1 years)											
Banning 2010[162] (SYNTAX)	randomised trials	no serious limitations (c)	no serious inconsistency	no serious indirectness	serious (b)	none	2/227 (0.9%)	5/204 (2.5%)	RR 0.36 (0.07 to 1.83)	16 fewer per 1000 (from 23 fewer to 20 more)	⊕⊕⊕O MODERATE
Sub group diabetes (MI) (follow-up 1 years)											
Banning 2010[162] (SYNTAX)	randomised trials	no serious limitations (c)	no serious inconsistency	no serious indirectness	serious (b)	none	11/227 (4.8%)	9/204 (4.4%)	RR 1.1 (0.46 to 2.6)	4 more per 1000 (from 24 fewer to 71 more)	⊕⊕⊕O MODERATE
Sub group diabetes (Repeat revascularisation) (follow-up 1 years)											
Banning 2010[162] (SYNTAX)	randomised trials	no serious limitations (c)	no serious inconsistency	no serious indirectness	no serious imprecision	none	46/227 (20.3%)	13/204 (6.4%)	RR 3.18 (1.77 to 5.71)	139 more per 1000 (from 49 more to 300 more)	⊕⊕⊕⊕ HIGH

Sub group no diabetes (Death) (follow-up 1 years)											
Banning 2010[162] (SYNTAX)	randomised trials	no serious limitations (c)	no serious inconsistency	no serious indirectness	serious (b)	none	20/664 (3%)	17/645 (2.6%)	RR 1.14 (0.6 to 2.16)	4 more per 1000 (from 11 fewer to 31 more)	⊕⊕⊕O MODERATE
Sub group no diabetes (no cardiac death) (follow-up 1 years)											
Banning 2010[162] (SYNTAX)	randomised trials	no serious limitations (c)	no serious inconsistency	no serious indirectness	serious (b)	none	17/664 (2.6%)	10/645 (1.6%)	RR 1.65 (0.76 to 3.58)	10 more per 1000 (from 4 fewer to 40 more)	⊕⊕⊕O MODERATE
Sub group no diabetes (stroke) (follow-up 1 years)											
Banning 2010[162] (SYNTAX)	randomised trials	no serious limitations (c)	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/664 (0.5%)	14/645 (2.2%)	RR 0.21 (0.06 to 0.72)	17 fewer per 1000 (from 6 fewer to 20 fewer)	⊕⊕⊕⊕ HIGH
Sub group no diabetes (MI) (follow-up 1 years)											
Banning 2010[162] (SYNTAX)	randomised trials	no serious limitations (c)	no serious inconsistency	no serious indirectness	serious (b)	none	32/664 (4.8%)	19/645 (2.9%)	RR 1.64 (0.94 to 2.86)	19 more per 1000 (from 2 fewer to 55 more)	⊕⊕⊕O MODERATE
Sub group no diabetes (Repeat revasc) (follow-up 1 years)											
Banning 2010[162] (SYNTAX)	randomised trials	no serious limitations (c)	no serious inconsistency	no serious indirectness	no serious imprecision	none	74/664 (11.1%)	37/645 (5.7%)	RR 1.94 (1.33 to 2.84)	54 more per 1000 (from 19 more to 106 more)	⊕⊕⊕⊕ HIGH

a) *Serruys 2009[153] (SYNTAX) : Randomised, allocation concealment reported, baseline comparisons made, nos. lost to follow-up reported ((5.4% in CABG and 1.3% in PCI group), Intention to treat analysis reported. Blind outcome assessment (adjudicated by an independent Clinical Events Committee).Patients aware of the intervention allocated.*

b) *95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.*

c) *Banning 2010[154] (SYNTAX): Randomised, ITT used, one year MACCE was evaluated in 849 (94.6%) CABG patients (645 non diabetic and 204 medically treated diabetes) and 891 (98.7%) PES patients (664 non diabetic and 227 with medically treated diabetes). Allocation concealment reported. Baseline comparisons made. This is a sub group analysis of the SYNTAX trial.*

d) *Authors note:*
   - *Most cases of stent thrombosis occurred within 30 days after the procedure, and the 12 month rate of stent thrombosis in the PCI group was similar to the rate of symptomatic graft occlusion in the CABG group. Stent thrombosis often has more serious consequences for patients (rate of death, approximately 30%, rate of MI approximately 60%) than does graft occlusion, which often results only in angina leading to revascularisation.*
   - *The use of antiplatelet medication was high among patients in the PCI group (with 71.1% receiving a thienopyridine at 12 months). The authors report that the low rate of stroke among patients with PCI may have resulted from the use of highly effective dual antiplatelet therapy which prevents thrombo embolic events.*
   - *More patients in the CABG group than in PCI declined to participate after proving consent; this imbalance was due to the greater invasiveness of CABG.*

Additional data for PCI vs. CABG - Left main coronary artery or 3 vessel disease – short term follow-up 1year

Serruys 2009[161] (SYNTAX)

No. of participants: Total (n=891 in PCI and n= 849 in CABG)

Data reported for subgroup of patients with left main coronary artery disease and three vessel disease separately. However, data could not be analysed as the exact number of patients in the subgroup of those with left main coronary artery disease and with 3 vessel disease not reported.

Left main coronary artery disease: The 12 month rate of major adverse cardiac or cerebrovascular events among patients with left main coronary artery disease was similar in the CABG and PCI groups (13.7% and 15.8% respectively; p=0.44). Although the rate of repeat revascularisation among patients with left main coronary artery disease was significantly higher in the PCI group (11.8% and 6.5% in the CABG group; p=0.02), this result was offset by a significantly higher rate of stroke in the CABG subgroup of patients with left main coronary artery disease (2.7% vs. 0.3% in the corresponding PCI subgroup; p=0.01).

Three vessel disease: The 12 month rate of major adverse cardiac or cerebrovascular events among patients with three vessel disease in the absence of left main coronary artery disease was significantly increased in the PCI group as compared with the CABG group (19.2% vs. 11.5%, p<0.001). The rate of death from any cause, stroke, or MI in this subgroup was similar with PCI and CABG (8% and 6.6% respectively; p =0.39).

Sub group interaction (SYNTAX trial for diabetes and non diabetes sub group)

The interaction p value for the effect of diabetes on death (p=0.77), cardiac death (p=0.88), stroke (p=0.61), MI (p=0.45) and repeat revascularisation (p=0.17) was not significant at short tem follow-up of 1 year.

12.5.2 Economic evidence

No economic studies were identified specifically on this population.

12.5.3 Evidence statements

Clinical

PCI vs. CABG - Three vessel disease or Left main coronary artery disease or both (Short term follow-up – 1year)

Serruys 2009[161] (SYNTAX): Evidence from one RCT shows that there was significantly higher repeat revascularisation [RR 2.29 (1.67 to 3.14)] in the PCI group compared to CABG. There were significantly more patients with stroke [RR 0.25 (0.09 to 0.67)] in the CABG group compared to PCI. There was no significant difference between PCI and CABG for death (all causes) [RR 1.24 (0.78 to 1.98)], cardiac mortality [RR 1.75 (0.99 to 3.08)], and MI

	[RR 1.46 (0.92 to 2.33)]. [1 year follow-up] **Banning 2010[162] (SYNTAX):** Evidence from one RCT shows that there was no significant difference between PCI with PES and CABG for death [RR 1.31 (0.67 to 2.59)], cardiac death [RR 1.8 (0.79 to 4.11)], stroke [RR 0.36 (0.07 to 1.83)], MI [RR 1.1 (0.46 to 2.6)]. There were significantly higher repeat revascularisations [RR 3.18 (1.77 to 5.71)] in the PCI group compared to CABG in a sub group of patients with diabetes. [1 year follow-up]. **Banning 2010[162] (SYNTAX):** Evidence from one RCT shows that there was no significant difference between PCI with PES and CABG for death [RR 1.14 (0.6 to 2.16)], cardiac death [RR 1.65 (0.76 to 3.58)], MI [RR 1.64 (0.94 to 2.86)]. There was significantly higher stroke* [RR 0.21 (0.06 to 0.72)] in the CABG group and higher repeat revascularisation [RR 1.94 (1.33 to 2.84)] in the PCI group compared to CABG in the sub group of patients with no diabetes. [1 year follow-up]. *Authors report that this value did not reach statistical significance in diabetes patients, possibly because of the small size in the diabetic group.
Economic	No economic studies were identified specifically on this population.

12.6 IPD Meta-analyses (PCI vs. CABG - Multi vessel disease - immediate, short and long term follow-up)

12.6.1 Clinical evidence

The "Review Protocol" for this topic can be found in Appendix C, the "Search Strategies" in Appendix D, the "List of Included and Excluded Studies" in Appendix E1, the "Clinical Evidence Tables" in Appendix E2, and the "Forest Plots" in Appendix F.

Table 12.12: IPD meta-analyses - PCI vs. CABG – Multi -vessel disease – Immediate, short and long term follow-up

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	PCI	CABG	RR/HR (95% CI)	Absolute	
Death (follow-up median 5.9 years)											
Hlatky 2009[122]	randomised trial	no serious limitations (a)	no serious inconsistency	serious (b)	no serious imprecision	none	628/3923 (16%)	575/3889 (14.8%)	HR 0.91 (0.82 to 1.02)	12 fewer per 1000 (from 25 fewer to 3 more)	⊕⊕⊕O MODERATE
Death - Age <55 years (follow-up 5.9 years)											
Hlatky 2009[122]	randomised trial	no serious limitations (a)	no serious inconsistency	serious (b)	no serious imprecision	none	88/1122 (7.8%)	107/1063 (10.1%)	HR 1.25 (0.94 to 1.66)	24 more per 1000 (from 6 fewer to 61 more)	⊕⊕⊕O MODERATE
Death- age 55-64 years (follow-up median 5.9 years)											
Hlatky 2009[122]	randomised trial	no serious limitations (a)	no serious inconsistency	serious (b)	no serious imprecision	none	220/1456 (15.1%)	201/1477 (13.6%)	HR 0.90 (0.75 to 1.09)	13 fewer per 1000 (from 32 fewer to 11 more)	⊕⊕⊕O MODERATE
Death->65 years (follow-up median 5.9 years)											
Hlatky 2009[122]	randomised trial	no serious limitations (a)	no serious inconsistency	serious (b)	no serious imprecision	none	319/1341 (23.8%)	267/1347 (19.8%)	HR 0.82 (0.7 to 0.97)	32 fewer per 1000 (from 5 fewer to 55 fewer)	⊕⊕⊕O MODERATE
Death- women (follow-up median 5.9 years)											
Hlatky 2009[122]	randomised trial	no serious limitations (a)	no serious inconsistency	serious (b)	no serious imprecision	none	164/992 (16.5%)	162/909 (17.8%)	HR 1.02 (0.82 to 1.27)	3 more per 1000 (from -30 fewer to 42 more)	⊕⊕⊕O MODERATE
Death- men (follow-up median 5.9 years)											
Hlatky 2009[122]	randomised trial	no serious limitations (a)	no serious inconsistency	serious (b)	no serious imprecision	none	464/3001 (15.5%)	413/2980 (13.9%)	HR 0.88 (0.77 to 1)	16 fewer per 1000 (from 30 fewer to 0 more)	⊕⊕⊕O MODERATE
Death- No diabetes (follow-up median 5.9 years)											
Hlatky 2009[122]	randomised trial	no serious limitations (a)	no serious inconsistency	serious (b)	no serious imprecision	none	448/3298 (13.6%)	432/3263 (13.2%)	HR 0.98 (0.86 to 1.12)	2 fewer per 1000 (from 17 fewer to 15 more)	⊕⊕⊕O MODERATE
Death- Diabetes (follow-up median 5.9 years)											
Hlatky 2009[122]	randomised trial	no serious limitations (a)	no serious inconsistency	serious (b)	no serious imprecision	none	179/618 (29%)	143/615 (23.3%)	HR 0.70 (0.56 to 0.87)	64 fewer per 1000 (from 27 fewer to 95 fewer)	⊕⊕⊕O MODERATE
Death- stable symptoms (follow-up median 5.9 years)											
Hlatky 2009[122]	randomised trial	no serious limitations (a)	no serious inconsistency	serious (b)	no serious imprecision	none	256/1900 (13.5%)	205/1840 (11.1%)	HR 0.83 (0.69 to 0.99)	18 fewer per 1000 (from 1 fewer to 33 fewer)	⊕⊕⊕O MODERATE
Death- unstable symptoms (follow-up median 5.9 years)											
Hlatky 2009[122]	randomised trial	no serious limitations (a)	no serious inconsistency	serious (b)	no serious imprecision	none	266/1306 (20.4%)	262/1347 (19.5%)	HR 0.95 (0.8 to 1.12)	9 fewer per 1000 (from 36 fewer to 21 more)	⊕⊕⊕O MODERATE
Death- Normal LV function (follow-up median 5.9 years)											

Hlatky 2009[122]	randomised trial	no serious limitations (a)	no serious inconsistency	serious (b)	no serious imprecision	none	398/2791 (14.3%)	375/2789 (13.4%)	HR 0.92 (0.8 to 1.06)	10 fewer per 1000 (from 25 fewer to 7 more)	⊕⊕⊕O MODERATE
Death- abnormal LV function (follow-up median 5.9 years)											
Hlatky 2009[122]	randomised trial	no serious limitations (a)	no serious inconsistency	serious (b)	no serious imprecision	none	151/615 (24.6%)	126/551 (22.9%)	HR 0.93 (0.73 to 1.18)	14 fewer per 1000 (from 56 fewer to 35 more)	⊕⊕⊕O MODERATE
Death- less than 3 diseased vessels (follow-up median 5.9 years)											
Hlatky 2009[122]	randomised trial	no serious limitations (a)	no serious inconsistency	serious (b)	no serious imprecision	none	371/2523 (14.7%)	325/2386 (13.6%)	HR 0.91 (0.78 to 1.06)	11 fewer per 1000 (from 28 fewer to 8 more)	⊕⊕⊕O MODERATE
Death- 3 vessel disease (follow-up median 5.9 years)											
Hlatky 2009[122]	randomised trial	no serious limitations (a)	no serious inconsistency	serious (b)	no serious imprecision	none	253/1376 (18.4%)	248/1477 (16.8%)	HR 0.91 (0.77 to 1.09)	14 fewer per 1000 (from 36 fewer to 14 more)	⊕⊕⊕O MODERATE
Death- No proximal LAD (follow-up median 5.9 years)											
Hlatky 2009[122]	randomised trial	no serious limitations (a)	no serious inconsistency	serious (b)	no serious imprecision	none	310/1636 (18.9%)	278/1567 (17.7%)	HR 0.92 (0.79 to 1.09)	13 fewer per 1000 (from 34 fewer to 14 more)	⊕⊕⊕O MODERATE
Death- Proximal LAD (follow-up median 5.9 years)											
Hlatky 2009[122]	randomised trial	no serious limitations (a)	no serious inconsistency	serious (b)	no serious imprecision	none	268/1684 (15.9%)	249/1707 (14.6%)	HR 0.90 (0.75 to 1.07)	14 fewer per 1000 (from 34 fewer to 9 more)	⊕⊕⊕O MODERATE
Death- balloon angioplasty trials (follow-up median 5.9 years)											
Hlatky 2009[122]	randomised trial	no serious limitations (a)	no serious inconsistency	serious (b)	no serious imprecision	none	481/2405 (20%)	436/2356 (18.5%)	HR 0.91 (0.8 to 1.03)	15 fewer per 1000 (from 34 fewer to 5 more)	⊕⊕⊕O MODERATE
Death- BMS trials (follow-up median 5.9 years)											
Hlatky 2009[122]	randomised trial	no serious limitations (a)	no serious inconsistency	serious (b)	no serious imprecision	none	147/1518 (9.7%)	139/1533 (9.1%)	HR 0.94 (0.74 to 1.18)	5 fewer per 1000 (from 23 fewer to 15 more)	⊕⊕⊕O MODERATE
Frequency of angina (Follow-up 1 year)											
Hlatky 2009[122]	randomised trial	no serious limitations (a)	no serious inconsistency	serious (b)	no serious imprecision	none	856/3240 (26.4%)	439/3228 (13.6%)	RR 1.94 (1.75 to 2.16)	128 more per 1000 (from 102 more to 158 more)	⊕⊕⊕O MODERATE
Stroke (Follow-up 90 days)											
Hlatky 2009[122]	randomised trial	no serious limitations (a)	no serious inconsistency	serious (c)	no serious imprecision	none	12/2269 (0.5%)	26/2268 (1.1%)	RR 0.46 (0.23 to 0.91)	6 fewer per 1000 (from 1 fewer to 8 fewer)	⊕⊕⊕O MODERATE

(a) Hlatky 2009[114]: *This is an IPD (Individual patient data) meta-analyses. Review addresses an appropriate and clearly focused question. The review included only RCTs which was relevant to the review question. There was adequate description of the methodology used in the meta-analysis. The papers report the search strategy used in detail. The authors report that all the included trials were reviewed and approved by ethics committees. All analyses followed the Intention to treat principle. This IPD meta analyses included 10 trials. Note: The IPD included 3 trials which were not included in the study level meta-analyses 1) BARI[123] -<30% with stable angina, 2) ERACI-II[124,125] - 92% unstable angina and 3) Toulouse[126]) - Study reports- Few patients presented with stable angina, whereas the majority complained of unstable angina or recent MI*

(b) *4 studies from the IPD meta-analyses did not have sufficient stable angina population (BARI[123], ERACI-II[124,125], Toulouse[126].*

(c) *Stroke data available from 7 trials*

Sub group interaction:
In patients with diabetes (CABG, n=615; PCI, n=618), mortality was substantially lower in the CABG group than in the PCI group (HR 0.70, 0.56-0.87); however, mortality was similar between groups in patients without diabetes (HR 0.98, 0.86-1.12; p=0.014 for interaction). Patient age modified the effect of treatment on mortality, with hazard ratios of 1.25 (0.94-1.66) in patients younger than 55 years, 0.90 (0.75-1.09) in patients aged 55-64 years, and 0.82 (0.70-0.97) in patients 65 years and older (p=0.002 for interaction). Treatment effect was not modified by the number of diseased vessels (p=0.98 for interaction), gender (p=0.25 for interaction), stable/unstable symptoms (p=0.30 for interaction), LV function (p=0.87 for interaction), involvement of proximal LAD (p=0.77 for interaction), and angioplasty/bare metal stents (p=0.19 for interaction).

12.6.2 Economic evidence

See 12.2.2.

12.6.3 Evidence statements

Clinical	**IPD meta analyses - Multi vessel disease – Immediate, short and long term follow-up** **Hlatky 2009[122]:** Evidence from one IPD meta-analyses shows that at 90 days stroke was significantly higher in the CABG group compared to PCI [RR 0.46 (0.23 to 0.91)] [90 days follow-up]. **Hlatky 2009[122]:** Evidence from one IPD meta-analyses shows that at 1 year angina was significantly less frequent in the CABG group compared to PCI [RR 1.94 (1.75 to 2.16)] [1 year] follow-up. **Hlatky 2009[122]:** Evidence from one IPD meta analyses shows that there was no significant difference between PCI and CABG for death [HR 0.91, 95% CI 0.82 to 1.02)]. There was significantly higher mortality in PCI compared to CABG in patients with diabetes [HR 0.70, 0.56 to 0.87)], however mortality was similar between PCI and CABG groups for patients with no diabetes [HR 0.98, 0.86 to 1.12; p=0.014 for interaction)]. There was no significant difference in mortality between PCI and CABG in patients younger than 55 years [HR 1.25, 0.94 to 1.66)] and in patients aged 55-64 years [HR 0.90 (0.75 to 1.09)], however mortality was significantly lower in CABG compared to PCI in patients 65 years and older [HR 0.82 (0.70 to 0.97) p=0.002 for interaction]. There was no significant difference in mortality between PCI and CABG groups when assessed by bare metal stents [HR 0.94 (0.74 to 1.18)] or balloon angioplasty [HR 0.91 (0.80 to 1.03)] (p=0.19 for interaction). There was no significant difference in mortality between PCI and CABG in patients less than 3 diseased vessels [HR 0.91 (0.78 to 1.06)] or 3 vessel disease [HR 0.91 (0.77 to 1.09)] (p=0.98 for interaction). There was no significant difference in mortality between PCI and CABG in patients with no proximal LAD [HR 0.92 (0.79 to 1.09)] or with proximal LAD [HR 0.90 (0.75 to 1.07)] (p=0.77 for interaction) [median 5.9 years follow-up].
Economic	In people with multi vessel disease who are suitable for both CABG and PCI, PCI is more cost-effective. This evidence has minor limitations and direct applicability but there is some uncertainty around this conclusion.

12.7 Recommendations and link to evidence

Recommendation	**Offer CABG to people with stable angina and suitable coronary anatomy when:** • **their symptoms are not satisfactorily controlled with optimal medical treatment and** • **revascularisation is considered appropriate and** • **PCI is not appropriate.** **Offer PCI to people with stable angina and suitable coronary anatomy when:** • **their symptoms are not satisfactorily controlled with optimal medical treatment and** • **revascularisation is considered appropriate and** • **CABG is not appropriate.** **When either procedure would be appropriate, explain to the person the risks and benefits of PCI and CABG for people with anatomically less complex disease whose symptoms are not satisfactorily controlled with optimal medical treatment. If the person does not express a preference, take account of the evidence that suggests that PCI may be the more cost-effective procedure in selecting the course of treatment.** **When either procedure would be appropriate, take into account the potential survival advantage of CABG over PCI for people with multivessel disease whose symptoms are not satisfactorily controlled with optimal medical treatment and who:** • **have diabetes or** • **are over 65 years or** • **have anatomically complex three-vessel disease, with or without involvement of the left main stem.**
Relative values of different outcomes	Outcomes of interest included long-term mortality (total and cardiovascular), rates of major adverse cardiovascular events (myocardial infarction, stroke, myocardial revascularisation), measures of symptom severity (frequency of angina, exercise test outcomes), and quality of life.

Trade off between clinical benefits and harms	The trials of myocardial revascularisation in this review compared an initial treatment strategy of coronary artery bypass surgery with initial strategies of coronary balloon angioplasty, or percutaneous coronary intervention using either bare-metal or drug-eluting coronary stents. The trials recruited highly selected patients who were considered suitable for either revascularisation strategy, and the trial results do not apply to all patients being considered for myocardial revascularisation procedures in contemporary practice. **Mortality** None of the individual trials of coronary artery bypass surgery versus percutaneous coronary intervention has sufficient statistical power to reliably detect potentially important differences in long-term mortality between the two treatment strategies. Our analysis of pooled data from the trials provides evidence that mortality in the medium to long term is comparable between the two treatment groups. The individual patient data meta-analysis combines data from all larger trials of bypass surgery versus percutaneous coronary intervention and reported no overall difference in mortality between the two treatment strategies. Subgroup analyses demonstrated a significant interaction between age and treatment effect, suggesting that CABG may confer a prognostic advantage in older patients (aged over 65 years). In addition there was a significant interaction between diabetes and treatment effect suggesting that coronary bypass surgery may additionally confer prognostic advantage in people with diabetes. **Stroke** Several trials reported on short term risk of stroke. In our analysis there was an excess risk of stroke in the coronary bypass surgery group (1.0% versus 0.3%) and this was confirmed in the individual patient data meta-analysis (1.1% versus 0.5% at 90 days). The GDG were concerned that the clinical significance of stroke (disabling versus non-disabling) is not reported consistently in the trials, and the difference in stroke risk may be partly due to bias resulting from different protocols for detection and diagnosis of stroke in the two treatment groups. There is no evidence of a difference in stroke risk between the treatment groups beyond the early follow-up phase. **Repeat revascularisation** The trials consistently reported higher rates of repeat (non-protocol) revascularisation in the percutaneous coronary

intervention group than in the surgery group. Revascularisation rates among patients assigned to percutaneous coronary intervention were higher in the early balloon angioplasty trials than in the later bare metal or drug-eluting stent trials (Figure 12.1- figure prepared for GDG)).

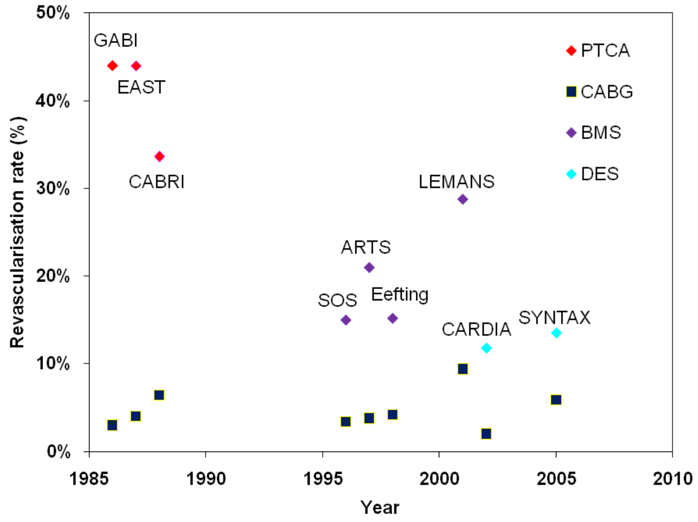

Figure 12.1: revascularisation rates at one year follow-up in trials of percutaneous coronary intervention versus coronary artery bypass surgery. The trials are plotted against the year in which trial recruitment started. For each trial the squares show the revascularisation rate for patients in the surgical group and the diamonds show the rate for patients in the percutaneous coronary intervention group.

Angina

The trials and the individual patient data meta-analysis provide evidence that initial strategies of coronary artery bypass surgery and percutaneous coronary intervention are effective treatments for angina in the medium and long-term. Nevertheless, freedom from angina was consistently higher among patients treated by coronary artery surgery than by percutaneous coronary intervention, both in trials of balloon angioplasty and in trials that used bare metal stents. The magnitude of the difference in angina prevalence between the two treatment strategies is small but was still evident in the ARTS trial after five years. We found no information from randomised trials about the effect of percutaneous coronary intervention with drug-eluting stents on the prevalence of angina.

The results of the trials of PCI versus CABG are consistent across subgroups with single and multi-vessel disease.

Limitations

The patients in the trials of percutaneous coronary intervention versus coronary artery bypass surgery were highly selected and considered angiographically suitable for either revascularisation procedure. For example in RITA-1 22800 patients with a clinical indication for myocardial revascularisation were considered for the trial, 4800 were eligible for the trial, but only 1011 were randomised. Also, eligibility for percutaneous treatment of coronary artery disease has evolved over time as improvements in technique and equipment have allowed treatment of more complex patterns of disease. The trial results may therefore not be generalisable to the wider population of people with stable angina and require cautious interpretation.

The IPD analysis included the BARI and ERACI trials, but these trials were excluded from our analysis because they enrolled a high proportion of patients with acute coronary syndrome. People with acute coronary syndrome are at higher risk of adverse cardiovascular events than people with stable angina and this may influence the relative effects of CABG and PCI on outcome.

Interpretation of the trials of CABG versus PCI is confounded by changes in surgical and interventional technique over time. In particular the introduction of bare-metal and drug-eluting stents has improved the acute results of PCI and reduces the subsequent risk of restenosis and repeat revascularisation procedures[64,66,163]. The IPD meta-analysis[122] included patients from the balloon angioplasty era and is therefore only partially applicable to current practice. On the other hand, inclusion of trials of balloon angioplasty allows analysis of longer term follow-up data, which is not currently available for trials of bare metal or drug-eluting stents.

The IPD meta-analysis reported an interaction between treatment effect and diabetes, with a survival advantage from CABG in people with diabetes. However, recent trials that used bare metal or drug-eluting stents have not demonstrated a survival advantage of surgical revascularisation over a PCI-based strategy (SYNTAX, CARDIA, LEMANS, ARTS, SOS), either in the entire trial populations or in the diabetic subgroups. SYNTAX and CARDIA used first-generation drug-eluting stents, but recent trials have shown that second generation drug-eluting stents are associated with superior clinical outcomes including reduced risks of stent thrombosis and requirement for repeat revascularisation[164,165]. The GDG concluded that the relative effects of PCI with drug-eluting stents and coronary artery bypass surgery on mortality in people with diabetes is uncertain and requires further investigation.

Conclusions

The GDG concluded that there is no definitive evidence that one revascularisation strategy confers a prognostic advantage over the other strategy in contemporary clinical practice.

The trials provide evidence that both revascularisation strategies relieve angina but coronary artery bypass surgery provides slightly better relief of angina in the medium term when compared with balloon angioplasty or percutaneous coronary intervention with bare metal stents.

The choice of revascularisation strategy will depend on many factors including angiographic suitability, patient choice, age, and the presence of diabetes and other comorbidities.

Economic considerations	An original economic model showed that PCI is more cost-effective than CABG in people with multi vessel disease eligible for both procedures. The model had a 10-year time horizon; the probabilities of clinical events at 6 months, 1 year. 2, 3, 5 and 10 years were obtained from the meta-analysis of the studies comparing PCI with stents to CABG included in the clinical review. In the model, patients in the CABG arm experienced overall fewer MI and repeat revascularisations compared to patients in the PCI arm; the incremental QALYs of CABG compared to PCI was 0.069. This small QALY gain does not justify the incremental cost of CABG compared to PCI (£2,427) as the incremental cost-effectiveness ratio is above £30,000/QALY. The higher cost of CABG is due to the higher initial cost of the procedure (£8,552 vs. £4,839 with PCI). There is however some uncertainty around this conclusion and some applicability issues (the population enrolled in the trials on which the model is based might not be representative of the wider population of patients with angina).Variation in patients' preference for one procedure or the other could play a decisive role when establishing the most cost-effective procedure. Therefore, patient preference should be assessed when discussing the revascularisation strategy.
Quality of evidence	We found significant heterogeneity between the trials included in this review, probably partly related to differences in inclusion criteria and to different revascularisation techniques. The economic evidence has minor limitations and direct applicability.
Other considerations	The economic evidence is based on an analysis of data from trials that recruited patients with multivessel disease, as we found only limited data from trials of PCI versus CABG in patients with single vessel disease. Patients undergoing PCI for

	single vessel disease generally require fewer stents than patients with multivessel disease and are therefore likely to incur lower costs. Patients undergoing CABG for single vessel disease may also incur lower costs than patients with multivessel disease, but there is no consistent evidence that the clinical results of the two revascularisation strategies differ between subgroups with single and multivessel disease. The GDG therefore considered that PCI is likely to be a cost-effective strategy in patients with single vessel disease who are suitable for either procedure. Results are available from the SYNTAX trial at one year. The GDG were aware that 3 year results have been presented at international meetings and that these results suggest that, using Syntax score to grade complexitiy, there is potential superiority of CABG for people with complex disease. As the Syntax score is not validated and the analysis of this subgroup was not pre-specified in the trial, the findings could not be considerd definitive. The GDG considered that NICE should be aware of this trial and its importance in the cardiac community.
Recommendation	**Ensure that there is a regular multidisciplinary team meeting to discuss the risks and benefits of continuing drug treatment or revascularisation strategy (CABG or PCI) for people with stable angina. The team should include cardiac surgeons and interventional cardiologists. Treatment strategy should be discussed for the following people, including but not limited to:** • **people with left main stem or anatomically complex three-vessel disease** • **people in whom there is doubt about the best method of revascularisation because of the complexity of the coronary anatomy, the extent of stenting required or other relevant clinical factors and comorbidities.** **Consider the relative risks and benefits of CABG and PCI for people with stable angina using a systematic approach to assess the severity and complexity of the person's coronary disease, in addition to other relevant clinical factors and comorbidities.**
Quality of evidence	No evidence was reviewed for this recommendation.
Other considerations	The GDG considered that review of treatment options for people with stable angina within a multidisciplinary team meeting that includes cardiac surgeons and an interventional

	cardiologists can be helpful. They did not think this is required for all patients but that risks and benefits in individual patients can be finely balanced and treatment decisions may best be made after review and discussion by professionals from different disciplines. The GDG considered that the review of treatment options should be approached systematically, taking account of the severity and complexity of the patient's coronary artery disease and any other relevant clinical factors and comorbidities. The GDG were aware that tools have been developed to support this process and scores that predict risk of revascularisation procedures are in clinical use (e.g. EUROSCORE [www.euroscore.org]). The SYNTAX score was developed to risk stratify participants in the SYNTAX clinical trial and in subgroup analyses high SYNTAX scores were associated with better one year outcome among patients assigned to CABG than among patients assigned to PCI. [153] Longer term follow-up data from the SYNTAX trial, and validation of the SYNTAX score in larger patient populations are not yet published. In the interim, the GDG considered that there is insufficient evidence to recommend the routine use of any particular score or method to decide on appropriate intervention.
Recommendation	**Ensure people with stable angina receive balanced information and have the opportunity to discuss the benefits, limitations and risks of continuing drug treatment, CABG and PCI to help them make an informed decision about their treatment. When either revascularisation procedure is suitable, explain to the person:** • **The main purpose of revascularisation is to improve the symptoms of stable angina.** • **CABG and PCI are effective in relieving symptoms.** • **Repeat revascularisation may be necessary after either CABG or PCI and the rate is lower after CABG.** • **Stroke is uncommon after either CABG or PCI, and the incidence is similar between the two procedures.** • **There is a potential survival advantage with CABG for some people with multivessel disease.** **Inform the person about the practical aspects of CABG and PCI. Include information about:**

	• **vein and/or artery harvesting** • **likely length of hospital stay** • **recovery time** • **drug treatment after the procedure.**
Quality of evidence	No evidence was specifically reviewed for these recommendations.
Other considerations	These recommendations were informed by the evidence from the reviews on medical versus revascularisation treatment and PCI versus CABG and by the professional opinion and views of the GDG The GDG considered it important that patients are given full information about the relative benefits and risks of continuing medical therapy or undergoing revascularisation. The areas of information listed by the GDG is not exhaustive but included the areas they considered should be included in informing patients.

12.8 Research recommendation A

The GDG recommended the following research question:

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

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

12.9 Research recommendation B

The GDG recommended the following research question:

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

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

13 Secondary prevention

13.1 Introduction

The aim of treatment for people with stable angina is to reduce symptoms suffered by patients and also to improve long term outcomes. Secondary prevention measures are important to reduce the progression of cardiovascular disease and are of established benefit for patients in certain circumstances e.g. post myocardial infarction – NICE Clinical Guideline 48 MI: Secondary prevention. NICE have also published a guideline NICE Clinical Guideline 67 Lipid modification which recommends statins for all patients with evidence of cardiovascular disease. This review therefore examined the evidence for use of aspirin and ace inhibitors in people with stable angina.

13.2 Aspirin

Aspirin is an anti-platelet agent. Anti-platelet agents decrease platelet aggregation and may inhibit thrombus formation. Clopidogrel and dypiridamole do not have licences for use in stable angina.

13.2.1 Clinical question

What is the clinical effectiveness of aspirin to improve long term outcomes in people with stable angina?

13.2.2 Clinical evidence

The "Review Protocol" for this topic can be found in Appendix C, the "Search Strategies" in Appendix D, the "List of Included and Excluded Studies" in Appendix E1, the "Clinical Evidence Tables" in Appendix E2, and the "Forest Plots" in Appendix F.

Table 13.1: Aspirin vs. placebo for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	Placebo	Relative (95% CI)	Absolute	
Non fatal MI (follow-up 50-60 months)											
Juul-Moller 1992[166]; Ridker 1991[167]	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	14/1187 (1.2%)	94/1181 (8%)	RR 0.14 (0.08 to 0.25)	69 fewer per 1000 (from 60 fewer to 74 fewer)	⊕⊕⊕O MODERATE
Fatal MI (follow-up 50-60 months)											
Juul-Moller 1992[166]; Ridker 1991[167]	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (g)	None	15/1187 (1.3%)	19/1181 (1.6%)	RR 0.79 (0.41 to 1.53)	3 fewer per 1000 (from 9 fewer to 8 more)	⊕⊕OO LOW
Cardiovascular death (follow-up 60.2 months)											
Ridker 1991[167] (d)	randomised trial	serious (b)	no serious inconsistency	no serious indirectness	serious imprecision (g)	None	6/178 (3.4%)	7/155 (4.5%)	RR 0.75 (0.26 to 2.17)	11 fewer per 1000 (from 33 fewer to 53 more)	⊕⊕OO LOW
Sudden death (follow-up median 50 months)											
Juul-Moller 1992[166]; (e)	randomised trial	serious (c)	no serious inconsistency	no serious indirectness	serious imprecision (g)	None	19/1009 (1.9%)	31/1026 (3%)	RR 0.62 (0.35 to 1.1)	11 fewer per 1000 (from 20 fewer to 3 more)	⊕⊕OO LOW
Vascular events (follow-up median 50 months) (f)											
Juul-Moller 1992[166];	randomised trial	serious (c)	no serious inconsistency	no serious indirectness	serious imprecision (h)	None	108/1009 (10.7%)	161/1026 (15.7%)	RR 0.68 (0.54 to 0.86)	50 fewer per 1000 (from 22 fewer to 72 fewer)	⊕⊕OO LOW
Vascular deaths (follow-up median 50 months)											
Juul-Moller 1992[166];	randomised trial	serious (c)	no serious inconsistency	no serious indirectness	serious imprecision (g)	None	51/1009 (5.1%)	70/1026 (6.8%)	RR 0.74 (0.52 to 1.05)	18 fewer per 1000 (from 33 fewer to 3 more)	⊕⊕OO LOW
All cause mortality (follow-up median 50 months)											
Juul-Moller 1992[166];	randomised trial	serious (c)	no serious inconsistency	no serious indirectness	serious imprecision (g)	None	82/1009 (8.1%)	106/1026 (10.3%)	RR 0.79 (0.6 to 1.04)	22 fewer per 1000 (from 41 fewer to 4 more)	⊕⊕OO LOW
Haemorrhagic adverse events (follow-up median 50 months)											
Juul-Moller 1992[166];	randomised trial	serious (c)	no serious inconsistency	no serious indirectness	serious imprecision (g)	None	27/1009 (2.7%)	16/1026 (1.6%)	RR 1.72 (0.93 to 3.17)	12 more per 1000 (from 1 fewer to 35 more)	⊕⊕OO LOW
Non haemorrhagic adverse events (follow-up median 50 months)											

Juul-Moller 1992[166];	randomised trial	serious (c)	no serious inconsistency	no serious indirectness	serious imprecision (g)	None	174/1009 (17.2%)	168/1026 (16.4%)	RR 1.05 (0.87 to 1.28)	8 more per 1000 (from 21 fewer to 46 more)	⊕⊕OO LOW

(a) Juul-Moller 1992[158]: Multicentre Randomised, double blind, low drop out rate (0.5% drop out after 50 months), sample size calculation reported, baseline comparisons made, Allocation concealment not reported, Intention to treat analysis not reported. Ridker 1991 Juul-Moller 1992[158]: Randomised, double blind, baseline comparisons made, Intention to treat analyses used. Allocation concealment not reported.

(b) Ridker 1991[159]: Randomised, double blind, baseline comparisons made, Intention to treat analyses used. Allocation concealment not reported.

(c) Juul-Moller 1992[158]: Multicentre randomised, double blind, low drop out rate (0.5% drop out after 50 months), sample size calculation reported, baseline comparisons made. Allocation concealment not reported, Intention to treat analysis not reported.

(d) Drug dosage: Alternate day aspirin therapy (325 mg)

(e) Drug dosage: Aspirin 75 mg daily. All patients were treated with Sotalol, median dose was 160 (40-480 mg) daily.

(f) Vascular events (first occurrence of MI, stroke or vascular death)

(g) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.

(h) 95% CI around the pooled estimate of effect includes appreciable benefit or appreciable harm.

13.2.3 Economic evidence

No economic studies were identified on this question. We calculated the daily and annual cost of aspirin based on the unit cost reported in the BNF59[19].

Table 13.2: Drug cost – aspirin

	Cost per day (£)	Cost per year (£)
Aspirin 75 mg, 1/day	0.035	12.8

The costs of adverse effects were not estimated.

13.2.4 Evidence statements

Clinical

Aspirin vs. placebo

Juul-Moller 1992[166]; Ridker 1991[167]: Evidence from 2 RCTs shows that there were significantly fewer patients with non fatal MI in the aspirin group compared to placebo. [RR 0.14 (0.08 to 0.25)] (Follow-up 50-60 months).

Juul-Moller 1992[166]; Ridker 1991[167]: Evidence from 2 RCTs shows that there was no significant difference between aspirin and placebo for fatal [MI RR 0.79 (0.41 to 1.53)]. (Follow-up 50-60 months)

Ridker 1991[167]: Evidence from one RCT shows that there was no significant difference between aspirin and placebo for cardiovascular death [RR 0.75 (0.26 to 2.17)](follow-up 60.2 months).

Juul-Moller 1992[166]: Evidence from one RCT shows that there were significantly fewer vascular events (first occurrence of MI, stroke or vascular death) in the aspirin group compared to placebo [RR 0.68 (0.54 to 0.86)] (Follow-up median 50 months).

Juul-Moller 1992[166]: Evidence from one RCT shows that there was no significant difference between aspirin and placebo for sudden death [RR 0.62 (0.35 to 1.1)], vascular deaths (i.e, fatal vascular events) [RR 0.74 (0.52 to 1.05)] and all cause mortality [RR 0.79 (0.6 to 1.04)] (Follow-up median 50 months).

Juul-Moller 1992[166]: Evidence from one RCT shows that there was no significant difference between aspirin and placebo for haemorrhagic adverse events [RR 1.72 (0.93 to 3.17)] and non-haemorrhagic adverse events [RR 1.05 (0.87 to 1.28)] (Follow-up median 50 months).

Economic	No economic evidence was found on this question. A simple cost analysis showed low drug costs of aspirin.

13.2.5 Recommendations and link to evidence

Recommendation	**Consider aspirin 75 mg daily for people with stable angina, taking into account the risk of bleeding and comorbidities.**
Relative values of different outcomes	The GDG were interested in a reduction in morbidity and mortality associated with use of aspirin for secondary prevention.
Trade off between clinical benefits and harms	Aspirin use was associated with statistically significant reduction of non fatal MI and vascular events. All cause mortality and vascular deaths were not statistically significant but the GDG was impressed by a clinically significant risk reduction which approached statistical significance. There was a trend towards increased bleeding risk associated with the use of aspirin. The GDG were aware of recent debates concerning the use of aspirin for primary prevention and considered it likely that within the population of people with stable angina some are at higher risk of future cardiovascular events than others. For those at lowest risk the harms from aspirin might outweigh the benefits but there is currently no way of risk stratifying people with stable angina
Economic considerations	The small drug cost of treatment with aspirin is likely to be offset by the improvement in clinical outcomes.
Quality of evidence	The quality for outcomes was low using GRADE methodology and the lack of precision contributed to this. The GDG however considered that the quality of the evidence was adequate to make a recommendation and consistent with what is known about use of aspirin across primary and secondary prevention.
Other considerations	The GDG agreed that aspirin should be considered for people with stable angina but did not think it should be offered to all patients. Healthcare professionals should take into consideration bleeding risk and co-morbidities when considering prescription of aspirin.

13.3 ACE Inhibitors

ACE inhibitors (angiotensin converting enzyme inhibitors) block the conversion of angiotensin 1 to angiotensin 11. They therefore lower arteriolar resistance and increase venous capacity; increase cardiac output and lower renovascular resistance. They are used to treat raised blood pressure but have been shown also to be beneficial for people with conditions such as heart failure.

13.3.1 Clinical question

What is the clinical /cost effectiveness of ACE inhibitors /ARBs for the management of angina?

13.3.2 Clinical evidence

The “Review Protocol” for this topic can be found in Appendix C, the “Search Strategies” in Appendix D, the “List of Included and Excluded Studies” in Appendix E1, the “Clinical Evidence Tables” in Appendix E2, and the “Forest Plots” in Appendix F.

Table 13.3: ACE inhibitors +background medication vs. placebo +background medication

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ACE +background medication	Placebo +background medication	Relative (95% CI)	Absolute		
Combined (death from CV causes or non fatal MI) (follow-up mean 4.8 years)												
Braunwald 2004 (PEACE)	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	344/4158 (8.3%)	352/4132 (8.5%)	RR 0.97 (0.84 to 1.12)	3 fewer per 1000 (from 14 fewer to 10 more)	⊕⊕⊕O MODERATE	
Combined (MI, stroke, or death from CV causes) (follow-up mean 5 years)												
Yusuf 2000 (HOPE trial)	randomised trials	no serious limitations[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	651/4645 (14%)	826/4652 (17.8%)	RR 0.79 (0.72 to 0.87)	37 fewer per 1000 (from 23 fewer to 50 fewer)	⊕⊕⊕⊕ HIGH	
Death from cardio vascular causes (follow-up 3-5 years)												
Braunwald 2004 (PEACE); Yusuf 2000 (HOPE trial); Pitt 2001(QUIET)[k]	randomised trials	Serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	441/9681 (4.6%)	543/9656 (5.6%)	RR 0.81 (0.72 to 0.92)	11 fewer per 1000 (from 4 fewer to 16 fewer)	⊕⊕⊕O MODERATE	
Death from non cardiovascular or unknown causes (follow-up 3-5 years)												
Braunwald 2004 (PEACE); Yusuf 2000 (HOPE trial); Pitt	randomised trials	Serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	367/9681 (3.8%)	387/9656 (4%)	RR 0.95 (0.82 to	2 fewer per 1000 (from 7 fewer to 4	⊕⊕⊕O MODERATE	

2001(QUIET)									1.09)	more)		
All causes death (follow-up 3-5 years)												
Yusuf 2000 (HOPE trial); Pitt 2001(QUIET)	randomised trials	Serious[d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	509/5523 (9.2%)	596/5524 (10.8%)	RR 0.85 (0.76 to 0.96)	16 fewer per 1000 (from 4 fewer to 26 fewer)	⊕⊕⊕O MODERATE	
Death from CHF (follow-up mean 4.8 years)												
Braunwald 2004 (PEACE)[j]	randomised trials	Serious[e]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/4158 (0.4%)	25/4132 (0.6%)	RR 0.6 (0.31 to 1.13)	2 fewer per 1000 (from 4 fewer to 1 more)	⊕⊕⊕O MODERATE	
Non fatal MI (MI in HOPE trial) (follow-up 3-5 years)												
Braunwald 2004 (PEACE); Yusuf 2000 (HOPE trial); Pitt 2001(QUIET)	randomised trials	Serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	717/9681 (7.4%)	830/9656 (8.6%)	RR 0.86 (0.78 to 0.95)	12 fewer per 1000 (from 4 fewer to 19 fewer)	⊕⊕⊕O MODERATE	
Stroke (follow-up mean 5 years)												
Yusuf 2000 (HOPE trial)[g], [h],[i]	randomised trials	no serious limitations (b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	156/4645 (3.4%)	226/4652 (4.9%)	RR 0.69 (0.57 to 0.84)	15 fewer per 1000 (from 8 fewer to 21 fewer)	⊕⊕⊕⊕ HIGH	
Revascularisation (follow-up mean 5 years)												
Yusuf 2000 (HOPE trial)	randomised trials	no serious limitations[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	742/4645 (16%)	852/4652 (18.3%)	RR 0.87 (0.8 to 0.95)	24 fewer per 1000 (from 9 fewer to 37	⊕⊕⊕⊕ HIGH	

										fewer)		
Hospitalised with unstable angina (follow-up mean 3-5 years)												
Yusuf 2000 (HOPE trial); Pitt 2001(QUIET)	randomised trials	Serious[d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	606/5523 (11%)	610/5524 (11%)	RR 0.99 (0.89 to 1.11)	1 fewer per 1000 (from 12 fewer to 12 more)	⊕⊕⊕O MODERATE	
Hospitalisation due to CHF (follow-up 4.8-5 years)												
Braunwald 2004 (PEACE); Yusuf 2000 (HOPE trial)	randomised trials	Serious[f]	no serious inconsistency	no serious indirectness	no serious imprecision	none	246/8803 (2.8%)	294/8784 (3.3%)	RR 0.84 (0.71 to 0.99)	5 fewer per 1000 (from 0 fewer to 10 fewer)	⊕⊕⊕O MODERATE	

(a) *PEACE trial 2004: block randomisation, double blind, sample size calculation reported, large sample (n=8290), Loss to follow-up (1.6% (68) in the placebo group and 1.6% (66) in the trandolapril group) and intention to treat analysis used. Allocation concealment not reported.*

(b) *Yusuf 2000 (HOPE trial): Large sample (n=9297, n=4645 in ramipril (10 mg o.d) and n=4652 in placebo) . Randomised. Double blind. Baseline comparisons made. ITT used.*

(c) *PEACE trial 2004: - block randomisation, double blind, sample size calculation reported, large sample (n=8290), Loss to follow-up (1.6% (68) in the placebo group and 1.6% (66) in the trandolapril group) and intention to treat analysis used. Allocation concealment not reported. QUIET trial 2001: Strengths - randomised, double blind, baseline comparisons made, sample size calculation reported, four patients lost to follow-up at 3 years, intention to treat analysis used, Weakness- Allocation concealment not reported. HOPE trial: Randomised. allocation concealment reported. sample size calculation reported. ITT used.*

(d) *QUIET 2001: randomised, double blind, baseline comparisons made, sample size calculation reported, four patients lost to follow-up at 3 years, intention to treat analysis used. Allocation concealment not reported. Qunapril 20/mg . Yusuf 2000 (HOPE trial): Large sample (n=9297). Randomised. baseline comparisons made. Double blind. ITT used.*

(e) *PEACE trial 2004: block randomisation, double blind, sample size calculation reported, large sample (n=8290), Loss to follow-up (1.6% (68) in the placebo group and 1.6% (66) in the trandolapril group) and intention to treat analysis used. Allocation concealment not reported.*

(f) *PEACE trial 2004: block randomisation, double blind, sample size calculation reported, large sample (n=8290), Loss to follow-up (1.6% (68) in the placebo group and 1.6% (66) in the trandolapril group) and intention to treat analysis used. Allocation concealment not reported. Yusuf 2000 (HOPE trial): Large sample (n=9297) . Randomised. Baseline comparisons made. Double blind. ITT used.*

(g) *stable angina: 2544/4645 in ramipril group and 2618/4652 in placebo.*

(h) *Permanent discontinuation of treatment: 1343/4645 in ramipril group, 1268/4652 in placebo. More patients in the ramipril group than in the placebo group stopped treatment because of cough or hypotension or dizziness. More patients in the placebo group than in the ramipril group stopped treatment because of uncontrolled hypertension or because of a clinical event.*

(i) *Background medication in HOPE trial: BB-39.2% in ramipril and 39.8% in placebo. Aspirin: 75.3% in ramipril and 76.9% in placebo. Lipid lowering agents: 28.4% in ramipril and 28.8% in placebo. CCB: 46.3% in ramipril and 47.9% in placebo.*
(j) *Background medication PEACE trial: CCB – 36% inTrandolapril and 35% in placebo; BB-60% in Trandolapril and placebo groups; Aspirin or antiplatelet medication-90% in Trandolapril and 91% in placebo; Lipid lowering drug- 70% in Trandolapril and placebo groups; digitalis- 4% in Trandolapril and placebo groups; antiarrhythmic agents-2% in Trandolapril groups; anticoagulant-5% in Trandolapril and placebo groups; Insulin- 4% in Trandolapril and placebo groups.*
(k) *Background medication QUIET trial: Lipid lowering agents: 0.1% ; BB- 26%; CCB- 0%; Nitrates- 41%; aspirin- 73%*

Table 13.4: ACE inhibitors+BB vs. BB

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ACE+BB	BB	Relative (95% CI)	Absolute	
Exercise time (min) (follow-up 12 weeks; better indicated by higher values)											
Klein 1990[168] (c)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	23	23	-	MD 0.2 higher (1.16 lower to 1.56 higher)	⊕⊕OO LOW
Time to 1mm ST segment depression (min) (follow-up 12 weeks; better indicated by higher values)											
Klein 1990[168]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	None	23	23	-	MD 0.2 higher (1.3 lower to 1.7 higher)	⊕⊕OO LOW

(a) *Klein 1990[162] : Randomised, cross over, double blind, baseline comparisons made. 6% (2/31) lost to follow-up. Allocation concealment not reported, Intention to treat analysis not used.*

(b) *95% CI includes no effect and the upper and lower CI crosses the MID.*

(c) *Drugs used: Benazepril 10 mg twice daily plus metoprolol OROS, 14/190 mg once daily or metoprolol OROS, 14/190 mg (release rate/total dose) once daily.*

Table 13.5: ACE inhibitors + background medication vs. nifedipine + background medication

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ACE +background medication	Nifedipine + background medication	Relative (95% CI)	Absolute	
Combined Cardiac events (follow-up 3 years) (f)											
Yui 2004[169] (e,i)	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	106/822 (12.9%)	116/828 (14%)	RR 0.92 (0.72 to 1.18)	11 fewer per 1000 (from 39 fewer to 25 more)	⊕⊕OO LOW
Sudden death or cardiac death (follow-up 3 years)											
Yui 2004[169]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	6/822 (0.7%)	6/828 (0.7%)	RR 1.01 (0.33 to 3.11)	0 more per 1000 (from 5 fewer to 15 more)	⊕⊕OO LOW
MI (follow-up 3 years)											
Yui 2004[169]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	13/822 (1.6%)	16/828 (1.9%)	RR 0.82 (0.4 to 1.69)	3 fewer per 1000 (from 12 fewer to 13 more)	⊕⊕OO LOW
Hospitalisation for angina pectoris (follow-up 3 years)											
Yui 2004[169]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	56/822 (6.8%)	50/828 (6%)	RR 1.13 (0.78 to 1.63)	8 more per 1000 (from 13 fewer to 38 more)	⊕⊕OO LOW
Hospitalisation for HF (follow-up 3 years)											
Yui 2004[169]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	9/822 (1.1%)	12/828 (1.4%)	RR 0.76 (0.32 to 1.78)	3 fewer per 1000 (from 10 fewer to 11 more)	⊕⊕OO LOW
Non cardiac death (follow-up 3 years)											
Yui 2004[169]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	9/822 (1.1%)	6/828 (0.7%)	RR 1.51 (0.54 to 4.23)	4 more per 1000 (from 3 fewer to 23 more)	⊕⊕OO LOW
Total mortality (follow-up 3 years)											
Yui 2004[169]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	15/822 (1.8%)	12/828 (1.4%)	RR 1.26 (0.59 to 2.67)	4 more per 1000 (from 6 fewer to 24 more)	⊕⊕OO LOW
Adverse events (follow-up 3 years) (g)											
Yui 2004[169]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (c)	none	121/822 (14.7%)	76/828 (9.2%)	RR 1.6 (1.22 to 2.1)	55 more per 1000 (from 20 more to 101 more)	⊕⊕OO LOW

Withdrawal due to adverse effects (follow-up 3 years) (h)											
Yui 2004[169]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (c)	none	72/822 (8.8%)	41/828 (5%)	RR 1.77 (1.22 to 2.56)	38 more per 1000 (from 11 more to 77 more)	⊕⊕OO LOW
Diabetes sub group (combined cardiac events) (follow-up 3 years)											
Yui 2004 (Subgroup Diabetes)[170]	randomised trials	serious (d)	no serious inconsistency	no serious indirectness	serious (b)	none	26/173 (15%)	30/199 (15.1%)	RR 1 (0.61 to 1.62)	0 fewer per 1000 (from 59 fewer to 93 more)	⊕⊕OO LOW
Diabetes sub group (cardiac death or sudden death) (follow-up 3 years)											
Yui 2004 (Subgroup Diabetes)[170]	randomised trials	serious (d)	no serious inconsistency	no serious indirectness	serious (b)	none	3/173 (1.7%)	1/199 (0.5%)	RR 3.45 (0.36 to 32.87)	12 more per 1000 (from 3 fewer to 160 more)	⊕⊕OO LOW
Diabetes sub group (MI) (follow-up 3 years)											
Yui 2004 (Subgroup Diabetes)[170]	randomised trials	serious (d)	no serious inconsistency	no serious indirectness	serious (b)	none	4/173 (2.3%)	4/199 (2%)	RR 1.15 (0.29 to 4.53)	3 more per 1000 (from 14 fewer to 71 more)	⊕⊕OO LOW
Diabetes sub group (hospitalisation for angina pectoris) (follow-up 3 years)											
Yui 2004 (Subgroup Diabetes)[170]	randomised trials	serious (d)	no serious inconsistency	no serious indirectness	serious (b)	none	12/173 (6.9%)	16/199 (8%)	RR 0.86 (0.42 to 1.77)	11 fewer per 1000 (from 47 fewer to 62 more)	⊕⊕OO LOW
Diabetes sub group (Hospitalisation for HF) (follow-up 3 years)											
Yui 2004 (Subgroup Diabetes)[170]	randomised trials	serious (d)	no serious inconsistency	no serious indirectness	serious (b)	none	5/173 (2.9%)	8/199 (4%)	RR 0.72 (0.24 to 2.16)	11 fewer per 1000 (from 31 fewer to 47 more)	⊕⊕OO LOW
Diabetes sub group (Total mortality)											
Yui 2004 (Subgroup Diabetes)[170]	randomised trials	serious (d)	no serious inconsistency	no serious indirectness	serious (b)	none	5/173 (2.9%)	2/199 (1%)	RR 2.88 (0.57 to 14.64)	19 more per 1000 (from 4 fewer to 137 more)	⊕⊕OO LOW

(a) Yui 2004[163]: Randomised, open, blinded endpoint design, sample size calculation reported, Intention to treat analysis used. concealment of allocation not reported
(b) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.
(c) 95% CI around the pooled estimate of effect includes appreciable benefit or appreciable harm.
(d) Yui 2004 (Subgroup Diabetes)[164]: Randomised, open, blinded endpoint design, sample size calculation reported, Intention to treat analysis used. Allocation concealment not used.
(e) Drugs used: nifedipine retard (long-acting nifedipine 20-40 mg/day) OR an ACE inhibitor (Enalapril 5-10 mg/day, Imidapril 5-10 mg/day, or Lisinopril 10-20 mg/day)
(f) Combined cardiac events (cardiac death or sudden death, MI, angina pectoris requiring hospitalisation, HF requiring hospitalisation, serious arrhythmia, performance of coronary interventions)
(g) The major adverse events occurring in the nifedipine group were those related to vasodilatory effect, including hypotension, facial erythema, and hot flushes. On the other hand dry cough accounted for most of the adverse events occurring in the ACE inhibitor group.

(h) The main reasons for withdrawal were vasodilatory effect in the nifedipine group and predominantly cough in the ACE inhibitor group.
(i) Medications used before the observation period- nifedipine group (67%) and ACE group (65%) on nitrates; nifedipine group (21%) and ACE group (18%) on BB; nifedipine group (52%) and ACE group (49%) o n CCB . If the anti anginal effect of the treatment was inadequate, long-acting or short-acting nitrates and/or BB were used concomitantly.

13.3.3 Economic evidence

No economic studies were identified on this question. We calculated the daily and annual cost of a standard treatment with the most used ACE inhibitor based on the unit cost reported in the BNF59[19].

Table 13.6: Drug cost - ACE inhibitors

	Additional cost per day (£)	Additional cost per year (£)
Ramipril tablets, 5mg, 1/day	0.07	25.6

The costs of adverse effects were not estimated.

13.3.4 Evidence statements

Clinical	**<u>ACE inhibitors +background medication vs. placebo + background medication</u>** **Braunwald 2004 (PEACE trial)**: Evidence from one RCT shows that there was no significant difference between ACE inhibitors and placebo for combined cardiac events (death from CV causes or non fatal MI) [RR 0.97 (0.84 to 1.12)], and death from CHF [RR 0.6 (0.31 to 1.13)] [Follow-up mean 4.8 years]. **Yusuf 2000 (HOPE trial):** Evidence from one RCT shows that there were significantly fewer combined cardiac events (MI, stroke or death from CV causes), revascularisation [RR 0.87 (0.8 to 0.95)] and stroke [RR 0.69 (0.57 to 0.84)] in the ACE inhibitor group compared to placebo group [RR 0.79 (0.72 to 0.87)] [Follow-up 5 years]. **Braunwald 2004 (PEACE trial); Pitt 2001 (QUIET trial); HOPE trial 2000:** Evidence from 3 RCT's shows that there were significantly fewer death from CV causes [RR 0.81 (0.72 to 0.92)], and non fatal MI [RR 0.86 (0.78 to 0.95)] in the ACE inhibitors group compared to placebo group. There was no significant difference between ACE inhibitors and placebo death from non cardiovascular or unknown causes [RR 0.95 (0.82 to 1.09)] [Follow-up 3–5 years]. **Yusuf 2000 (HOPE trial); Pitt 2001 (QUIET trial):** Evidence from 2 RCTs shows that there were significantly fewer all causes death [RR 0.85 (0.76 to 0.96)], in the ACE inhibitors group compared to placebo group. There was no significant difference between ACE inhibitor group and placebo for hospitalisation due to unstable

angina [RR 0.99 (0.89 to 1.11)] [Follow-up 3- 5 years]

Yusuf 2000 (HOPE trial); Braunwald 2004 (PEACE trial): Evidence from 2 RCTs shows that there were significantly fewer hospitalisation due to CHF in the ACE inhibitors group compared to placebo group [RR 0.84 (0.71 to 0.99)] [Follow-up 4.8–5 years].

ACE inhibitors+BB vs. BB

Klein 1990[168]: Evidence from one underpowered RCT shows that there was no significant difference between ACE + BB compared to BB for exercise time (min) [MD 0.2 (-1.16 to 1.56)] and time to 1 mm ST segment depression (min) [MD 0.2 (-1.3 to 1.7)] [Follow-up 12 weeks].

ACE inhibitors+ background medication vs. nifedipine + background medication

Yui 2004[169]: Evidence from one RCT shows that there was no significant difference between ACE inhibitor and nifedipine for combined cardiac events (cardiac death or sudden death, MI, angina pectoris requiring hospitalisation, HF requiring hospitalisation, serious arrhythmia, performance of coronary interventions) [RR 0.92 (0.72 to 1.18)], sudden death or cardiac death [RR 1.01 (0.33 to 3.11)], MI [RR 0.82 (0.4 to 1.69)], hospitalisation for angina pectoris [RR 1.13 (0.78 to 1.63)], hospitalisation for HF [RR 0.76 (0.32 to 1.78)], non cardiac death [RR 1.51 (0.54 to 4.23)] and total mortality [RR 1.26 (0.59 to 2.67)] [Follow-up 3 years].

Yui 2004 (Diabetes Subgroup)[170]: Evidence from one RCT shows that there was no significant difference between ACE inhibitor and nifedipine in diabetes sub group of patients for combined cardiac events (cardiac death or sudden death, MI, angina pectoris requiring hospitalisation, HF requiring hospitalisation, serious arrhythmia, performance of coronary interventions) [RR 1 (0.61 to 1.62)], cardiac death or sudden death [RR 3.45 (0.36 to 32.87)], MI [RR 1.15 (0.29 to 4.53)], hospitalisation for angina pectoris [RR 0.86 (0.42 to 1.77)], hospitalisation for HF [RR 0.72 (0.24 to 2.16)] and total mortality [RR 2.88 (0.57 to 14.64)] [Follow-up 3 years].

Yui 2004[169]: Evidence from one RCT shows that there were significantly more adverse events [RR 1.6 (1.22 to 2.1)] and more withdrawals due adverse events [RR 1.77 (1.22 to 2.56)] in the ACE inhibitor group compared to nifedipine group [Follow-up 3 years]

Economic	No economic evidence was found on this question. A simple cost analysis showed a low additional cost of adding ACE-inhibitors to standard treatment.

13.3.5 Recommendations and link to evidence

Recommendation	**Consider angiotensin-converting enzyme (ACE) inhibitors for people with stable angina and diabetes. Offer or continue ACE inhibitors for other conditions, in line with relevant NICE guidance.**
Relative values of different outcomes	The GDG were interested in intermediate and longterm morbidity and mortality outcomes when evaluating the value of ACE inhibitors for people with stable angina.
Trade off between clinical benefits and harms	Evidence from one large trial (HOPE) suggests that ACE inhibitors reduce the combined end point of MI, stroke or death from cardiovascular causes, and the rates of stroke and revascularisation. Two RCTs (HOPE, QUIET) showed lower all cause death with ACE inhibitors. Two large trials (HOPE, PEACE) showed significantly lower rates of hospitalisation due to heart failure with ACE inhibitors. Combined evidence from three randomised trials (HOPE, QUIET, PEACE) showed death from cardiovascular causes, non fatal MI, and revascularisation to be significantly lower with use of ACE inhibitors. There was no evidence available for ARB's in the management of stable angina.
Economic considerations	There is a low additional cost of adding ACE-inhibitors to standard treatment while the clinical evidence showed significant improvements in health outcomes for some patients. Therefore ACE-inhibitors are likely to be cost-effective.
Quality of evidence	Moderate and high quality evidence for outcomes was available. No economic evidence was available on this question.
Other considerations	The GDG noted that use of other medications and some population characteristics differed in the studies available for this review. In the PEACE trial 90% of patients were taking aspirin and 70% were taking lipid lowering drugs. 18% of the population was diabetic. In this trial there was no significant effect from ACE inhibitors on major end points. In the HOPE trial 38% of the population was diabetic and 75% were

taking aspirin and 28% lipid lowering drugs. This trial showed reduced combined cardiac events. The GDG considered that the evidence did not indicate that all people with angina should be offered an ACE inhibitor. The GDG considered that patients who have had a myocardial infarction will already be on an ACE inhibitor as will many patients for hypertension, heart failure or kidney disease. The GDG considered that the evidence suggested potential benefit for diabetic patients and if diabetic patients are not already taking ACE inhibitor health care professionals should consider offering ACE inhibitors.

13.4 Further secondary prevention approaches covered by other NICE Clinical Guidelines

The use of statins and the treatment of high blood pressure are the subjects of other NICE Clinical Guidelines. Listed below are the details of the interventions and the recommendations made in the NICE TA.

13.4.1 Statins–NICE Clinical Guideline 67 (March 2010)

“Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease”

Recommendation	**Offer statin treatment in line with 'Lipid modification' (NICE clinical guideline 67).**

13.4.2 Hypertension- NICE Clinical Guideline 34 (June 2006)

“Management of hypertension in adults in primary care”

Recommendation	**Offer treatment for high blood pressure in line with 'Hypertension' (NICE clinical guideline 34)*.** * NICE is updating clinical guideline 34 on hypertension (publication expected August 2011).

14 Risk scores

14.1 Introduction

The GDG were interested in whether there were scoring systems available that would predict adverse outcomes. Ideally clinicians would like to be able to predict which patients were likely to have an adverse outcome and to intervene in those patients. In the absence of clear evidence for benefit of pharmacological or revascularistion strategies this might mean providing more intensive education and rehabilitation and support programmes to help patients to engage in secondary prevention strategies.

In this chapter we address the following key clinical question:

In adults with stable angina which tables, equations, engines, models or scoring systems are most reliable/effective for prognostic-risk stratification in prediction of adverse cardiac outcomes?

Two risk scoring systems were found that have been developed to predict adverse outcomes in patients with stable angina. The two risk scoring systems are: ACTION score-derived from a clinical trial population (ACTION trial)[171] and Euro heart Angina score - derived from a large cohort population (Euro Heart survey[172]).

14.2 Clinical Evidence

The "Review Protocol" for this topic can be found in Appendix C, the "Search Strategies" in Appendix D, the "List of Included and Excluded Studies" in Appendix E1, and the "Clinical Evidence Tables" in Appendix E2.

Derivation of risk scores

For each risk score, multivariate analysis of baseline characteristics was performed to ascertain those characteristics which were most strongly associated with adverse outcomes- death or MI in Euro heart Angina score; and death all causes, MI or disabling stroke in the ACTION score. Risk scores were generated from the coefficients with an appropriate number of points given for the presence of each risk factor.

The components of each of the risk scores are shown below:

A. ACTION risk score for death, MI or disabling stroke at 4.9 years follow-up:

Age, left ventricular ejection fraction, smoking, white blood cell count, diabetes, casual blood glucose concentration, creatinine concentration, previous stroke, at least one attack a week, coronary angiographic findings (if available), lipid lowering treatment, QT interval, systolic blood pressure ≥ 155 mm Hg, number of drugs used for angina, previous MI, sex.

B. Euro heart Angina score for death or MI at one year follow-up:

co-morbidity, diabetes, duration of symptoms, severity of symptoms, resting electrocardiogram abnormalities, abnormal ventricular function

14.2.1 ACTION risk score

Clayton 2005[171]

This study used data from the ACTION trial (a coronary disease trial investigating outcome with nifedipine GITS), which followed 7665 patients with stable symptomatic angina for a mean of 4.9 years, to develop a score for predicting the combined risk of death from any cause, MI or stroke.

Participants: The Model was based on 7311 patients with values for all variables in model, of who 1063 had the combined event of death, MI, or disabling stroke.

Inclusion criteria In the ACTION trial: Eligible patients had stable symptomatic angina requiring treatment and either previous MI or proved angiographic coronary artery disease. Patients without a previous MI or coronary angiography could participate only if there was a positive result on an exercise or perfusion test. Key exclusions were ejection fraction below 40%, clinically significant heart failure, major cardiovascular event or intervention within the past 3 months, planned coronary angiography or intervention, and known intolerance to dihydropyridines. The patients were recruited from outpatient cardiology clinics in Western Europe, Israel, Canada, Australia, and New Zealand.

Outcomes and follow-up: The outcome measures were death from any cause or MI or disabling stroke with a follow-up of 4.9 years.

Statistical analysis: Multivariate Cox proportional hazard models used for the outcome time to death, MI, or disabling stroke as adjudicated by the critical events committee, using patients who had no missing values for the predictor variables. Each variables strength of predictive contribution was expressed by its z score (the model co-efficient divided by its standard error) and quantified each variables predictive power as hazard ratio with 95% CI.

For each patient, the risk score was calculated by multiplying each coefficient in the final model by 10, then by the patient's variable value, and then summed up the results.

Results: Table 1 shows the 16 variables, with the risk scores and Cox regression coefficients that were in the final model as derived for 7311 patients (95%) with complete information

Table 14.1: Predictors of death, MI, or disabling stroke for 7311 participants in the ACTION trial

(Cox proportional hazard analysis) – figures are numbers (%)

Risk factors	**Death, MI or stroke **(n=1063)**	**No death, MI, or stroke (n=6248)**	**Z score***	**Co-efficient**	**Contribution to risk score**
Mean age SD (year)	66.5 (9.5)	63 (9.2)	10.77	0.55	0 when age≤60 years or add per 10 years>60 years
Mean SD (ejection fraction)	46.7 (6.6)	48.6 (6.3)	6.47	0.17	0 when ≤60 years or add per 5% <60%
Smoking					
Never	260 (24)	1784 (29)	-	-	
Ex smoker	560 (53)	3417 (55)	1.54	0.12	Add if applicable
current	243 (23)	1047 (17)	6.12	0.60	Add if applicable
Mean (SD) white blood cells (109 /l)	7.4 (2.5)	7 (1.8)	6.07	0.068	0 when ≤5109/l >5
Diabetes					
No diabetes	848 (80)	5393 (86)	-	-	
Non- ID diabetes	167 (16)	727 (12)	1.06	0.13	Add if applicable
ID diabetes	48 (5)	128 (2)	5.61	0.85	Add if applicable
Mean (SD) glucose, no diabetes (mg/dl)	103 (26)	99 (20)	4.68	0.072	0 when ≤100 mg/dl or add per 10mg/dl >100 mg/dl.
Mean (SD) glucose, non-ID diabetes (mg/dl)	189 (79)	168 (65)	3.36	0.032	0 when ≤100 mg/dl or add per 10mg/dl >100 mg/dl.
Mean (SD) creatinine (mg/dl)	1.14 (0.25)	1.08 (0.21)	4.27	0.078	0 when ≤1.15 mg/dl or add per 0.1 mg/dl >1.15 mg/dl.
Previous stroke	50 (5)	116 (2)	3.59	0.53	Add if yes
Angina attack ≥1 /week	364 (34)	1750 (28)	3.42	0.22	Add if applicable
Previous angiography					
Never done	350 (33)	1842 (29)	1.50	0.11	Add if applicable
0-2 vessel disease	421 (40)	3069 (49)	-	-	Add 0 if applicable
≥3 vessel disease	292 (27)	1337 (21)	3.23	0.25	Add if applicable
No lipid lowering therapy	406 (38)	1950 (31)	3.20	0.21	Add if applicable
QT interval (12 lead ECG) ≥ 430msec	238 (22)	1096 (18)	3.05	0.23	Add if applicable
Systolic blood	275 (26)	1097 (18)	2.84	0.21	Add if

pressure ≥ 155 mmHg					applicable
No of drugs for angina					
0	8 (1)	53 (1)			
1	268(25)	1953 (31)	2.76	0.13	Add once for each drug used
2	626 (59)	3487 (56)			
3	161 (15)	755 (12)			
Previous MI	597 (56)	3118 (50)	2.16	0.14	Add if yes
Male	863 (81)	4944 (79)	1.87	0.16	Add if male

**Z score- co-efficient divided by its SE. Larger values indicate more highly significant risk factor: z scores of 1.96, 2.58, 3.29 and 3.89 correspond to p=0.05, p=0.01, p=0.001 and p=0.0001.*
***The definition of stroke excluded events without lasting disability. MI- did not include patients with chest pain and raised troponin concentrations.*
***Note:** Age was the strongest predictor. Male sex was of borderline significance (p=0.06) but was retained for completeness. Diabetes and stroke were the strongest predictors from clinical history. Patients with known three or more vessel disease had raised risk. Other predictors included were left ventricular ejection fraction, a prolonged QT interval, use of lipid lowering drugs, and the number of drugs used for angina (including past use of CCB).*

The table below presents hazard ratios for the individual events of death, MI, and disabling stroke with the same variables as for the combined endpoint.

Table 14.2: Predictors of death, MI, and disabling stroke

(Cox proportional hazard analysis) - figures are hazard ratios (95% CI)

Risk factor	**Death, MI, or stroke (n=1063)**	**Death (n=569)**	**MI (n=495)**	**Stroke (n=170)**
Age per 10 years >60	1.73 (1.57 to 1.92)	2.30 (2.01 to 2.64)	1.45 (1.25 to 1.69)	1.75 (1.37 to 2.24)
Ejection fraction per 5%<60	1.19 (1.13 to 1.25)	1.26 (1.17 to 1.35)	1.14 (1.06 to 1.23)	1.24 (1.09 to 1.41)
Smoking				
Never	1.00	1.00	1.00	1.00
Ex smoker	1.13 (0.97 to1.32)	1.19 (0.96 to 1.48)	0.99 (0.79 to 1.24)	1.42 (0.95 to 2.13)
current	1.82 (1.50 to 2.20)	2.20 (1.69 to 2.85)	1.39 (1.05 to 1.84)	2.44 (1.49 to 3.99)
White blood cells per 109 /l>5	1.07 (1.05 to 1.09)	1.09 (1.07 to 1.12)	1.05 (1.01 to 1.10)	1.00 (0.92 to 1.09)
Diabetes				
No diabetes	1.00	1.00	1.00	1.00
Non ID diabetes	1.14 (0.90 to 1.44)	0.93 (0.66 to 1.32)	1.14 (0.81 to 1.60)	1.75 (1.06 to 2.90)
ID diabetes	2.33 (1.74 to 3.14)	3.44 (2.40 to 4.94)	2.62 (1.75 to 3.93)	0.56 (0.14 to 2.29)
Glucose per 10 mg/dl >100† (no diabetes)	1.08 (1.04 to 1.11)	1.10 (1.06 to 1.14)	1.05 (1.00 to 1.10)	1.07 (0.98 to 1.15)
Glucose per 10 mg/dl >100† (non-ID diabetes)	1.03 (1.01 to 1.05)	1.04 (1.01 to 1.01 to 1.07)	1.03 (1.00 to 1.06)	1.03 (0.99 to 1.07)
Creatinine per 0.1 mg/dl >1.5	1.08 (1.04 to 1.12)	1.09 (1.04 to 1.14)	1.08 (1.02 to 1.14)	1.06 (0.97 to 1.16)
Previous stroke	1.70 (1.27 to 2.28)	1.74 (1.19 to 2.54)	1.50 (0.95 to 2.36)	4.28 (2.60 to 7.06)
Angina attack ≥1 /week	1.25 (1.10 to 1.42)	1.27 (1.07 to 1.51)	1.21 (1.00 to 1.46)	1.16 (0.84 to 1.61)
Previous				

angiography				
Never done	1.12 (0.97 to 1.30)	1.16 (0.95 to 1.41)	1.20 (0.96 to 1.49)	1.10 (0.77 to 1.58)
0-2 vessel disease	1.00	1.00	1.00	1.00
≥3 vessel disease	1.28(1.10 to 1.50)	1.14 (0.92 to 1.41)	1.50 (1.21 to 1.87)	1.06 (0.72 to 1.57)
No lipid lowering therapy	1.23 (1.08 to 1.40)	1.33 (1.12 to 1.58)	1.10 (0.91 to 1.33)	1.09 (0.79 to 1.51)
QT interval (12 lead ECG) ≥ 430msec	1.26 (1.08 to 1.45)	1.52 (1.26 to 1.84)	1.08 (0.87 to 1.35)	1.69 (1.22 to 2.36)
Systolic blood pressure ≥ 155 mmHg	1.23 (1.07 to 1.42)	1.18 (0.98 to 1.43)	1.09 (0.88 to 1.35)	1.69 (1.22 to 2.36)
For each additional drug for angina	1.14 (1.04 to 1.25)	1.09 (0.96 to 1.24)	1.20 (1.05 to 1.38)	1.21 (0.96 to 1.54)
Previous MI	1.15 (1.01 to 1.30)	1.10 (0.92 to 1.30)	1.16 (0.96 to 1.39)	1.01 (0.74 to 1.38)
Male	1.17 (0.99 to 1.39)	1.21 (0.96 to 1.52)	1.24 (0.97 to 1.59)	0.88 (0.59 to 1.30)

***Note:** Patterns of risk factors were broadly similar, though risk of stroke was more strongly linked to raised blood pressure but unrelated to white cell count, angiographic data, previous MI and sex.*

Limitations of the score: The risk score did not seem to predict the nature of the event (death in 39%, myocardial infarction in 46%, and disabling stroke in 15%) or the incidence of angiography or revascularisation, which occurred in 29% of patients.

Summary: The risk score combined 16 routinely available variables: age, left ventricular ejection fraction, smoking, white blood cell count, diabetes, casual blood glucose concentration, creatinine concentration, previous stroke, at least one attack a week, coronary angiographic findings (if available), lipid lowering treatment, QT interval, systolic blood pressure ≥ 155 mm Hg, number of drugs used for angina, previous MI, and sex. The patients risk is calculated by using ACTION score which is a number in the range of 0 to 60.

14.2.2 Euro heart angina score

Daly 2006[172]

The Euro heart survey of stable angina was designed as a prospective observational cohort study of patients presenting to cardiology services with stable angina. Participating centres were a mix of academic and non academic institutions, and hospitals with and without interventional and cardiac surgical facilities.

Participants: N=3031 patients enrolled from 156 centres in 34 countries.

Inclusion criteria: Patients attending cardiology services with a new presentation of stable angina were considered for enrolment, and consecutive patients in whom the cardiologist made a clinical diagnosis of stable angina caused by myocardial ischemia due coronary disease were included in the survey. Exclusion criteria included unstable angina, admission to hospital within 24 hours of assessment, myocardial infarction within one year, previous revascularisation, or a cause of angina other than coronary disease.

Baseline characteristics: The population was relatively young 61 years and 58% male. Most patients had mild to moderate symptoms of angina for 6 months or less before presentation to a cardiologist, although only 48 (1.7%) patients had symptoms for less than one month before cardiology assessment. 10496 (40%) of patients were in class 1.

At baseline 1602 (47%) of patients were on aspirin, 1429 (21%) patients on statins and 1142 (38%) on BBs.

Confirmation of coronary disease: Coronary angiography was done at least once during follow-up in 1253 (41%) patients. At the end of the follow-up period, approximately one third (n=994) of patients had had coronary disease confirmed angiographically and a further third (n=1023) had negative investigations. One sixth of patients had no definitive diagnostic test to confirm the presence or absence of coronary disease.

Outcome: The primary outcome of interest was death or non fatal MI.

Follow-up: The median duration of follow-up was -13 months (interquartile range 12–15 months).

Statistical analysis: Cox's proportional hazards models were used to determine the effects of clinical and investigative variables on the occurrence of death or non fatal MI in both univariate and multivariate analysis. Starting with clinical variables, stepwise regression was done (using entry/removal P value = 0.15) to determine the factors predictive of death or infarction during follow-up. Models were developed separately for clinical and investigative parameters and then for a combination of clinical and investigative parameters. Final model was refitted for all patients without missing values for the variables selected.

Results: The Euro heart Angina score involves six characteristics: co-morbidity, diabetes, severity of symptoms, duration of symptoms, resting electrocardiogram abnormalities, and abnormal ventricular function.

The major clinical events occurring during follow-up in the overall population with stable angina (N=3031) are shown in the table below.

Table 14.3: Major clinical events occurring during follow-up in the overall population with stable angina

Endpoint	No of events	Event rate (95% CI) per 100 patient
Death*	50	1.5 (1.1 to 1.9)
Non cardiovascular death	14(28%)	
Non fatal MI	48	1.4 (1.1 to 1.9)
Death and non fatal MI	93	2.3 (1.9 to 2.8)
Cerebro vascular event	34	1.1 (0.8 to 1.5)
Heart failure	49	1.5 (1.1 to 2.0)
Unstable angina	164	5.2 (4.4 to 6.0)
All cardiovascular events	328	10.3 (9.3 to 11.5)

**of 50 deaths, the cause of death was classified as unknown or missing in 6 and cardiac or cardiovascular in 29. Note: Comparisons with clinical trial populations with stable angina: The annual incidence of death in the survey was 1.5% and the incidence of non fatal MI was 1.4%. In the subgroup with proved coronary disease these rates were 1.8% and 3.2%. Estimates of annual mortality from modern clinical trials of secondary prevention, anti anginal treatment, or revascularisation range from 0.9% to 1.7%, with a higher mortality in populations with more severe symptoms. Reported annual incidences of non fatal MI range from 1.1% to 1.5%.*

The table below shows the risk of death or myocardial infarction associated with baseline clinical characteristics and results of investigations. Previous myocardial infarction, signs of heart failure, or a past history of diabetes, hypertension, or any co-morbidity were significant predictors of adverse outcome, as were increasing severity of symptoms and shorter duration of symptoms. Resting electrocardiographic abnormalities (Q wave or ST/T wave changes) were associated with approximately double the risk of death or myocardial infarction, but positive non-invasive stress test results were not significantly associated with adverse outcome.

Table 14.4: Unadjusted hazard ratio of death or MI associated with clinical and investigative parameters in general population with stable angina (n=3031)

Clinical variables	Hazard ratio	P value
Age (per 1 year increment)	1.03 (1.01 to 1.05)	0.001
Sex (female v male)	1.19 (0.79 to 1.79)	0.40
Diabetes	2.40 (1.55 to 3.70)	<0.001
Hypertension	2.12 (1.29 to 3.48)	0.002

Hyperlipidaemia	1.00 (0.63 to 1.58)	0.99
Ever smoked	1.53 (1.00 to 2.36)	0.05
Previous myocardial infarction	3.24 (1.72 to 6.13)	0.002
Comorbidity	2.98 (1.98 to 4.52)	<0.001
Symptom severity:		
Class II versus class I	2.34 (1.37 to 4.00)	0.0002
Class III versus class I	3.44 (1.80 to 6.55)	
Symptom duration >6 months	0.60 (0.39 to 0.94)	0.03
Signs of heart failure	2.67 (1.56 to 4.57)	0.001
Body mass index >30	0.82 (0.49 to 1.37)	0.43
Tertiary education	0.78 (0.40 to 1.52)	0.46
Investigative variables		
Left bundle branch block	1.50 (0.66 to 3.43)	0.34
Q wave	2.37 (1.38 to 4.06)	0.002
ST or T wave changes	2.26 (1.50 to 3.41)	<0.001
Ischaemic ECG changes	2.27 (1.50 to 3.43)	<0.001
Result of individual stress tests:		
Positive exercise ECG (n=2299)	1.44 (0.80 to 2.61)	0.22
Positive stress echocardiogram (n=119)	1.24 (0.24 to 6.40)	0.80

Positive perfusion scan (n=420)	3.55 (0.77 to 16.47)	0.07
Result of any stress test		
Positive test	1.50 (0.82 to 2.73)	<0.0001
No test done	4.42 (2.50 to 7.82)	
Echocardiography (before events):		
Abnormal left ventricular function	5.21 (3.19 to 8.49)	<0.001

The table below shows stepwise regression selected co-morbidity, diabetes, recent onset of symptoms, more severe symptoms, ST or T wave abnormalities on the resting electrocardiogram, not having any stress test done, and abnormal ventricular function as the variables most predictive of outcome

Table 14.5: Clinical and investigative parameters independently predictive of death or MI, determined by using stepwise selection procedures in general population with stable angina**

Clinical variables (n=2183)	Hazard ratio (95% CI)	P- value
Comorbidity	2.41 (1.49 to 3.91)	<0.001
Signs of heart failure	1.62 (0.85 to 3.07)	0.14
Previous myocardial infarction	2.19 (1.08 to 4.42)	0.03
Diabetes	2.03 (1.25 to 3.31)	0.004
Symptom duration >6 months	0.54 (0.33 to 0.87)	0.01
Symptom severity:		
Class II versus class I	1.95 (1.07 to 3.54)	0.005
Class III versus class I	2.65 (1.29 to 5.50)	
Investigative variables (n=2963)		
Stress testing:		
Positive test	1.43 (0.76 to 2.70)	0.0001
No stress test done	3.78 (2.04 to 7.00)	

Echocardiography:		
Abnormal left ventricular function	2.57 (1.62 to 4.08)	<0.0001
Electrocardiography:		
ST or T wave changes	1.63 (1.06 to 2.50)	0.03
Combined clinical and investigative variables (n=2528)		
Comorbidity	2.25 (1.43 to 3.56)	0.0008
Diabetes	1.95 (1.22 to 3.11)	0.007
Previous myocardial infarction	—	
Symptoms >6 months	0.48 (0.30 to 0.77)	0.002
Symptom severity:		
Class II versus class I	1.76 (1.00 to 3.09)	0.05
Class III versus class I	2.18 (1.10 to 4.33)	
ST or T wave changes	1.56 (0.99 to 2.45)	0.05
Stress test:		
Positive stress test result	1.29 (0.63 to 2.67)	<0.0001
No stress test done	3.48 (1.71 to 7.07)	
Abnormal left ventricular function	2.11 (1.29 to 3.46)	0.004

*** As non performance of a test is not an objective measure of a patient but can be influenced by many physician related and non clinical factors. A further stepwise selection process was used to consider only the non invasive investigations that had been done. A positive versus negative or inconclusive non-invasive stress test result was not selected as a significant predictor of outcome when combined with information from echocardiography and resting echocardiography.*

In the model developed to derive the clinical risk score the final predictors of death or MI were co-morbidity, diabetes, severity of symptoms, duration of symptoms, resting electrocardiogram abnormalities, and abnormal ventricular function.

Validity: Applying the model developed on 75% of the population to the remaining 25% of the population gave a C-statistic for the angina score to predict outcome of 0.74.

Cox's proportional hazards models were used to determine the effects of clinical and investigative variables on the occurrence of death or non fatal MI in both univariate and multivariate analysis.

To develop a scoring system for predicting probability of death or infarction during the first year after presentation that was based only on objective information generally available to clinicians and not on whether a test was done a further multivariate model was developed without the stress test done/not done variable. The performance of the model was assessed by calculating the Harrels C-statistics (comparable to the area under the receiver operating characteristics curve).

Table 14.6: Score for each factor to calculate risk score for patients presenting with stable angina

Risk factor	Score contribution
Comorbidity*	
No	0
Yes	86
Diabetes	
No	0
Yes	57
Angina score	
Class 1	0
Class 2	54
Class 3	91
Duration of symptoms	
>6 months	0
<6 months	80
Abnormal ventricular function	
No	0
Yes	114
ST depression or T wave inversion on resting electrocardiogram	
No	0
Yes	34

**One or more of previous cerebrovascular event; hepatic disease defined as chronic hepatitis or cirrhosis, or other hepatic disease causing elevation of transaminases more than three times upper limit of normal; peripheral vascular disease defined as claudication either at rest or on exertion, amputation for arterial vascular insufficiency, vascular surgery (reconstruction or bypass) or angioplasty to the extremities, documented aortic aneurysm, or non-invasive evidence of impaired arterial flow; chronic renal failure defined as chronic dialysis or renal transplantation or serum creatinine greater than 200 mol/l; chronic respiratory disease defined as a diagnosis previously made by physician or patient receiving bronchodilators or FEV1<75%, arterial pO2<60%, or arterial pCO2>50% predicted in previous studies; chronic inflammatory conditions defined as a diagnosis of rheumatoid arthritis, systemic lupus erythematosis or other connective tissue diseases, polymyalgia rheumatica, and so on; malignancy defined as a diagnosis of malignancy within a year or active malignancy.*

Limitations: Small sample. The Euro heart survey of stable angina population differs from a general selection of people with angina in the community, many of whom may not have a diagnosis, and differs from the overall primary care angina population in that they have been selected for specialist assessment. However, the population is comparatively less highly selected than those in randomised controlled trials. The score has not been validated so far in a stable angina population.

Summary: In the model developed to derive the clinical risk score the final predictors of death or MI were co-morbidity, diabetes, shorter duration of symptoms, increasing severity of symptoms, abnormal ventricular function, resting electrocardiographic changes, or not having any stress test done. Results of the non invasive stress tests did not significantly predict outcome in the population who had tests done. A score was constructed using the parameters predictive of outcome to estimate the probability of the death or myocardial infarction within one year of presentation of stable angina. Applying the model developed on 75% of the population to the remaining 25% of the population gave a C-statistic for the angina score to predict outcome of 0.74.

14.3 Economic evidence

No economic studies were found on this question.

14.4 Evidence statements

Clinical There was evidence from 2 studies[171,172] that reported the derivation of ACTION risk score and Euro heart Angina score. However, there was no evidence available that validated the ACTION risk score and Euro heart Angina score in a stable angina population.

Economic No economic evidence was found on this question.

14.5 Recommendations and link to evidence

Recommendation	No recommendation was made
Relative values of different outcomes	Not applicable
Trade off between clinical benefits and harms	Not applicable
Economic considerations	No economic evidence was identified. If routine clinical indicators are used, costs are negligible.
Quality of evidence	Both risk scores were derived from selected patient populations that may not be representative of the wider population of patients with stable angina. The Euroheart score was developed from 75% of the total Euroheart survey population (derivation cohort) and tested in the remaining 25% of the population. The population used to develop the ACTION score was

	derived from the randomised ACTION trial, which enrolled patients with previous MI, or angiographic or other evidence of coronary heart disease. The available risk scores have not been validated in populations other than the cohorts in which they were developed.
Other considerations	The GDG recognised that given the low event rate in stable angina a large cohort is required when developing a predictive model in a general angina population. The GDG did not consider that the evidence was sufficient to recommend using clinical risk scores but acknowledged that the clinical factors identified in the Euroheart study can result in a poorer outcome.

15 Functional and anatomical investigations

15.1 Introduction

NICE Clinical Guideline 'Chest pain of recent onset' emphasizes the importance of clinical assessment in establishing a diagnosis in people with chest pain. When the diagnosis is uncertain functional tests for the demonstration of inducible myocardial ischaemia and anatomical tests to confirm the presence of obstructive coronary artery disease are also recommended.

In people with an established diagnosis of stable angina non-invasive functional testing has also been recommended before invasive coronary angiography or revascularisation procedures for detection of myocardial ischaemia, risk stratification, and selection of appropriate treatment.[173].

In this chapter we review whether functional or anatomical tests in people with an established diagnosis of stable angina provide incremental value for the prediction of adverse cardiovascular outcomes and/or influence management to improve outcome. To add incremental value a test must provide additional prognostic information over and above that provided by standard clinical variables alone. Studies that did not assess incremental prognostic value were excluded.

The following tests were assessed in this review:

- Exercise electrocardiography – 2 papers
- Exercise echocardiography – 2 papers
- Myocardial Perfusion Imaging – 9 papers
- Ambulatory electrocardiography – 2 papers

Tests in patients with normal coronary arteries and chest pain

- Stress echocardiography – 1 paper

Exercise electrocardiography is carried out with an exercise treadmill or bicycle ergometer, with step-wise increases in workload and continuous electrocardiographic monitoring. The test is continued to maximal exercise tolerance or development of clinical and/or electrocardiographic evidence of myocardial ischaemia (ST segment depression).

Stress echocardiography is carried out during exercise stress on a treadmill or bicycle ergometer, or during pharmacological stress induced by intravenous administration of dobutamine or dipyridamole. Detection of new wall motion abnormalities on the echocardiogram during stress is interpreted as evidence of inducible myocardial ischaemia.

Myocardial perfusion scintigraphy requires intravenous administration of a radioactive tracer [labelled with thallium-201 or technetium-99m (as tetrofosmin or sestamibi)] that is taken up by myocardial cells. A gamma camera is used to image the distribution of the tracer within the myocardium and to detect abnormalities of myocardial perfusion before and after exercise or pharmacological stress. Myocardial perfusion scintigraphy was originally developed as a planar imaging technique, but more recently single photon emission computed tomography (SPECT) has facilitated acquisition of tomographic images of the myocardium. In addition, ECG gating synchronises image acquisition with cardiac contraction, which reduces cardiac motion artefacts and facilitates measurement of left ventricular ejection fraction.

Ambulatory electrocardiography involves continuous electrocardiography, usually over 24-48 hours, and allows detection of spontaneous symptomatic or asymptomatic episodes of ST segment depression (myocardial ischaemia) during normal daily activities.

We found no evidence assessing the incremental prognostic value of cardiac computed tomography, cardiac magnetic resonance stress imaging, or invasive coronary angiography in patients with stable angina.

In this evidence review studies were not combined in a meta-analysis, because all of the included studies were observational studies. Additionally there was poor reporting of results in studies and heterogeneity across studies. The review is presented narratively with details of the test, population, end points, follow-up, results, and evidence statements for each study.

The following criteria were taken into consideration to give an overall quality rating of the primary studies: representativeness of the cohort; loss to follow-up being unrelated to key characteristics sufficient to limit potential bias ; adequate measurement of outcome of interest in study participants; prospectiveness of the study; adjustment for confounding factors in the analysis and at least 10 events per factor in the analysis (the study had to have at least 8 to 10 events per factor and analysis was adjusted for at least 3 of 4 relevant factors in the analysis). However, if there were insufficient relevant factors taken into account, the quality of the study was downgraded. All these factors were taken into consideration to give an overall quality rating.

Table 15.1: List of studies with test, test variables, clinical variables, and outcomes - for patients with stable angina

Study	Tests	Test variables considered in the analysis	Clinical variables considered in the analysis	Outcomes	Follow-up
Exercise Electrocardiography					
Forslund 2000[174]	Exercise electrocardiography (bicycle ergometry)	Univariate analysis: Exercise duration (s) Maximal heart rate during exercise (beats.min) Time to onset of chest pain (s) Time to 1 mm ST segment depression (s) Maximal ST segment depression (mm) Maximal ST segment depression (mm) after 2 min rest (mm) Multivariate analysis: Maximal ST segment depression ST segment depression after exercise Exercise duration.	Univariate analysis: Age, sex, smoking habits, hypertension, previous MI, congestive heart failure, diabetes, mellitus. Multivariate analysis: Sex, MI, history of hypertension and diabetes mellitus.	1) CV death 2) CV death and MI	Median 40 months (6 months to 75 months)
Sekhri 2008[175]	Exercise electrocardiography (treadmill ergometry)	Univariate analysis: <u>Resting ECG:</u> Abnormal axis Q waves Change in ST segment or T wave Left ventricular hypertrophy Bundle branch block <u>Exercise ECG:</u> Exercise time (mins) Maximum workload % predicted heart rate Maximum blood pressure Multivariate analysis: <u>Resting ECG:</u> Q waves Bundle branch block Change in ST segment or T wave	Univariate analysis: Age (10 year increase) Sex (female vs. male) Typicality of chest pain Heart rate per second increase Systolic blood pressure Hypertension Diabetes Current smoker Multivariate analysis: Age (10 year increase) Sex (female vs. male) Typicality of chest pain Diabetes	Composite of death due to coronary heart disease or non fatal acute coronary syndrome.	Median 2.46 years

		Exercise ECG: Exercise time (min)			
Exercise echocardiography					
D'Andrea 2005[176]	Exercise stress echocardiography (bicycle ergometry)	Univariate and multivariate analysis: Rest echo: Rest WMSI Exercise echo: Positive ESE Peak WMSI Low workload Angina during ESE	Multivariable analysis included significant variables in univariate analysis: Age, hypercholesterolemia, cigarette smoking.	1) Cardiac death 2) Cardiac death and non fatal MI	Mean 46.9 months (range 12-60 months).
Elhendy 2004[177]	Exercise echocardiography (treadmill ergometry)	Univariate analysis: Echocardiographic variables: Wall motion abnormality during exercise New wall motion abnormality (ischaemia) Percent ischaemic segments Wall motion score index during exercise Mean motion score index Exercise test variables: 85% age predicted heart rate Systolic blood pressure during exercise Rate pressure product during exercise Workload (METs) Exercise induced angina Ischaemic electrocardiographic changes Multivariate analysis: - Echocardiographic variables: Wall motion abnormalities Exercise test variables: Workload	Univariate analysis: Age, gender, diabetes mellitus, smoking. Multivariate analysis included significant variables in univariate analysis: Age, gender, diabetes	1) Any cardiac event defined as coronary artery revascularisation, non fatal MI, and cardiac death) 2) Cardiac death and non fatal MI	Median 2.7 years (1 to 7.8 years)

		Ischaemic electrocardiographic changes			
Myocardial Perfusion Imaging					
Groutars 2002[178]	Myocardial perfusion scintigraphy using technetium-99m tetrofosmin with bicycle ergometry	Multivariate analysis: Abnormal SPECT (Summed stress score SSS >3) Summed stress score (SSS) Summed difference score (SDS) Severe ischaemia (SDS >12) *	Univariate analysis: History of MI, history of PTCA, history of CABG, type of chest pain (indeterminate, atypical angina, typical angina, shortness of breath), age and gender, hypercholesterolemia, smoking, diabetes mellitus, hypertension. Exercise variable: Post exercise test likelihood of coronary artery disease. Multivariate analysis included significant variables in univariate analysis: History of MI, history of PTCA, history of CABG, typical angina symptoms, age and gender. Exercise variable: Post exercise test likelihood of coronary artery disease.	Death, caused by any cardiac disorder with underlying coronary artery disease, including sudden death (confirmed by review of death certificate or hospital chart), or non fatal MI	Mean 23±9 months
Elhendy 2005[179]	Myocardial perfusion scintigraphy (SPECT) using technetium-99m tetrofosmin with bicycle ergometry	Univariate and multivariate analysis: Reversible perfusion defects Fixed perfusion defects	Univariate and multivariate analysis: Age Male sex History of heart failure Diabetes mellitus Smoking	1) Death from any cause 2) Cardiac death and non fatal MI	Mean 6±1.7 years
Stratmann 1992[180]	Dipyridamole thallium-201 scintigraphy	Univariate analysis: Normal scan Abnormal scan Reversible defect ≥1 segment ≥3 segments Fixed defect	Univariate analysis: Age Sex History of old MI History of congestive cardiac failure History of diabetes mellitus History of systemic hypertension	Cardiac event (development of unstable angina, occurrence of a nonfatal MI, or death resulting from a primary cardiac	Mean 18±9 months

		≥1 segment ≥3 segments Reversible and fixed defects Multivariate analysis: Fixed defect Abnormal scan	History of peripheral vascular disease History of cigarette smoking Pre study coronary angiography Pre study CABG Pre study coronary angioplasty Multivariate analysis: History of MI History of peripheral vascular disease History of congestive heart failure Pre test CABG	cause) and cardiac death.	
Wiersma 2009[181]	Myocardial perfusion scintigraphy (SPECT) using several isotopes and bicycle or treadmill ergometry	Univariate analysis: Abnormal rest ECG MPS: severe ischaemia Multivariate analysis MPS: severe ischaemia	Univariate analysis: Male gender CCS II/IV BMI≥29.9 kg/m2 Age 65 years or older Previous MI Previous revascularisation Aspirin Statin Insulin Multivariable analysis: Insulin	Cardiac death or non fatal MI	Mean 2.2±0.7 years
Stratmann 1994[182]	Myocardial perfusion scintigraphy (SPECT) using technitiun-99 m sestamibi and pharmacological (dipyridamole) stress	Univariate analysis: Occurrence of dipyridamole-induced chest pain, or MIBI perfusion defects. Multivariate analysis: Abnormal scan Reversible defect Fixed defect Chest pain during test	Univariate analysis: Age, gender, history of previous MI, congestive heart failure, diabetes mellitus treated with medication, systemic hypertension, peripheral vascular disease, cigarette smoking, or pre-test coronary revascularisation. CAD documented by coronary angiography before or ≤2 months after dipyridamole testing. Q waves on the pre test Electrocardiogram consistent with prior MI Electrocardiographic changes consistent with	Cardiac death or non fatal acute MI	Mean 13±5 months

			ischaemia Multivariate analysis: History of congestive heart failure History of diabetes mellitus CAD by coronary angiography Q waves on pre-test ECG		
Stratmann 1994[183]	Myocardial perfusion scintigraphy (SPECT) using techetium-99m sestamibi and treadmill ergometry	Univariate analysis: <u>Exercise treadmill test:</u> Chest pain during exercise Ischaemic ST depression≥2 mm Peak HR, beats per minute peak HR≥85% of age predicted maximal Peak SBP, mm Hg Peak DP, beats-mm Hg/minx103 Exercise duration (Sec) Exercise duration ≥360 sec <u>MPS</u>: Abnormal scan Reversible defect Fixed defect Reversible and fixed defects Multivariate analysis: Abnormal scan Reversible defect Fixed defect Ischaemic ST depression	Univariate analysis: Age, sex, history of congestive heart failure, history of old MI, history of diabetes mellitus, history of systemic hypertension, history of peripheral vascular disease, history of cigarette smoking, CAD by coronary angiography, pre study revascularisation, Q wave on pre test ECG, mediactions Multivariate analysis: History of congestive heart failure History of MI History of diabetes mellitus.	Cardiac death or non fatal MI	Mean 13±5 months (range 1 to 24 months)
Poornima 2004[184]	Myocardial perfusion scintigraphy (SPECT) using thallium-201 and treadmill	Univariate and bi-variate analysis: A global stress score (GSS) was obtained by adding the scores on all the stress short axis images.	Univariate and bi-variate analysis: <u>Clinical score:</u> A simple five-point scoring system was developed after consideration of 16 clinical	Cardiac death, MI, late revascularisation.	Mean 7±1 year

	ergometry		and ECG variables. The variables included in the five point scoring were male gender, history of MI (clinical event and Q waves on ECG), diabetes, insulin use, and typical angina.		
Vanzetto 1999[185]	Myocardial perfusion scintigraphy (SPECT) using thallium-201 and treadmill ergometry	Univariate analysis: <u>ETT variables:</u> Maximal heart rate, bpm Percentage of MPHR Maximum workload, W Negative ETT Positive ETT Strongly positive ETT Non diagnostic ETT Maximum ST segment depression, mm <u>SPECT variables:</u> Abnormal T1201 SPECT Mean number of abnormal segments Mean number of fixed segments Mean number of reversible segments Multivariate analysis- <u>ETT variables:</u> Negative ETT Positive ETT Strongly positive ETT Non diagnostic ETT Maximum ST segment depression, mm <u>SPECT variables:</u> Normal T1201 SPECT 1 or 2 abnormal segments on T1201-SPECT ≥3 abnormal segments on T1201-SPECT	Univariate analysis: Age >60 years, sex, patients with >1 risk factor, previous history of MI, typical angina. Multivariate analysis included significant variables in univariate analysis: Age >60 years, patients with >1 risk factor, previous history of MI	Overall mortality; cardiac mortality (sudden death or death of demonstrated cardiac origin); occurrence of MI	Mean 72± SD 18 months
Lima 2004[186]	Myocardial perfusion scintigraphy (SPECT) with tecnitium-99 m and pharmacological	Univariate analysis: <u>ETT variables:</u> Peak rate pressure product V02 (METS) Peak heart rate (beats/min) Peak % MAPHR	Univariate variables: Not specifically reported Multivariate analysis included significant variables in univariate analysis: Gender, pre scan likelihood of CAD.	Cardiac events (cardiac death, MI, or myocardial revascularisation)	Mean 34±15 months

	(dipyridamole) or exercise stress	Peak systolic arterial pressure (mmHg) ETT duration (min) MPS: abnormal scan (Perfusion defects) Left ventricular enlargement			
Ambulatory Electrocardiography					
Forslund 1999[187]	Ambulatory electrocardiography	Univariate analysis: No. of VPCs No. of segment depressions/24 hr Duration of ST segment depression/24 hr (min) Multivariate analysis: ST segment depression over 24 hours.	Univariate analysis: Age, sex, smoking, hypertension, previous MI, congestive heart failure, diabetes mellitus Multivariate analysis: Sex, previous MI, hypertension and diabetes.	CV death, non fatal MI, and revascularisation	Median 40 months (6 to 75 months)
Conti 1997[188]	Exercise test and Ambulatory electrocardiography	Univariate analysis: Number of ambulatory ECG episodes Mean heart rate and maximum change in heart rate on baseline ambulatory ECG monitoring Abnormal 12 lead electrocardiogram at rest. Multivariate analysis: Exercise time Ambulatory ECG episodes	Univariate analysis: Mean heart rate and maximum change in heart rate on baseline ambulatory ECG monitoring, history of revascularisation, history of MI, history of congestive cardiac failure, family history of coronary artery disease before age 55, diabetes mellitus, demographic variables (age, gender, race), certain variables related to history and disease (stenosis 50% in 1,2 or 3 vessels), ejection fraction <50%, history of hypertension, abnormal 12 lead electrocardiogram at rest and history of smoking. Multivariate analysis included variables in univariate analysis p<0.05 (specific variables not reported).	Death, MI or hospitalisation for ischaemic event.	1 year

[1] SSS was obtained by calculating the sum of the scores of the 20 segments of the stress technetium-tetrofosmin images. The SRS was calculated on a similar basis. The SDS was calculated as the sum of the differences between SSS and the SRS for each segment.

Table 15.2: For patients with chest pain and normal coronary arteries (Cardiac syndrome X)

Study	Tests	Test variables	Clinical variables considered in the analysis	Outcomes	Follow-up
Stress echocardiography					
Bigi 2002[189]	Pharmacological stress echocardiography (dobutamine or dipyridamole)	Univariate analysis: Positive SE Rest WMSI Peak WMSI Multivariate analysis: Positive SE Rest WMSI Peak WMSI	Univariate analysis: Clinical Age sex Previous infarction hypertension Diabetes Hypercholesterolemia Multivariate analysis included significant variables in univariate analysis: Hypertension	Target events were cardiac death, non fatal infarction, and unstable angina. Only the worst event was taken in to account for statistical analysis.	Mean 36 months

15.2 Exercise Electrocardiography

15.2.1 Clinical question

In adults with stable angina what is the incremental value/effectiveness of exercise electrocardiography for prognostic risk stratification in prediction of adverse cardiac outcomes?

15.2.2 Clinical evidence

The "Review Protocol" for this topic can be found in Appendix C, the "Search Strategies" in Appendix D, the "List of Included and Excluded Studies" in Appendix E1, and the "Clinical Evidence Tables" in Appendix E2.

Two papers[174,175] assessed the incremental value of exercise electrocardiography for prediction of adverse cardiac outcomes.

Forslund 2000[174] (n=809) evaluated the prognostic value of exercise tolerance testing (ETT) among patients with chronic stable angina.

The end-points were cardiovascular death, and cardiovascular death+MI. Cardiovascular death was defined as death from acute MI, sudden death (within 2 hours of onset of symptoms) or death from other vascular causes (e.g. fatal cerebrovascular disease, pulmonary emboli). At follow-up ranging from 6 to 75 months (median 40 months) there were 32 cardiovascular deaths and 29 MIs.

Prognostic implications of results from exercise tests were assessed in a multivariate Cox model which included sex, previous MI, hypertension and diabetes mellitus. After adjustment for these variables, maximal ST depression during exercise, ST segment depression 2 min after exercise, and exercise duration all carried independent relationships to both cardiovascular death and the combined endpoint of cardiovascular death + MI.

Table 15.3: Prognostic evaluation of exercise variables –multivariate analysis for CV death

Prognostic factors	Odds ratio (95% CI)	p value
Maximal ST depression	1.450 (1.15 to 1.83)	0.0018
Maximal ST depression 1-2 mm	0.827 (0.30 to 2.30)	0.71
Maximal ST depression ≥ 2 mm	1.619 (0.73 to 3.59)	0.23
ST segment depression after exercise:	1.850 (1.43 to 2.39)	0.00

ST segment depression 1-2 mm	1.502 (0.63 to 3.59)	0.36
ST segment depression ≥2 mm	5.180 (2.12 to 12.67)	0.0003
Exercise duration (male patients)	0.786 (0.69 to 0.90)	0.0006
Exercise duration 9-13 min	0.358 (0.16 to 0.82)	0.015
Exercise duration ≥ 13 min	0.250 (0.08 to 0.77)	0.016

Table 15.4: Prognostic evaluation of exercise variables – multivariate analysis for CV death +MI

Prognostic factors	**Odds ratio (95% CI)**	**p value**
Maximal ST depression	1.33 (1.12 to 1.58)	0.001
Maximal ST depression 1-2 mm	1.36 (0.66 to 2.80)	0.402
Maximal ST depression ≥ 2 mm	2.06 (1.11 to 3.83)	0.02
ST segment depression after exercise:	1.54 (1.26 to 1.91)	0.00
ST segment depression 1-2 mm	1.59 (0.89 to 2.85)	0.11
ST segment depression ≥2 mm	3.03 (1.46 to 6.31)	0.002
Exercise duration (male patients)	0.834 (0.76 to 0.92)	0.0002
Exercise duration 9-13 min	0.506 (0.28 to 0.92)	0.02
Exercise duration ≥ 13 min	0.314 (0.14 to 0.71)	0.005

Sekhri 2008[175] (n=1422) evaluated the prognostic value of exercise electrocardiograms (ECG) among patients with suspected angina and no previous diagnosis of coronary artery disease.

The primary end point was a composite of death due to coronary heart disease or non-fatal acute coronary syndrome. There were a total of 353 events at 1 year and the median follow-up was 2.46 years.

Adjusted hazard ratios for three models were reported: basic clinical assessment, basic clinical assessment plus resting electrocardiogram (ECG), and basic clinical assessment plus resting ECG plus exercise ECG (table X). In the final models (clinical assessment plus resting ECG plus exercise ECG) the major contributors to the risk of the primary end point were typical symptoms and abnormalities on the exercise ECG, with age, sex, and diabetes making variable additional contributions depending on whether the summary ECG subset or detailed ECG subset were analysed.

In the summary ECG subset only the clinicians' assessment of ischaemia was recorded (positive, negative, or equivocal). In the detailed ECG subset, data recorded included exercise time, maximum workload, maximum heart rate, maximum blood pressure, diagnostic change in ST segment, arrhythmias, and reason for stopping (limiting symptoms, ST segment displacement of more than 1 mm 0.08 seconds after the J point, or target heart rate achieved).

Table 15.5: Sekhri 2008[175], Multivariate analysis for coronary heart disease death + MI

Covariate	Coefficient	Adjusted hazard ratio (95% CI)	P value
Clinical assessment with significant variables (whole cohort)			
Age (10 year increase)	0.26	1.30 (1.21 to 1.39)	<0.001
Sex (female v male)	–0.28	0.75 (0.64 to 0.89)	0.0008
Typical v atypical	1.13	3.09 (2.58 to 3.71)	<0.001
Non-cardiac v atypical chest pain	–0.38	0.68 (0.50 to 0.93)	
Diabetes	0.45	1.58 (1.28 to 1.94)	<0.001
Clinical assessment plus resting ECG (whole cohort)			
Age (10 year increase)	0.23	1.26 (1.17 to 1.35)	<0.001
Sex (female v male)	–0.27	0.76 (0.65 to 0.90)	0.0013
Typical v atypical chest pain	1.04	2.82 (2.34 to 3.40	<0.001
Non-cardiac v atypical chest pain	–0.37	0.69 (0.50 to 0.95)	

Diabetes	0.41	1.50 (1.22 to 1.86)	0.0002
Q waves	0.57	1.77 (1.24 to 2.53)	0.0037
Bundle branch block	0.30	1.36 (0.95 to 1.94)	0.1089
Change in ST segment or T wave	0.45	1.57 (1.28 to 1.94)	<0.001
Clinical assessment plus resting ECG plus summary exercise ECG			
Age (10 year increase)	0.10	1.11 (1.00 to 1.22)	0.048
Sex (female v male)	–0.05	0.95 (0.76 to 1.18)	0.64
Typical v atypical chest pain	0.75	2.12 (1.66 to 2.71)	<0.001
Non-cardiac v atypical chest pain	–0.54	0.58 (0.29 to 1.19)	
Diabetes	0.36	1.44 (1.09 to 1.89)	0.0134
Q waves	0.75	2.12 (1.28 to 3.49)	0.051
Bundle branch block	–0.11	0.90 (0.40 to 2.02)	0.79
Change in ST segment or T wave	0.29	1.34 (1.01 to 1.79)	0.0078
Positive v negative exercise ECG	0.92	2.53 (1.95 to 3.30)	<0.001
Equivocal v negative exercise ECG	0.44	1.55 (1.06 to 2.28	
Clinical assessment plus resting ECG plus detailed exercise ECG			
Age (10 years increase)	0.03	1.03 (0.85 to 1.25)	0.76
Sex (female v male)	–0.59	0.55 (0.37 to 0.83)	0.0036

Typical v atypical chest pain	0.90	2.45 (1.62 to 3.70)	<0.001
Non-cardiac v atypical chest pain	–0.52	0.59 (0.14 to 2.45)	
Diabetes	0.03	1.03 (0.63 to 1.70)	0.9023
Q waves	0.49	1.64 (0.64 to 4.18)	0.3338
Bundle branch block	0.42	1.53 (0.48 to 4.89)	0.5022
Change in ST segment or T wave	0.32	1.37 (0.83 to 2.27)	0.2264
Exercise time (minutes)	–0.15	0.86 (0.79 to 0.93)	0.0005
Diagnostic change in ST segment	0.81	2.26 (1.44 to 3.53)	0.0005

Summary: Two moderate quality prognostic studies showed that exercise electrocardiography (ECG) offered incremental prognostic value in prediction of CV death, CV death + MI, and death due to CHD + non fatal ACS. However it should be noted that in one of the studies the study sample did not entirely represent the population of interest. Also both studies reported composite outcomes and may overemphasize the incremental prognostic value of the tests.

15.2.3 Economic evidence

No relevant studies were found. Studies reporting the cost per case detected were not included as this question was addressed in the Chest Pain Guideline (CG95).

We looked for the costs of the individual tests from UK sources. We found that the unit cost of exercise test is £69 (NHS Reference Costs 2008-09 – Diagnostic Services - Exercise Test (including Treadmill, etc.) / Stress Test)[24].

15.2.4 Evidence statements

Clinical

Exercise electrocardiography

Forslund 2000[174]: Evidence from one study shows that exercise electrocardiography offers incremental prognostic information in prediction of CV death and CV death +MI [follow-up median (median 40 months)].

Sekhri 2008[175] : Evidence from one study shows that exercise ECG variables are independent predictors of death due to coronary heart disease or non-fatal acute coronary syndrome. [median

	follow-up 2.46 years].
Economic	No economic evidence was found on this question. A simple cost analysis showed that exercise electrocardiography has a cost of £69 per test.

15.3 Exercise echocardiography

15.3.1 Clinical question

In adults with stable angina what is the incremental value/effectiveness of exercise echocardiography for prognostic risk stratification in prediction of adverse cardiac outcomes?

15.3.2 Clinical evidence

The "Review Protocol" for this topic can be found in Appendix C, the "Search Strategies" in Appendix D, the "List of Included and Excluded Studies" in Appendix E1, the "Clinical Evidence Tables" in Appendix E2, and the "Forest Plots" in Appendix F.

Two papers[176,177] assessed the incremental prognostic value of exercise echocardiography for prediction of adverse cardiac outcomes.

D'Andrea[176] 2005 (n=607) assessed the long term predictive values of supine bicycle stress echocardiography (ESE) in patients with low, intermediate and high pretest risk of cardiac events.

The primary outcomes were cardiac death, and cardiac death and non fatal MI at a mean follow-up of 46.9 months (range 12-60 months). During the follow-up there 48 deaths (21.6%) and 34 acute non fatal MIs (15.3%).

Table 15.6: Multivariate predictive value of clinical risk factors and exercise stress echocardiography (ESE) results for cardiac death

Variables	**Chi square (X^2)**	**p value**	**variables selected (partial X^2; 95% CI; p)**
Clinical	9.3	0.01	cigarette smoking (2.8; 1.8 to 4.1; <0.01)
Clinical +rest echo	11.8	0.001	rest WMSI* (3.0; 2.1 to 4.1 ;< 0.01)
Clinical +rest echo+ ESE:	37.9	0.00001	positive ESE (4.1; 3.6 to 4.4;

			<0.0001) Peak WMSI* (3.5; 2.8 to 4.1); <0.0001 Low workload (3.1; 2.7 to 3.7; <0.01)

*wall motion score index

Table 15.7: Multivariate predictive value of clinical risk factors and exercise stress echocardiography (ESE) results for cardiac death+MI

Variables	Chi-square (X^2)	p value	variables selected (partial X^2; 95% CI; p)
Clinical	9.6	0.01	hypercholesterolemia (2.5; 1.6 to 3.3; <0.01)
Clinical +rest echo	12.5	0.001	rest WMSI (3.1; 2.4 to 3.8 ;< 0.01)
Clinical +rest echo+ ESE	39.6	0.00001	Positive ESE (4.5; 3.6 to 5.3 ;< 0.0001) Peak WMSI (3.7 ; 2.6 to 4.4; <0.0001) Angina during ESE (2.9; 2.3 to 3.8; <0.01)

Multivariate analysis identified ESE positive for ischaemia, peak WMSI, low workload, as the strongest independent predictors of cardiac death. Multivariate analysis identified positive ESE, peak WMSI, angina during the test and hypercholesterolemia as independent determinants of cardiac death or MI. The results demonstrate that predictive information provided by ESE is additional and independent to that provided by clinical and rest echocardiographic data.

Elhendy 2004[177] (n=437) assessed the incremental value of exercise echocardiography in risk stratification of patients with a high pre-test probability of coronary artery disease. Exercise echocardiography was done during symptom limited treadmill exercise testing (Bruce protocol 89%, Naughton protocol 6%, modified Bruce protocol 5%) with 12 channel electrocardiographic monitoring.

The end points were 1) non fatal MI and cardiac death and 2) coronary artery revascularisation, non fatal MI, and cardiac death assessed at a median follow-up of 2.7 years (1 to 7.8 years). Cardiac events occurred in 68 patients (16%) and included four cardiac deaths, 15 non fatal MIs, and 53 revascularisation procedures (4 subsequently had non fatal MI).

Table 15.8: Independent predictors of cardiac events using a three step multivariate analysis model

Parameters	Chi-square (X^2)	p-value*; model chi-square **
Clinical model		
Age	0.01	0.9; 36
Gender	14	0.0002
Diabetes mellitus	1.9	0.2
Clinical and exercise test model		
Ischaemic electrocardiographic changes	3.2	0.07; 62 ***
Workload	4.8	0.03
Clinical, exercise stress and echocardiography model		
Wall motion abnormalities		78 *****
In multi vessel regions****	13.4	0.0003
In single vessel region****	2.8	0.1

**Chi square and p value based on final model.*
*** Overall model chi-square at each phase of the modelling process*
**** p=0.0001 versus the clinical model.*
***** The reference group consisted of subjects with no wall motion abnormalities*
****** p=0.001 versus the clinical plus exercise stress model.*

In a multivariate analysis of clinical, exercise, and echocardiographic parameters, independent predictors of cardiac death and non-fatal MI were Q waves on the stress electrocardiogram and the presence of wall motion of abnormalities during exercise in multi-vessel distribution. In a separate analysis of clinical, exercise and echocardiographic variables for the prediction of all cardiac events, the addition of echocardiographic data increased the chi-square for the model from 62 to 78 (p=0.0003).

Summary: Two moderate quality studies showed that **exercise echocardiography** offered incremental value in prediction of cardiac death, MI and coronary revascularisation. The outcomes of interest were adequately assessed in both studies, but one of the studies used composite outcomes and did not report individual cardiac outcomes separately. This may cause bias as it offers an exaggerated perception of the incremental prognostic value of the tests.

15.3.3 Economic evidence

No relevant studies were found. Studies reporting the cost per case detected were not included as this question was addressed in the Chest Pain Guideline (CG95).

We looked for the costs of the individual tests from UK sources. We found that the unit cost of stress echocardiography is £435[190].

15.3.4 Evidence statements

Clinical	**<u>Exercise echocardiography</u>** **D'Andrea 2005[176]:** Evidence from one cohort study shows that exercise stress echocardiography offered incremental prognostic information in prediction of cardiac death [follow-up mean 46.9 months]. **Elhendy 2004[177] :** Evidence from one cohort study shows that exercise echocardiography offered incremental prognostic information in prediction of cardiac events (cardiac death, non fatal MI, coronary revascularisation) in addition to clinical and exercise variables [follow-up median 2.7 years (1 to 7.8 years)].
Economic	No economic evidence was found on this question. A simple cost analysis showed that stress echocardiography has a cost of £435 per test.

15.4 Myocardial perfusion imaging

15.4.1 Clinical question

In adults with stable angina what is the incremental value/effectiveness of Myocardial Perfusion Imaging for prognostic risk stratification in prediction of adverse cardiac outcomes?

15.4.2 Clinical evidence

The "Review Protocol" for this topic can be found in Appendix C, the "Search Strategies" in Appendix D, the "List of Included and Excluded Studies" in Appendix E1 and the "Clinical Evidence Tables" in Appendix E2.

Nine studies assessing the incremental prognostic value of myocardial perfusion imaging were included in this review [178-186]

Groutars 2002[178] evaluated the incremental prognostic value of myocardial perfusion scintigraphy using technetium-99m tetrofosmin with bicycle ergometry in 597patients with known or suspected coronary artery disease. Three nuclear variables were evaluated, including the summed stress score (SSS), the summed rest score (SRS), and the summed difference score (SDS). The SSS was obtained by calculating the sum of the scores of the 20 segments of the stress technetium-tetrofosmin images. The SRS was calculated on a similar basis. The SDS was calculated as the sum of the differences between SSS and the SRS for each segment. An SDS score between 2 and 12 was defined as moderate myocardial ischaemia and an SDS score of >12 as severe ischaemia. The endpoints were death, caused by any cardiac disorder with underlying coronary artery disease, including sudden death (confirmed by review of death certificate or hospital chart), or non fatal MI (documented by appropriate electrocardiographic and cardiac enzyme changes) assessed at a mean follow-up of 23±9 months. A total of 46 events occurred: 16 cardiac deaths and 30 non fatal MI.

Multivariate analysis included four different nuclear variables, the SSS, SDS, abnormal SPECT, and severe ischaemia. Abnormal SPECT was defined as an SSS greater than 3 and severe ischaemia as SDS greater than 12. Abnormal SPECT (HR 5.438, CI 1.882 to 15.72, p=0.002) and SSS (HR 1.019, CI 1.001 to 1.038, p=0.035) were significant independent predictors of cardiac death and MI.

Table 15.9: Groutars 2002[178], Multivariate analysis of nuclear variables

	Events (n=46)	No event (n=551)	HR	95% CI	P
Abnormal SPECT (SSS) summed stress score >3)	41 (89%)	278 (50%)	5.438	1.882 to 15.72	0.002
Summed stress score (SSS)	28±20	13±17	1.019	1.001 to 1.038	0.035
Summed difference score (SDS)	12±14	7±11	1.036	1.036	0.110
Severe ischaemia (SDS >12)	15 (33%)	96 (17%)	0.342	0.342	0.072

Elhendy 2005[179] (N=455) assessed the independent value of SPECT imaging using technetium-99m tetrofosmin with bicycle ergometry in predicting death from any cause, cardiac death, and cardiac death and non-fatal MI (defined by cardiac enzyme levels and electrocardiographic changes) in patients with stable angina pectoris. During a mean follow-up of 6±1.7 years 93 (20%) patients died. Death was considered cardiac in 46 patients (10%) and non fatal MI occurred in 40 patients (9%).

Table 15.10: Predictors of outcome events by Cox models

Parameter	Univariate [RR (95% CI)]	Multivariate [RR (95% CI)]
All cause mortality		
Age	1.05 (1.02 to 1.09)	1.05 (1.03 to 1.08)
Male sex	2.5 (1.5 to 3.1)	2.1 (1.3 to 3.4)
History of heart failure	5.1 (2.7 to 10)	2.7 (1.6 to 4.5)
Diabetes mellitus	2 (1.2 to 3.4)	2.2 (1.4 to 3.5)
Smoking	1.9 (1.2 to 3.1)	1.7 (1.1 to 2.6)
Reversible perfusion defects	2 (1.2 to 3.1)	1.9 (1.1 to 2.8)
Fixed perfusion defects	2.3 (1.3 to 4.1)	2 (1.2 to 3.1)
Cardiac mortality		
Age	1.04 (1.01 to 1.09)	1.04 (1.02 to 1.07)
Male sex	2.5 (1.2 to 3.4)	1.8 (1.2 to 3.8)
History of heart failure	7.3 (3.5 to 15)	4.2 (2.1 to 7)
Diabetes mellitus	2.3 (1.2 to 4.4)	1.7 (1.2 to 3.9)
Abnormal perfusion	2.9 (1.8 to 5.1)	2.5 (1.5 to 3.5)
Cardiac death or non-fatal MI		
Age	1.03 (1.01 to 1.06)	1.03 (1.01 to 1.06)
Male sex	2.2 (1.3 to 3.6)	2.3 (1.3 to 4)
History of heart failure	2.9 (1.7 to 4.9)	2.8 (1.6 to 4.9)
Diabetes mellitus	1.6 (1.1 to 2.8)	1.8 (1.1 to 3.1)
Hypertension	1.7 (1.1 to 2.6)	1.9 (1.2 to 3)
Reversible perfusion defects	2 (1.2 to 3.1)	1.7 (1.1 to 2.4)

In a multivariate model, independent predictors of death were age, male sex; diabetes, history of heart failure; smoking and MPS variables- reversible perfusion defects and fixed perfusion defects.

Stratmann 1992[180] (N=373) evaluated the usefulness of thallium -201 scintigraphy with dypridamole stress for predicting the occurrence of cardiac events in patients with stable chest pain. The outcomes assessed were cardiac event (development of unstable angina, nonfatal MI, or death resulting from a primary cardiac cause) and cardiac death at a mean follow-up of 18±9 months. Cardiac events occurred in 59 patients during the follow-up period, including unstable angina in 27, non fatal MI in 11, and cardiac death in 21.

Regression analysis showed that a history of previous CABG and the presence of a fixed perfusion defect were the only independent predictors of a subsequent cardiac event. The presence of a fixed perfusion defect and a history of peripheral vascular disease were found to be independent predictors of cardiac death.

Table 15.11: Stratmann 1992[180], Predictors of cardiac events

All cardiac events	**Chi square**	**P value**
Fixed defect	4.09	0.04
Abnormal scan (presence of a reversible defect, a fixed defect, or both reversible and fixed defects)	2.20	0.13
History of old MI	2.88	0.09
History of congestive heart failure	2.46	0.11
Pretest CABG	3.87	0.04
Cardiac death		
Fixed defect	7.04	0.008
Abnormal scan	0.36	0.54
History of old MI	5.46	0.02
History of peripheral vascular disease	8.54	0.004

Wiersma 2009[181] (N=319) determined the prognostic value of myocardial perfusion scintigraphy in a population with type 2 diabetes mellitus and mild stable angina (CCS class I-II). The outcome assessed was cardiac death or spontaneous, non procedure-related, non fatal MI. During a mean follow-up of 2.2±0.6 years 14 patients had a non fatal MI or died from a cardiac cause. Multivariate analysis identified the presence of severe myocardial ischaemia (SDS ≥8) (HR 5.45, 95% CI 1.89 to 15.71) and insulin use (HR 4.00 95% CI 1.25 to 12.75) as independent predictors of cardiac events.

Table 15.12: Wiersma 2009[181], Multivariable Analysis

Characteristic	Present	Absent	HR (95% CI)
Insulin use	11/158	3/161	4.00 (1.25 to 12.75)
MPS: severe ischaemia	8/63	6/256	5.446 (1.89 to 15.71)

Stratmann 1994[182] (N=534) evaluated technitium-99 m sestamibi SPECT using dipyridamole stress for assessing risk of subsequent cardiac events in patients with stable chest pain who were unable to perform diagnostically useful levels of exercise stress. Cardiac events included non fatal MI and cardiac death, and occurred in 58 patients at a mean follow-up of 13±5 months

Stepwise logistic regression was used to evaluate the independent predictive value of clinical and test variables. In Model 1, the only scintigraphic variable included was the presence of an abnormal scan. In the second model the scintigraphic variables entered were specific types of myocardial perfusion defects , either reversible or fixed. the In the first model, the presence of an abnormal scan, a history of congestive heart failure or diabetes mellitus, Q waves on the pre test electrocardiogram, and an abnormal MIBI study were identified as independent predictors of cardiac events. In the second model, reversible and fixed myocardial perfusion defects retained independent predictive value for cardiac events, as did congestive heart failure, Q waves on the pre-test electrocardiogram and dipyridamole induced chest pain.

Table 15.13: Stratmann 1994[182], multivariate analysis

Multivariate analysis	RR (95% CI)
Model I	
Abnormal scan	5.8 (1.8 to 19) *
Chest pain during test	1.8 (0.9 to 3.6)
History of congestive heart failure	1.8 (1.1 to 3.1) *
History of diabetes mellitus	1.8 (1.0 to 3.1)
CAD by coronary angiography	1.3 (0.8 to 2.3)
Q waves on pre-test ECG	1.8 (1.0 to 3.1) *
Model II	
Reversible defect	2.1 (1.2 to 3.5) *
Fixed defect	1.8 (1.0 to 3.4) *
Chest pain during test	1.7 (0.8 to 3.5)
History of congestive heart failure	2.0 (1.1 to 3.5) *
History of diabetes mellitus	1.9 (1.1 to 3.2) *
CAD by coronary angiography	1.4 (0.8 to 2.3)
Q waves on pre-test ECG	(1.0 to 3.2) *

Stratmann 1994[183] (n=548) assessed the relative prognostic value of exercise stress with myocardial perfusion imaging in a large population of patients presenting for the evaluation of stable chest pain consistent with angina pectoris. The outcomes assessed were cardiac events (cardiac death or non fatal MI) at a mean follow-up 13±5 months (range 1 to 24 months). During follow-up 24 patients had a cardiac event including non fatal MI in 11 and death from a cardiac cause in 13.

In the first regression model, the only scintigraphic variable included in the analysis was the presence of an abnormal perfusion scan. In the second model, patients with an abnormal perfusion scan result were classified into those with either reversible or fixed perfusion defects.

Table 15.14: Stratmann 1994[183] (Exercise MIBI imaging), Univariate & multivariate analysis

Multivariate analysis	RR (95% CI)
Multivariate analysis- Model I	
Abnormal scan	11.9 (1.6 to 89.4)
Ischaemic ST depression	2.2 (0.9 to 5)
History of congestive heart failure	1.6 (0.6 to 4.2)
History of old MI	1.2 (0.5 to 2.8)
history of diabetes mellitus	1.5 (0.6 to 4.1)
Multivariate analysis- Model II	
Reversible defect	2.9 (1.2 to 7)
Fixed defect	1.4 (0.6 to 3.3)
Ischaemic ST depression	2.0 (0.8 to 4.6)
History of congestive heart failure	1.9 (0.7 to 5.2)
History of old MI	1.3 (0.6 to 3.2)
history of diabetes mellitus	1.6 (0.6 to 4.2)

**In Model I, scintigraphic variable included 'abnormal scan'; In Model II, scintigraphic variables included were 'reversible defect' and 'fixed defect'.*

Poornima 2004[184] (N=1,461) assessed the incremental value of SPECT using thallium-201 and treadmill ergometry in symptomatic patients with low-risk Duke treadmill scores ($\geq$5). Most of the patients had atypical angina (71%). The outcomes assessed were: 1) cardiac death, non-fatal MI, late revascularisation and 2) cardiac death or non fatal MI at a mean follow-up of 7$\pm$1 years. The total number of events was 211 and included 30 deaths, 55 non fatal MIs and 124 revascularisation procedures.

Table 15.15: Poornima 2004[184] Univariate analysis

Univariate results	Chi square (X^2)	p-value
Clinical score (CS) [1]		
Cardiac death	41.9	0.0001
Cardiac death/MI	102.7	0.0001
Cardiac death/MI/ late	102.7	0.0001

revascularisation		
global stress score (GSS) [2]		
Cardiac death	24.9	0.0001
Cardiac death/MI	14.2	0.0002
Cardiac death/MI/ late revascularisation	65.6	0.0001

Table 15.16: Poornima 2004[184] Bivariate analysis

Bivariate results (including both CS and GSS)	**Chi square (X^2) (Adjusted)**	**p-value**
Clinical score (CS)[1]		
Cardiac death	31	0.0001
Cardiac death/MI	40.5	0.0001
Cardiac death/MI/ late revascularisation	73.5	0.0001
global stress score (GSS)[2]		
Cardiac death	7.74	0.005
Cardiac death/MI	2.71	0.10
Cardiac death/MI/ late revascularisation	23.6	0.0001

1Clinical score (CS): A simple five-point scoring system was developed after consideration of 16 clinical and ECG variables. The variables included in the five point scoring were male gender, history of MI (clinical event and Q waves on ECG), diabetes, insulin use, and typical angina.

2A global stress score (GSS) was obtained by adding the scores of perfusion on all the stress short axis images. A global rest score (GRS) was obtained by adding the scores of all the redistribution short axis images. A global difference score (GDS) was obtained by subtracting GSS from GRS.

The CS (clinical score) and GSS (Global stress score) were significant independent predictors of cardiac death.

Vanzetto 1999[185] (N=1137) evaluated the prognostic value of Thallium 201SPECT and exercise treadmill test in patients with low to intermediate-likelihood of future cardiac events.

The outcomes assessed were mortality, cardiac mortality (sudden death or death of demonstrated cardiac origin) and occurrence of MI (on the basis of characteristic chest pain, ECG changes, and serum creatine kinase level >twice the upper limit of normal). During follow-up (72±18 months [11 days to 8 years]) 88 patients died, 46 from a cardiac cause. MI occurred in 57 patients, 7 of whom died from a cardiac cause 8±4 months later.

Age (p=0.04), exercise treadmill test (p=0.03), and thallium-201 SPECT (p=0.003) were independent predictors of overall mortality. Thallium-201 SPECT and exercise treadmill test were independent predictors of cardiac death. Thallium-201 SPECT was also predictive of future MI, whereas exercise treadmill test was not.

In multivariate analysis, SPECT was of incremental prognostic value over clinical and exercise treadmill test data for predicting overall mortality and major cardiac events.

Table 15.17: Multivariate predictors of cardiac death

	Odds ratio	**95% CI**	**P value**
Age >60 years	1.78	1.02 to 3.11	0.05
Previous MI	3.50	2.06 to 5.96	0.006
Positive ETT	0.83	0.25 to 2.80	Ns
Strongly positive ETT	2.66	1.23 to 5.76	0.02
Non diagnostic ETT	2.48	1.31 to 4.69	0.006
1 or 2 abnormal segments on T1201 SPECT	2.20	0.97 to 4.98	0.08
≥ 3 abnormal segments on T1201 SPECT	4.83	2.22 to 9.54	0.001

Table 15.18: Multivariate predictors of non fatal MI

	Odds ratio	**95% CI**	**P value**
Presence of ≥ 1 risk factor	2.50	1.50 to 4.17	0.03
Previous MI	2.89	1.78 to 4.69	0.01
Positive Exercise Treadmill Test (ETT)	1.14	0.60 to 2.18	Ns
Strongly positive Exercise Treadmill Test (ETT)	0.89	0.43 to 1.85	Ns

Non diagnostic Exercise Treadmill Test (ETT)	0.93	1.54 to 1.60	Ns
Maximum ST segment depression ≥ 2	1.34	0.76 to 2.37	Ns
1 or 2 abnormal segments on T1201 SPECT	4.20	1.93 to 9.14	0.002
≥ 3 abnormal segments on T1201 SPECT	4.97	2.15 to 11.49	0.004

Lima 2003[186] (N=328) evaluated the value of pharmacological (dipyridamole) or exercise stress SPECT with technitium-99m for risk stratification of patients aged ≥75 years with suspected CAD.

The outcomes assessed were cardiac death or MI, and cardiac death, MI or myocardial revascularisation. During follow-up, 56 patients had cardiac events including 24 cardiac deaths, 11 non fatal MIs and 21 revascularisation procedures.

Logistic regression analysis of clinical, exercise treadmill test and MPS data was used to identify significant predictors of cardiac events, with separate models for cardiac death, cardiac death and MI, and any cardiac event. For cardiac death, the MPS result was the most significant predictor variable (x^2=17.7, 95% CI: 5.9 to 30.6, p=0.0001), followed by LV enlargement (x^2=10.3, 95% CI: 2.26 to 46.7, p=0.0004).

For cardiac death and MI MPS result was also the most predictive variable ($\mathbf{X}^2$=12.9, 95% CI 5.3 to 3.19, p=0.0001), followed by male gender ($\mathbf{X}^2$=3.7, 95% CI 1.5 to 8.9, p=0.0001) and pharmacologic stress ($\mathbf{X}^2$=2.8, 95% CI 1.15 to 6.4, p=0.03).

The independent predictors of any cardiac event were an abnormal scan ($\mathbf{X}^2$=18.7, 95% CI 8.9 to 39.6, p=0.0001) and male gender ($\mathbf{X}^2$=2.6, 95% CI 1.3 to 5.2, p=0.009).

Summary: Nine studies (2 high quality, 2 moderate quality, and 5 low quality) showed that **Myocardial Perfusion Imaging** offered incremental prognostic value in prediction of cardiac death, MI, and/or revascularisation. Most of the studies were not of high quality as they did not have sufficient number of events (for validity the study should have at least 10 patients (continuous) or 10 events (dichotomous) per variable). Some studies did not include relevant risk factors (e.g. CCS class, LV function) and had short follow-up periods. Also many studies reported composite outcomes as their primary endpoint, and the components of these outcomes have been inconsistently defined, and inadequately reported. This may cause an exaggerated perception of the incremental prognostic value of the test being evaluated.

15.4.3 Economic evidence

No relevant studies were found. Studies reporting the cost per case detected were not included as this question was addressed in the Chest Pain Guideline (CG95).

We looked for the costs of the individual tests from UK sources. We found that the unit cost of MPS with SPECT is £293[191].

15.4.4 Evidence statements

Clinical

Myocardial perfusion imaging:

Groutars 2002[178] (Myocardial SPECT using technitiun-99m tetrofosmin): Evidence from one study shows that myocardial perfusion scanning using technetium 99m tetrofosmin offered incremental prognostic information in prediction of cardiac death or non fatal MI [follow-up 2 years].

Elhendy 2005[179] (Myocardial SPECT using technitiun-99m tetrofosmin): Evidence from one study shows that stress technetium-tetrofosmin myocardial perfusion imaging is an independent predictor of all cause mortality in patients with stable angina. [mean follow-up 6±1.7 years].

Stratmann 1992[180] (Dipyridamole thallium-201 scintigraphy): Evidence from one study shows that presence of a fixed perfusion defect during dipyridamole stress and a history of CABG are independent predictors of cardiac events. The presence of a fixed perfusion defect and a history of peripheral vascular disease were independent predictors of cardiac death [mean follow-up 18 months].

Wiersma 2009[181] (Myocardial SPECT): Evidence from one study shows that the presence of severe myocardial ischaemia and insulin use were independent predictors of cardiac death or non fatal MI [follow-up 2.2±0.6 years].

Stratmann 1994[182] (Myocardial SPECT using technetium-99m sestamibi and dipyridamole stress): Evidence from one study shows that reversible and fixed perfusion defects on SPECT, history of congestive heart failure, history of diabetes mellitus, and Q waves on pre-test ECG were independent predictors of cardiac death or MI [mean follow-up 13±5 months].

Stratmann 1994[183] (Myocardial SPECT using technetium-99m sestamibi and exercise stress): Evidence from one study shows that exercise perfusion abnormalities and reversible perfusion defects were independent predictors of cardiac death or non-fatal MI) [mean follow-up 13±5 months].

Poornima 2004[184] (Myocardial SPECT and treadmill ergometry):

Evidence from one prognostic study shows that the clinical score (CS) and global stress score (GSS) were significant independent predictors of cardiac death, cardiac death or MI; and cardiac death, MI or revascularisation The independent predictive power of CS appeared to be greater than that of GSS [follow-up 7±1 year].

Vanzetto 1999[185] (Myocardial SPECT using thallium 201 and exercise treadmill test): Evidence from one prognostic cohort study shows that exercise tolerance test and SPECT were independent predictors of overall mortality. Exercise tolerance test and SPECT were independent predictors of cardiac death and SPECT was an independent predictor of MI [Follow-up 72±18 months]

Lima 2004[186] (Myocardial SPECT using technetium-99m and exercise treadmill test): Evidence from one study shows that SPECT was an independent predictor of cardiac death or MI, and of total cardiac events (cardiac death, MI or myocardial revascularisation). [mean follow-up 34±15 months]

Economic No economic evidence was found on this question. A simple cost analysis showed that MPS with SPECT has a cost of £293 per test.

15.5 Ambulatory ECG

15.5.1 Clinical question

In adults with stable angina what is the incremental value/effectiveness of "exercise tests and ambulatory ECG" for prognostic risk stratification in prediction of adverse cardiac outcomes?

15.5.2 Clinical evidence

The "Review Protocol" for this topic can be found in Appendix C, the "Search Strategies" in Appendix D, the "List of Included and Excluded Studies" in Appendix E1, and the "Clinical Evidence Tables" in Appendix E2.

Two papers assessed the incremental prognostic value of ambulatory ECG for prediction of adverse cardiac outcomes [187,188].

Forslund 1999[187] (N=686) investigated whether ambulatory ECG and exercise testing provide complementary prognostic information in patients with stable angina pectoris.

The outcomes assessed were CV death, non fatal MI, and revascularisation. CV death was defined as death from acute MI, sudden death, or death from other vascular diseases. The criteria for MI were typical clinical presentation, significant increase in cardiac enzymes, and/or development of a new Q wave on the electrocardiogram.

During follow-up (median 40 months, range 6 to 75 months) 29 patients had CV death, 27 had a nonfatal MI, and 89 underwent revascularisation.

The duration of ST segment depression over 24 hours (log transformed) was independently related to CV death (OR 1.23, 95% CI 1.04 to 1.46, p=0.018) and to CV death+ MI (OR 1.13, 95% CI 1.00 to 1.27, p=0.050). The odds ratio for revascularisation was 1.11 (CI 1.01 to 1.22, p=0.035), and for the composite endpoint was 1.11 (CI 1.04 to 1.20, p=0.004).

Conti 1997[188] (n=558) assessed the prognostic value of exercise test and ambulatory ECG among patients enrolled in the ACIP trial. The outcome event (a composite of death, MI, or hospitalisation for ischaemic event at 1 year) occurred in 73 cases.

Table 15.19A: Model 1: (=angina history, ischaemia guided therapy, revascularisation strategy - all baseline variables with p<0.05) (n=548)

Variable	p value	RR; 99% CI
History of angina(within 6 weeks of randomisation)	0.01	1.95
Exercise time	0.01	0.89
Ambulatory ECG episodes	0.39	1.03
Duration of ischaemia	0.33	1.00
Ischaemia guided strategy	0.32	0.76
Revascularisation strategy	0.04	0.55

Table 15.19B: Model 2: (=angina history, ischaemia guided therapy, revascularisation strategy- all baseline variables stepwise)

Variable	p value	RR (99% CI interval)
History of angina (within 6 weeks of randomisation)	0.008	2.00; 1.02 to 3.94
Exercise time	0.006	0.88; 0.78 to 0.99
Ambulatory ECG episodes	NA	
Duration of ischaemia	NA	
Ischaemia guided strategy	0.32;	0.76
Revascularisation strategy	0.04; 0.55	

The model indicates that a history of angina in the 6 weeks before randomisation and a short total time on exercise treadmill at baseline were highly significant predictors of adverse events (death, MI, or hospitalization for iscahemic event) within 1 year.

Summary: Of the two studies (one moderate and one low quality) , one of the studies showed that **ambulatory ECG** offered incremental prognostic value in prediction of cardiac death and MI; and the other study showed that ambulatory ECG was not an independent predictor of death, MI or hospitalisation for ischaemic events) . The studies were not of high quality as they had very few events (for validity the study should have at least 10 patients (continuous) or 10 events (dichotomous) per variable). Also both studies reported composite outcomes as their primary endpoint instead of reporting individual cardiac outcomes.

15.5.3 Economic evidence

No relevant studies were found. Studies reporting the cost per case detected were not included as this question was addressed in the Chest Pain Guideline (CG95).

We looked for the costs of the individual tests from UK sources. We found that the unit cost of ambulatory ECG is £56 (NHS Reference Costs 2008-09 – Diagnostic Services – 24 Hour ECG/BP monitoring)[24].

15.5.4 Evidence statements

Clinical	**Ambulatory ECG** **Forslund 1999[187]:** Evidence from one study shows that duration of ST segment depression during the ambulatory electrocardiograph was an independent predictor of CV death and CV death+MI. **Conti 1997[188] [exercise test and ambulatory ECG]:** Evidence from one study shows that history of angina in the 6 weeks before randomisation and a short total time on exercise treadmill at baseline were statistically significant predictors of adverse events (death, MI or hospitalisation for ischaemic events) within 1 year. Angina during ambulatory ECG or stress test was not predictive of an adverse event [follow-up 1 year].
Economic	No economic evidence was found on this question. A simple cost analysis showed that ambulatory ECG has a cost of £56 per test.

15.6 Recommendations and link to evidence

Recommendation	**Please see sections 11.5 and 11.6 for recommendations on the use of anatomical and functional tests in the management of patients with stable angina.**
Relative values of different outcomes	The review indicates that functional tests provide modest incremental prognostic information. The magnitude of the increment in prognostic value is however unclear. The GDG were interested in identifying prognostic information and whether acting on this prognostic information would be beneficial to patients. Since this guideline recommends that patients are given anti-anginal drugs and secondary prevention measures, the ability to identify patients who would benefit from revascularisation is critical. However neither this review nor the evidence reviews examining medical and revascularisation strategies (see chapter 10 and 11) provided robust evidence to identify patients who gain prognostic benefit from revascularisation.
Economic considerations	All of the tests considered in this review are associated with some costs but there is no evidence that routine functional or anatomical testing provides additional clinical benefit. Routine functional testing was therefore considered not cost-effective.
Quality of evidence	The study inclusion criteria varied widely and the study participants may not be representative of the wider population of people with stable angina. The studies were generally small with relatively short follow-up times. Consequently most of the studies had relatively few outcome events and limited statistical power to reliably identify predictor variables. For validity of the results the analysis should have at least 10 patients (continuous) or 10 events (dichotomous) per variable. The studies generally did not include all potentially important clinical predictors of risk in the univariate and multivariate analyses and it is therefore not possible to accurately quantify the incremental predictive value of any of the functional tests. Several of the studies used composite outcomes. The use of revascularisation as a component of a composite outcome is problematic when assessing the prognostic value of a functional test because the test result may directly influence the likelihood that individual patients will undergo revascularisation.
Other considerations	The GDG discussed whether it was appropriate to routinely perform tests that would provide prognostic information but

that would not influence treatment. The GDG agreed the need to inform patients of the purpose and potential therapeutic implications of all investigations, particularly those associated with risk. The GDG agreed that functional and anatomical testing for prognostic information alone was unlikely to be justified or appropriate for the majority of patients. The GDG made recommendations for the use of these tests within a wider management strategy and these recommendations are found in section 11.5 and 11.6

The GDG were aware of a historical understanding in cardiology that functional testing in people with a confirmed diagnosis of stable angina is important in clinical assessment, including risk stratification and decisions about treatment. This strategy is recommended by other groups. [173]

The GDG discussed evidence that did not fulfill the inclusion criteria for the review but is influential in the discussion within cardiology about the benefit of functional testing. One study reports evidence from a registry of 10627 patients (of whom 39.7% had angina) who underwent exercise or adenosine myocardial perfusion SPECT[192]. Myocardial revascularisation was carried out within six weeks of the scan in 671 patients, and 9956 patients were initially managed medically. All patients were followed for a mean of 1.9 years and multivariate modelling was used to assess the effect of the extent of inducible myocardial ischaemia on the relationship between treatment strategy (revascularisation or medical therapy) and cardiac mortality. Above a threshold of 10%-12.5% ischaemic myocardium revascularisation was associated with lower cardiac death rate than medical therapy.

In the nuclear substudy of COURAGE (n=314) percutaneous coronary intervention produced more effective resolution of ischaemia than optimal medical treatment, and in multivariate analyses reduction of ischaemia was associated with greater event-free survival[193].

The GDG considered evidence from these studies to be hypothesis-generating rather than definitive evidence on which recommendations could be based. The GDG considered this area a high priority for further research.

The GDG were aware that people with a confirmed diagnosis of stable angina may have had a functional or anatomical test during diagnostic assessment and that functional testing can be part of the assessment when deciding on revascularisation strategy.

16 Rehabilitation

16.1 Introduction

Cardiac rehabilitation programmes have been shown to be of benefit to people with cardiovascular disease in certain circumstances e.g. those who have had a myocardial infarction (Myocardial infarction: secondary prevention. NICE clinical guideline 48 (2007). The GDG were interested in whether there was evidence that patients with stable angina would similarly benefit from cardiac rehabilitation programmes.

The aim of this review was to address the question, "what is the clinical/cost effectiveness of cardiac rehabilitation programmes for patients with stable angina?"

There is no universal definition of cardiac rehabilitation. Cardiac rehabilitation can be defined 'as the process by which patients with cardiac disease, in partnership with a multidisciplinary team of health professionals, are encouraged and supported to achieve and maintain optimal physical and psychosocial health'[194].

The following are the domains of cardiac rehabilitation programmes described by the Department of Health and British Association for Cardiac Rehabilitation:

a. Department of Health (Department of Health 2010).

Cardiac rehabilitation is a professionally supervised programme consisting of:

- a medical assessment to determine risk factors, patient needs and limitations
- a menu-based programme covering six components, namely: lifestyle, risk factor management, cardio-protective drug therapy and implantable devices, psychosocial status and quality of life , education and long-term management.

b. British Association for Cardiac Rehabilitation (2007) (BACR 2007) describe the core components of cardiac rehabilitation as follows:

1. Lifestyle:

    I) Physical activity and exercise

    II) Diet and weight management

    III) Smoking cessation

2. Education

3. Risk factor management

4. Psychosocial

5. Cardio protective drug therapy and implantable devices

6. Long-term management strategy

This evidence review has used broad criteria when considering what evidence should be included. The main criteria were that the patients had stable angina and had an active intervention that could be considered important for rehabilitation and/or secondary prevention. Outcomes sought were those which represented improvement in angina, cardiovascular outcomes and quality of life. Programmes where patients were given advice only e.g. to exercise, to change diet are included in the review on effect of lifestyle factors in chapter 17.

A total of 20 papers were included in this review, with the trials evaluating a range of rehabilitation programmes. The studies have been analysed and presented separately according to the following themes:

- Exercise only – 4 papers
- Health Education – 2 papers
- Stress management programmes– 4 papers
- Intensive lifestyle programme – 1 paper
- Yoga life style programme– 1 paper
- Nurse led cardiac rehabilitation programme – 1 paper
- Angina management programme – 1 paper
- Angina Plan- 2 paper

Only 2 papers [195,196] included Phases 1 and 2. The majority of the papers examined phases 3 and 4 and included exercise, education and advice on risk factors.

The main results of the review are presented according to the content of rehabilitation programmes and their relevant comparisons as follows:

Exercise programmes

- Intensive exercise programme vs. control for stable angina
- Exercise and placebo vs. placebo for stable angina
- Exercise and BB vs. BB for stable angina
- Exercise plus low fat diet vs. control for stable angina

- Exercise vs. PCI

Health education

- Health education vs. control for stable angina

Stress management

- Stress management vs. routine care control for stable angina
- Stress management + exercise vs. routine care control for stable angina

Yoga life style

- Yoga life style intervention programme vs. control for stable angina

Intensive lifestyle programme

- Intensive life style intervention programme vs. control for stable angina

Nurse led cardiac rehabilitation

- Nurse led cardiac rehabilitation vs. routine care for stable angina

Angina management programme

- Angina management programme (AMP) vs. control for stable angina

Angina Plan

- Angina Plan vs. education session for stable angina

16.2 Clinical Evidence

16.2.1 Exercise Programmes

The “Review Protocol” for this topic can be found in Appendix C, the “Search Strategies” in Appendix D, the “List of Included and Excluded Studies” in Appendix E1, the “Clinical Evidence Tables” in Appendix E2, and the “Forest Plots” in Appendix F.

There were 4 papers with 5 relevant comparisons (Intensive exercise programme vs. control; Exercise and placebo vs. placebo; Exercise and BBs vs. BB; Exercise plus low fat diet vs. control; PCI vs. exercise +medical therapy) evaluating effectiveness of exercise training programmes for stable angina. Of these 4 papers 2 papers compared the effectiveness of exercise training with medical therapy[197] and PCI[198]. These studies could be considered as treatment options rather than rehabilitation but are included here for simplicity.

Table 16.1: Intensive exercise programme vs. control

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise (1 year intensive)	Control	Relative (95% CI)[9]	Absolute	
Max ST depression (mm) (follow-up 1 years; better indicated by lower values)											
Todd 1990[199] (a,b,c,d,e)	randomised trials	serious (f)	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	20	-	MD 0.2 higher (-0.43 to 0.83)	⊕⊕⊕O MODERATE
Time to 1mm ST depression (s) (follow-up 1 years; better indicated by higher values)											
Todd 1990[199] (a,b,c,d,e)	randomised trials	serious (f,g)	no serious inconsistency	no serious indirectness	serious imprecision (i)	none	20	20	-	MD 166 higher (-221.71 to 553.7)	⊕⊕OO LOW
Treadmill time (s) (follow-up 1 years; better indicated by higher values)											
Todd 1990[199] (a,b,c,d,e)	randomised trials	serious (f,h)	no serious inconsistency	no serious indirectness	serious imprecision (i)	none	20	20	-	MD 262 higher (66.64 to 590.64)	⊕⊕OO LOW

(a) The intervention is a one-year intensive exercise training programme. The training group undertook the Canadian Air force Programme for Physical Fitness. It is a brief (11 minutes) daily exercise programme of five callisthenic type exercises. Exercise levels increase in intensity each week to achieve a progressive increase in physical fitness.

(b) All study patients were given atenolol for 2 weeks and then atenolol was stopped 4 wks before they were randomised to the exercise or control group. The main comparison is between the exercise training programme (n=20) and B-blockers (same patients at baseline) with regard to exercise tolerance. In addition, a further comparison is made between the exercise training programme patients and those who did not receive the exercise programme. A modified Naughton protocol exercise program was used to assess tolerance. Randomisation produced groups whose baseline measurements differed statistically in only one respect. The mean (SD) maximum ST depression for the control group (1.5 (0.8) mm) was significantly less than that for the exercise group (1.9 (0.9) mm). Quite large variations in other variables were, however, not statistically significant. Most notable among these differences was the time to 1 mm ST depression, which was twice as long in the controls as in the exercise group. The overall trend was for the exercise group to be less fit, as judged by resting and submaximal heart rate, and to have more severe disease, judged by maximum heart rate and double product, maximum ST depression, and double product ST threshold.

(c) All patients had an exercise test at baseline then received 100 mg atenolol daily for one week and had another exercise test thereafter. Atenolol was then withdrawn and patients were randomised. With regards to exercise compared to β blockers the authors conclude that regular exercise training was as good as atenolol in antianginal efficacy since both improved Max ST depression, time to 1 mm ST depression and treadmill time equally well.

(d) Within the exercise group maximum ST depression was (1.9±0.9 to 1.6±1.2, p<.05), time to 1mm ST depression (374±369 to 881±668, p<.001) and total treadmill time (741±356 to 1272±514, p<.001) improved significantly.

(e) All patients in the exercise group reported an improvement in their anginal symptoms.

(f) Todd 1990[193] : No information was reported for methods of randomisation, or concealment of allocation to investigators - small sample size

(g) Time to 1 mm ST depression increased significantly from baseline for the exercise, but not the control group. Change score statistics not provided

(h) Treadmill time increased significantly from baseline for the exercise, but not the control group (p<0.001). Change score statistics not provided

i) 95% CI includes no effect and the upper and lower CI crosses the MID.

Table 16.2: Exercise and placebo vs. placebo for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise (and placebo)	Placebo	Relative (95% CI)	Absolute	
Maximal working capacity kpm/min (follow-up 4 months; better indicated by higher values)											
Malmborg 1974[197]	randomised trials	serious (a,b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	8	8	-	MD 4 lower (43.5 lower to 35.5 higher)	⊕⊕OO LOW
Anginal attacks / week (follow-up 4 months; better indicated by lower values)											
Malmborg 1974[197]	randomised trials	serious (a,b)	no serious inconsistency	no serious indirectness	serious imprecision (c)	none	8	8	-	MD 25 lower (82.38 lower to 32.38 higher)	⊕⊕OO LOW
Nitroglycerin tablets/ week (follow-up 4 months; better indicated by lower values)											
Malmborg 1974[197]	randomised trials	serious (a,b)	no serious inconsistency	no serious indirectness	serious imprecision (c)	none	8	8	-	MD 4 higher (96.75 lower to 104.75 higher)	⊕⊕OO LOW

(a) Malmborg 1974[191]: This is a small pilot study (n=29 with n=8 maximum in the 4 groups).
(b) It did not specify a primary outcome and did not perform a power calculation.
(c) 95% CI includes no effect and the upper and lower CI crosses the MID.

Table 16.3: Exercise and BBs vs. BB for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise and BBs	BB	Relative (95% CI)	Absolute	
Maximal working capacity kpm/min (follow-up 4 months; better indicated by higher values)											
Malmborg 1974[197]	randomised trials	serious (a,b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	6	7	-	MD 6 lower (55.60 lower to 43.60 higher)	⊕⊕OO LOW
Anginal attacks / week (follow-up 4 months; better indicated by lower values)											
Malmborg 1974[197]	randomised trials	serious (a,b)	no serious inconsistency	no serious indirectness	serious imprecision (c)	none	6	7	-	MD 41 higher (1.93 lower to 83.93 higher)	⊕⊕OO LOW
Nitroglycerin tablets/ week (follow-up 4 months; better indicated by lower values)											
Malmborg 1974[197]	randomised trials	serious (a,b)	no serious inconsistency	no serious indirectness	serious imprecision (c)	none	6	7	-	MD 58 higher (37.02 lower to 153.02 higher)	⊕⊕OO LOW

(a) Malmborg 1974[191]: This is a small pilot study (n=29 with n=8 maximum in the 4 groups).
(b) It did not specify a primary outcome and did not perform a power calculation.
(c) 95% CI includes no effect and the upper and lower CI crosses the MID.

Table 16.4: Exercise plus low fat diet vs. control

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise + low fat diet	Control	Relative (95% CI)	Absolute	
Cardiac mortality (follow-up 12 months)											
Schuler 1992[200]	randomised trials	serious (a,b)	no serious inconsistency	no serious indirectness	serious imprecision (c)	none	2/56 (3.6%)	0/57 0%	RR 5.09 (0.25 to 103.66)	40 more per 1000 (from 20 fewer to 90 more)	⊕⊕OO LOW
Mortality (all) (follow-up 12 months)											
Schuler 1992[200]	randomised trials	serious (a,b)	no serious inconsistency	no serious indirectness	serious imprecision (c)	none	2/56 (3.6%)	1/57 1.8%	RR 2.04 (0.19 to 21.82)	19 more per 1000 (from 15 fewer to 375 more)	⊕⊕OO LOW
Non-fatal MI (follow-up 12 months)											
Schuler 1992[200]	randomised trials	serious (a,b)	no serious inconsistency	no serious indirectness	serious imprecision (c)	none	0/56 (0%)	2/573.5%	RR 0.2 (0.01 to 4.15)	28 fewer per 1000 (from 35 fewer to 110 more)	⊕⊕OO LOW

(a) Only compliant and responsive subjects were selected for this study, so results are likely to be better than those which would be found in a general population of patients with angina.

(b) Schuler 1992[194]: Method of randomisation reported. No blinding. More patients dropped out of the study before treatment was complete in the exercise group (29% vs. 9% in the control group). No allowance was made for this in analysis of final dataset. Therefore, the health benefits gained in the exercise group will be an overestimate.

(c) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.

Table 16.5: Exercise vs. PCI

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise	PCI	Relative (95% CI)	Absolute	
Death of cardiac causes (follow-up 12 months)											
Hambrecht 2004[198]	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/51 (0%)	0/50 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE
Cerebrovascular accident (follow-up 12 months)											
Hambrecht 2004[198]	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (b)	none	2/51 (3.9%)	3/50 (6%)	RR 0.65 (0.11 to 3.75)	21 fewer per 1000 (from 53 fewer to 165 more)	⊕⊕OO LOW
Revascularisation (follow-up 12 months)											
Hambrecht 2004[198]	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (b)	none	3/51 (5.9%)	10/50 (20%)	RR 0.29 (0.09 to 1.01)	142 fewer per 1000 (from 182 fewer to 2 more)	⊕⊕OO LOW
Hospitalisation and coronary angiography owing to worsening angina (follow-up 12)											
Hambrecht 2004[198]	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (b)	none	1/51 (2%)	7/50 (14%)	RR 0.14 (0.02 to 1.1)	120 fewer per 1000 (from 137 fewer to 14 more)	⊕⊕OO LOW

(a) Hambrecht 2004[192]: Even though allocation concealment is reported the method of randomisation is not clearly described
(b) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm

Additional data:

Todd 1990[199]

No. of participants: n= 40 (Exercise (n=20); Control (n=20)).

No information was reported for methods of randomisation, allocation concealment and blinding.

All study patients were given atenolol for 2 weeks and then atenolol was stopped 4 wks before they were randomised to the two groups. The intervention was a one-year intensive exercise training programme.

All patients in the exercise group noted an improvement in their symptoms within 6-8 weeks of starting training. At one year six patients were symptom free during normal activities these six and two others had stopped taking all antianginal agents except sublingual glyceryl trinitrate [no values were reported for these outcomes].

16.2.2 Health Education

The "Review Protocol" for this topic can be found in Appendix C, the "Search Strategies" in Appendix D, the "List of Included and Excluded Studies" in Appendix E1, the "Clinical Evidence Tables" in Appendix E2, and the "Forest Plots" in Appendix F.

There were 2 papers comparing Health Education programmes with control for stable angina [201,202].

Table 16.6: Health education vs. control

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Health Education	Control	Relative (95% CI)	Absolute	
Mortality (follow-up 2 years)											
Cupples 1994[201]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (d)	none	13/342 (3.8%) (a)	29/346 (8.4%)	RR 0.45 (0.24 to 0.86)	46 fewer per 1000 (from 12 fewer to 64 fewer)	⊕⊕OO LOW
Increase in frequency of exercise (follow-up 2 years)											
Cupples 1994[201]	randomised trials	serious	no serious inconsistency	no serious indirectness	serious imprecision (d)	none	108/342 (31.6%)	63/346 (18.2%)	RR 1.73 (1.32 to 2.28)	133 more per 1000 (from 58 more to 233 more)	⊕⊕OO LOW
Nottingham Health Profile (follow-up 2 years; measured with: Nottingham Health Profile (NHP); better indicated by higher values)											
O'Neill 1996[202]	randomised trials	serious (b,c)	no serious inconsistency	no serious indirectness	no serious imprecision	none	221 MD -7.64	212 MD -20.43	-	confidence interval cannot be calculated – missing standard deviations	⊕⊕⊕O MODERATE

(a) Cupples 1994[195]: Allocation concealment not reported. 25/342(7%) in intervention group and 46/346(13%) in the control group lost to follow-up. 10/13 deaths in the intervention group and 28/29 deaths in the control group were due to cardiovascular causes

(b) The conclusions reached in the abstract do not match the statistics in the result section.

(c) The mean differences in overall NHP scores did not reach statistical significance (p=0.0659), but were described in the abstract as significant. Mean differences of two subscales reached statistical significance. Physical Mobility (MD intervention -1.49 and MD control -6.19, p=0.0015) and Social Isolation (MD intervention +1.42 and MD control -3.01, p=0.0408) in favour of the intervention group

(d) 95% CI around the pooled estimate of effect includes appreciable benefit or appreciable harm.

Additional data:

Cupples 1994[201]: Angina episodes per week

For this outcome SD not reported along with the mean values hence data was not analysed. Data reported as in the paper.

The mean number of episodes of angina per week in the intervention group decreased from 3.2 (95% CI 2.7 to 3.7) at baseline to 2.6 (1.7 to 3.5) at review (p=0.04), but no significant change was seen in the control group 2.5 (2.1 to 2.9) at baseline and 2.14 (1.7 to 2.5) at review.

16.2.3 Stress management

The "Review Protocol" for this topic can be found in Appendix C, the "Search Strategies" in Appendix D, the "List of Included and Excluded Studies" in Appendix E1, the "Clinical Evidence Tables" in Appendix E2, and the "Forest Plots" in Appendix F.

There were 4 papers with 2 relevant comparisons (stress management vs. routine care control and; stress management + exercise vs. routine care control) evaluating the effectiveness of stress management programmes for stable angina[203-206].

Table 16.7: Stress management vs. routine care control

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Stress management	routine care control	Relative (95% CI)	Absolute	
Frequency of angina (average no. of. daily attacks) (8 weeks) (follow-up 8 weeks; better indicated by lower values)											
Bundy 1998[206]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	42	16	-	MD 0.00 higher (2.92 lower to 2.92 higher)	⊕⊕⊕O MODERATE
Average duration of angina per attack (mins) (8 weeks) (follow-up 8 weeks; better indicated by lower values)											
Bundy 1998[206]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	42	16	-	MD 0.40 lower (4.70 lower to 3.90 higher)	⊕⊕⊕O MODERATE
Frequency of chest pain at rest (days per fortnight) (6 months) (follow-up 6 months; better indicated by lower values)											
Gallacher 1997[204]	randomised trials	serious limitations (b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	158	179	-	MD 0.59 lower (1.24 lower to 0.06 higher)	⊕⊕⊕O MODERATE
Frequency of chest pain on exertion (days per fortnight) (6 months) (follow-up 6 months; better indicated by lower values)											
Gallacher 1997[204]	randomised trials	serious limitations (b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	158	179	-	MD 0.54 lower (1.35 lower to 0.27 higher)	⊕⊕⊕O MODERATE

(a) Bundy 1998[200]: Allocation concealment not clear. N=120 patients were randomised but only data for 99 patients was included in the analysis. It is not clear how the excluded patients were distributed among the groups or if there were systematic differences in excluded patients between groups.This is a relatively small, short term study aimed at assessing stress mgt, exercise training, stress mgt + exercise training combined with a waiting list control group. Patients were male and all had angina. No primary outcome measures were specified.Rather the study measured exercise workload anginal symptoms and glyceryltrinitrate usage.17% of patients were excluded from the analysis because they had only partial outcome data. No description of these patients was given or the distribution among treatment groups.
(b) This is a large (n=452), well conducted study. Analysis however, was performed on data for only 70% of patients in the SMP group and 80% of those in the control group. Randomisation method was well described. Blinding was not described but relevant study results are based on patient diaries and not investigator assessment

Table 16.8: Stress management + exercise vs. routine care control

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Stress management + exercise	routine care control (8 weeks)	Relative (95% CI)	Absolute	
Frequency of angina (average no. of daily attacks (follow-up 8 weeks; better indicated by lower values) (final scores)											
Bundy 1998[206]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	16	-	MD 0.6 higher (2.97 lower to 4.17 higher)	⊕⊕⊕O MODERATE

Duration of angina (min) (follow-up 8 weeks; better indicated by lower values) (final scores)											
Bundy 1998[206]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	16	-	MD 4.4 lower (9.08 lower to 0.28 higher)	⊕⊕⊕O MODERATE
Frequency of angina (follow-up 8 weeks; better indicated by lower values) (change scores)											
Bundy 1994[205]	randomised trials	serious (b)	no serious inconsistency	no serious indirectness	serious imprecision (c)	none	14	15	-	MD 2.70 lower (5.98 lower to 0.58 higher)	⊕⊕OO LOW
Duration of angina (follow-up 8 weeks; better indicated by lower values) (change scores)											
Bundy 1994[205]	randomised trials	serious (b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	14	15	-	MD 0.70 lower (1.06 to 0.34 lower)	⊕⊕⊕O MODERATE

(a) Bundy 1998[200]: Allocation concealment not clear. N=120 patients were randomised but only data for 99 patients was included in the analysis. It is not clear how the excluded patients were distributed among the groups or if there were systematic differences in excluded patients between groups. This is a relatively small, short term study aimed at assessing stress mgt, exercise training, stress mgt + exercise training combined with a waiting list control group. Patients were male and all had angina. No primary outcome measures were specified. Rather the study measured exercise workload anginal symptoms and glyceryltrinitrate usage.17% of patients were excluded from the analysis because they had only partial outcome data. No description of these patients was given or the distribution among treatment groups

(b) No description of method of randomisation or of "blinding" reported. All patients randomised completed the study. This is a small study (n=29) which aims to evaluate the effects of Stress Management Training (SMT) compared to routine care (RC) on exercise tolerance, angina symptoms, medication use and anxiety. All patients completed the study and the intervention is well described. Follow-up was relatively short (8 weeks after study end) and the study did not specify a primary outcome. It simply reports results for all study outcomes measured. Only exercise tolerance was reported at 8 weeks follow up. The remaining outcomes (medication use, angina symptoms and anxiety) were only reported at baseline and at study end (8 weeks from start of treatment).

(c) 95% CI includes no effect and the upper and lower CI crosses the MID.

Additional data

Amarosa-Tupler 1989[203]

Number of angina incidents: Data not given but plotted on a line graph. No change in the weekly number of incidents of angina for the group which listened to the tape which contained information. Groups which listened to the tape containing relaxation and/or imagery instructions showed a marked decrease in the weekly number of angina incidents. When the subjects stopped listening to the tapes the incidents of chest pain remained low for 1 or 2 weeks, then began to increase. Pain intensity and number of medications: for the three groups with relaxation and/or imagery tapes, the results followed the same pattern as the number of weekly incidents of angina described previously, i.e. a decrease during the tape exposure followed by an increase.

16.2.4 Yoga life style intervention programme

The “Review Protocol” for this topic can be found in Appendix C, the “Search Strategies” in Appendix D, the “List of Included and Excluded Studies” in Appendix E1, the “Clinical Evidence Tables” in Appendix E2, and the “Forest Plots” in Appendix F.

There was one paper[207] comparing Yoga Lifestyle programmes with control (conventional medical therapy) for stable angina.

Table 16.9: Yoga life style intervention programme vs. control

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Yoga life style intervention programme	Control (1 year)	Relative (95% CI)	Absolute	
Mortality (follow-up 1 years)											
Manchanda 2000[207]	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/21 (0%)	0/21 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE
Angina episodes per week (follow-up 1 years; range of scores: -; better indicated by less)											
Manchanda 2000[207] (b)	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	21	21	-	MD 3.3 lower (4.82 to 1.78 lower)	⊕⊕⊕O MODERATE
Exercise duration (sec) (follow-up 1 years; range of scores: -; better indicated by less)											
Manchanda 2000[207]	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (d)	none	21	21	-	MD 39 higher (46.78 lower to 124.78 higher)	⊕⊕OO LOW
ST segment depression (mm) (follow-up 1 years; range of scores: -; better indicated by less)											
Manchanda 2000[207]	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	21	21	-	MD 2.52 lower (2.95 to 2.09 lower)	⊕⊕⊕O MODERATE
Revascularisation (follow-up 1 years)											
Manchanda 2000[207] (c)	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (e)	none	1/21 (4.8%)	8/21 (38.1%)	RR 0.13 (0.02 to 0.91)	335 fewer per 1000 (from 34 fewer to 373 fewer)	⊕⊕OO LOW

(a) *Manchanda 2000[201]: Strengths: prospective randomised ; no attrition ; independent observers blinded to treatment allocation ; good compliance Weaknesses: small sample size ; randomisation and allocation concealment methods unclear ; blinding not possible due to nature of intervention ; groups significantly different at baseline in number of anginal episodes and exercise duration*

(b) *At baseline patients in yoga group had significantly more anginal episodes per week (6.7±3 vs. 4.1±2.1).*

(c) *Only 1 in the yoga group needed revascularisation (PTCA) against 8 in the control group (2 PTCA and 6 CABG) (RR 5.45 p=0.001)*

(d) *95% CI includes no effect and the upper and lower CI crosses the MID.*

(e) *95% CI around the pooled estimate of effect includes appreciable benefit or appreciable harm.*

16.2.5 Intensive life style programme

The "Review Protocol" for this topic can be found in Appendix C, the "Search Strategies" in Appendix D, the "List of Included and Excluded Studies" in Appendix E1, the "Clinical Evidence Tables" in Appendix E2, and the "Forest Plots" in Appendix F.

There was one paper comparing Intensive lifestyle programme with control for stable angina[208].

Table 16.10: Intensive lifestyle programme vs. control for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intensive lifestyle programme	control (5 years)	Relative (95% CI)	Absolute	
Angina frequency (times per week) (follow-up 5 years; range of scores: -; better indicated by less)											
Ornish 1998[208]	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	18	14	-	MD 0.7 higher (0.9 lower to 2.3 higher)	⊕⊕⊕O MODERATE
Chest pain duration (min) (follow-up 5 years; range of scores: -; better indicated by less)											
Ornish 1998[208]	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	18	14	-	MD 0.1 lower (1.64 lower to 1.44 higher)	⊕⊕⊕O MODERATE
MI (follow-up 5 years)											
Ornish 1998[208]	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (b)	none	2/28 (7.1%)	4/20 (20%)	RR 0.36 (0.07 to 1.76)	128 fewer per 1000 (from 186 fewer to 152 more)	⊕⊕OO LOW
PTCA (follow-up 5 years)											
Ornish 1998[208]	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (b)	none	8/28 (28.6%)	14/20 (70%)	RR 0.41 (0.21 to 0.78)	413 fewer per 1000 (from 154 fewer to 553 fewer)	⊕⊕OO LOW
CABG (follow-up 5 years)											
Ornish 1998[208]	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (b)	none	2/28 (7.1%)	5/20 (25%)	RR 0.29 (0.06 to 1.33)	178 fewer per 1000 (from 235 fewer to 83 more)	⊕⊕OO LOW
Death (follow-up 5 years)											
Ornish 1998[208]	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (b)	none	2/28 (7.1%)	1/20 (5%)	RR 1.43 (0.14 to 14.7)	21 more per 1000 (from 43 fewer to 685 more)	⊕⊕OO LOW

(a) Ornish 1998[202]: Strengths -RCT conducted from 1986 to 1992 using a randomised invitational design. Quantitative coronary arteriograms were blindly analysed without knowledge of group assignment. Baseline comparisons made. No loss to follow-up . Limitations- small sample size, Allocation concealment not reported.

(b) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.

Additional data:

Ornish 1998[208]:

There was significantly more frequent cardiac hospitalisation in the control group (44/20) compared to intervention group (23/28) at 5 years ($p<0.001$). Cardiac hospitalisation included hospitalisation for MI, PTCA and CABG.

16.2.6 Nurse led cardiac rehabilitation

The "Review Protocol" for this topic can be found in Appendix C, the "Search Strategies" in Appendix D, the "List of Included and Excluded Studies" in Appendix E1, the "Clinical Evidence Tables" in Appendix E2, and the "Forest Plots" in Appendix F.

There was one paper comparing nurse led cardiac rehabilitation with routine care for stable angina[196].

Table 16.11: Nurse led cardiac rehabilitation vs. routine care for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Nurse led cardiac rehab	routine care (6 months)	Relative (95% CI)	Absolute	
Walking performance (Jenkins activity checklist for walking) (follow-up 6 months; range of scores: -; better indicated by more) (b)											
Jiang 2007[196]	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	83	84	-	MD 2.01 higher (1.23 to 2.79 higher)	⊕⊕⊕O MODERATE

(a) *Jiang 2007[190]: This is a relatively short term study of patients (n=167) .Very little information is given about whether investigators were "blinded" to patients' allocation to intervention or control group. Most of the outcomes measured in the study were not relevant to the review question for which this study was included. No description of routine care was given or even if it included advice on diet, exercise and smoking cessation.*

(b) *Jenkins Activity check list used: There were 16 activities on the scale, ranging from walking from bed to bathroom to walking 6.5 km. Subjects were required to indicate whether they had performed each activity in the previous 24 hour period. For scoring, the number of 'yes' responses was summed to provide an activity total score, ranging from 0 to 16.*

16.2.7 Angina management programme (AMP)

The "Review Protocol" for this topic can be found in Appendix C, the "Search Strategies" in Appendix D, the "List of Included and Excluded Studies" in Appendix E1, the "Clinical Evidence Tables" in Appendix E2, and the "Forest Plots" in Appendix F.

There was one paper comparing the Angina management programme (AMP) with waiting list control for stable angina[209].

Intervention: For the Angina Management Programme (AMP) patients attended the hospital for two mornings per week for eight weeks. The AMP included the following elements: Exercise - consisted of 10 movements designed to improve general fitness and flexibility. Number of repetitions increased as patients felt fitter up until "somewhat hard"; Psychological elements of the programme included : Stress management - using relaxation, breathing re-training, bio-feedback, yoga exercises and behaviour modification; Psychological status - a self help rehab programme designed to reverse beliefs known to predict poor psychological recovery from MI; Behavioural change - help to return to appropriate but abandoned activities using goal setting and pacing; and education - Patients received extensive information about CAD, secondary prevention and angina.

Table 16.12: AMP vs. control for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Angina management programme (AMP)	control (at the end of 8 week treatment period)	Relative (95% CI)	Absolute	
Mean no. of Episodes of angina per week (follow-up 8 weeks; range of scores: -; better indicated by less)											
Lewin 1995[209]	randomised trial	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	34	31	-	MD 12.1 lower (18.65 to 5.55 lower)	⊕⊕⊕⊕ HIGH
Severity of angina (self rated out of 100 with scores being worse) (follow-up 8 weeks; range of scores: -; better indicated by less)											
Lewin 1995[209]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	34	31	-	MD 11.7 lower (23.04 to 0.36 lower)	⊕⊕⊕⊕ HIGH
Duration of angina (mins) (follow-up 8 weeks; range of scores: -; better indicated by less)											
Lewin 1995[209]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	34	31	-	MD 9.7 lower (25.8 lower to 6.4 higher)	⊕⊕⊕⊕ HIGH
Disability (Sickness Impact Profile) (100 being completely medically dependent and 0 indicating no measurable impairment) (follow-up 8 weeks; range of scores: -; better indicated by less)											
Lewin 1995[209]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	34	31	-	MD 12.7 lower(17.71 to 7.69 lower)	⊕⊕⊕⊕ HIGH

(a) Lewin 1995[203]: Randomised. Allocation concealment reported. For investigator measured outcome such as the exercise tolerance test, results were analysed by a doctor not otherwise involved in the trial and blinded to occasion and group. 5/39(13%) in treatment group and 7/38(18%) in the control group lost to follow-up. This paper reports summary results of 5 small (n=16) trials which took place over 2 years. Each trial was exactly the same design. In total n=77 patients were randomised to the Angina Management Programme (AMP) or to Waiting List Controls (WLC) for 8 weeks. After 8 weeks of being in the WLC group patients went on to the AMP for 8 weeks. Further assessments were carried out for all patients at 4 months and 1 year. However, at the latter two time points all patients had had treatment with AMP. Therefore, the only relevant results are for the initial 8 week controlled phase of the study. That is, there was no long term control group.

16.2.8 Angina Plan

The “Review Protocol” for this topic can be found in Appendix C, the “Search Strategies” in Appendix D, the “List of Included and Excluded Studies” in Appendix E1, the “Clinical Evidence Tables” in Appendix E2, and the “Forest Plots” in Appendix F.

There were 2 papers comparing the Angina Plan with education only for stable angina[195,210].

‘The Angina Plan’ consisted of a 70-page, patient-held ‘work-book’ and an audio-taped relaxation programme which was introduced to the patient during a 30 to 40-minute structured interview. Before commencing, the nurse asked the patient to complete a questionnaire designed to establish if he or she had any of the common misconceptions about angina. Any misconceptions were discussed with the patient to correct their understanding of the illness and to explain how such beliefs can lead to undue invalidism. The nurse then worked with the patient to identify all of his or her personal risk factors for coronary heart disease in the normal manner.

A method of gradually and systematically reducing these and increasing activity levels, ‘goal setting and pacing’ that we have developed in previous research with angina patients, was used to negotiate gradual return to abandoned activities or to increase the patients’ capacity for that activity. The same method was used to introduce lifestyle change; improved diet and walking.

Patients were asked to practice relaxation, using the audio cassette, for 20 minutes each day. The nurse contacted the patient with a brief phone call at the end of weeks 1, 4, 8, and 12. Any success with the goals the patients had set was rewarded with praise and encouragement and they were asked if they wished to extend the goal.

The Plan also contained written information about the role of frightening thoughts and misconceptions in triggering adrenaline release and anxiety and how this can result in poor coping strategies (such as the ‘over activity-rest cycle’), as well as an explanation of the symptoms of hyperventilation and panic. Standard advice on risk factors, medication, and what to do in the event of a suspected heart attack were also included.

Educational sessions: The nurse identified the patients’ risk factors for coronary heart disease from the research clinic measurements and a personal history and discussed ways in which each of them could be reduced. Patients were invited to ask questions about each risk factor and about angina or heart disease in general. They were also encouraged to discuss how it had affected their lives. Any questions they had were answered in an honest and factual manner by the nurse. If she did not know the answer at the time then she found it later and telephoned or wrote to them.

Every patient was given a package of written information, designed for people with coronary heart disease and angina and produced by authoritative sources, including the British Heart Foundation, the Chest Heart and Stroke Association, and the Family Heart Association.

Zetta 2009[195]:

N=218 (n=109- standard care) (n=109 Angina Plan)

Angina Plan – During a 45 minute in-hospital consultation the AP nurse completed an assessment and initiated the AP intervention, which was then facilitated over the next 12 weeks. The patients' cardiac misconceptions were identified using the brief questionnaire within the AP pack at the start of the consultation to allow the nurse to proactively target and correct these misconceptions. Individual cardiovascular risk was assessed and advice on risk factor modification given. Participants received the AP, which included a patient-held 'work-book' and an audio taped relaxation and information programme. The work-book provided information on angina and its management, cardiovascular risk, relaxation, exercise and goal setting and pacing techniques. Over the following 12 weeks a method of 'goal setting and pacing' based on the principles of CBT was used by the AP facilitator introduce lifestyle changes and support recovery during telephone follow-up at weeks 1,4, 8 and 12 for all participants in the AP group.

Standard care – A minimal intervention by nurses during their admission which identified patients risk factors , provided advice on their condition and risk factor reduction where possible depending on staff workload and skill mix.

Table 16.13: Angina Plan vs. education session for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Angina Plan	Education session (6 months) (change scores)	Relative (95% CI)	Absolute	
Anxiety (HAD scale) (follow-up 6 months; better indicated by lower values) (f)											
Lewin 2002[210], Zetta 2009[195]	randomised trials	no serious limitations (a)	serious inconsistency (b)	no serious indirectness	no serious imprecision	None	177	183	-	MD 0.16 lower (0.39 lower to 0.06 higher)	⊕⊕⊕O MODERATE
Depression (HAD scale) (follow-up 6 months; better indicated by lower values)											
Lewin 2002[210], Zetta 2009[195]	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	177	183	-	MD 0.86 lower (1.07 to 0.66 lower)	⊕⊕⊕⊕ HIGH
Angina attacks per week (angina diary- self reported) (follow-up 6 months; better indicated by lower values)											
Lewin 2002[210]	randomised trials	no serious limitations (c)	no serious inconsistency	no serious indirectness	no serious imprecision	None	68	74	-	MD 2.57 lower (4.46 to 0.68 lower)	⊕⊕⊕⊕ HIGH
Mean pain score (follow-up 6 months; better indicated by lower values)											
Lewin 2002[210]	randomised trials	no serious limitations (c)	no serious inconsistency	no serious indirectness	no serious imprecision	None	68	74	-	MD 1.79 higher (3.5 lower to 7.08 higher)	⊕⊕⊕⊕ HIGH
Mean duration of pain (follow-up 6 months; better indicated by lower values)											
Lewin 2002[210]	randomised trials	no serious limitations (c)	no serious inconsistency	no serious indirectness	no serious imprecision	None	68	74	-	MD 2.43 lower (12.23 lower to 7.37 higher)	⊕⊕⊕⊕ HIGH
Physical limitation (Seattle Angina questionnaire)(follow-up 6 months; better indicated by higher values) (g)											
Lewin 2002[210]	randomised trials	no serious limitations (c)	no serious inconsistency	no serious indirectness	no serious imprecision	None	68	74	-	MD 9.85 higher (4.84 to 14.86 higher)	⊕⊕⊕⊕ HIGH
Angina stability (Seattle Angina questionnaire) (follow-up 6 months; better indicated by higher values)											
Lewin 2002[210]	randomised trials	no serious limitations (c)	no serious inconsistency	no serious indirectness	no serious imprecision	None	68	74	-	MD 4.56 higher (5.56 lower to 14.68 higher)	⊕⊕⊕⊕ HIGH
Angina frequency (Seattle Angina questionnaire) (follow-up 6 months; better indicated by higher values)											
Lewin 2002[210], Zetta 2009[195]	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	177	183	-	MD 3.78 higher (1.82 lower to 9.39 higher)	⊕⊕⊕⊕ HIGH
Treatment satisfaction (Seattle Angina questionnaire) (follow-up 6 months; better indicated by higher values)											
Lewin 2002[210]	randomised trials	no serious limitations (c)	no serious inconsistency	no serious indirectness	no serious imprecision	None	68	74	-	MD 1.94 lower (6.99 lower to 3.11 higher)	⊕⊕⊕⊕ HIGH
Disease perception (Seattle Angina questionnaire) (follow-up 6 months; better indicated by higher values)											

Lewin 2002[210], Zetta 2009[195]	randomised trials	no serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	177	183	-	MD 2.86 higher (1.24 lower to 6.96 higher)	⊕⊕⊕⊕ HIGH
Misconceptions/knowledge (follow-up 6 months; better indicated by lower values) (h)											
Zetta 2009[195]	randomised trials	no serious limitations (d)	no serious inconsistency	no serious indirectness	no serious imprecision	None	109	109	-	MD 5.50 lower (7.39 to 3.61 lower)	⊕⊕⊕⊕ HIGH
CLASP angina (follow-up 6 months; better indicated by lower values) (i)											
Zetta 2009[195]	randomised trials	no serious limitations (d)	no serious inconsistency	no serious indirectness	no serious imprecision	None	109	109	-	MD 0.80 higher (0.01 lower to 1.61 higher)	⊕⊕⊕⊕ HIGH
Physical limitation (SF-36) (follow-up 6 months; better indicated by higher values) (k)											
Zetta 2009[195]	randomised trials	no serious limitations (d)	no serious inconsistency	no serious indirectness	no serious imprecision	None	109	109	-	MD 3.67 higher (2.31 lower to 9.65 higher)	⊕⊕⊕⊕ HIGH
Energy and vitality (SF- 36) (follow-up 6 months; better indicated by higher values)											
Zetta 2009[195]	randomised trials	no serious limitations (d)	no serious inconsistency	no serious indirectness	no serious imprecision	None	109	109	-	MD 4.52 higher (1.02 lower to 10.06 higher)	⊕⊕⊕⊕ HIGH
Pain (SF-36) (follow-up 6 months; better indicated by higher values)											
Zetta 2009[195]	randomised trials	no serious limitations (d)	no serious inconsistency	no serious indirectness	no serious imprecision	None	109	109	-	MD 11.87 higher (4.04 to 19.7 higher)	⊕⊕⊕⊕ HIGH
GH perception (SF-36) (follow-up 6 months; better indicated by higher values)											
Zetta 2009[195]	randomised trials	no serious limitations (d)	no serious inconsistency	no serious indirectness	no serious imprecision	None	109	109	-	MD 5.03 higher (0.12 to 9.94 higher)	⊕⊕⊕⊕ HIGH
Change in health (SF-36) (follow-up 6 months; better indicated by higher values)											
Zetta 2009[195]	randomised trials	no serious limitations (d)	no serious inconsistency	no serious indirectness	no serious imprecision	None	109	109	-	MD 5.25 higher (2.52 lower to 13.02 higher)	⊕⊕⊕⊕ HIGH
SE1 QOL- DW QOL score (follow-up 6 months; better indicated by higher values) (e)											
Zetta 2009[195]	randomised trials	no serious limitations (d)	no serious inconsistency	no serious indirectness	no serious imprecision	None	109	109	-	MD 1.70 higher (2.5 lower to 5.9 higher)	⊕⊕⊕⊕ HIGH

(a) (Lewin 2002)[204]: Randomised. Allocation concealment reported. Baseline and follow-up measures were collected, scored, and entered into the computer by research staff blinded to group allocation. 5/68 (7%) in the Angina Plan group and 7/74 (9%) in the Education Programme group lost to follow-up.The data were analysed by a medical statistician not otherwise involved in the research. The study had 80% power to detect a difference of 0.5 units on the Hospital Anxiety and Depression Scale. . However, the study acknowledges that the mean reduction in anxiety and depression is slight, even though for some patients it was profound. Follow up was 6 months so the study was not capable of determining if the observed benefits continue beyond this time. In Zetta 2009[189] random allocations were computer generated, allocated to permuted fixed blocks of 20 and stratified for site. The researcher was blinded to group allocation throughout the trial. ITT reported.

(b) $I^2 = 71\%$

(c) Lewin 2002[204]: Randomised. Allocation concealment reported. Baseline and follow-up measures were collected, scored, and entered into the computer by research staff blinded to group allocation. 5/68 (7%) in the Angina Plan group and 7/74 (9%) in the Education Programme group lost to follow-up. The data were analysed by a

medical statistician not otherwise involved in the research.. The study had 80% power to detect a difference of 0.5 units on the Hospital Anxiety and Depression Scale. However, the study acknowledges that the mean reduction in anxiety and depression is slight, even though for some patients it was profound. Follow up was 6 months so the study was not capable of determining if the observed benefits continue beyond this time.

(d) Zetta 2009[189]: Random allocations were computer generated, allocated to permuted fixed blocks of 20 and stratified for site. The researcher was blinded to group allocation throughout the trial. ITT reported.

(e) SEI Qol-DW (Schedule for the Evaluation of Individual Quality of Life-Direct weighting) is an interview based tool specifically designed for the assessment of individual quality of life. Using the SEIQoL-DW participants define five areas that comprise individual 'quality of life'. These items are rated in terms of level of importance. An overall score ranging from 0-100 is then calculated with higher scores reflecting better quality of life. The SE1QoL-DW is totally subjective and patient centred and provides a relatively unique measure of quality of life.

(f) Hospital Anxiety and Depression scale (HADS): 14 item tool with 2, seven item subscales to measure anxiety and depression within a non psychiatric population. A score from 0 to 3 for each item generated a total score (range 0 to 21 for each sub scale. Scores between 8 and 10 indicate borderline presence of anxiety or depression and score above 10 suggest that anxiety or depression may be present.

(g) The Seattle Angina Questionnaire is a disease specific health related quality of life measure comprised of a 19 item questionnaire measuring five dimensions of coronary artery disease: physical limitation, angina stability, anginal frequency, treatment satisfaction and disease perception. Each dimension is scored separately on a 0-100 scale with higher scores indicating better functioning.

(h*) Knowledge and misconceptions were assessed using the 14 item York Angina Beliefs Questionnaire. This uses a Likert scale response format ranging 'strongly agree' to 'strongly disagree'. Items targeted the cause, physiology and coping with angina. Summation and transformation of the item scores generated a scale total ranging from 0-56 with higher numbers indicating more misconceptions.*

(i) The Cardiovascular Limitations and Symptoms Profile (CLASP) measures nine physical and functional dimensions, including four symptom subscales (angina, shortness of breath, tiredness, ankle swelling) and five subscales focusing on functional limitations (mobility, social life and leisure activities, activities within the home, concerns and worries, sexual activity). Each of the nine subscales is scored separately to calculate a specific measure of impairment.

(j) The Short Form 36 Health Survey (SF-36) is a 36 item questionnaire assessing general health and QoL. The 8 dimensions of SF-36 (physical functioning, role limitations caused by emotional problems, bodily pain, social functioning, mental health, role limitations caused by emotional problems, vitality-energy/fatigue and general health perception) generates scores on each dimension between 0 and 100, with higher scores representing better health status.

16.3 Economic evidence

Two studies were included, one comparing stent angioplasty with exercise training[198] and one comparing health education with control[211]. These are summarised in the economic evidence profile below. See also Economic Evidence Tables in Appendix G.

Table 16.14: PCI vs. exercise - Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
Hambrecht 2004[198]	Potentially serious limitations (a)	Partial applicability (b)	Based on a RCT included in our review (see 16.2.1)

c) *Limited follow-up (1 year). A breakdown of the cost items was not reported. A sensitivity analysis was not conducted. The study received an unconditional grant from Aventis.*
d) *Study conducted in Germany. Effectiveness was not reported in terms of QALYs.*

Table 8.15: PCI vs. exercise - Economic summary of findings

Study	*Incremental cost (£)*	*Incremental effects*	*ICER*	*Uncertainty*
Hambrecht 2004[198]	1,502 (a)	- (b)	- (c)	No sensitivity analyses were performed.

(d) *2003 GBP; cost of interventions including hospital charges, expenses for supervised training sessions, bicycle ergometer, coronary angiographies, and rehospitalisation. P value <0.001*
(e) *Outcomes considered were deaths of cardiac causes, cerebrovascular accidents, and revascularisation. None of them was statistically significant.*
(f) *An overall summary of cost-effectiveness was provided only in the text but the details of the effectiveness measure were not reported anywhere. To gain one CCS class the cost was £4,396 in the PCI group and £2,167 in the exercise group.*

Table 8.16: Health education vs. control - Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
O'Neill 1996[211]	Potentially serious limitations (a)	Partial applicability (b)	Based on a RCT included in our review (see 16.2.1). Funded by the Medical Research Council.

(a) *Not all the important outcomes were evaluated (e.g. angina symptoms, MI).*
(b) *Relatively old study; medical treatment might have not been optimal at that time. Unclear what the control group received. Effectiveness was not reported in terms of QALYs.*

Table 8.17: Health education vs. control - Economic summary of findings

Study	*Incremental cost (£)*	*Incremental effects (deaths saved)*	*ICER*	*Uncertainty*
O'Neill 1996[211]	39 (a)	4.6% (b)	NR	No sensitivity analyses were performed.

(a) *1996 GBP; cost of intervention (staff time and travel-related costs), drugs, GP visits, hospital visits, tests and other treatments. Community care costs were excluded. Difference in costs was not statistically significant.*

(b) *Not statistically significant.*

16.4 Evidence statements

Clinical **A. <u>Exercise programmes:</u>**

<u>Intensive exercise programme vs. control</u>

Todd 1990[199]: Evidence from one RCT shows that the differences between exercise group and control group at time of follow- up were not statistically significant for max ST depression (mm) [MD 0.2 (-0.43 to 0.83)], time to 1 mm ST depression (sec) [MD 166 (-221.71 to 553.71)] and treadmill time (sec) [MD 262 (-66.64 to 590.64)]. [1 year follow-up]

<u>Exercise plus placebo vs. placebo</u>

Malmborg 1974[197]: Evidence from one small scale pilot RCT shows that the differences in proportion of change in maximal working capacity kpm/min [MD -4 (-43.5 to 35.5)], angina attacks per week [MD -25 (-82.38 to 32.38)], and nitro-glycerine tablet intake per week [MD 4 (-96.75 to 104.75)] were not significantly different in an exercise group compared to a placebo group. [follow-up 4 months]

<u>Exercise plus BB and vs. BB</u>

Malmborg 1974[197]: Evidence from one small scale pilot RCT shows that the differences in proportion of change in maximal working capacity kpm/min [MD -6 (-55.60 to 43.60)], angina attacks per week [MD 41 (-1.93 to 83.93)] and nitro-glycerine tablet intake per week [MD 58 (-37.02 r to 153.02)] were not significantly different in an exercise group compared to a placebo group. [follow-up 4 months] [moderate quality]

<u>Exercise plus low fat diet vs. control</u>

Schuler 1992[200]: Evidence from one RCT shows that cardiac mortality [RR 5.09 (0.25 to 103.66)] ,total mortality [RR 2.04 (0.19 to 21.82)] and non-fatal MI [RR 0.2 (0.01 to 4.15)] did not significantly differ between the an exercise + low fat diet compared to a control group [follow-up

12 months]

Exercise programme vs. PCI

Hambrecht 2004[198]: Evidence from one RCT shows that there was no significant differences between Exercise group and PCI group for cerebrovascular accidents [RR 0.65 (0.11 to 3.75)], hospitalisation and also no significant difference in coronary angiography owing to worsening angina [RR 0.14 (0.02 to 1.1)] there were no deaths of cardiac causes in either group [0/51 in Exercise group and 0/50 in PCI group]. There was a significantly higher proportion of patients needing revascularisation in the PCI group compared to the exercise group [RR 0.29 (0.09 to 1.01)]. [1 year follow-up].

B. Health Education

Health education vs. control – mortality and frequency of exercise

Cupples 1994[201]: Evidence from one RCT shows that total mortality was significantly lower in the health education group compared to control group [RR 0.45 (0.24 to 0.86)]. Significantly more patients in the health education group increased their frequency of exercise compared to the control group [RR 1.73 (1.32 to 2.28)]. [Follow-up 2 years]

Health education vs. control for stable angina – Quality of life

O'Neill 1996[202]: Evidence from one RCT shows that the mean differences in overall Nottingham Health Profile (NHP) scores did not reach statistical significance (p=0.0659) . Mean differences of two NHP subscales reached statistical significance. Physical Mobility [MD intervention -1.49 and MD control -6.19, p=0.0015] and Social Isolation [MD intervention +1.42 and MD control -3.01, p=0.0408] with better self ratings associated with the intervention group. [follow-up 2 years]

C. Stress management

Stress management vs. routine care control

Bundy 1998[206]: Evidence from one RCT shows that there was no significant difference between stress management and routine care control for frequency of angina [(MD 0.00 (-2.92 to 2.92)] and average duration of angina attack (mins) [MD -0.40 (-4.70 to 3.90)] [follow-up 8 weeks]

Gallacher 1997[204]: Evidence from one RCT shows that there was no significant difference between stress management and control, group for frequency of chest pain at rest (days per fortnight) [MD -0.59 (-1.24 to 0.06)] and frequency of chest pain on exertion (days per fortnight) [MD -0.54 (-1.35 to 0.27)] [Follow-up 6 months]

Stress management + exercise vs. routine care control

Bundy 1998 [206]: Evidence from one RCT shows that there was no significant difference between stress management along with exercise compared to routine care control for frequency of angina (average no. of daily attacks) [MD 0.6 (-2.97 to 4.17)] and duration of angina (min) [MD -4.4 (-9.08 to 0.28)] [finalscores]. [8 weeks follow-up]

Bundy 1994 [205]: Evidence from one RCT shows that there was no significant difference between stress management along with exercise compared to routine care control for frequency of angina (average no. of daily attacks) [MD -2.70 (-5.98 to 0.58)] . Duration of angina (min) was significantly lower in the stress management group compared to routine care control [MD -0.70 (-1.06 to -0.34)] [change scores]. [8 weeks follow-up]

D. Yoga lifestyle

Yoga lifestyle vs. control

Manchanda 2000[207]: Evidence from one RCT shows that there was no mortality in either the Yoga life style intervention programme and control group [0/21 in intervention and 0/21 in control group]. There was significantly fewer angina episodes per week in the Yoga intervention group compared to control group MD -3.3 (-4.82 to -1.782).There was no significant difference between yoga life style and control group for exercise duration (sec) [MD 39 (-46.78 to 124.78)]. ST-Segment depression was significantly lower in the Yoga Lifestyle group compared to control [MD -2.52 (-2.95 to -2.09)]. Revascularisation was significantly lower in the Yoga lifestyle compared to control group [RR 0.12 (0.02 to 0.91] [1 year follow-up].

E. Intensive lifestyle

Intensive style vs. control

Ornish 1998[208]: Evidence from one RCT shows that there was no statistically significant difference between intensive lifestyle programme and control for angina frequency (times per week) [MD 0.7 (-0.9 to 2.3)], chest pain duration (min) [MD -0.1 (-1.64 to 1.44)] , MI [RR 0.36 (0.07 to 1.76)], CABG [RR 0.29 (0.06 to 1.33)] and death [RR 1.43 (0.14 to 14.7)] . There was significantly lower PTCA in the lifestyle programme compared to control [RR 0.41 (0.21 to 0.78)] [5 years follow-up]

F. Nurse led cardiac rehabilitation

Nurse led cardiac rehab vs. routine care

Jiang 2007[196]: Evidence from one RCT shows that 'walking performance' [measured using Jenkins Activity check list] was significantly higher in the

Nurse cardiac rehab group compared to control [MD 2.01 (1.23 to 2.79)] [6 months follow-up]

G. Angina management Programme (AMP)

AMP vs. control

Lewin 1995[209]: Evidence from one RCT shows that significantly fewer mean no. of episodes of angina per week in the AMP group compared to control [MD -12.1 (-18.65 to -5.55)], severity of angina was significantly lower in the AMP group compared to control [MD -11.7 (-23.04 to -0.36)], there was no significant difference between AMP and control group for duration of angina (mins) [MD -9.7 (-25.8 to 6.4)] and disability [measured by Sickness Impact Profile] was significantly lower in the AMP group compared to control [MD -12.7 (-17.71 to -7.69)] [follow-up – at the end of 8 weeks treatment period]

H. Angina Plan

Angina Plan vs. education session

Lewin 2002[210]: Evidence from one RCT shows that there was significantly greater reduction angina attacks per week (from angina diary of patients) [MD -2.57 (-4.46 to -0.68)], physical limitation (Seattle Angina Questionnaire) [MD 9.85 (4.84 to 14.86)], in the Angina Plan group compared to standard care/education session control group. There was no significant difference between angina plan and standard care/education session for mean duration of pain [MD -2.43 (-12.23 to 7.37)], mean pain score [MD 1.79 (-3.5 to 7.08)] , Angina stability (Seattle Angina Questionnaire) [MD 4.56 (-5.56 to 14.68)] treatment satisfaction (Seattle Angina Questionnaire) [MD -1.94 (-6.99 to 3.11)] [6 months follow-up]

Lewin 2002[210]; Zetta 2009[195]: Evidence from 2 RCTs shows that depression (HAD scale) was found to be significantly reduced in the Angina Plan group compared to standard care group/education session [MD -0.86 (-1.07 to -0.66)]. There was no significant between the Angina Plan and standard care/education session group for Anxiety (HAD scale) [MD 0.16 lower (0.39 lower to 0.06 higher)], angina frequency (Seattle Angina Questionnaire) [MD 3.78 higher (-1.82 to 9.39)] , disease perception (Seattle Angina Questionnaire) [MD 3.51 (-1.64 to 8.66)] [6 months follow-up]

Zetta 2009[195]: Evidence from one RCT shows that significantly more patients in the Angina Plan group reported increased knowledge and less misconceptions compared to standard care/education session group [MD -5.50 (-7.39 to -3.61 lower)] and significant improved General Health perception (SF-36) [MD 5.03 (0.12 to 9.94)] in angina plan group compared to standard care/education session group . There was no significant difference between angina plan and standard care/education session group for CLASP angina [MD 0.80 (-0.01 to

	1.61)], Physical function (SF-36) [MD 3.67 (-2.31 to 9.65)], energy and vitality (SF-36) [MD 4.52 (-1.02 to 10.06)], Pain (SF-36) [MD 11.87 (4.04 to 19.70)], change in health (SF-36) [MD 5.25 (-2.52 to 13.02)], SEI Qol-DW Qol (Schedule for the Evaluation of Individual Quality of Life-Direct Weight) Score [MD 1.70 (-2.50 to 5.90)]. [6 months follow-up]
Economic	No economic evidence was found on comprehensive cardiac rehabilitation programmes. Exercise training reduces costs compared to PCI while health education does not generate additional costs compared to control. This evidence has potentially serious limitations and partial applicability.

16.5 Recommendations and link to evidence

Recommendation	**Assess the person's need for lifestyle advice (for example about exercise, stopping smoking, diet and weight control) and psychological support, and offer interventions as necessary.**
Relative values of different outcomes	The GDG were interested in whether cardiac rehabilitation programmes would influence mortality and morbidity outcomes as well as quality of life. The GDG recognised that intermediate outcomes such as change in diet and exercise may indicate potential benefit but considered that harder outcomes were required if they were to recommend rehabilitation to the NHS as standard treatment for people with stable angina.
Trade off between clinical benefits and harms	
Economic considerations	No economic evidence was found on comprehensive cardiac rehabilitation programmes. Some economic evidence was found on components of rehabilitation programmes (exercise training and health education). The evidence on these two components shows that exercise training and health education could improve outcomes without creating additional costs. As the benefits from the single components might vary among individuals, the GDG thought it would be more cost-effective to assess the need for interventions on an individual basis.

Quality of evidence	The quality and quantity of evidence for comprehensive programmes of cardiac rehabilitation was not adequate to suggest these could be recommended for people with stable angina. In particular the number of patients included in the studies was small and the length of follow up was extremely short. Yoga/lifestyle programme, angina management programme and angina plan did result in a reduction in angina frequency. In the yoga lifestyle programme[207] at one year, the yoga groups showed significant reduction in number of anginal episodes per week, improved exercise capacity and decrease in body weight. Revascularisation procedures (coronary angioplasty or bypass surgery) were also less frequently required in the yoga group (one vs. eight patients RR 5.45 p=0.01). The study had a very small sample size (n=42) and follow-up of only 1 year. Also by nature of the interventions the study could not be blinded, and hence a placebo effect of yoga interventions cannot be excluded. Further, the study did not look at differential effects of yogic exercises, dietary control and aerobic exercises, and the study considered yoga lifestyle modification as a composite incorporating all the above mentioned components. The study by Lewin 1995[209] on the angina management programme showed significantly fewer episodes of angina per week compared to control, and lower severity of angina compared to control. However the study sample was very small (65 patients completed the study) and the follow-up period of 8 weeks was too short to determine whether the programme provides long term benefit. The study by Cupples 1994[201] showed that the education programme reduced angina episodes per week and increased frequency of exercise in people with angina. The study also reports that percentage of patients who took drugs prophylactically increased significantly by the end of the study, which could have caused a reduction in symptoms. Further, the study did not validate the patients reporting of the frequency of exercise and some reporting bias may have occurred. Nevertheless, the study was relatively large (n=688) and well conducted. The study by Lewin 2002[210] on the self-management programme- Angina Plan was a small (n=142), well conducted study. Most of the patients who received Angina Plan reported a reduction of three episodes of

	angina per week; this is clinically worthwhile reduction of nearly 50%from the baseline mean of seven episodes per week. The authors propose that increased activity levels and daily walking may have raised the Angina Plan patients' threshold for exercise induced pain. There was significant reduction in anxiety and depression. Follow up was 6 months, so the study was not capable of determining if the observed benefits continue beyond this time. The study by Zetta (2009)[195] recruited patients who were admitted to medical admission or coronary care units. These patients were not considered to be representative of people with chronic stable angina. The economic evidence has potentially serious limitations and partial applicability.
Other considerations	The GDG concluded that the evidence did not indicate benefit for patients from comprehensive cardiac rehabilitation programmes. There was no evidence to support any model of care for delivering individual interventions that patients might benefit from. The self management programme (Angina Plan) includes a brief, cognitive-behavioural programme comprising a 76-page patient-held workbook (contains information about risk factor reduction, stress management, angina management and how to use goal setting and pacing to increase activity safely), a tape or CD based relaxation programme, an advice tape to introduce the concepts in the Angina Plan to the patient before they see the facilitator, and a misconceptions questionnaire. The Angina Plan is introduced to the patient (and their partner) in an interview lasting thirty or forty minutes, and followed up by four, ten to fifteen minute appointments or phone calls over three months. The GDG considered that the components of the Angina plan were beneficial to people with stable angina but the evidence was not adequate to recommend the programme based on a small study sample with a short follow-up. People with angina are likely to need a variety of interventions geared to understanding and coping with their diagnosis and helping them to engage in activities for secondary prevention. The GDG preferred the idea of a menu of health needs that may need to be

addressed and patients should be directed to services they individually require. It is the GDG opinion that a tailored approach (i.e. offer only the rehabilitation components that are required rather than a comprehensive programme) is likely to be cost-effective.

The GDG considered that many of the aspects of care that would be of benefit to people with stable angina are available via primary care and via services such as the National Exercise Referral Scheme in Wales[212].

16.6 Research recommendation

The GDG recommended the following research question:

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

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

17 Lifestyle Adjustments

17.1 Introduction

Lifestyle interventions such as exercise are known to have a positive effect on cardiovascular health. The GDG were interested in whether there were specific lifestyle interventions that would reduce mortality and morbidity in people with stable angina.

The aim of our evidence review was to address the question: "What is the clinical/cost effectiveness of angina specific interventions to modify lifestyle/CVD risk factors to reduce symptoms, morbidity and mortality and improve quality of life in angina patients?"

The following lifestyle factors were considered for this review:

- Diet (including folic acid, vitamin E, C, beta carotene supplements, Omega 3-acid ethyl esters, Mediterranean diet, low saturated diet, low glycaemic diet, fruit and vegetables, fish diet)

- Physical activity

A total of 5 papers (3 RCTs and 2 cross over trials) have been included in this review. Three papers (2 RCTs and one cross over trial) evaluated the effectiveness of fish oil diet/capsules and two papers (one RCT and one cross over trial) evaluated the effectiveness of Vitamin E in people with stable angina. However we did not identify any papers looking at the following interventions in people with stable angina: Folic acid, Vitamin C, beta carotene supplements, Mediterranean diet, low saturated fat diet, and low glycaemic diet.

There was significant overlap between review of lifestyle interventions and review of rehabilitation programmes. The evidence relating to the effect of exercise primarily came from supervised programmes and these are therefore reported in the chapter on rehabilitation (chapter 16).

17.2 Fish oils

17.2.1 Clinical question

What is the clinical /cost effectiveness of fish oils for reducing symptoms, morbidity, mortality and improving quality of life in stable angina patients?

17.2.2 Clinical evidence

The "Review Protocol" for this topic can be found in Appendix C, the "Search Strategies" in Appendix D, the "List of Included and Excluded Studies" in Appendix E1, the "Clinical Evidence Tables" in Appendix E2, and the "Forest Plots" in Appendix F.

There were 3 studies evaluating the effectiveness of fish oil. One RCT[213] and one cross over trial[214] (analysed as a parallel RCT) evaluated the effectiveness of fish oil capsules compared to placebo and one RCT[215] evaluated the effectiveness of both dietary fish advice and fish oil capsules compared to fruit advice and sensible eating.

Table 17.1: Fish oil capsules vs. placebo for stable angina (Follow-up at end of treatment period)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Fish oil capsules	Placebo (Follow-up at end of treatment period)	Relative (95% CI)	Absolute	
Anginal episodes per week (better indicated by lower values) (Follow-up at the end of 12 weeks treatment period)											
Salachas 1994[213]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (c)	none	20	19	-	MD 3 lower (54.01 lower to 48.01 higher)	⊕⊕OO LOW
GTN consumption per week (better indicated by lower values) (Follow-up at the end of 12 weeks treatment period)											
Salachas 1994[213]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (c)	none	20	19	-	MD 1.99 lower (10.69 lower to 6.71 higher)	⊕⊕OO LOW
Exercise test duration (min) (better indicated by higher values) (Follow-up at the end of 12 weeks treatment period)											
Salachas 1994[213]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (c)	none	20	19	-	MD 0.99 higher (2.01 lower to 3.99 higher)	⊕⊕OO LOW
Number of anginal attacks per 30 days (better indicated by lower values) (Follow-up at the end of 12 weeks treatment period)											
Aucamp 1993[214]	randomised trials	very serious (b)	no serious inconsistency	no serious indirectness	serious imprecision (c)	none	12	11	-	MD 9.2 lower (29.15 lower to 10.75 higher)	⊕OOO VERY LOW
Duration of angina attacks per minute (better indicated by lower values) (Follow-up at the end of 12 weeks treatment period)											
Aucamp 1993[214]	randomised trials	very serious (b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	12	11	-	MD 0.4 lower (0.95 lower to 0.15 higher)	⊕⊕OO LOW
Intensity of pain per attack per patient (on a 10 cm visual analogue scale) (better indicated by lower values) (Follow-up at the end of 12 weeks treatment period)											
Aucamp 1993[214]	randomised trials	very serious (b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	12	11	-	MD 1 lower (2.12 lower to 0.12 higher)	⊕⊕OO LOW
No. of sublingual isosorbide dinitrate tablets taken per 30 days (better indicated by lower values) (Follow-up at the end of 12 weeks treatment period)											
Aucamp 1993[214]	randomised trials	very serious (b)	no serious inconsistency	no serious indirectness	serious imprecision (c)	none	12	11	-	MD 0 higher (16.14 lower to 16.14 higher)	⊕OOO VERY LOW

(a) *Salachas 1994[207]: Randomised. Double blind. Allocation concealment not reported. Numbers lost to follow-up not reported. No ITT reported. Baseline comparison between groups not made.*

(b) *Aucamp 1993[208]: Placebo controlled cross-over trial. Single blind. 23 patients completed the trial: 11 patients taking placebo in phase 1(group A) and 12 patients taking the active fish oil in phase 1 (group B). Very little baseline characteristics reported. No ITT reported. No method of randomisation and allocation concealment reported. Very poorly reported trial.*

(c) *95% CI includes no effect and the upper and lower CI crosses the MID*

Table 17.2: Fish advice (dietary fish advice + fish oil capsule) vs. fruit advice for stable angina (Follow-up after 3 to 9 yrs)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Fish advice (dietary fish advice + fish oil capsule)	Fruit advice (Follow-up 6 months after entering the trial)	Relative (95% CI)	Absolute	
All death (Follow-up after 3 to 9 years)											
Burr 2003[215]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (b)	None	141/764 (18.5%)	133/779 (17.1%)	RR 1.08 (0.87 to 1.34)	14 more per 1000 (from 22 fewer to 58 more)	⊕⊕OO LOW
Cardiac death (Follow-up after 3 to 9 years)											
Burr 2003[215]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (b)	None	94/764 (12.3%)	72/779 (9.2%)	RR 1.33 (1 to 1.78)	31 more per 1000 (from 0 more to 72 more)	⊕⊕OO LOW
Sudden death (Follow-up after 3 to 9 years)											
Burr 2003[215]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (b)	None	42/764 (5.5%)	30/779 (3.9%)	RR 1.43 (0.9 to 2.26)	17 more per 1000 (from 4 fewer to 49 more)	⊕⊕OO LOW

(a) Burr 2003[209]: Randomised. Baseline characteristics reported, Loss to follow-up not reported. ITT not reported. Allocation concealment not reported.
(b) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.

Table 17.3: Fish advice (dietary fish advice + fish oil capsule) vs. fish +fruit advice for stable angina (Follow-up after 3 to 9 yrs)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Fish advice (dietary fish advice + fish oil capsule) (Follow-up 6 months after entering the trial)	Fish +Fruit advice	Relative (95% CI)	Absolute	
All death (Follow-up after 3 to 9 years)											
Burr 2003[215]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (b)	None	141/764 (18.5%)	142/807 (17.6%)	RR 1.05 (0.85 to 1.3)	9 more per 1000 (from 26 fewer to 53 more)	⊕⊕OO LOW
Cardiac death (Follow-up after 3 to 9 years)											
Burr 2003[215]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (b)	None	94/764 (12.3%)	86/807 (10.7%)	RR 1.15 (0.88 to 1.52)	16 more per 1000 (from 13 fewer to 55 more)	⊕⊕OO LOW
Sudden death (Follow-up after 3 to 9 years)											
Burr 2003[215]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (b)	None	42/764 (5.5%)	31/807 (3.8%)	RR 1.43 (0.91 to 2.25)	17 more per 1000 (from 3 fewer to 48 more)	⊕⊕OO LOW

(a) *Burr 2003[209]: Randomised. Baseline characteristics reported, Loss to follow-up not reported. ITT not reported. Allocation concealment not reported.*
(b) *95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.*

Table 17.4: Fish advice (dietary fish advice + fish oil capsule) vs. sensible eating (non -specific advice) for stable angina (Follow-up after 3 to 9 yrs)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Fish advice (dietary fish advice + fish oil capsule)	Sensible eating (non - specific advice) (Follow-up 6 months after entering the trial)	Relative (95% CI)	Absolute	
All deaths (Follow-up after 3 to 9 years)											
Burr 2003[215]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (b)	None	141/764 (18.5%)	109/764 (14.3%)	RR 1.29 (1.03 to 1.63)	41 more per 1000 (from 4 more to 90 more)	⊕⊕OO LOW
Cardiac death (Follow-up after 3 to 9 years)											
Burr 2003[215]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (b)	None	94/764 (12.3%)	67/764 (8.8%)	RR 1.4 (1.04 to 1.89)	35 more per 1000 (from 4 more to 78 more)	⊕⊕OO LOW
Sudden death (Follow-up after 3 to 9 years)											
Burr 2003[215]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	None	42/764 (5.5%)	17/764 (2.2%)	RR 2.47 (1.42 to 4.3)	33 more per 1000 (from 9 more to 73 more)	⊕⊕⊕O MODERATE

(a) Burr 2003[209]: Randomised. Baseline characteristics reported, Loss to follow-up not reported. ITT not reported. Allocation concealment not reported.
(b) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.

In order to attempt to explain the unexpected excess mortality associated with fish advice, ad hoc subgroup analyses were carried out by the study authors. The apparently adverse e effect of fish advice was confine d to the second phase of the trial (data not shown), when a much higher proportion of participants were given fish capsules than in the first phase. During this phase some of the participants in the fish advice group were sub randomised to receive fish oil capsules, so survival analysis was carried out to examine the effect on those sub randomised to capsules rather than to dietary fish advice.

Table 17.5: Survival analysis of subjects advised on dietary fish or fish oil

Outcome	Dietary fish (n=1109)	Fish oil capsules (n=462)
All death	n=198 (HR 1.13 (0.94 to 1.37) p=0.20	n=85 (HR 1.19 (0.92 to 1.54) p=0.19
Cardiac death	n=121 (HR 1.20 (0.93 to 1.53) p=0.16	n=59 (HR 1.45 (1.05 to 1.99) p=0.02
Sudden death	n=49 (HR 1.43 (0.95 to 2.15) p=0.08	n=24 (HR 1.84 (1.11 to 3.05); p=0.01

*hazard ratios adjusted for age, smoking, previous MI, history of high blood pressure, diabetes, BMI, serum cholesterol, medication and fruit advice.

The hazard ratios for each mortality category were higher in the fish oil capsules than in the dietary fish group. The possibility was considered that dietary fish or fish oil could adversely interact with drugs commonly given for heart disease. Hazard ratios of cardiac deaths were calculated in relation to fish advice, with subjects classified in to those receiving and those not receiving various types of drugs at recruitment in to the trial. No evidence was found of any adverse interactions; treatment with BB showed a significant favourable interaction with fish advice.

17.2.3 Economic evidence

No economic studies were retrieved on this question.

17.2.4 Evidence statement

Clinical <u>**Fish oil capsule vs. placebo**</u>

Salachas 1994[213]: Evidence from one RCT shows that there was no significant difference between Fish oil capsules and placebo for number of anginal attacks per week [MD -3.00 [-54.01 to 48.01], GTN consumption per week [MD -1.99 [-10.69 to 6.71] and exercise duration (min) [MD 0.99 [-2.01 to 3.99]. [Follow-up end of 12 weeks treatment period]

Aucamp 1992[214]: Evidence from one RCT shows that there was no significant difference between fish oil capsules and placebo for number of anginal attacks per 30 days [MD -9.20 [-29.15 to 10.75], duration of angina attacks per minute [MD -0.40 [-0.95 to 0.15], intensity of pain per attack per patient (on a 10 cm visual analogue scale)[MD -1.00 [-2.12 to 0.12], no. of sublingual isosorbide dinitrate tablets taken per 30 days [MD 0.00 [-16.14 to 16.14] [Follow-up at end of 12 weeks treatment period]

Fish advice (dietary fish+ fish oil capsule) vs. fruit advice

Burr 2003[215]: Evidence from one RCT shows that there was significantly higher cardiac death in the fish advice group [RR 1.33 [1.00 to 1.78] compared to fruit advice group; and there was no significant difference between fish advice and fruit advice group for all death [RR 1.08 [0.87 to 1.34] and sudden death [RR 1.43 [0.90 to 2.26] [Follow-up after 3 to 9 yrs]

Fish advice (dietary fish+ fish oil capsule) vs. fish +fruit advice

Burr 2003[215]: Evidence from one RCT shows that there was no significant difference between fish advice and fish+fruit advice for all death [RR 1.05 [0.85 to 1.30], cardiac death [RR 1.15 [0.88 to 1.52] and sudden death [RR 1.43 [0.91 to 2.25] [Follow-up after 3 to 9 yrs]

Fish advice (dietary fish+ fish oil capsule) vs. sensible eating (non - specific advice)

Burr 2003[215]: Evidence from one RCT shows that there was significantly lower all causes death [RR 1.29 [1.03 to 1.63], cardiac death [RR 1.40 [1.04 to 1.89] and sudden death [RR 2.47 [1.42 to 4.30] in the sensible eating group compared to fish advice group [Follow-up after 3 to 9 yrs]

Economic No economic studies were retrieved on this question.

17.2.5 Recommendations and link to evidence

Recommendation	**Do not offer vitamin or fish oil supplements to treat stable angina. Inform people that there is no evidence that they help stable angina.**
Relative values of different outcomes	The outcomes considered as important during the development of the review protocol for lifestyle adjustments included mortality, major cardiac events, angina frequency/severity,

	exercise tolerance, hospitalisation, revascularisation, QoL.
Trade off between clinical benefits and harms	Evidence showed that there was no significant improvement in angina and exercise duration with the use of fish oil capsules. Fish oil capsules (long term use) when compared to fruit advice showed a statistically significant increase in cardiac death. When compared to sensible eating fish oil capsules showed statistically significant increases in all cause death, cardiac death and sudden death. There is no evidence of clinical benefit from the use of fish oils in stable angina patients and some evidence of harm when compared to advice on sensible eating
Economic considerations	The use of fish oils would generate costs without improving outcomes.
Quality of evidence	The evidence was of moderate quality except for the cross over trial where evidence was low quality.
Other considerations	

17.3 Vitamin E

17.3.1 Clinical question

What is the clinical /cost effectiveness of Vitamin E for reducing symptoms, morbidity, mortality and improving quality of life in stable angina patients?

17.3.2 Clinical evidence

The "Review Protocol" for this topic can be found in Appendix C, the "Search Strategies" in Appendix D, the "List of Included and Excluded Studies" in Appendix E1, the "Clinical Evidence Tables" in Appendix E2, and the "Forest Plots" in Appendix F.

There were 2 studies (one RCT and one cross over trial) evaluating the effectiveness of Vitamin E compared to placebo[216,217].

Table 17.6: Vitamin E vs. placebo for stable angina (Follow-up at the end of treatment period)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin E	Placebo (Follow-up at the end of treatment period)	Relative (95% CI)	Absolute	
Improved anginal symptoms (Follow-up at the end of 9 week treatment period)											
Anderson 1974[216]	randomised trials	very serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (c)	none	5/18 (27.8%)	5/18 (27.8%)	RR 1 (0.35 to 2.87)	0 fewer per 1000 (from 181 fewer to 519 more)	⊕OOO VERY LOW
No change in anginal symptoms (Follow-up at the end of 9 week treatment period)											
Anderson 1974[216]	randomised trials	very serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (c)	none	13/18 (72.2%)	12/18 (66.7%)	RR 1.08 (0.7 to 1.67)	53 more per 1000 (from 200 fewer to 447 more)	⊕OOO VERY LOW
Slightly worse anginal symptoms (Follow-up at the end of 9 week treatment period)											
Anderson 1974[216]	randomised trials	very serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (c)	none	0/18 (0%)	1/18 (5.6%)	RR 0.33 (0.01 to 7.68)	37 fewer per 1000 (from 55 fewer to 371 more)	⊕OOO VERY LOW
Duration treadmill (min) (better indicated by higher values) (Follow-up end of 6 months treatment period)											
Gillilan 1977[217]	randomised trials	serious (b)	no serious inconsistency	no serious indirectness	serious imprecision (d)	none	48	40	-	MD 0.18 higher (0.51 lower to 0.87 higher)	⊕⊕ OO LOW
Angina attacks per week (better indicated by lower values) (Follow-up end of 6 months treatment period)											
Gillilan 1977[217]	randomised trials	serious (b)	no serious inconsistency	no serious indirectness	serious imprecision (d)	none	48	48	-	MD 0.6 higher (4.04 lower to 5.24 higher)	⊕⊕OO LOW
Nitroglycerin consumption per week (better indicated by lower values) (Follow-up end of 6 months treatment period)											
Gillilan 1977[217]	randomised trials	serious (b)	no serious inconsistency	no serious indirectness	serious imprecision (d)	none	48	48	-	MD 0.1 lower (5.38 lower to 5.18 higher)	⊕⊕OO LOW

(a) Anderson 1974[210]: Randomised. Double blind. 33/40 completed 9 full weeks of records. In 5 cases (3 vitamin and 2 placebo) only 8 weeks of records could be used because one record card was incomplete or missing, in one (vitamin group) only 7 weeks of records were available, and one other patient (vitamin) withdrew from the study after 7 weeks because of persistent diarrhoea. allocation concealment not reported. Randomisation was not carried out properly, patients randomised after giving the intervention. Baseline characteristics not well reported. Only subjective data available. Blinding process unclear. ITT not reported.

(b) Gillilan 1977[211]: Double blind cross over study. Blinding of outcome assessors. Baseline comparison between groups not reported. Method of randomisation and allocation concealment not reported. No ITT reported.

(c) 95% CI around the pooled estimate of effect includes both: 1) no effect and 2) appreciable benefit or appreciable harm.

(d) 95% CI includes no effect and the upper and lower CI crosses the MID.

Additional data from two studies :

Anderson 1974[216] (Vitamin E capsules vs. placebo)

- **Nitroglycerin consumption:** Mean nitroglycerin consumption was higher in the vitamin E group from the start, and increased from 18.7 to 23.5 between the first and last weeks. In the placebo group the mean intake was 10.9 tablets in the first week and this declined to 6.4 in the last week (Standard deviation not reported). The authors report that these differences were largely due to one or two patients in each group who had a large initial intake and showed great variation. Thus the increase in the Vitamin E group was attributed entirely due to one patient, whose consumption of NTG averaged 180 tablets per week-more than that of the entire placebo group. Most of the patients in each group showed little change in NTG consumption during the trial.

- **Pain score:** The net pain score for the placebo group was lower than that for the vitamin group in 7 out of the 9 weeks. Comparing the last and first weeks, the overall mean change in score was -0.81 for the vitamin group and +0.17 for the placebo group (Standard deviation not reported).

- **Side effects:** There were no side effects with Vitamin E reported by the patients. Headache and constipation were reported by two patients who were in the placebo group.

Gillilan 1977[217] (Vitamin E capsules vs. placebo)

- There were 4 deaths during the study, two of which occurred suddenly at home (apparently cardiac death) and two of which occurred during hospitalisation for recurrent MI (established at autopsy).

- No deleterious side effects were observed resulting from the use of Vitamin E during the study. There were slightly more complaints of mild gastrointestinal disturbances during placebo phase (6%) than during vitamin E phase (4%). No exacerbation of hypertension, congestive heart failure, or skeletal-muscular complaints could be attributed to vitamin E therapy.

17.3.3 Economic evidence

No economic studies were retrieved on this question.

17.3.4 Evidence statements

Clinical	**Vitamin E vs. placebo** **Anderson 1974[216]:** Evidence from one RCT shows that there was no significant difference between Vitamin E and placebo for improved anginal symptoms [RR 1.00 [0.35 to 2.87], no change in anginal symptoms [RR 1.08 [0.70 to 1.67], slightly worse anginal symptoms [RR 0.33 [0.01 to 7.68] [Follow-up at the end of 9 weeks treatment period]

Gillilan 1977[217]**:** Evidence from one RCT shows that there was no significant difference Vitamin E and placebo for duration treadmill (min) [MD 0.18 [-0.51 to 0.87], angina attacks per week [MD 0.60 [-4.04 to 5.24], and nitroglycerin consumption per week [MD -0.10 [-5.38 to 5.18] [Follow-up at the end of 6 months treatment period]

Economic No economic studies were retrieved on this question.

17.3.5 Recommendations and link to evidence

Recommendation	**Do not offer vitamin or fish oil supplements to treat stable angina. Inform people that there is no evidence that they help stable angina.**
Relative values of different outcomes	The outcomes considered as important during the development of the review protocol for lifestyle adjustments included mortality, major cardiac events, angina frequency/severity, exercise tolerance, hospitalisation, revascularisation, QoL.
Trade off between clinical benefits and harms	Evidence showed that there was no significant difference between Vitamin E and placebo for any of the anginal or exercise test outcomes. There is no evidence of clinical benefits arising from the use of Vitamin E in stable angina patients.
Economic considerations	The use of Vitamin E would generate costs without improving outcomes.
Quality of evidence	The available studies had short follow-up and were of low to moderate quality (based on GRADE). No evidence for other vitamin supplements in the treatment of stable angina that met our inclusion criteria for review was identified.
Other considerations	The GDG considered the evidence on Vitamin E did not show any benefit and patients should be informed of this. No evidence was found for other supplements. The GDG considered that absence of evidence of benefit does not exclude the possibility of benefit, but both patients and healthcare practitioners should be aware of the lack of any evidence of benefit. Supplements are a cost either to patients or to the health service and there is no evidence of benefit.

18 Pain Interventions and Refractory angina

18.1 Introduction

Stable angina presents as chest pain. Interventions are primarily related to addressing cardiac work by for example improving blood flow by medical treatment or revascularisation and by addressing the progression of underlying coronary artery disease. Chronic refractory angina has been defined as angina that cannot be controlled with optimal medical therapy and where revascularisation is unfeasible[21]. The decision as to when revascularisation is unfeasible is a decision made by interventional radiologists and cardiac surgeons. Revascularisation will also carry risks and an informed patient may decide that these risks outweigh possible benefits. The current UK national chronic refractory angina group's definition of chronic refractory angina is, "Chronic stable angina that persists despite optimal medication and when revascularisation is unfeasible or where the risks are unjustified. Interventions directed towards pain rather than towards coronary artery disease have been used for people with 'refractory' angina.

The GDG choose not to make a decision on a definition of refractory angina. They considered that different definitions and inclusion criteria might have been used in different studies and considered it more appropriate to examine evidence for use of pain interventions in as wide a population of people with angina as possible. The evidence review therefore describes the populations included in each study. The GDG were addressed by Professor Michael Chester and Dr. Austin Leach from the National Angina Refractory Centre who also advised on the interventions to include in the evidence review.

The following pain interventions have been included in the review:

- TENS (Transcutaneous electric nerve stimulation),
- EECP (Enhanced external counter pulsation)
- Acupuncture
- Self-pain management programmes

The evidence review includes 1 paper on TENS (Transcutaneous Electric Nerve Stimulation), 3 papers on EECP (Enhanced external counter pulsation) and 3 papers on Acupuncture, 2 papers on self-management of pain. No studies were identified evaluating the effectiveness of opioids in the management of people with angina.

Table 18.1: Pain interventions – Summary of evidence

Study	Intervention	Comparison	Duration of intervention	Study design	No of participants	Follow-up	Outcomes
Manheimer 1985[218]	TENS	Control group did not receive TENS	10 weeks. Three TENS treatment sessions of at least 1 hr each per day (morning, noon and evening)	RCT	N=23 (n=12 TENS and n=11). Severe angina pectoris (duration 1 to 20 years, functional class III or IV, NYHA). The antianginal pharmacological treatment taken at the beginning of the study was regarded as optimal. All patients had been considered for aortocoronary bypass surgery: one patient had undergone such a operation, five were waiting for surgery, and the remaining were being considered for surgical treatment.	After 2 weeks	Maximal total work during exercise was determined as a product of workload in watts and time in mins (W.min); ST segment depression during and after exercise; pain and dyspnea reported by the patient during and after exercise..; frequency of anginal attacks and consumption of short- acting nitroglycerin per week.
Arora 1999[219]	EECP	Inactive counterpulsation (CP)	35 hours of (once or twice/day) of active counterpulsation over a 4 to 7-week period.	RCT	N = 139 (n=EECP 72, n=67 inactive counterpulsation. Chronic stable angina- CCS I, II or III. More than 70% of patients in each	3 days after follow-up for angina pain counts, one week after treatment for exercise duration.	Exercise test, Anginal pain counts, Nitroglycerin use.

					group had CCS class II or III and over 70% of each group had undergone prior CABG or angioplasty.		
Arora 2002[219]	EECP	Inactive counterpulsation (CP).	35 hours of (once or twice/day) of active counterpulsation over a 4 to 7-week period.	RCT	N = 139 (n=EECP 72, n=inactive counterpulsation 67); n=71 (36 in EECP and n=35 inactive CP). Chronic stable angina - CCS I, II or III	At end of treatment and 1 year after treatment	Health related quality of life (HRQOL)
Loh 2008[220]	EECP	No comparison	A standard course of 35 one hour treatment sessions. The patients received a mean of 33.3±9.6 hours of treatment over a mean period of 48 days.	Before-After study	N=1427, CCS I, I, III angina. Anginal status: [CCS class I: 2.2% CCS class II: 8.6% CCS class III: 62.8% CCS class IV: 26.4%]. 88% had prior PCI or CABG and 88% were unsuitable for further coronary intervention.	3 years (median 37 months)	Anginal status (CCS class), weekly angina episode, nitroglycerin use , QOL (using a simple 5 point scale where 1 represents the worst and 5 represents the best QOL), clinical events (PCI, CABG, MI, death, MACE (composite of death/MI/CABG/PCI) and hospitalisation.
Ballegaard 1990[221]	Acupuncture	Sham acupuncture.	Ten (10) treatments in the supine position within 3 weeks	RCT	N=49 (n=24 in genuine acupuncture and n=25 sham acupuncture). Clinically stable exercise induced angina pectoris for more than 6 months (2 or more anginal attacks per week). All	Just after the treatment period	Exercise test; no. of anginal attacks; activity at the time of the pain; nitroglycerin consumption (diaries); daily well being on an ordinal scale; global evaluation of the effect of the treatment on an ordinal scale:

					patients on medical treatment.		
Ballegaard 1986[222]	Acupuncture	Sham acupuncture.	Seven (7) treatments in the supine position for 3 weeks	RCT	N=26 (n=13 in active acupuncture and n=13 in sham acupuncture). Stable, medically resistant, exercise provoked angina pectoris (functional class II-1V NYHA). The patients were selected among 56 consecutive patients with a positive evaluation with regard to aortocoronary bypass surgery	Immediately after the 9 week treatment period.	Exercise tests variables (Exercise tolerance, difference in pressure rate product between rest and maximum exercise, maximal PRP during exercise, maximum ST depression and length of time maximum ST depression); anginal attacks, activity at the time of the pain attack and nitroglycerin consumption (from diaries); subjective global evaluation by the patient at the end of the trial : improvement of general well-being after treatment /no improvement of general well-being after treatment.
Richter 1991[223]	Acupuncture	Tablet placebo.	The treatment was given 3 times per week during the 4 week period.	RCT (cross over trial)	N=21 (cross over). Patients with stable effort angina and at least five anginal attacks per week during the last 6 months, inspite of intensive antianginal treatment. Bypass surgery had been performed in 8 patients, in two of them repeatedly, while 5 patients were still waiting for	Immediately after the 4 treatment period	Exercise test, self rating quality of life questionnaire, no. of anginal attacks.

					operation.		
McGillion 2008[224]	Chronic Angina Self-Management Program (CASMP)	Waiting list control (offered entry into the next available CASMP once post-test measures were completed).	The psycho education programme given in two-hour sessions weekly, over a six-week period by a registered nurse using a group format.	RCT	n=130 were randomised, n=66 to the CASMP and n=64 to the waiting list control group. Chronic stable angina patients.	3 months from start of treatment	Health Related Quality of Life (HRQOL) which included the SF-36 and the SAQ (Seattle Angina Questionnaire)
Payne 1994[225]	Pain management programme	standard medical care	The pain management programme administered over three consecutive weekly sessions (length of sessions not reported).	RCT	N =52 (N=26 pain management treatment and N=26 controls). Episodes of chest pain or discomfort in the previous 4 weeks in patients with diagnosed coronary artery disease.	6 months.	Pain frequency and intensity; frequency of NTG usage; mood and psychological distress.

18.2 Transcutaneous electric nerve stimulation (TENS)

18.2.1 Clinical question

What is the clinical/cost effectiveness of TENS in people with stable angina?

18.2.2 Clinical evidence

The “Review Protocol” for this topic can be found in Appendix C, the “Search Strategies” in Appendix D, the “List of Included and Excluded Studies” in Appendix E1, the “Clinical Evidence Tables” in Appendix E2, and the “Forest Plots” in Appendix F.

There was one RCT[218] evaluating the effectiveness of TENS in patients with severe angina pectoris.

The “Review Protocol” for this topic can be found in Appendix C, the “Search Strategies” in Appendix D, the “List of Included and Excluded Studies” in Appendix E1, the “Clinical Evidence Tables” in Appendix E2, and the “Forest Plots” in Appendix F.

Table 18.2: TENS vs. control (no TENS) for stable angina – Quality assessment & Summary of findings

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	TENS vs. control (no TENS) (Follow-up 2 weeks after treatment)	control	Relative (95% CI)	Absolute	
Exercise tolerance (W.min) (follow-up 2 weeks; better indicated by higher values)											
Mannheimer 1985[218]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	11	10	-	MD 9 lower (170.42 lower to 152.42 higher)	⊕⊕OO LOW
ST segment depression (mm) during exercise (follow-up 2 weeks; better indicated by lower values)											
Mannheimer 1985[218]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	11	10	-	MD 0.2 lower (1.36 lower to 0.96 higher)	⊕⊕OO LOW
ST segment depression (mm) after exercise (follow-up 2 weeks; better indicated by lower values)											
Mannheimer 1985[218]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	11	10	-	MD 0.2 higher (0.97 lower to 1.37 higher)	⊕⊕OO LOW
Frequency of angina attacks per week (follow-up 2 weeks; better indicated by lower values)											
Mannheimer 1985[218]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	11	10	-	MD 4 lower (21.98 lower to 13.98 higher)	⊕⊕OO LOW
Nitroglycerin consumption per week (follow-up 2 weeks; better indicated by lower values)											
Mannheimer 1985[218]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	11	10	-	MD 17 higher (9.31 lower to 43.31 higher)	⊕⊕OO LOW

(a) *Mannheimer 1985[212]: Randomised. Blind outcome assessment (ST segment changes were measured blindly by two independent observers). Method of randomisation not reported. Allocation concealment not reported. Small sample size. Loss to follow-up not reported. ITT not reported. No blinding of participants (not possible due to the kind of intervention)*

(b) *Upper and lower confidence limit crosses the minimal important difference.*

18.2.3 Economic evidence

No relevant economic evaluations comparing TENS with any other intervention were identified.

18.2.4 Evidence statement

Clinical	**TENS vs. control** **Mannheimer 1985[212]:** Evidence from one RCT shows that there was no significant difference between TENS treatment and control group for exercise tolerance (W.min) (MD -9.00 [-170.42, 152.42]); ST segment depression (mm) during exercise (MD -0.20 [-1.36, 0.96]); ST segment depression after exercise (MD 0.20 [-0.97, 1.37]); frequency of angina attack per week (MD -4.00 [-21.98, 13.98]); and nitroglycerin consumption per week (MD 17.00 [-9.31, 43.31]) [follow-up 2 weeks after treatment]
Economic	No economic evidence was found.

18.2.5 Recommendations and link to evidence

Recommendation	**Do not offer the following interventions to manage stable angina:** • **transcutaneous electrical nerve stimulation (TENS)** • **enhanced external counterpulsation (EECP)** • **acupuncture.**
Relative values of different outcomes	The outcomes considered as important during the development of the review protocol for pain interventions included: improvement in anginal symptoms (angina frequency and nitroglycerin consumption), exercise tolerance, mortality, major cardiac events, hospitalisation, revascularisation, QoL and adverse events.
Trade off between clinical benefits and harms	The evidence identified on TENS reported on three outcomes including frequency of anginal attacks, exercise tolerance and nitroglycerin consumption. TENS is not clinically effective with respect to any of these three outcomes. There is no evidence of clinical benefit arising from the use of TENS in stable angina patients.
Economic considerations	No published health-economic evaluation of TENS was identified. The intervention is associated with costs to the NHS but there is no evidence of clinical benefit. TENS was therefore

	considered not cost-effective.
Quality of evidence	The available evidence was of low quality as assessed by GRADE with a very small sample size (n=23) and short follow-up period (2 weeks).
Other considerations	The GDG considered that current evidence base is weak and shows no effectiveness of TENS. TENS should not be used unless new evidence emerges that demonstrates that TENS is clinically and cost-effective in people with stable angina.

18.3 Enhanced external counterpulsation (EECP)

18.3.1 Clinical question

What is the clinical/cost effectiveness of EECP in people with stable angina?

18.3.2 Clinical evidence

The “Review Protocol” for this topic can be found in Appendix C, the “Search Strategies” in Appendix D, the “List of Included and Excluded Studies” in Appendix E1, the “Clinical Evidence Tables” in Appendix E2, and the “Forest Plots” in Appendix F.

There were 3 papers (1 RCT, one sub-study of the RCT and one Before-After study) evaluating the effectiveness of EECP in patients with chronic stable angina and refractory angina.

Table 18.3: EECP vs. inactive CP for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	EECP	inactive CP (Follow-up 3 days after treatment for angina pain counts, one week after treatment for exercise duration)	Relative (95% CI)	Absolute	
Exercise duration (sec) (change scores) (follow-up after 1 week) (follow-up 1 weeks; better indicated by higher values)											
Arora 1999[219]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (d)	none	57	58	-	MD 16 higher (15.86 lower to 47.86 higher)	⊕⊕OO LOW
Time to >1mm ST segment depression (Sec) (change scores) (follow-up after 1 week) (follow-up 1 weeks; better indicated by higher values)											
Arora 1999[219]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	56	-	MD 41 higher (9.13 to 72.87 higher)	⊕⊕⊕O MODERATE
Angina episodes/day (change scores) (follow-up after 3 days) (follow-up 3 days; better indicated by lower values)											
Arora 1999[219]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious imprecision (d)	none	71	66	-	MD 0.24 lower (0.83 lower to 0.35 higher)	⊕⊕OO LOW
NTG use/day (change scores) (follow-up after 3 days) (follow-up 3 days; better indicated by lower values)											
Arora 1999[219]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	71	66	-	MD 0.22 lower (0.55 lower to 0.11 higher)	⊕⊕⊕O MODERATE
Adverse events (no. of patients) (up to the end of treatment) (c)											
Arora 1999[219]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	39/71 (54.9%)	17/66 (25.8%)	RR 2.13 (1.35 to 3.38)	291 more per 1000 (from 90 more to 613 more)	⊕⊕OO LOW

(a) *Arora 1999[213]: Multicentre randomised study. Baseline characteristics reported. The EECP group and inactive CP group were not balanced at baseline, the patients in the EECP group had significantly longer duration of angina and higher proportion of patients with previous MI. Allocation concealment reported. 2 /139 withdrew prior to first treatment. 1/66 in inactive CP and 12/71 in EECP lost to follow-up [more drop out from the EECP than the control group] . No data reported on long term outcomes* *especially cardiac mortality. Completed trial: N = 124: EECP,n= 59; Inactive CP ,n=65. ITT analysis used (but not for all outcomes). ITT was not reported for ST segment depression and exercise duration. This may overestimate the treatment effect. Data not well reported. Very short follow-up*

(b) *Less than 300 events*

(c) *The adverse experiences (device related) were: Paresthesia, edema, swelling, skin abrasion, bruise, blister, pain (legs, back). The adverse experiences (non device related) were: viral syndrome, anxiety, dizziness, tinnitus, GI disturbance, headache, blood pressure change, epitaxis, angina, other chest pain, A/V arrhythmia, heart rate change, respiratory.*

(d) *95% CI includes no effect and the upper and lower CI crosses the MID.*

ARORA 2002[226] (MUST EECP trial; EECP vs. control)

This is a sub-study of the (MUST EECP trial assessing HRQOL [Health related quality of life] at one year follow-up).

Population:

MUST EECP trial N=138 (n=EECP 71, n=inactive counterpulsation n= 66) 119 male. Age (mean): 62±9 (no EECP); 64±9 (EECP); p<0.1.

Data for sudstudy with HRQoL was available only for n=71 (35 in no EECP and n=36 EECP, 65 male. Age (mean ±SD): 62.7 ± 9.7 (no EECP), 65.3± 8.1 [Hence there is a high risk that this sample is not representative of the study population]

Outcome: Health related quality of life (HRQOL). Four primary outcomes were used in the analysis: the physical functioning, bodily pain and social functioning subscales of the SF-36, and QOL score. The 36 item Short-Form Health Survey (SF-36) and the cardiac version of the Quality of Life Index (QIL) used for measuring HQOL. The SF-36 comprises 36 items that yield 8 multi item scales that measure physical functioning, work role disability due to emotional problems, bodily pain, general health perceptions, vitality, social functioning, work role disability due to emotional problems, mental health, and a single item evaluation of change in health. The QIL is in 2 parts: Part 1 measures satisfaction with various aspects of life as they are impacted by the respondent's cardiac health. Part 2: Measures the importance of these same aspects of life to the respondent personally.

Results:

A. Baseline to end of treatment: Both EECP and inactive CP groups reported significant improvements in physical functioning, bodily pain, and cardiac specific health and functioning from baseline to end of treatment. The size of the improvement in HQOL parameters was always larger for the EECP than for inactive CP; however, this difference was only statistically significant for one of the four primary parameters: social functioning. Those in the EECP group reported a substantially greater increase in their abilities to participate in social activities with family and friends than did those in the inactive CP, who, on average, reported a decrease in social activity. [Values not reported]

B. Baseline to 1 year follow-up: At 1 year follow-up, the EECP group maintained statistically significant improvements in HQOL across all primary HQOL parameters, where as the inactive CP group only maintained a significant improvement in the physical functioning scale. At 1 year follow-up, improvements for the EECP group were significantly greater than those for the inactive CP group on 3 of 4 primary parameters: bodily pain, social functioning, and cardiac specific health and functioning [no values reported]

Loh 2008[220] (International EECP Patient Registry [IPER]):

This is a Before-After study. This study is the 3 year follow-up of the patients in the International EECP Patient Registry (IEPR)

Population: N=1427. Five thousand patients from 99 American and 9 international centres were enrolled between Jan 1998 and July 2001. Consecutive patients from each centre who had at least 1 hour of EECP treatment were enrolled. The mean age was 66.3±10.8 years and 72% were men.76% had multivessel coronary disease.88% had prior PCI or CABG and 88% were unsuitable for further coronary intervention. The Anginal status of patients was: CCS class I: 2.2%; CCS class II: 8.6%; CCS class III: 62.8%; CCS class IV: 26.4%.

Intervention: EECP. A standard course of 35 one hour treatment sessions was recommended. The patients received a mean of 33.3±9.6 hours of treatment over a mean period of 48 days.

Follow-up: 3 years (median 37 months)

Outcome: The primary outcome measure was Anginal status (CCS class). The other outcomes were weekly angina episode, nitroglycerin use , QOL (using a simple 5 point scale where 1 represents the worst and 5 represents the best QOL), clinical events (PCI, CABG, MI, death, MACE (composite of death/MI/CABG/PCI) and hospitalisation.

Results: Immediately post EECP, the proportion of patients who suffered from CCS Class III/IV angina reduced from 89.2% to 24.9%, p<0.001. The CCS class improved by at least 1 class in 77.9% of the patients and by 2 classes in 38%. 16.3% of patients had no angina. These were sustained in 74% patients whose anginal status was documented at 3 year follow-up. At 3 years, 36.4% of the patients had class II or milder angina. The Cumulative 3 year repeat EECP and major cardiovascular event rates: (Percentage (95% CI)) was: Repeat EECP: 22.5% (20.1% -24.9%); PCI: 16.4% (14.3% -18.5%); CABG: 7.5% (6%-9%); MI: 11.8% (10%-13.7%); Death- 17% (14.9%-19.1%); MACE: 40.8% (38.8%-43.5%). Of the patients who responded to the QOL questionnaires there was sustained improvement in their QOL after 3 years, p<0.001(results reported graphically).

18.3.3 Economic evidence

One study[227] was included that compared EECP with no treatment. This is summarised in the economic evidence profile below. See also Economic Evidence Tables in Appendix G.

Table 8.4: EECP vs. no treatment- Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
McKenna 2009[227]	Potentially serious limitations (a)	Direct applicability	Decision model based on the MUST-EECP trial, included in the review of clinical effectiveness.

a) *The analysis was based on limited data (one small RCT). Utilities were obtained from an algorithm converting SF-36 to EQ-5D. Durability of benefits obtained from expert opinion. The model does not consider: the effect of the intervention on mortality or myocardial infarction, the cost of escalating medical treatment over time, costs associated with no intervention.*

Table 8.5: EECP vs. no treatment - Economic summary of findings

Study	Incremental cost (£)	Incremental effects (QALYs)	ICER	Uncertainty
McKenna 2009[227]	4,750 (a)	0.255 (b)	£18,643/QALY	One-way sensitivity analysis: results were sensitive to the probability of sustaining QoL benefits over time and to the cost of EECP. Results were not sensitive to the rate of repeat EECP within two years or to the discount rates used. Worst/best case scenario: if QoL benefits from EECP are only sustained in the first year, the ICER was £63,000. If QoL benefits are sustained over a lifetime, the ICER becomes £5,830. Monte-Carlo simulation: EECP was cost-effective in 44.4% of the simulations.

(a) *2008 GBP. Costs included were capital cost of EECP machine, equipment replacement costs, consumables, staffing costs, overheads, repeat operations. Cost of no treatment was assumed to be null. Cost data were obtained from personal communication and price list of supplier.*

(b) *Quality of life improvements were calculated as EQ-5D scores using an algorithm to convert the SF-36 scores from the study into EQ-5D. Utilities after one year were estimated with expert elicitation techniques (frequency chart).*

18.3.4 Evidence statements

Clinical **EECP vs. inactive CP**

Arora 1999[219] **(MUST EECP trial):** Evidence from one RCT shows that time to >1 mm ST segment depression (sec) increased significantly in the EECP compared to inactive CP (MD 41.00 [9.13 to 72.87]). Adverse events were significantly higher in the EECP group compared to inactive CP (RR 2.13 (1.35 to 3.38).There was no significant difference between EECP and inactive CP for exercise duration (sec) (MD 16.00 [-15.86 to 47.86]); angina episodes/day (MD -0.24 [-0.83 to 0.35]) ; NTG use/day (MD -0.22 [-0.55 to 0.11]) [follow-up 3 days after treatment for angina pain counts, one week after treatment for exercise duration].

EECP vs. control

Arora 2002[226] **(MUST EECP trial):** Evidence from one RCT shows that both EECP and inactive CP groups reported statistically significant improvements in physical functioning, bodily pain, and cardiac specific health and functioning from baseline to end of treatment. At 1 year follow-up, the EECP group maintained statistically significant improvements in HQOL across all primary HQOL parameters, where as the inactive CP group only maintained a statistically significant

	improvement in the physical functioning scale. At 12 month follow-up, improvements in HQOL for the EECP were significantly greater than those for the inactive CP group on three of four primary parameters (SF-36 scale): bodily pain, social functioning and cardiac specific health and functioning but not physical functioning. [Follow-up 12 months] **EECP Patient Registry (no comparison group)** **Loh 2008[220] (International EECP Patient Registry [IPER])** : Evidence from one Before-After study shows that immediately post EECP, the proportion of patients who suffered from CCS Class III/IV angina reduced from 89.2% to 24.9%, p<0.001. The CCS class improved by at least 1 class in 77.9% of the patients and by 2 classes in 38%. 16.3% of patients had no angina. These were sustained in 74% patients whose anginal status was documented at 3 year follow-up. Immediately post EECP, 76% of the patients experienced at least 50% reduction in frequency of angina. This was sustained at 3 year follow-up. Of the patients who responded to the QOL questionnaires there was sustained improvement in their QOL after 3 years, p<0.001(no values reported) [follow-up 3 years]
Economic	The cost-effectiveness of EECP is very uncertain depending on the sustained effectiveness of the intervention. This evidence is directly applicable but it has potentially serious limitations.

18.3.5 Recommendations and link to evidence

Recommendation	**Do not offer the following interventions to manage stable angina:** • **transcutaneous electrical nerve stimulation (TENS)** • **enhanced external counterpulsation (EECP)** • **acupuncture.**
Relative values of different outcomes	The outcomes considered important during the development of the review protocol for pain interventions included: improvement in anginal symptoms (angina frequency and nitroglycerin consumption), exercise tolerance, mortality, major cardiac events, hospitalisation, revascularisation, QoL and adverse events.
Trade off between clinical benefits and harms	Evidence from the MUST EECP trial showed a statistically significant improvement in one exercise test variable (time to ST depression) in the EECP group relative to the control group (one week follow-up period). The GDG did not consider this improvement to be clinically significant. Furthermore there were more adverse events in the EECP group when compared

	to the control group over the 7 week treatment period. The registry study (International EECP Patient Registry (IPER)) showed significant improvement in CCS angina class after 3 years. During this follow-up period there was repeat EECP in 22.5% of patients, PCI in 16.4% patients, CABG in 7.5% of patients and death in 17% of patients. Adverse events were significantly higher in the EECP group when compared to the control group over the 7 week treatment period.
Economic considerations	There is high uncertainty over the cost-effectiveness of EECP in people with stable angina mainly due to the unknown long-term benefits of the intervention.
Quality of evidence	The available evidence on EECP is weak. It is based on one RCT (MUST EECP) and one registry study (International EECP Patient Registry (IPER)). The MUST EECP trial was a small study with a high risk of bias. The randomisation scheme was not explained and the short follow-up period (1 year) limits conclusions regarding the durability of treatment effects. The IPER registry study has serious limitations. Only patients from centres with at least 80% compliance in follow-up data were included (5000 patients were enrolled but only 1427 patients were analysed). No evidence was available on the long-term safety of EECP. The economic evidence was directly applicable but it had potentially serious limitations.
Other considerations	The GDG considered that people with angina that has not responded to drug or revascularisation options or for whom these options are inappropriate or undesirable present a significant clinical problem. They considered it important, however, that interventions offered to these patients should have robust evidence base. Without such an evidence base the GDG considered it misleading to offer such interventions to patients and it was more appropriate for healthcare professionals to acknowledge the limitations of interventions available and provide information, education and support for patients.

18.4 Acupuncture

18.4.1 Clinical question

What is the clinical/cost effectiveness of Acupuncture in people with stable angina?

18.4.2 Clinical evidence

The "Review Protocol" for this topic can be found in Appendix C, the "Search Strategies" in Appendix D, the "List of Included and Excluded Studies" in Appendix E1, the "Clinical Evidence Tables" in Appendix E2, and the "Forest Plots" in Appendix F.

There were 3 RCTs[221-223] evaluating the effectiveness of acupuncture in people with stable angina.

Data for the 3 RCTS could not be analysed as the standard deviations were not reported. Hence results have been reported narratively.

Ballegaard 1990 [221]

Population: N=49 (n=24 in genuine acupuncture and n=25 sham acupuncture). The Median age (years) of the patients was 67 yrs in genuine and 66 yrs in sham acupuncture.

Intervention: Genuine acupuncture. The genuine acupuncture was given according to traditional Chinese medicine, each patient receiving 10 treatments in the supine position within 3 weeks.

Comparison: Sham acupuncture.

Outcome: Exercise test; no. of anginal attacks; activity at the time of the pain; nitroglycerin consumption (diaries); daily well being on an ordinal scale, using the terms very good (given value 1), good (2), fair (3), not good (4), bad (5) ; global evaluation of the effect of the treatment on an ordinal scale: much improved, somewhat improved, slightly improved, unchanged, slightly worse, somewhat worse, much worse.

Follow-up: Immediately after treatment

Results:

A. Exercise test variables

There was no significant between group differences for any of the exercise variables. Exercise variables (genuine (n=24) vs. sham acupuncture (n=25): Exercise tolerance (%): median change +9 , range -25 to +184 vs. median change +4 (-16 to +135); Maximal PRP (%): -1 (-12 to +47) vs. +5 (-22 to +25); Delta PRP (%): + 3 (-38 to +145) vs. +4 (-28 to + 78); Time to ST segment depression (%): median change 0 (-42 to +100) vs. median change 0 (-40 to +40); Time to end of ST depression (%):median change +9 (-75 to +600) vs. median change 0 (-58 to +300); Maximum ST depression (mm): median change 0 (-1.0 to +0.5) vs. 0 median change (-1.0 to

+1.5); Time with minimum 1 mm ST depression (%):median change +15 (-79 to +490) vs. median change +5 (-72 to +200); Time to onset of pain (%):median change +10 (-32 to +107) vs. median change +10 (-39 to +55); Post exercise pain duration (%): median change 0 (-47 to +700) vs. median change 0 (-77 to +78).

B. Subjective variables

Within both groups there was a significant decrease in both anginal attack rate and nitroglycerin consumption. After treatment all patients receiving genuine acupuncture decreased nitroglycerin consumption (median change -54%, range -14 to -100%). Anginal attack rate was reduced in 13 of 14 patients (93%) (median change -41%, range +18 to -95%). Nitroglycerin consumption and anginal attack rate were reduced in 15 of 16 patients (94%) receiving sham acupuncture. The median change being -53% (range +20 to -100%) and -55% (range +23% to -100%) respectively. Daily well being was improved in 14 out of 23 (61%) in both groups (median improvement +1 arbitrary value in both groups). Concerning global evaluation, 75% of the patients treated by genuine acupuncture reported improvement in their general condition after the end of the treatment and 6m months later 67% still felt the improvement. Among those treated by sham acupuncture 84% reported improvement and 6 months later 72% still felt it.

Ballegaard 1986[222]

Population: N=26 (n=13 in active acupuncture and n=13 in sham acupuncture).

Intervention: Active acupuncture. During the 3 weeks treatment period all patients received seven treatments in the supine position.

Control: Sham acupuncture.

Follow-up: Immediately after the 9 week treatment period.

Results: Patients receiving genuine acupuncture had a significantly higher dPRP (Pressure rate product) than patients receiving sham acupuncture, respectively. [Maximal PRP (mmHgmin-1): 24.640 vs. 13.530 ; Delta PRP (mmHgmin-1): 12.580 vs. 6.592]. There was no significant difference between genuine and sham acupuncture, respectively for : Exercise tolerance (Wmin): 550 (150 to 1300) vs. 256 (100 to 1700); Time to maximal ST depression (min): 2 (0 to 7.5) vs. 2 (0 to 4.5); and Size of maximal ST depression (mm): 1 (0 to 3) vs. 1 (0 to 2); No. of anginal attacks per 3 weeks: 55 (8 to 168) vs. 66 (41 to 149); and nitroglycerin consumption (0.25 mg tablets per 3 weeks): 39 (1 to 193) vs. 30 (0 to 152). Six of the 12 patients in the active treatment group and one of 12 patients in the sham treatment group reported improvement in general well being after treatment (p=0.10). No complications or adverse effects were observed. The study period consisted of: 3 weeks of pre treatment control; after randomisation 3 weeks of treatment, during which the patients received either active or sham acupuncture, and 3 weeks of post treatment control.

Richter 1991[223]

Population: N=21 (cross over study).

Intervention: Acupuncture. The treatment was given 3 times per week during the 4 week period.

Comparison: Tablet placebo.

Follow-up: Immediately after the 4 week treatment period (2 weeks wash out period between the treatment periods)

Results: During acupuncture treatment, 14 patients showed a reduced number of anginal attacks compared with placebo. The no. of attacks was unchanged in the remaining 7 patients; no worsening was observed in any of the patients. In the whole group, the average number of anginal attacks/week was 12.1 during the run-in period, 6.1 during the acupuncture period and 10.6 during the placebo period. The differences between acupuncture and both run-in and placebo periods were statistically significant ($p<0.01$). The results of the exercise tests did not show any significant difference in maximal physical performance at the end of the acupuncture period compared with placebo, the mean values being 104.2 W and 101.4 W respectively. However, maximal workload until onset of chest pain was significantly increased after acupuncture compared with placebo (94.3 W vs. 81.9 W, $P<0.05$). Mean chest pain score at maximal workload improved significantly after acupuncture compared with placebo (mean (0.81 W and 1.38, $p<0.01$). ST segment depression at maximal workload was significantly reduced after acupuncture compared with placebo (mean 0.71 mm vs. 1.03 mm, $p<0.01$). Similar results were obtained for ST segment depression at maximal comparable workload (mean 0.63 mm vs. 0.87 mm, $p<0.01$). [Standard deviations not reported]. Concerning the self-rating life quality questionnaire, the score was significantly improved for chest pain, physical performance, peripheral coldness, pessimism, vertigo and relaxation ($p<0.05$). The statistical significance could not be proved for anxiety, tiredness, sleep disturbances and gastro-intestinal symptoms. No adverse effect of acupuncture was observed. [mean values and standard deviations not reported]

18.4.3 Economic evidence

One study[228] focusing on the addition of acupuncture and self-education to medical treatment was found but it was excluded as it had serious limitations due to the study design (within-group comparison) and it was partially applicable (cost estimates from the USA).

18.4.4 Evidence statements

Clinical	<u>**Acupuncture vs. sham acupuncture**</u> **Ballegaard 1990[221]:** Evidence from one RCT shows that there was no significant difference between genuine acupuncture and sham acupuncture for exercise variables ; anginal attack rate ; and nitroglycerin consumption [follow-up 3 days after treatment for angina pain counts, one week after treatment for exercise duration].

	Ballegaard 1986[222]**:** Evidence from one RCT shows that compared to patients receiving sham acupuncture the patients receiving active acupuncture increased cardiac work capacity significantly,. There was no significant difference between the groups for exercise tolerance , time to maximal ST depression (min); size of maximal ST depression (mm) : and nitroglycerin consumption [Follow-up immediately after 9 week treatment period] **<u>Acupuncture vs. placebo</u>** **Richter 1991**[223]**:** Evidence from one randomised cross over trial shows that compared to placebo treatment acupuncture significantly reduced anginal attacks per week); maximal workload until onset of chest pain was significantly increased after acupuncture compared with placebo chest pain at maximal workload improved significantly after acupuncture compared with placebo ST segment depression at maximal workload was significantly reduced after acupuncture compared with placebo and ST segment depression at maximal comparable workload was significantly reduced after acupuncture compared with placebo. There was no significant difference in maximal physical performance at the end of the acupuncture period compared with placebo [follow-up immediately after 4 week treatment period]
Economic	No economic evidence was included on this intervention.

18.4.5 Recommendations and link to evidence

Recommendation	**Do not offer the following interventions to manage stable angina:** • **transcutaneous electrical nerve stimulation (TENS)** • **enhanced external counterpulsation (EECP)** • **acupuncture.**
Relative values of different outcomes	The outcomes considered as important during the development of the review protocol for pain interventions included: improvement in anginal symptoms (angina frequency and nitroglycerin consumption), exercise tolerance, mortality, major cardiac events, hospitalisation, revascularisation, QoL and adverse events.
Trade off between clinical benefits and harms	One RCT[223] showed some improvement in angina and exercise test variables when compared to tablet placebo. However there was no improvement in angina or exercise test variables in two RCTs[221,222] that compared acupuncture to sham

	acupuncture. There is no other evidence of clinical benefit arising from the use of acupuncture in stable angina patients.
Economic considerations	No published health-economic evaluation of acupuncture was included. The intervention is not cost-effective as it generates costs without being effective at improving the outcomes considered.
Quality of evidence	Evidence was obtained from 3 low quality RCTs[221-223]. Each of these RCTs had small sample size (<50 patients); outcomes were measured immediately after treatment with no longer term follow-up. The methodology of the trials was not well reported and the derived data was not analysable. Hence the GDG was not confident in the results of these trials.
Other considerations	The GDG considered that people with angina which has not responded to drug or revascularisation options or for whom these options are inappropriate or undesirable present a significant clinical problem. They considered it important however, that interventions offered to these patients should have robust evidence base. The GDG did not consider that the evidence for acupuncture supported its use in people with angina. The GDG recognised that some people with angina may also experience chest pain that is not cardiac in origin and that acupuncture may have some role in these circumstances.

18.5 Self management of pain

18.5.1 Clinical question

What is the clinical/cost effectiveness of self management of pain in people with stable angina?

18.5.2 Clinical evidence

The "Review Protocol" for this topic can be found in Appendix C, the "Search Strategies" in Appendix D, the "List of Included and Excluded Studies" in Appendix E1, the "Clinical Evidence Tables" in Appendix E2, and the "Forest Plots" in Appendix F.

There were 2 RCTs[224,225] comparing Psycho educational programmes with control/standard medical care for self management of pain in stable angina.

McGillion 2008[224] (CASMP vs. control)

Population: n=130 were randomised, n=66 to the CASMP and n=64 to the waiting list control group.

Intervention: The Chronic Angina Self-Management Program (CASMP) is a standardized psycho education programme given in two-hour sessions weekly, over a six-week period.

The CASMP is an adaptation of Lorig et al.'s Chronic Disease Self-Management Program (CDSMP, 1999 Stanford University). The programme was delivered by a registered nurse using a group format (e.g., 8-15 patients) in a comfortable classroom setting. Key pain related content includes relaxation and stress management techniques, energy conservation, symptom monitoring and management techniques, medication review, seeking emergency assistance, diet, and managing emotional responses to cardiac pain. Programme sessions were offered both day and evening and participants were encouraged to bring a family member or friend if they wished. A facilitator manual specified the intervention protocol in detail to ensure consistent delivery of the CASMP across sessions.

Comparison: Waiting list control: The patients in this group were offered entry into the next available CASMP once post-test measures were completed.

Outcomes: The primary outcome was Health Related Quality of Life (HRQOL) which included the SF-36 and the SAQ (Seattle Angina Questionnaire). The secondary outcome was enabling skill, reflected by CSA patients' self-efficacy and resourcefulness to self-manage their pain.

Follow-up: 3 months

Table 18.6: Chronic angina self management Program (CASMP) vs. control (Follow-up 3 months from start of treatment) for stable angina

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chronic angina self management Program (CASMP)	control (Follow-up 3 months from start of treatment)	Relative (95% CI)	Absolute	
Physical functioning (SF-36) (range 0-100 -higher score better functioning) (change scores) (follow-up 3 months; range of scores: 0-100; better indicated by higher values)											
McGillion 2008[224]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	57	60	-	MD 5.98 higher (2.59 to 9.37 higher)	⊕⊕OO LOW
Role physical functioning (SF-36) (change scores) (range 0-100) (follow-up 3 months; range of scores: 0-100; better indicated by higher values)											
McGillion 2008[224]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	57	60	-	MD 1.6 higher (2.5 lower to 5.7 higher)	⊕⊕⊕O MODERATE
Bodily pain (SF-36) (change scores) (range 0-100) (follow-up 3 months; range of scores: 0-100; better indicated by higher values)											
McGillion 2008[224]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	57	60	-	MD 2.3 higher (0.94 lower to 5.54 higher)	⊕⊕⊕O MODERATE
General Health (SF-36) (change scores) (0-100) (follow-up 3 months; range of scores: 0-100; better indicated by higher values)											
McGillion 2008[224]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	57	60	-	MD 3.87 higher (1.3 to 6.44 higher)	⊕⊕OO LOW
Angina frequency (SAQ) (range 0-100- higher scores better functioning) (change scores) (follow-up 3 months; range of scores: 0-100; better indicated by higher values)											
McGillion 2008[224]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	57	60	-	MD 9.2 higher (1.48 to 16.92 higher)	⊕⊕⊕O MODERATE
Angina stability (SAQ) (range 0-100) (change scores) (follow-up 3 months; range of scores: 0-100; better indicated by higher values)											
McGillion 2008[224]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	57	60	-	MD 15.1 higher (4.11 to 26.09 higher)	⊕⊕⊕O MODERATE
Disease perception (SAQ) (range 0-100) (change scores) (follow-up 3 months; range of scores: 0-100; better indicated by higher values)											
McGillion	randomised	serious(a)	no serious	no serious	no serious	none	57	60	-	MD 6.6 higher	⊕⊕⊕O

2008[224]	trials		inconsistency	indirectness	imprecision					(1.18 lower to 14.38 higher)	MODERATE
Physical limitation (SAQ) (range 0-100) (change scores) (follow-up 3 months; range of scores: 0-100; better indicated by higher values)											
McGillion 2008[224]	randomised trials	serious(a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	57	60	-	MD 5.5 higher (0.24 lower to 11.24 higher)	⊕⊕⊕O MODERATE
Treatment satisfaction (SAQ) (range 0-100) (change scores) (follow-up 3 months; range of scores: 0-100; better indicated by higher values)											
McGillion 2008[224]	randomised trials	serious(a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	57	60	-	MD 4.9 higher (3.05 lower to 12.85 higher)	⊕⊕⊕O MODERATE
Self-Efficacy to manage disease (Self-efficacy Scale)range scores 10- 100 -higher scores better) (change scores) (follow-up 3 months; range of scores: 10-100; better indicated by higher values)											
McGillion 2008[224]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	serious (b)	none	57	60	-	MD 8.6 higher (2.76 to 14.44 higher)	⊕⊕OO LOW

(a) McGillion 2008[218]: Randomised. Allocation concealment reported. 9/66 (14%) in the intervention group and 4/64 (6%) in the control group. There are more patients in the intervention group who were lost to follow-up but there are no systematic differences between the two groups with respect to loss of participants. The study follow-up period was limited to three months after baseline for both groups. ITT used. No blinding of participants and outcome assessors.

(b) Lower CI crosses MID.

Additional data:

Payne 1994[225] (Self Pain management programme vs. control)

Data was not analysed for the following study as it was poorly reported:

Population: n=52. Participants were 52 male veterans (26 in the treatment and 26 controls). To qualify for the study, patients were required to meet the following criteria: (a) diagnosis of CAD, or positive diagnostic evaluation, such as an exercise stress test, thallium 201 scan or coronary angiogram (b) self report of at least 4 episodes of chest pain or discomfort in the previous 4 weeks (c) 18-65 yrs of age (d) no hospitalisation within past 30 days (e) no current physical disorder associated with severely disabling symptoms or a recent change in symptoms (f) no history of heart valve replacement (g) no history of cardiac transplant surgery.

Intervention: A pain management programme administered over three consecutive weekly sessions (length of sessions not reported). The goals were to 1) educate patients regarding the role of psychological factors in pain and pain control and 2) teach participants an integrated set of self management skills to modify cognitions, behaviours and affective responses considered likely to adversely impact on the experience of chest pain. Specific skills taught included pacing of physical activities (e.g. taking scheduled breaks), modification of dysfunctional, stress engendering thoughts using cognitive reframing and problem solving techniques, and relaxation training via diaphragmatic breathing.

Control: Received standard medical care

Follow-up: 6 months.

Primary outcomes: No primary or secondary outcomes specified. Outcomes included: pain frequency and intensity; frequency of NTG usage; mood and psychological distress.

Results: There were no significant differences between groups with regard to pain frequency, pain intensity, psychological and other factors at 6 months. Actual data for results not reported.

18.5.3 Economic evidence

No economic studies were found on this question.

18.5.4 Evidence statements

Clinical	**Self management programme vs. control** **McGillion 2008[224]:** Evidence from one RCT shows that Physical functioning (SF-36) (MD 5.98 [2.59 to 9.37]) , General Health (SF-36) (MD 3.87 [1.30 to 6.44]), Angina frequency (SAQ) (MD 9.20 [1.48 to16.92], Angina stability (SAQ) (MD 15.10 [4.11 to 26.09]); and self-efficacy to manage disease (self-efficacy scale) (MD 8.60 [2.76 to 14.44]) were significantly improved in the CASMP compared to control . There was no significant difference

	between CASMP and control for Role physical functioning (SF-36) (MD 1.60 [-2.50 to 5.70]); bodily pain (SF-36) (MD 2.30 [-0.94 to 5.54]);disease perception (SAQ) (MD 6.60 [-1.18 to14.38]) ; physical limitation (SAQ) (MD 5.50 [-0.24 to11.24]) and treatment satisfaction (SAQ) (MD 4.90 [-3.05 to12.85]) [Follow-up 3 months from start of treatment] **Payne 1994[225]:** Evidence from one RCT shows that there were no significant differences between Pain management programme compared to control (standard care) with regard to pain frequency, pain intensity, psychological and other factors. (actual values for results not reported). [Follow-up 6 months]
Economic	No economic evidence was available on this question.

18.5.5 Recommendations and link to evidence

Recommendation	**Offer people whose stable angina has not responded to drug treatment and/or revascularisation comprehensive re-evaluation and advice, which may include:** • **exploring the person's understanding of their condition** • **exploring the impact of symptoms on the person's quality of life** • **reviewing the diagnosis and considering non-ischaemic causes of pain** • **reviewing drug treatment and considering future drug treatment and revascularisation options** • **acknowledging the limitations of future treatment** • **explaining how the person can manage the pain themselves** • **specific attention to the role of psychological factors in pain** • **development of skills to modify cognitions and behaviours associated with pain.**
Relative values of different outcomes	Quality of Life outcomes were considered to be most important in assessing the effectiveness of self-management including various outcomes measured by the SF-36 health survey (physical functioning, bodily pain and general health), as well as those of the Seattle Angina Questionnaire (angina frequency and stability, disease perception, physical limitation and treatment satisfaction) and self-efficacy to manage disease.
Trade off between clinical benefits and harms	One RCT[224] showed statistically significant improvements in some Quality of Life variables including physical functioning, general health, angina frequency and stability, and self-efficacy to manage disease. The studies reviewed do not provide a report on harms arising from self-management. The GDG considered it unlikely that significant harms would occur from

	involvement in a self-management programme.
Economic considerations	The small increase in staff time cost is likely to be offset by the improvement in quality of life shown by the clinical review.
Quality of evidence	Clinical evidence on self-management of pain that met our inclusion criteria for reviewing was obtained from one moderate quality RCT (n=117) and one low quality RCT (n=52) study as assessed by GRADE. McGillion 2008[224] conducted a small RCT of a psycho education programme [Chronic Angina Self-Management Program (CASMP)] in which those treated were compared to patients in a waiting list control group. The study found statistically reliable short-term improvements in some components of HRQL for those who participated in the CASMP as compared to the control group. The follow-up period was limited to three months after baseline and the long-term durability of the observed intervention effects is not known. Due to the nature of the treatment, the patients undergoing EECP could not be blinded, increasing the likelihood of a placebo effect. Further, all psycho education sessions were delivered by a single facilitator increasing the risk to external validity. Payne 1994[225] conducted a very small RCT evaluating a pain management programme and standard medical care compared with standard medical care alone. It found that there were short-term reductions in the number of self-reported chest pain episodes in treated subjects but this benefit was not evident at 6 month follow-up. The study however had a high risk of bias which would make the results unreliable. No economic evidence was included on this intervention.
Other considerations	The GDG made a recommendation on intervention for patients whose angina has not responded to treatment or for whom revascularisation is undesirable or inappropriate using the information presented by Professor Michael Chester and the evidence from the reviews on self management strategies. The evidence for self-management strategies comes from two studies[224,225]. These programmes included a range of self management skills to modify cognitions, behaviours and affective responses considered likely to adversely impact on the experience of chest pain. Specific skills

taught included components such as pacing of physical activities (e.g. taking scheduled breaks), modification of dysfunctional, stress engendering thoughts using cognitive reframing and problem solving techniques, and relaxation training via diaphragmatic breathing, energy conservation, symptom monitoring and management techniques, medication review, seeking emergency assistance, diet, and managing emotional responses to cardiac pain.

19 Cardiac syndrome X

19.1 Introduction

Cardiac syndrome X can be defined as angina in the presence of normal coronary arteries. Diagnostic criteria may also include evidence of ischaemia. The term microvascular angina is also used as it is thought that the pathology may lie within the microvasculature. Abnormalities of endothelial function have also been described.

The GDG were interested in the efficacy of standard anti-anginal drug treatment and drugs for secondary prevention for people with syndrome X and for the evidence on benefit of rehabilitation programmes. This chapter reports on the results of these questions:

A. What is the clinical /cost effectiveness of using standard anti-angina drug therapy (short-acting nitrates, BB, CCB, long-acting nitrates, ACE/ARBs, nicorandil, Ivabradine, Ranolazine,) and /or drugs for secondary prevention in people with syndrome X.

B. What is the clinical/cost effectiveness and safety of cardiac rehabilitation programmes for people with syndrome X?

C. What is the incremental value/effectiveness of anatomical/functional tests for prognostic risk stratification in prediction of adverse cardiac outcomes in people with cardiac syndrome X?

The studies included in the review are all of patient with exertional angina who had positive exercise tests and normal coronary arteries on angiography.

19.2 Clinical/Cost effectiveness of standard anti-anginal drug therapy for management of syndrome X

This review explores use of standard anti-anginal drug therapies for treating angina patients who have normal coronary arteries (cardiac syndrome X). This evidence review included a total of 7 papers. No economic evidence was available to assess cost-effectiveness; therefore this review focuses only on clinical effectiveness.

The results of the review have been analysed based on the type of drug involved (BBs, CCBs, nitrates, nicorandil, aminophylline, ACE inhibitors) and whether they were compared to placebo or to each other.

The main outcomes analysed were number of ischemic episodes, duration of ischemic episodes, exercise duration, time to 1mm-ST segment depression and consumption of nitroglycerin tablets.

19.2.1 Clinical Evidence

The "Review Protocol" for this topic can be found in Appendix C, the "Search Strategies" in Appendix D, the "List of Included and Excluded Studies" in Appendix E1, the "Clinical Evidence Tables" in Appendix E2, and the "Forest Plots" in Appendix F.

The results of the review are presented as follows:

- BBs vs. placebo
- CCBs vs. placebo
- BB vs. CCB
- BB vs. CCB in people with pressure-rate product variation <1050
- BB vs. CCB in people with pressure-rate product variation >1050
- BB vs. nitrates
- CCB vs. nitrates
- Nicorandil vs. placebo
- Aminophylline vs. nitroglycerin
- Angiotensin-converting enzyme inhibitors + statins vs. placebo

Table 19.1: BBs vs. placebo for Cardiac Syndrome X

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	BB	control	Relative (95% CI)	Absolute	
ischemic episodes - propanolol vs. placebo (follow-up 7 days; range of scores: -; better indicated by less)											
Bugiardini 1989[229] (c)	randomised trial (b)	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	16	16	-	MD3.2 lower (4.13 to 2.27 lower)	⊕⊕OO LOW
ischemic duration (min) - propanolol vs. placebo (follow-up 7 days; range of scores: -; better indicated by less)											
Bugiardini 1989[229]	randomised trial (b)	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	16	16	-	MD 25 lower (34.15 to 15.85 lower)	⊕⊕OO LOW

(a) Bugiardini 1989[223]: Randomisation and allocation concealment unclear, small sample size
(b) Crossover design
(c) Propanolol 120-160mg daily (optimal dose for each patient determined 2-3 weeks before the double blind study ; beta blockade occurred at 120mg a day in 6 patients and at 160mg in 10)

Table 19.2: CCBs vs. placebo for Cardiac Syndrome X

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CCBs	control	Relative (95% CI)	Absolute	
ischemic episodes (verapamil vs. placebo ; verapamil or nifedipine vs. placebo) (follow-up 7-28 days; range of scores: -; better indicated by less)											
Bugiardini 1989[229] (c) Cannon 1985[230] (d)	randomised trial (a)	serious (b)	serious inconsistency (e)	no serious indirectness	no serious imprecision	none	38	38		MD 0.6 lower (1.81 lower to 0.61 higher) (e)	⊕⊕OO LOW
ischemia duration (min) (verapamil vs. placebo; - verapamil or nifedipine vs. placebo) (follow-up 7-28 days; range of scores: -; better indicated by less)											
Bugiardini 1989[229] (c) Cannon 1985[230] (d)	randomised trial (a)	serious (b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	38	38	-	MD 0.74 higher (0.55 lower to 2.04 higher) (f)	⊕⊕⊕O MODERATE
Nitroglycerin tablets consumption - verapamil or nifedipine vs. placebo (follow-up 28 days; range of scores: -; better indicated by less)											
Cannon 1985[230] (d)	randomised trial (a)	serious (b)	no serious inconsistency	no serious indirectness	serious imprecision (f)	none	22	22	-	MD 18 lower (41.74 lower to 5.74 higher)	⊕⊕OO LOW
presence of chest pain during exercise - verapamil or nifedipine vs. placebo (follow-up 28 days)											
Cannon 1985[230] (d)	randomised trial (a)	serious (b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/25 (36%)	16/22 (72.7%)	RR 0.49 (0.28 to 0.89)	371 fewer per 1,000 (from 80 fewer to 524 fewer)	⊕⊕⊕O MODERATE

(a) Crossover design
(b) Bugiardini 1989[223] ; Cannon 1985[224] : Randomisation and allocation concealment unclear, small sample size
(c) Propanolol 120-160mg daily (optimal dose for each patient determined 2-3 weeks before the double blind study ; beta blockade occurred at 120mg a day in 6 patients and at 160mg in 10)
(d) The drug and dosage used were determined from the unblinded lead-in phase: 17 patients received verapamil, 40-160mg 4 times a day (mode 80) and 9 patients received nifedipine 10-30mg 4 times a day (mode 10)
(e) There was substantial heterogeneity (I^2=71%) indicating that these results must be carefully interpreted
(f) 95% CI includes no effect and the upper and lower CI crosses the MID.

Table 19.3: BBs vs. CCBs for Cardiac Syndrome X

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	BBs	CCBs	Relative (95% CI)	Absolute	
Number of anginal episodes (per 4 weeks per patient) (propanolol vs. verapamil; atenolol vs. amlodipine) (follow-up 1-4 weeks; range of scores: -; better indicated by less)											
Bugiardini 1989[229] Lanza 1999 (c)	randomised trial (a)	serious (b)	no serious inconsistency	no serious indirectness	no serious imprecision	None	26	26	-	MD 2.71 lower (3.6 to 1.83 lower)	⊕⊕⊕O MODERATE
Chest pain episodes duration (min) (propanolol vs. verapamil ; atenolol vs. amlodipine) (follow-up 1-4 weeks; range of scores: -; better indicated by less)											
Bugiardini 1989[229] Lanza 1999 (c)	randomised trial (a)	serious (b)	serious inconsistency (d)	no serious indirectness	no serious imprecision	none	26	26	-	MD 17.66 lower (24.35 to 10.97 lower)	⊕⊕OO LOW
severity of chest pain (scale 1-5) - atenolol vs. amlodipine (follow-up 4 weeks; range of scores: -; better indicated by less)											
Lanza 1999[231] (c)	randomised trial (a)	serious (b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	10	10	-	MD 0.20 lower (1.17 lower to 0.77 higher)	⊕⊕OO LOW
quality of life (scale 0-100 mm) - atenolol vs. amlodipine (follow-up 4 weeks; range of scores: -; better indicated by less)											
Lanza 1999[231] (c)	randomised trial (a)	serious (b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	10	10	-	MD 8 higher (15.73 lower to 31.73 higher)	⊕⊕OO LOW

(a) Crossover design
(b) Bugiardini 1989[223] Lanza 1999 : Unclear randomisation and allocation concealment, small sample size
(c) Bugiardini 1989[223]: propanolol 120-160mg/day (optimal dose for each patient determined 2-3 weeks before the double blind study ; beta blockade occurred at 120mg a day in 6 patients and at 160mg in 10). Lanza 1999[225]: atenolol 100mg/day, amlodipine 10mg/day
(d) There was substantial heterogeneity (I^2=86%) indicating that these results must be carefully interpreted

Table 19.4: BBs vs. CCBs in patients with pressure-rate product variation <1050 for Cardiac Syndrome X

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	BBs	CCBs in patients with pressure-rate product variation <1050	Relative (95% CI)	Absolute	
exercise duration (sec) - acebutolol vs. verapamil in patients with pressure-rate product variation >1050 (follow-up 4 weeks; range of scores: -; better indicated by less)											
Romeo 1988[232] (c)	randomised trial (a)	serious (b)	no serious inconsistency	no serious indirectness	serious imprecision (d)	none	15	15	-	MD 44 lower (113.48 lower to 25.48 higher)	⊕⊕OO LOW

(a) Crossover design
(b) Romeo 1988[226]: Randomisation, allocation concealment and blinding not reported, small sample size
(c) Acebutolol 400mg a day, verapamil 80mg 4 times a day
(d) 95% CI includes no effect and the upper and lower CI crosses the MID.

Table 19.5: BBs vs. CCBs in patients with pressure-rate product variation >1050 for Cardiac Syndrome X

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	BBs	CCBs in patients with pressure-rate product variation >1050	Relative (95% CI)	Absolute	
exercise duration (sec) - acebutolol vs. verapamil in patients with pressure-rate product variation <1050 (follow-up 4 weeks; range of scores: -; better indicated by less)											
Romeo 1988[232] (c)	randomised trial (a)	serious (b)	no serious inconsistency	no serious indirectness	serious imprecision (d)	none	15	15	-	MD 0 higher (52.48 lower to 52.48 higher)	⊕⊕OO LOW

(a) Crossover design
(b) Romeo 1988[226] : Randomisation, allocation concealment and blinding not reported, small sample size
(c) Acebutolol 400mg a day, verapamil 80mg 4 times a day
(d) 95% CI includes no effect and the upper and lower CI crosses the MID.

Table 19.6: BBs vs. nitrates for Cardiac Syndrome X

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	BBs	Nitrates	Relative (95% CI)	Absolute	
Number of anginal episodes (per 4 weeks per patient) - atenolol vs. ISMN (follow-up 4 weeks; range of scores: -; better indicated by less)											
Lanza 1999[231] (c)	randomised trial (a)	serious (b)	no serious inconsistency	no serious indirectness	serious imprecision (d)	none	10	10	-	MD 9 lower (24.84 lower to 6.84 higher)	⊕⊕OO LOW
Chest pain episodes duration (min) - atenolol vs. ISMN (follow-up 4 weeks; range of scores: -; better indicated by less)											
Lanza 1999[231] (c)	randomised trial (a)	serious (b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	10	10	-	MD 3 higher (6.15 lower to 12.15 higher)	⊕⊕OO LOW
severity of chest pain (scale 1-5) - atenolol vs. ISMN (follow-up 4 weeks; range of scores: -; better indicated by less)											
Lanza 1999[231] (c)	randomised trial (a)	serious (b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	10	10	-	MD 0.2 higher (0.85 lower to 1.25 higher)	⊕⊕OO LOW
quality of life (scale 0-100 mm) - atenolol vs. ISMN (follow-up 4 weeks; range of scores: -; better indicated by less)											
Lanza 1999[231] (c)	randomised trial (a)	serious (b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	10	10	-	MD 29 higher (4.44 to 53.56 higher)	⊕⊕OO LOW

(a) Crossover design
(b) Lanza 1999[225]: Randomisation and allocation concealment unclear, small sample size
(c) Atenolol 100mg/day, ISMN 50mg/day
(d) 95% CI includes no effect and the upper and lower CI crosses the MID

Table 19.7: CCBs vs. nitrates for Cardiac Syndrome X

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CCBs	Nitrates	Relative (95% CI)	Absolute	
Number of anginal episodes (per 4 weeks per patient) - amlodipine vs. ISMN (follow-up 4 weeks; range of scores: -; better indicated by less)											
Lanza 1999[231] (c)	randomised trial (a)	serious (b)	no serious inconsistency	no serious indirectness	serious imprecision (d)	none	10	10	-	MD 2 lower (21.28 lower to 17.28 higher)	⊕⊕OO LOW
Chest pain episodes duration (min) - amlodipine vs. ISMN (follow-up 4 weeks; range of scores: -; better indicated by less)											
Lanza 1999[231] (c)	randomised trial (a)	serious (b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	10	10	-	MD 5 higher (6.39 lower to 16.39 higher)	⊕⊕OO LOW
severity of chest pain (scale 1-5) - amlodipine vs. ISMN (follow-up 4 weeks; range of scores: -; better indicated by less)											
Lanza 1999[231] (c)	randomised trial (a)	serious (b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	10	10	-	MD 0.4 higher (0.57 lower to 1.37 higher)	⊕⊕OO LOW
quality of life (scale 0-100 mm) - amlodipine vs. ISMN (follow-up 4 weeks; range of scores: -; better indicated by less)											
Lanza 1999[231] (c)	randomised trial (a)	serious (b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	10	10	-	MD 21 higher (1.81 lower to 43.81 higher)	⊕⊕OO LOW

(a) Crossover design
(b) Lanza 1999[225]: Randomisation and allocation concealment unclear, small sample size
(c) Amlodipine 10mg/day, ISMN 50mg/day
(d) 95% CI includes no effect and the upper and lower CI crosses the MID.

Table 19.8: Nicorandil vs. placebo for Cardiac Syndrome X

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Nicorandil	control	Relative (95% CI)	Absolute	
Time to 1mm ST-segment depression (sec) (follow-up 2 weeks; range of scores: -; better indicated by less)											
Chen 1997[233] (c)	randomised trial (a)	serious (b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	13	13	-	MD 69 higher (0.24 to 137.76 higher)	⊕⊕OO LOW
maximum ST-segment depression (mm) (follow-up 2 weeks; range of scores: -; better indicated by less)											
Chen 1997[233] (c)	randomised trial (a)	serious (b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	13	13	-	MD 0.4 lower (0.99 lower to 0.19 higher)	⊕⊕OO LOW
Total exercise duration (sec) (follow-up 2 weeks; range of scores: -; better indicated by less)											
Chen 1997[233] (c)	randomised trial (a)	serious (b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	13	13	-	MD 38 higher (16.85 lower to 92.85 higher)	⊕⊕OO LOW

(a) Crossover design
(b) Chen 1997[227]: Randomisation, allocation concealment and blinding unclear, small sample size
(c) Nicorandil 5mg 3 times a day

Table 19.9: Aminophylline vs. nitroglycerine for Cardiac Syndrome X

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Aminophylline	Nitroglycerine	Relative (95% CI)	Absolute	
Time to 1mm ST depression (follow-up 5min post nitroglycerin or 90min post aminophylline; range of scores: -; better indicated by less)											
Radice 1996[234] (c)	randomised trial (a)	serious (b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	20	-	MD 1.9 higher (0.88 to 2.92 higher)	⊕⊕OO LOW

(a) Crossover design
(b) Radice 1996[228] : Randomisation, allocation concealment and blinding unclear, small sample size
(c) Aminophylline 400mg or nitroglycerin (sublingual) 0.3mg administered once

19.2.2 Economic evidence

No economic studies were identified on this question.

19.2.3 Evidence statements

Clinical

BBs vs. placebo for cardiac syndrome X

Bugiardini 1989[229]: Evidence from one RCT shows that there were significantly lower number of ischemic episodes [MD -3.2 (-4.13 to -2.27)] and smaller ischemic duration (min) [MD -25 (-34.15 to -15.85)] in the BBs group compared to placebo group. [7-day follow-up].

CCBs vs. placebo for cardiac syndrome X

Bugiardini 1989[229]; Cannon 1985[230]: Evidence from two RCTs shows that there was no significant difference between CCBs and placebo for number of ischemic episodes [MD-0.6 (-1.81 to0.61)] and ischemic duration [MD 0.74 (-0.55 to 2.04)]. [follow-up 7-28 days]

Cannon 1985[230]: Evidence from one RCT shows that there was no significant difference between CCBs and placebo for consumption of nitroglycerin tablets [MD -18 (-41.74 to 5.74)] . Patients in the CCBs group had significantly less chest pain during exercise compared to those receiving placebo [RR 0.49 (0.0.28 to 0.89)]. [follow-up 28 days]

BBs vs. CCBs for cardiac syndrome X

Bugiardini 1989[229]; Lanza 1999[231]: Evidence from two RCTs shows that there was a significantly lower number of anginal episodes [MD-2.71 (-3.6 to -1.83)] and shorter chest pain episode duration(min) [MD -17.66 (-24.35 to -10.97)]in the BBs compared to CCBs group. [follow up 1-4 weeks]

Lanza 1999[231]: Evidence from one RCT shows that there was no significant difference in severity of chest pain [MD-0.2 (-1.17 to 0.77)] and quality of life [MD8 (-15.73 to 31.73)] between BBs and CCBs [follow up 4 weeks]

BBs vs. CCBs in patients with pressure-rate product variation <1050

Romeo 1988[232]: Evidence from one RCT shows that there was no significant difference between BBs and CCBs for exercise duration (sec) [MD -44 (-113.48 to 25.48)] in patients with pressure-rate product variation <1050 [follow up 4 weeks]

BBs vs. CCBs in patients with pressure-rate product variation >1050

Romeo 1988[232]: Evidence from one RCT shows that there was no significant difference between BBs and CCBs for exercise duration (sec) [MD 0 (-52.48 to 52.48)] in patients with pressure-rate product variation

>1050 [follow up 4 weeks]

BBs vs. nitrates for cardiac syndrome X

Lanza 1999[231]: Evidence from one RCT shows that there was no significant difference between BBs and nitrates for number of anginal episodes [MD -9 (-24.84 to 6.84)], chest pain duration (min) [MD 3 (-6.15 to 12.15)], severity of chest pain [MD0.2 (-0.85 to 1.25)]. Quality of life was significantly improved in the BBs group compared to the nitrates group [MD 29 (4.44 to 53.56)] [follow up 4weeks]

CCBs vs. nitrates for cardiac syndrome X

Lanza 1999[231]: Evidence from one RCT shows that there was no significant difference between CCBs and nitrates for number of anginal episodes [MD - (-21.28 to 17.28)], chest pain duration (min) [MD 5 (-6.39 to 16.39)], severity of chest pain [MD 0.4 (-0.57 to 1.37)] or quality of life [MD 21 (-1.81 to 43.81)] [follow up 4weeks]

Nicorandil vs. placebo for cardiac syndrome X

Chen 1997[233]: Evidence from one RCT shows that time to 1mm ST segment depression (sec) was significantly longer in the Nicorandil group compared to placebo [MD 69 (0.24 to 137.76)], and there was no significant difference between Nicorandil and placebo for maximum ST segment depression (mm) [MD -0.4 (-0.99 to 0.19)] and total exercise duration (sec) [MD38 (-16.85 to 92.85)]. [follow up 2 weeks]

Aminophylline vs. nitroglycerine for cardiac syndrome X

Radice 1996[234]: Evidence from one RCT shows that there was a significant increase in time to 1mm ST depression [MD 1.9 (0.88 to 2.92)] in the aminophylline group compared to the nitroglycerin group [follow up 5-90min after administration of drug]

Economic No economic evidence was found on this question.

19.2.4 Recommendations and link to evidence

Recommendation	**In people with angiographically normal coronary arteries and continuing anginal symptoms, consider a diagnosis of cardiac syndrome X.** **Continue drug treatment for stable angina only if it improves the symptoms of the person with suspected cardiac syndrome X.**
Relative values of different outcomes	The GDG were interested in evidence for short and long term outcomes for interventions in people with syndrome X

Trade off between clinical benefits and harms	The evidence available in this review only included evidence for limited outcomes over short periods of time. Longer term morbidity and mortality outcomes were not available. Evidence from placebo controlled trials indicated improvement of ischaemic episodes and duration over a short time period.
Economic considerations	No economic evidence was found on this question.
Quality of evidence	The evidence for available outcomes was of low quality.
Other considerations	Syndrome X is a diagnosis made following investigation with coronary angiography. Patients are therefore already likely to be taking or to have tried one or more standard anti-anginal drugs. The GDG made a consensus recommendation that patients should stay on anti-anginal drugs only if they obtain symptomatic benefit from the drugs. The evidence does not support use of standardanti-anginal drugs for longer term benefit.

19.3 Drugs for secondary prevention for people with syndrome X

The use of aspirin, statins and ACE inhibitors have resulted in significant benefits for many people with cardiac conditions. The GDG were interested in whether these drugs were beneficial to patients who do not have evidence of coronary artery disease but have angina type pain and evidence of ischaemia. Studies were found examining the benefit of statins and a combination of statins and ace inhibitors.

19.3.1 Clinical evidence

The “Review Protocol” for this topic can be found in Appendix C, the “Search Strategies” in Appendix D, the “List of Included and Excluded Studies” in Appendix E1, the “Clinical Evidence Tables” in Appendix E2, and the “Forest Plots” in Appendix F

Table 19.10: Statins vs. placebo for Cardiac Syndrome X

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Statins	Placebo	Relative (95% CI)	Absolute	
Total exercise time (Sec) (follow-up 3 months; range of scores: -; better indicated by more)											
Kayikcioglu 2003[235] (d)	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	19	19	-	MD 78 higher (11.17 lower to 167.17 higher)	⊕⊕⊕O MODERATE
Time to 1mm ST depression (Sec) (follow-up 3 months; range of scores: -; better indicated by more)											
Kayikcioglu 2003[235]; Fabian 2004[236] (c)	randomised trial	serious (b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	39	39	-	MD 48.36 lower (60.71 to 36.02 lower)	⊕⊕⊕O MODERATE
Hospitalisation for worsening of angina (follow-up 3 months)											
Kayikcioglu 2003[235]	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/19 (5.3%)	1/19 (5.3%)	RR 1 (0.07 to 14.85)	0 fewer per 1000 (from 49 fewer to 734 more)	⊕⊕⊕O MODERATE

(a) Kayikcioglu 2003[229]: Single blind, randomised, baseline comparisons made. Allocation concealment not reported, 0.5% drop out, intention to treat analysis not reported.
(b) Fabian 2004[230]: Randomised, baseline comparisons made. Allocation concealment not reported, blinding not reported, drop out rate not reported, intention to treat analysis not reported. Kayikcioglu 2003[229]: Single blind, randomised, baseline comparisons made. Allocation concealment not reported, 0.5% drop out, intention to treat analysis not reported.
(c) Drug dosage: Fabian 2004[230] - Simvastatin 20 mg/day
(d) Drug dosage: Pravastatin 40 mg/day.

Table 19.11: Angiotensin-Converting Enzyme Inhibitors + statins vs. placebo for Cardiac Syndrome X

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Angiotensin-Converting Enzyme Inhibitors and statins	placebo	Relative (95% CI)	Absolute	
Seattle Angina Questionnaire angina frequency score (follow-up 6 months; range of scores: -; better indicated by less)											
Pizzi 2004[237] (a)	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	22	23	-	MD 19.7 higher (12.51 to 26.89 higher)	⊕⊕⊕⊕ HIGH
Seattle Angina Questionnaire Quality of life score (follow-up 6 months; range of scores: -; better indicated by less)											
Pizzi 2004[237] (a)	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	22	23	-	MD 24.6 higher (18.38 to 30.82 higher)	⊕⊕⊕⊕ HIGH
Seattle Angina Questionnaire summary score (follow-up 6 months; range of scores: -; better indicated by less)											
Pizzi 2004[237] (a)	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	22	23	-	MD 20.9 higher (15.5 to 26.3 higher)	⊕⊕⊕⊕ HIGH
Peak exercise time (s) (follow-up 6 months; range of scores: -; better indicated by less)											
Pizzi 2004[237] (a)	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	22	23	-	MD 67.2 higher (19.27 to 115.13 higher)	⊕⊕⊕⊕ HIGH
ST depression (mV) (follow-up 6 months; range of scores: -; better indicated by less)											
Pizzi 2004[237] (a)	randomised trial	no serious limitations				none	22	23	-	MD 0.09 lower (0.44 lower to 0.26 higher)	⊕⊕⊕⊕ HIGH
Flow-mediated Dilation of brachial artery (%) (follow-up 6 months; range of scores: -; better indicated by less)											
Pizzi 2004[237] (a)	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	22	23	-	MD 1.9 higher (1.04 to 2.76 higher)	⊕⊕⊕⊕ HIGH

(a) Drug dosage: ramipril (10mg/d) and atorvastatin (40mg/d)

19.3.2 Economic evidence

No economic studies were identified on this question.

19.3.3 Evidence statements

Clinical	<u>**Statins for cardiac syndrome X**</u> **Kayikcioglu 2003[235]; Fabian 2004[236]:** Evidence from 2 underpowered RCTs shows that time to 1mm ST depression (sec) was significantly longer in the statins group compared to placebo [MD -48.36 (-60.71 to -36.02). [Follow-up 3 months] **Kayikcioglu 2003[235]:** Evidence from one underpowered RCT shows that there was no significant difference between Statins and placebo for total exercise time (sec) [MD 78 (-11.17 to 167.17)] and hospitalisation for worsening of angina [RR 1 (0.07 to 14.85)] [Follow-up 3 months]. <u>**ACE Inhibitors + Statins for cardiac syndrome X**</u> **Pizzi 2004[237]:** Evidence from one RCT shows that angina frequency [MD 19.70 [12.51, 26.89]], Quality of Life [MD 24.60 [18.38, 30.82]], peak exercise time [MD 67.20 [19.27, 115.13]] and flow mediated dilation of brachial artery [MD1.90 [1.04, 2.76]] were significantly improved in the ACE inhibitors + statins group compared to placebo. There was no significant difference between groups for ST segment depression [MD -0.09 [-0.44 to 0.26]]. [follow up 6 months]
Economic	No economic evidence was found on this question.

19.3.4 Recommendations and link to evidence

Recommendation	**Do not routinely offer drugs for the secondary prevention of cardiovascular disease to people with suspected cardiac syndrome X.**
Relative values of different outcomes	The GDG were interested in morbidity and mortality outcomes for interventions for people with syndrome X. They were aware however that this evidence was unlikely to be available and accepted evidence on short term outcomes.
Trade off between clinical benefits and harms	

Economic considerations	Secondary prevention was not shown to add any benefits in people with suspected cardiac syndrome X. Therefore it is unlikely that this therapy is cost-effective.
Quality of evidence	
Other considerations	No evidence was found examining the benefit of aspirin or ACE inhibitors in people with syndrome X. The GDG considered that given the lack of evidence and potential risks and cost of using these drugs they should not be offered to people with syndrome X. The study outcome available for the comparison of statins versus placebo was ECG changes only and the GDG did not consider this adequate evidence to recommend use of statins. Quality of Life and angina score outcomes were available for combination of statin and ACE inhibitor versus placebo but the study was small.

19.4 Clinical/cost-effectiveness and safety of non-pharmacological treatments for syndrome X

19.4.1 Clinical Evidence

The “Review Protocol” for this topic can be found in Appendix C, the “Search Strategies” in Appendix D, the “List of Included and Excluded Studies” in Appendix E1, the “Clinical Evidence Tables” in Appendix E2, and the “Forest Plots” in Appendix F.

Table 19.12: Exercise programme + symptoms monitoring vs. symptoms monitoring for Cardiac Syndrome X

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Cardiac rehabilitation exercise programme + symptoms monitoring	symptoms monitoring	Relative (95% CI)	Absolute	
HADS total score (follow-up 8 weeks; range of scores: -; better indicated by less)											
Asbury 2008[238] (b)	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	32	32	-	MD 1.4 higher (1.14 lower to 3.94 higher)	⊕⊕⊕O MODERATE
SF36 physical functioning (follow-up 8 weeks; range of scores: -; better indicated by more)											
Asbury 2008[238]	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	32	32	-	MD 1.8 higher (8.48 lower to 12.08 higher)	⊕⊕⊕O MODERATE
SF-36 pain (follow-up 8 weeks; range of scores: -; better indicated by more)											
Asbury 2008[238]	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	32	32	-	MD 1.3 higher (9.15 lower to 11.75 higher)	⊕⊕⊕O MODERATE
SF-36 general health (follow-up 8 weeks; range of scores: -; better indicated by more)											
Asbury 2008[238]	randomised trial	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	32	32	-	MD 3.9 higher (5.86 lower to 13.66 higher)	⊕⊕⊕O MODERATE
Symptom frequency (better indicated by lower values)											
Asbury 2008[238]	randomised trials	serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	32	32	-	MD 2.6 lower (4.1 to 1.1 lower)	⊕⊕⊕O MODERATE

(a) Small pilot study
(b) Cardiac rehabilitation: 8-week group-based phase III CR exercise programme: outpatient cardiovascular exercise programme designed to improve aerobic conditioning, functional capacity, muscular strength, endurance and flexibility. Each class was approx 80minutes long

Table 19.3: Physical training vs. normal activity for Cardiac Syndrome X

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Cardiac rehabilitation physical training	normal activity	Relative (95% CI)	Absolute	
Distance walked (m) (follow-up 8 weeks; range of scores: -; better indicated by more)											
Tyni-Lenne 2002[239] (c)	randomised trial	very serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	7	7	-	MD 42 higher (7.79 lower to 91.79 higher)	⊕⊕OO LOW
peak heart rate (beats/min) (follow-up 8 weeks; range of scores: -; better indicated by less)											
Tyni-Lenne 2002[239]	randomised trial	very serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	7	7	-	MD 4 lower (18.61 lower to 10.61 higher)	⊕⊕OO LOW
exertion (Borg RPE) (follow-up 8 weeks; range of scores: -; better indicated by less)											
Tyni-Lenne 2002[239]	randomised trial	very serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	7	7	-	MD 1 lower (3.67 lower to 1.67 higher)	⊕⊕OO LOW
pain onset (min) after exercise (follow-up 8 weeks; range of scores: -; better indicated by more)											
Eriksson 2000[240]	randomised trial	very serious (b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	7	10	-	MD 3 higher (2.03 to 3.97 higher)	⊕⊕OO LOW
max pain (Borg CR-10 after exercise) (follow-up 8 weeks; range of scores: -; better indicated by less)											
Eriksson 2000[240]	randomised trial	very serious (b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	7	10	-	MD 1 lower (1.97 to 0.03 lower)	⊕⊕OO LOW

(a) Tyni-Lenne 2002[239]: Very small sample size, unclear randomisation and allocation concealment methods
(b) Eriksson 2000[240]: Very small sample size, no description of randomisation, allocation concealment or blinding
(c) Physical programme: outpatient group-based under supervision by physical therapist. Endurance training on cycle ergometer 3 times a week for 8 weeks at the intensity of 50% of the peak work rate achieved in VO2 max test. The training was 30 minutes.

Table 19.14: Physical training vs. relaxation therapy for Cardiac Syndrome X

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	cardiac rehabilitation physical training	relaxation therapy	Relative (95% CI)	Absolute	
Distance walked (m) (follow-up 8 weeks; range of scores: -; better indicated by less)											
Tyni-Lenne 2002[239]	randomised trial (b)	very serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	7	7	-	MD 22 higher (28.3 lower to 72.3 higher)	⊕⊕OO LOW
peak heart rate (beats/min) (follow-up 8 weeks; range of scores: -; better indicated by less)											
Tyni-Lenne 2002[239]	randomised trial	very serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	7	7	-	MD 11 lower (28.29 lower to 6.29 higher)	⊕⊕OO LOW
exertion (Borg RPE) (follow-up 8 weeks; range of scores: -; better indicated by less)											
Tyni-Lenne 2002[239]	randomised trial	very serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	7	7	-	MD 1 lower (4.14 lower to 2.14 higher)	⊕⊕OO LOW

(a) Tyni-Lenne 2002[239]: Very small sample size, unclear randomisation and allocation concealment methods

(b) Interventions in the study: physical programme: outpatient group-based under supervision by physical therapist. Endurance training on cycle ergometer 3 times a week for 8 weeks at the intensity of 50% of the peak work rate achieved in VO2 max test. The training was 30minutes. Relaxation training consisted of a modified Jacobson approach and autogenous training for one hour at a time.

Table 19.15: Relaxation therapy vs. normal activity for Cardiac Syndrome X

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	cardiac rehabilitation relaxation therapy	normal activity	Relative (95% CI)	Absolute	
Distance walked (m) (follow-up 8 weeks; range of scores: -; better indicated by less)											
Tyni-Lenne 2002[239] (b)	randomised trial	very serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	7	7	-	MD 20 higher (28.72 lower to 68.72 higher)	⊕⊕OO LOW
peak heart rate (beats/min) (follow-up 8 weeks; range of scores: -; better indicated by less)											
Tyni-Lenne 2002[239]	randomised trial	very serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	7	7	-	MD 7 higher (6.98 lower to 20.98 higher)	⊕⊕OO LOW
exertion (Borg RPE) (follow-up 8 weeks; range of scores: -; better indicated by less)											
Tyni-Lenne 2002[239]	randomised trial	very serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	7	7	-	MD 0 higher (2.67 lower to 2.67 higher)	⊕⊕OO LOW

(a) Tyni-Lenne 2002[239]: Very small sample size, unclear randomisation and allocation concealment methods
(b) Relaxation training consisted of a modified Jacobson approach and autogenous training for one hour at a time

Table 19.16: Exercise + relaxation training vs. exercise training for Cardiac Syndrome X

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	cardiac rehabilitation exercise + relaxation training	exercise training	Relative (95% CI)	Absolute	
pain onset after exercise (min) (follow-up 8 weeks; range of scores: -; better indicated by more)											
Eriksson 2000[240] (b)	randomised trial	very serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	7	10	-	MD 0 higher (2.34 lower to 2.34 higher)	⊕⊕OO LOW
max pain (Borg CR-10) after exercise (follow-up 8 weeks; range of scores: -; better indicated by less)											
Eriksson 2000[240]	randomised trial	very serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	7	10	-	MD 1 higher (0.05 lower to 2.05 higher)	⊕⊕OO LOW

(a) Eriksson 2000[240] : Very small sample size, no description of randomisation, allocation concealment or blinding
(b) Outpatient activity in outpatient setting supervised by physical therapist. Body awareness training consisted of body and mind relaxation performed twice a week for 8 weeks. Exercise training was performed on cycle ergometer 3 times a week for 8 weeks. Training was 30minutes and intensity was 50% of peak work rate determined at onset of study

Table 19.17: Exercise + relaxation training vs. normal activity for Cardiac Syndrome X

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	cardiac rehabilitation exercise + relaxation training	normal activity	Relative (95% CI)	Absolute	
pain onset after exercise (min) (follow-up 8 weeks; range of scores: -; better indicated by more)											
Eriksson 2000[240] (b)	randomised trial	very serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	7	7	-	MD 3 higher (0.69 to 5.31 higher)	⊕⊕OO LOW
max pain (Borg CR-10) after exercise (follow-up 8 weeks; range of scores: -; better indicated by less)											
Eriksson 2000[240]	randomised trial	very serious (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	7	7	-	MD 0 higher (0.97 lower to 0.97 higher)	⊕⊕OO LOW

(a) Eriksson 2000[240] : Very small sample size, no description of randomisation, allocation concealment or blinding
(b) Outpatient activity in outpatient setting supervised by physical therapist. Body awareness training consisted of body and mind relaxation performed twice a week for 8 weeks. Exercise training was performed on cycle ergometer 3 times a week for 8 weeks. Training was 30minutes and intensity was 50% of peak work rate determined at onset of study

Additional data:

Psychological treatment vs. control for Cardiac syndrome X:

Potts 1999[241]

The data from the study could not be analysed as SD for the eman values were not reported.

N=60 (n=34 immediate treatment and n=26 waiting control)

Intervention: Psychological treatment package consisting of education, relaxation, breathing training, graded exposure to activity and exercise, and the use of thought diaries to record and challenging automatic thoughts about heart disease.

Groups met weekly for 4 weeks, then every 2 weeks for a further 4 weeks. Each session lasted 2 hours, with a short break. Subjects were asked to practice various exercises at home between sessions, and to report their progress at the beginning of subsequent sessions. Treatment was broadly behavioural in orientation, based on a manual developed via an initial pilot group, and was supplemented by written material given to subjects at each session.

Control group was assigned to a waiting period before being reassessed and then entering treatment.

Results:

Treatment was associated with a significantly greater reduction in chest pain episode frequency (-3 vs. 0; p=0.01), than waiting control group. There was no significant difference between the treatment and control groups in changes in chest pain severity (-5.9 vs. 0.8; NS) or duration (min) (-1.6 vs. -0.5; NS,) although there were non significant trends to improvement in the treatment group, and the range of variation was very wide. Treatment was also associated with significant reductions in both the anxiety (-1.5 vs.0; p=0.05) and depression (-2 vs. 0; p=0.05) subscales of the HAD*, the total disability score of the SIP** (6.5 vs. 1.4; p=0.05), and two of the 4 subscales of the NHP *** (pain: 5 vs.0; p=0.05 and energy: -24 vs.0; p=0.01). Exercise duration (min) improved significantly. (1.3 vs. 0.1; p=0.5).

Note: All above values are medians, negative values indicating reductions.

*Hospital anxiety Depression scale (HAD)-A 14 item inventory covering non somatic symptoms of anxiety and depression, intended for use in medical populations. It yields separate scores for anxiety and depression, with cut offs indicating caseness above 11.

**Sickness Impact Profile (SIP) – A 136 item inventory yielding measures of the impact of illness on various domains of everyday life, as well as an overall disability score.

***Nottingham Health Profile (NHP) – A 24 item inventory quantifying the impairments due to illness in six areas.

19.4.2 Economic evidence

No economic studies were found on this question.

19.4.3 Evidence statements

Clinical

Exercise programme + symptoms monitoring vs. symptoms monitoring for cardiac syndrome X

Asbury 2008[238]: Evidence from one RCT shows that there was significantly lower symptom frequency in the exercise programme +symptom monitoring group compared to control [MD -2.6 (-4.1 to -1.1)]. No significant difference was found for the other outcomes (HADS total score, SF-36 physical function, SF-36 pain, SF-36 general health). [follow-up 8 weeks]

Physical training vs. normal activity for cardiac syndrome X

Tyni-Lenne 2002[239]; Eriksson 2000[240]: Evidence from two RCT shows that max pain after exercise [MD-1.00 [-1.97, -0.03]] and pain onset after exercise [MD 3.00 [2.03 to 3.97]]) was significantly reduced in the physical training group compared to the normal activity group. There was no significant difference between physical training and normal activity for all other outcomes (distance walked [MD [42.00 [-7.79 to 91.79]], peak heart rate [MD -4.00 [-18.61to10.61]], exertion [MD -1.00 [-3.67 to 1.67]]. [follow-up 8 weeks]

Physical training vs. relaxation therapy for cardiac syndrome X

Tyni-Lenne 2002[239]: Evidence from one RCT shows that there was no significant difference between physical training and relaxation therapy for distance walked [MD 22 (-28.3 to 72.3)], peak heart rate [MD -11 (-28.29 to 6.29)] and exertion [MD -1 (-4.14 to 2.14)] [follow up 8 weeks]

Relaxation therapy vs. normal activity for cardiac syndrome X

Tyni-Lenne 2002[239]: Evidence from one RCT shows that there was no significant difference between relaxation therapy and normal activity for distance walked [MD 20 (-28.72 to 68.72)] , peak heart rate [MD 7 (-6.98 to 20.98)] and exertion [MD 0 (-2.67 to 2.67)] [follow up 8 weeks]

Exercise +relaxation training vs. exercise training for cardiac syndrome X

Eriksson 2000[240]: Evidence from one RCT shows that there was no significant difference between exercise +relaxation training and exercise training for pain onset after exercise [MD 0.00 (-2.34 to 2.34] and max pain after exercise [MD 1 (-0.05 to 2.05)] [follow up 8 weeks]

Exercise +relaxation training vs. normal activity for cardiac syndrome X

Eriksson 2000[240]: Evidence from one RCT shows that that there was no significant difference between exercise +relaxation training and for normal activity pain onset after exercise [MD 3 (0.69 to 5.31)] and max pain after exercise [MD 0 (-0.97 to 0.97) were significantly longer in the [follow up 8 weeks]

Economic No economic evidence was found on this question.

19.4.4 Recommendations and link to evidence

Recommendation	No recommendation was made
Relative values of different outcomes	When considering the value of rehabilitation for people with syndrome X, the GDG were interested in improvements in quality of life as well as longer term outcomes such as angina frequency and morbidity and mortality.
Trade off between clinical benefits and harms	
Economic considerations	Rehabilitation is associated with important costs. The clinical evidence review did not indicate effectiveness of programmes of rehabilitation, which are therefore not likely to be cost effective.
Quality of evidence	The GDG considered that the available evidence mainly assessed exercise and exercise programmes for people with syndrome X, and the evidence did not address the benefit of comprehensive programmes of cardiac rehabilitation. The quality of evidence available was low.
Other considerations	The GDG did not make a recommendation about cardiac rehabilitation for people with syndrome X. The quality of evidence was low but one moderate quality evidence study did suggest that exercise was beneficial but the review did not support any particular exercise programme over normal activity. The GDG did not consider that exercise was harmful to people with syndrome X and that it was important people with syndrome X are given positive encouragement to take part in exercise and to be as active as possible. The study by Potts 1999[241] reported only mean data but suggested that people with syndrome X might benefit from

programmes which include attention to beliefs about angina. The GDG considered that people with syndrome X would be similar to those with stable angina in their needs for and response to appropriate information and support tailored to their individual needs.

19.5 Stress echocardiography in people with cardiac syndrome X

19.5.1 Clinical question

In adults with cardiac Syndrome X (i.e. those with chest pain and normal coronary arteries) what is the incremental value/effectiveness of functional tests for prognostic risk stratification in prediction of adverse cardiac outcomes?

19.5.2 Clinical evidence

The "Review Protocol" for this topic can be found in Appendix C, the "Search Strategies" in Appendix D, the "List of Included and Excluded Studies" in Appendix E1, and the "Clinical Evidence Tables" in Appendix E2.

Bigi 2002[189] (N=125) assessed the incremental prognostic value of dobutamine and dipyridamole stress echocardiography in patients with known or suspected coronary artery disease.

The outcome events were cardiac death, non fatal infarction, and unstable angina assessed at a mean follow-up of 36 months (range 6 to 80).

Target events occurred in 9 patients: 2 cardiac deaths, 5 non fatal MI, and 2 hospitalisations for unstable angina. Six of the 9 patients with cardiac events had positive stress echocardiography.

Hypertension, positive stress echocardiography, and peak wall motion score index were multivariate predictors of outcome, but stress echocardiography provided an 87.5% increase in the global chi-square ($p<0.001$). The event free survival of patients with positive stress echocardiography was significantly lower compared with those with negative test (Hazard ratio 4.7 95% CI 1.3 to 47)

Table 19.18: Bigi 2002[189], Multivariate predictors of outcome

Variables	Chi-square	Odds ratio	95% CI	P-value
Clinical				
Hypertension	5.7	13	1.6 to 105	0.01
Echocardiographic				
Positive SE	3.8	3.6	1to 14	0.05
Peak WMSI	8.1	5.0	1.6 to 15	0.004

Summary: One low quality study showed that **stress echocardiography** offered incremental prognostic value in prediction of adverse cardiac outcomes (cardiac death, non fatal infarction or unstable angina) in people with chest pain and normal or slightly narrowed coronary arteries. The results should be considered with caution as the study had very few events, small sample size, and a short follow-up period.

19.5.3 Economic evidence

No relevant studies were found. Studies reporting the cost per case detected were not included as this question was addressed in the Chest Pain Guideline (CG95).

We looked for the costs of the individual tests from UK sources. We found that the unit cost of stress echocardiography is £435[190].

19.5.4 Evidence statements

Clinical	<u>**Stress echocardiography**</u> **Bigi 2002[189]:** Evidence from one study shows that stress echocardiography offers incremental prognostic information in prediction of cardiac outcomes (cardiac death, non fatal infarction or unstable angina) in patients with chest pain and normal or slightly narrowed coronary arteries. [Mean follow-up 36 months (range 6 to 80)].
Economic	No economic evidence was found on this question. A simple cost analysis showed that stress echocardiography has a cost of £435 per test.

19.5.5 Recommendations and link to evidence

Recommendation	No recommendation was made
Relative values of different outcomes	
Trade off between clinical benefits and harms	
Economic considerations	No health economic evidence was available but the cost of testing is significant.
Quality of evidence	One low quality study was found.
Other considerations	The GDG agreed not to make a recommendation. The care of people with cardiac syndrome X is difficult. The diagnosis is made after angiography. The evidence does not support routine use of stress ECHO but the GDG recognized that further investigation may have a role in individual patients.

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