ClinicalEvidence

Angina (chronic stable)

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ABSTRACT

INTRODUCTION: Stable angina is usually caused by coronary atherosclerosis, and affects up to 16% of men and 10% of women aged 65–74 years in the UK. Risk factors include hypertension, elevated serum cholesterol levels, smoking, physical inactivity, and overweight. People with angina are at increased risk of other cardiovascular events and mortality compared with people without angina. Among people not thought to need coronary artery revascularisation, annual mortality is 1–2% and the annual non-fatal myocardial infarction (MI) rate is 2–3%. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are effects of long-term drug treatment for stable angina? We searched: Medline, Embase, The Cochrane Library, and other important databases up to June 2007 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found nine systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the long-term effectiveness and safety of the following interventions: beta-blockers, calcium channel blockers, long-acting nitrates, potassium channel openers, combinations of these anti-anginal drug treatments and the use of these anti-anginal drug treatment as an adjunct to existing therapies.

QUESTIONS

INTERVENTIONS

SINGLE-DRUG TREATMENT

Likely to be beneficial

COMBINATION DRUG TREATMENT

Likely to be beneficial

ADJUNCTIVE DRUG TREATMENT

Likely to be beneficial

Unknown effectiveness

Covered elsewhere in Clinical Evidence

Secondary prevention of ischaemic cardiac events.

To be covered in future updates

Ivabradine

Ranolazine

Trimetazidine

Statins

Non-drug interventions

Refractory angina

Footnote

*Based on consensus.

Key points

- Stable angina is a sensation of discomfort or pain in the chest, arm, or jaw brought on predictably by factors that increase myocardial oxygen demand, such as exertion, and relieved by rest or nitroglycerin.

  Stable angina is usually caused by coronary atherosclerosis, and affects up to 16% of men and 10% of women aged 65–74 years in the UK. Risk factors include hypertension, elevated serum cholesterol levels, smoking, physical inactivity, and overweight.

  People with angina are at increased risk of other cardiovascular events and mortality compared with people without angina.

Among people not thought to need coronary artery revascularisation, annual mortality is 1–2% and annual non-fatal MI rates are 2–3%.

We found no long-term, adequately powered RCTs of anti-anginal drugs versus placebo or comparing the use of a single anti-anginal drug versus combinations of anti-anginal drug classes. There is a consensus that monotherapy with beta-blockers, calcium channel blockers, nitrates, and potassium channel openers are effective for treating the symptoms of stable angina in the long term, although we found few studies to confirm this. There is also consensus that the concurrent use of two of these classes of drug has an additional beneficial effect on anginal symptoms and quality of life. It has not been established that this approach reduces cardiovascular events.

Monotherapy with beta-blockers or calcium channel blockers seems equally effective at reducing angina attacks, and they are equally well tolerated in the long term.

Adding a calcium channel blocker to existing anti-anginal drug treatments slightly reduces the need for coronary artery surgery, but has no effect on other cardiovascular events.

Monotherapy with nitrates may be as effective as monotherapy with calcium channel blockers at reducing angina attacks and improving quality of life.

We found no RCTs on the effects of long-term monotherapy with potassium channel openers in people with stable angina, but a large RCT of a potassium channel opener as an adjunct to existing anti-anginal drug treatments found a reduction the number of cardiovascular events compared with placebo.

Clinical context

DEFINITION

Angina pectoris, often simply known as angina, is a clinical syndrome characterised by discomfort in the chest, shoulder, back, arm, or jaw. [1] Angina is usually caused by coronary artery atherosclerotic disease. Rarer causes include valvular heart disease, hypertrophic cardiomyopathy, uncontrolled hypertension, or vasospasm or endothelial dysfunction not related to atherosclerosis. The differential diagnosis of angina includes non-cardiac conditions affecting the chest wall, oesophagus, and lungs. Angina may be classified as stable or unstable. **Stable angina** is defined as regular or predictable angina symptoms that have been occurring for over 2 months. Symptoms are transient and typically provoked by exertion, and alleviated by rest or nitroglycerin. Other precipitants include cold weather, eating, or emotional distress. This review deals specifically with stable angina caused by coronary artery atherosclerotic disease. For management of **unstable angina**, see separate review on acute coronary syndromes.

INCIDENCE/ PREVALENCE

The prevalence of stable angina remains unclear. [1] [2] Epidemiological studies in the UK estimate that 6–16% of men and 3–10% of women aged 65–74 years have experienced angina. [3] [4] [5] Annually, about 1% of the population visit their general practitioner with symptoms of angina, [4] and 23,000 people with new anginal symptoms present to their general practitioner each year in the UK. [6] These studies did not distinguish between stable and unstable angina. [3] [4] [5] [6]

AETIOLOGY/ RISK FACTORS

Stable angina resulting from coronary artery disease is characterised by focal atherosclerotic plaques in the intimal layer of the epicardial coronary artery. The plaques encroach on the coronary lumen and may limit blood flow to the myocardium, especially during periods of increased myocardial oxygen demand. The major risk factors that lead to the development of stable angina are similar to those that predispose to CHD. These risk factors include increasing age, male sex, overweight, hypertension, elevated serum cholesterol level, smoking, and relative physical inactivity. [7]

PROGNOSIS

Stable angina is a marker of underlying CHD, which accounts for 1 in 4 deaths in the UK. [8] People with angina are 2–5 times more likely to develop other manifestations of CHD than people who do not have angina. [7] [9] One population-based study (7100 men aged 51–59 years at entry) found that people with angina had higher mortality than people with no history of coronary artery disease at baseline (16-year survival rate: 53% with angina *v* 72% without coronary artery disease *v* 34% with a history of MI). [10] Clinical trials in people with stable angina have tended to recruit participants who were not felt to be in need of coronary revascularisation, and prognosis is better in these people, with an annual mortality of 1–2%, and an annual rate of non-fatal MI of 2–3%. [11] [12] [13] [14] Features that indicate a poorer prognosis include: more-severe symptoms, male sex, [15] abnormal resting ECG [16] (present in about 50% of people with angina), [17] previous MI, [10] [18] left ventricular dysfunction, [19] easily provoked or widespread coronary ischaemia on stress testing (present in about a third of people referred to hospital with stable angina), and significant stenosis of all three major coronary arteries or the left main coronary artery. [6] [19] In addition, the standard coronary risk factors continue to exert a detrimental and additive effect on prognosis in people with stable angina. [9] [20] [21] Control of these risk factors is dealt with in the *Clinical Evidence* review on secondary prevention of ischaemic cardiac events.

AIMS OF INTERVENTION To prevent death and future cardiovascular events, and to improve symptoms, exercise capacity, and quality of life.

OUTCOMES **Primary outcomes:** mortality, non-fatal MI, and unstable angina. **Secondary outcomes:** anti-anginal efficacy (as determined by symptom frequency and total exercise time on treadmill testing), quality of life (assessed by questionnaire), and adverse effects of treatment.

METHODS *BMJ Clinical Evidence* search and appraisal June 2007. The following databases were used to identify studies for this systematic review: Medline 1966 to June 2007, Embase 1980 to June 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 2. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded where possible, and containing more than 50 people, of whom more than 80% were followed up for a minimum of 6 months. We excluded all studies described as "open", "open label", or not blinded. We included RCTs that compared single-drug anti-anginal treatment versus placebo or another single-drug anti-anginal treatment, single drug-class treatment versus dual drug-class treatment, and single drug-class treatment used as an adjunct to existing treatment versus existing treatment alone in people with stable angina believed to be caused by coronary artery atherosclerotic disease. The anti-anginal drug classes covered by the search were beta-blockers, calcium channel blockers, long-acting nitrate preparations, and potassium channel openers. Systematic reviews and RCTs that cover secondary prevention in mixed manifestations of atherosclerotic coronary artery disease are reported in the review on secondary prevention of ischaemic cardiac events. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA, and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 14).

QUESTION What are effects of long-term single-drug treatment for stable angina?

OPTION BETA-BLOCKERS AS MONOTHERAPY

Symptom improvement
Beta-blockers compared with placebo We don't know whether propranolol is more effective at reducing the frequency of angina attacks, at reducing serious cardiac events (cardiac death, MI, or angina deterioration), or at improving the duration of exercise at 6 months (very low-quality evidence).

Beta-blockers compared with calcium channel blockers We don't know whether beta-blockers are more effective at reducing the frequency of angina attacks or improving exercise duration at 6 months, at improving exercise capacity at 32 weeks, or at improving a composite outcome of non-fatal cardiovascular events or mortality at 3.4 years, or the combined outcome of unstable angina, MI, or mortality, at 2 years (very low-quality evidence).

Mortality
Beta-blockers compared with calcium channel blockers Metoprolol and verapamil seem equally effective at reducing mortality after a median follow up of 3.4 years (high-quality evidence).

Quality of life
Beta-blockers compared with calcium channel blockers Metoprolol and verapamil seem equally effective at improving quality-of-life scores (moderate-quality evidence).

Note
There is consensus that beta-blockers are effective for treating the symptoms of stable angina.

For GRADE evaluation of interventions for angina (stable), see table, p 14 .

Benefits: We found one systematic review (search date 1996). [22]

Beta-blockers versus placebo:
The review [22] identified one RCT [23] (191 people aged less than 70 years with abnormal exercise stress test or previous MI). It compared three treatments: beta-blockers (propranolol; 78 people), calcium channel blockers (bepridil; 78 people), and placebo (35 people). It found no significant

difference between propranolol and placebo in the reduction in frequency of angina attacks, or improvement in duration of exercise at 6 months (mean reduction in weekly angina attacks from baseline: 71% with propranolol *v* 77% with placebo; P reported as not significant; increase in exercise duration from baseline: 24% with propranolol *v* 8% with placebo; P = 0.09). Serious cardiac events (cardiac death, MI, or angina deterioration) were more common with propranolol than with placebo, but the significance of this difference was not reported (AR for serious cardiac events: 8/78 [10%] with propranolol *v* 2/35 [6%] with placebo; P value not reported).

Beta-blockers versus calcium channel blockers:
The systematic review [22] identified five RCTs that met our inclusion criteria (1818 people). The first RCT (191 people ages less than 70 years, with abnormal exercise stress test or previous MI), [23] compared three treatments: beta-blockers (propranolol 60–240 mg/day; 78 people), calcium channel blockers (bepridil 100–400 mg/day; 78 people), and placebo (35 people). It found no significant difference between propranolol and bepridil in the reduction in the frequency of angina attacks or improvement in duration of exercise at 6 months (reduction in weekly angina attacks from baseline: 69% with bepridil *v* 71% with propranolol; P reported as not significant; increase in exercise duration from baseline: 24% with propranolol *v* 31% with bepridil; P = 0.26). The incidence of serious cardiac events (cardiac death, MI, or angina deterioration) was similar with propranolol and bepridil (AR for serious cardiac events: 8/78 [10%] with propranolol *v* 6/78 [8%] for bepridil; P value not reported). The second RCT (80 people aged up to 80 years with abnormal exercise stress test) [24] compared a beta-blocker (nadolol 40–160 mg once daily) versus a calcium channel blocker (amlodipine 2.5–10 mg once daily) in people with stable angina. It found no significant difference in the reduction in frequency of angina attacks or change in exercise duration at 6 months (change in median number of angina attacks/week from baseline to 6 months: from 3.0 to 0.3 with nadolol *v* from 4.0 to 0.3 with amlodipine; P reported as not significant; change in total exercise treadmill time from baseline to 6 months: 490 seconds to 475 seconds [–3%] with nadolol *v* 454 seconds to 462 seconds [+2%] with amlodipine; P reported as not significant). The third RCT (56 people aged less than 80 years with abnormal exercise stress test) compared a beta-blocker (metoprolol 100 mg twice daily; 26 people) with a calcium channel blocker (diltiazem 120 mg twice daily; 30 people) in people with stable angina. [25] It found no significant difference between groups at 32 weeks in the change in exercise capacity (39 people evaluable: 19 people with metoprolol *v* 20 people with diltiazem; analysis not by intention to treat; mean change in duration of exercise from baseline to 32 weeks: +0.2 minutes with metoprolol *v* +0.3 minutes with diltiazem; P reported as not significant). The effect of treatments on the frequency of angina symptoms was not reported. The fourth RCT (809 people aged less than 70 years selected on the basis of typical clinical history and response to nitroglycerin or, if history was not typical, an abnormal stress test) compared a beta-blocker (metoprolol 200 mg once daily) with a calcium channel blocker (verapamil 240 mg twice daily). [26] It found no significant difference in either mortality or the combined outcome of mortality or non-fatal cardiovascular event between metoprolol and verapamil after a median follow up of 3.4 years (AR for mortality: 22/406 [5%] with metoprolol *v* 25/403 [6%] with verapamil; OR 0.87, 95% CI 0.48 to 1.56; AR for mortality or non-fatal cardiovascular event: 128/406 [32%] with metoprolol *v* 123/403 [30%] with verapamil; OR 1.03, 95% CI 0.84 to 1.30. It also found no significant difference in three quality-of-life variables between metoprolol and verapamil (Cornell Medical Index psychomatic symptom index, score range 39–195: mean score change –1.1 with metoprolol *v* –2.2 with verapamil; P = 0.34; overall life satisfaction, score range 0–120: mean score change –3.0 with metoprolol *v* –2.5 with verapamil; P = 0.85; sleep disturbances, score range 9–36: mean score change –0.7 with both treatments: P = 0.97). The fifth RCT (682 people with stable angina who were not immediately being considered for coronary revascularisation) compared three treatments: atenolol (50 mg twice daily), nifedipine (20 or 40 mg twice daily as tolerated), and atenolol plus nifedipine. [13] It found no significant difference between atenolol alone and nifedipine alone in the combined outcome of mortality, MI, or unstable angina, after a mean follow-up of 2 years (AR for combined death, MI, or unstable angina: 29/226 [13%] with atenolol *v* 25/232 [11%] with nifedipine; log rank P = 0.32).

Beta-blockers versus nitrates or potassium channel openers:
We found no RCTs.

Harms:

Beta-blockers versus placebo:
The RCT identified by the review found no significant difference between propranolol and placebo in the proportion of people experiencing at least one non-cardiac adverse effect (AR 23/78 [29%] with propranolol *v* 6/35 [17%] with placebo; P = 0.08). [23] There was no significant difference between groups in treatment withdrawal caused by lack of efficacy or severe adverse effects (17/78 [22%] with propranolol *v* 6/35 [17%] with placebo; P = 0.58).

Beta-blockers versus calcium channel blockers:
The first RCT identified by the review found that the proportion of people experiencing at least one non-cardiac adverse event was significantly higher with propranolol than with bepridil (AR for at least one non-cardiac adverse event: 23/78 [30%] with propranolol *v* 9/78 [12%] with bepridil;

P = 0.003). [23] This was mostly due to an increased incidence of fatigue in the propranolol group (14/78 [18%] with propranolol *v* 6/78 [8%] with bepridil; P = 0.05). However, there was no significant difference between groups in treatment withdrawal caused by lack of efficacy or severe adverse effects (17/78 [22%] with propranolol *v* 15/78 [19%] with bepridil; P = 0.69). The second RCT found that significantly more people taking nadolol than amlodipine had adverse effects (AR 33/40 [83%] with nadolol *v* 17/40 [43%] with amlodipine; P less than 0.0001). [24] However, similar numbers of people in both groups were withdrawn from treatment owing to adverse effects (4/40 [10%] with nadolol *v* 3/40 [8%] with amlodipine; P value not reported). The third RCT reported that most adverse events were mild, and that there was no significant difference in the incidence of adverse events between metoprolol and diltiazem (figures not reported, P reported as non-significant). [25] The fourth RCT (809 people) found that significantly more people withdrew from the study because of gastrointestinal upset with verapamil than with metoprolol (AR 22/403 [6%] with verapamil *v* 10/406 [3%] with metoprolol; P = 0.029). However, it found no significant difference between the two treatments in overall withdrawal due to adverse effects (AR 59/403 [15%] with verapamil *v* 45/406 [11%] with metoprolol; P = 0.13). The fifth RCT (682 people) found that, over an average of 2 years' follow-up, significantly more people stopped treatment because of adverse effects in the nifedipine group than in the atenolol group (AR 93/232 [40%] with nifedipine *v* 60/226 [27%] with atenolol; log rank P = 0.001). [13]

Beta-blockers versus nitrates or potassium channel openers:
We found no RCTs.

Comment: Many of the RCTs included in the review were unlikely to have been sufficiently powered to detect a clinically important difference between groups. [22]

Clinical guide:
There is consensus that beta-blockers are effective for treating the symptoms of stable angina.

OPTION CALCIUM CHANNEL BLOCKERS AS MONOTHERAPY

Symptom improvement
Calcium channel blockers compared with placebo Bedpridil may be more effective at increasing the duration of exercise at 6 months, but we don't know whether it is more effective at reducing serious cardiac events (defined as unstable angina, MI, or death) or the frequency of angina attacks (very low-quality evidence).

Calcium channel blockers compared with beta-blockers We don't know whether calcium channel blockers are more effective at reducing the frequency of angina attacks or improving exercise duration at 6 months, at improving exercise capacity at 32 weeks, or at improving a composite outcome of non-fatal cardiovascular events or mortality at 3.4 years or the combined outcome of unstable angina, MI, or mortality, at 2 years (very low-quality evidence).

Calcium channel blockers compared with nitrates Amlodipine may be more effective than isosorbide mononitrate at improving exercise duration at 6 months, but we don't know whether amlodipine is more effective at reducing the number of weekly anginal attacks at 6 months (low-quality evidence).

Mortality
Calcium channel blockers compared with beta-blockers Verapamil and metoprolol seem equally effective at reducing mortality after a median follow up of 3.4 years (high-quality evidence).

Quality of life
Calcium channel blockers compared with beta-blockers Verapamil and metoprolol seem equally effective at improving quality-of-life scores (moderate-quality evidence).

Calcium channel blockers compared with nitrates We don't know whether amlodipine is more effective than isosorbide mononitrate at improving quality-of-life scores at 6 months (low-quality evidence).

Note
There is consensus that calcium channel blockers are effective for treating the symptoms of stable angina.

For GRADE evaluation of interventions for angina (stable), see table, p 14 .

Benefits: We found one systematic review (search date 1996). [22]

Calcium channel blockers versus placebo:
The review [22] identified one RCT (191 people of people aged less than 70 years with abnormal exercise stress test or previous MI). [23] It compared three treatments: calcium channel blocker (bepridil; 78 people), beta-blocker (propranolol; 78 people), and placebo (35 people). It found no significant difference between bepridil and placebo in the reduction in frequency of angina attacks

at 6 months (mean reduction in weekly angina attacks from baseline: 69% with bepridil *v* 77% with placebo; P reported as not significant). It found that bepridil significantly increased duration of exercise at 6 months compared with placebo (increase in exercise duration from baseline: 31% with bepridil *v* 8% with placebo; P = 0.03). It found that the rate of serious cardiac events (defined as death, MI, or unstable angina) was higher with bepridil than with placebo, but the significance of this difference was not reported (AR for major cardiac events: 6/78 [8%] with bepridil *v* 2/35 [6%] with placebo; P value not reported).

Calcium channel blockers versus beta-blockers:
See benefits of beta-blockers versus calcium channel blockers, p 3 .

Calcium channel blockers versus nitrates:
The systematic review found no RCTs. [22] We found one subsequent RCT (196 people, aged at least 65 years with an abnormal exercise stress test) comparing amlodipine (5–10 mg once daily) versus isosorbide mononitrate (25–50 mg once daily). [27] It found no significant difference either in the number of weekly anginal attacks or in quality of life (assessed using the short form 36 [SF-36] questionnaire) between amlodipine and isosorbide mononitrate at 6 months (median weekly number of angina attacks: 0 for both groups; P reported as not significant; mean improvement in SF-36 bodily pains scale score from baseline: about 5 for both groups; P reported as not significant; mean improvement in SF-36 health transition score from baseline: about 11 for both groups; P reported as not significant). It found a significant improvement in exercise duration with amlodipine compared with isosorbide mononitrate at 6 months (mean change in exercise duration from baseline to 6 months: from 436 seconds to 548 seconds [+112 seconds] with amlodipine *v* from 462 seconds to 494 seconds [+32 seconds] with isosorbide mononitrate; P = 0.016).

Calcium channel blockers versus potassium channel openers:
We found no RCTs.

Harms:

Calcium channel blockers versus placebo:
The RCT [23] found no significant difference between bepridil and placebo in the proportion of people experiencing at least one non-cardiac adverse effect at 6 months (AR 9/78 [12%] with bepridil *v* 6/35 [17%] with placebo; P = 0.22).

Calcium channel blockers versus beta-blockers:
See harms of beta-blockers versus calcium channel blockers, p 3 .

Calcium channel blockers versus nitrates:
The RCT found no significant difference between amlodipine and isosorbide mononitrate in the proportion of people reporting any adverse event at 6 months. The proportion of people with serious adverse effects was also similar in both groups (AR for any adverse event: 58% with amlodipine *v* 53% with isosorbide mononitrate; P value reported as not significant; AR for a serious adverse event: reported as about 7% in both groups; P value not reported). [27] About 8% of people in the amlodipine group and 18% of people in the isosorbide mononitrate group withdrew because of adverse events (significance not reported). Only two withdrawals (2%; both oedema) in the amlodipine group and seven withdrawals (7%; all headache) in the isosorbide mononitrate group were considered treatment related (significance not reported). The RCT found that peripheral oedema was more common with amlodipine than with isosorbide mononitrate, whereas headache was more common with isosorbide mononitrate than with amlodipine (AR for peripheral oedema: 14% with amlodipine *v* 0% with isosorbide mononitrate; AR for headache: 13% with isosorbide mononitrate *v* 2% with amlodipine; P value not reported for either comparison).

Calcium channel blockers versus potassium channel openers:
We found no RCTs.

Comment:

Clinical guide:
There is consensus that calcium channel blockers are effective for treating the symptoms of stable angina.

OPTION NITRATES AS MONOTHERAPY

Symptom improvement
Nitrates compared with calcium channel blockers Isosorbide mononitrate may be less effective than amlodipine at improving exercise duration at 6 months, but we don't know whether isosorbide mononitrate is more effective than amlodipine at reducing the number of weekly anginal attacks at 6 months (low-quality evidence).

Quality of life

Nitrates compared with calcium channel blockers We don't know whether isosorbide mononitrate is more effective than amlodipine at improving quality-of-life scores at 6 months (low-quality evidence).

Note
We found no direct information about whether nitrates are better than no active treatment. There is consensus that nitrates are effective for treating the symptoms of stable angina.

For GRADE evaluation of interventions for angina (stable), see table, p 14 .

Benefits:

Nitrates versus placebo, beta-blockers, or potassium channel openers:
We found no systematic review or RCTs (see comment below).

Nitrates versus calcium channel blockers:
See benefits of calcium channel blockers versus nitrates, p 5 .

Harms:

Nitrates versus placebo, beta-blockers, or potassium channel openers:
We found no systematic review or RCTs.

Nitrates versus calcium channel blockers:
See harms of calcium channel blockers versus nitrates, p 5 .

Comment:

Clinical guide:
There is consensus that nitrates are effective for treating the symptoms of stable angina.

OPTION POTASSIUM CHANNEL OPENERS AS MONOTHERAPY

We found no direct information about potassium channel openers in the treatment of people with stable angina.

Note
There is consensus that potassium channel openers are effective for treating the symptoms of stable angina.

For GRADE evaluation of interventions for angina (stable), see table, p 14 .

Benefits:

Potassium channel openers versus placebo, beta-blockers, calcium channel blockers, or nitrates:
We found no systematic review or RCTs (see comment below).

Harms:

Potassium channel openers versus placebo, beta-blockers, calcium channel blockers, or nitrates:
We found no systematic review or RCTs.

Comment:

Clinical guide:
There is consensus that potassium channel openers are effective for treating the symptoms of stable angina.

QUESTION What are the effects of long-term combination drug treatment for stable angina?

OPTION BETA-BLOCKERS PLUS OTHER ANTI-ANGINAL DRUG TREATMENTS VERSUS BETA-BLOCKERS ALONE New

Symptom improvement
Beta-blockers plus calcium channel blockers compared with beta-blockers alone We don't know whether atenolol plus nifedipine is more effective than atenolol alone at improving a composite outcome (including unstable angina, MI, or mortality) at 2 years (low-quality evidence).

Note
We found no direct information about whether beta-blockers plus nitrates are more effective than beta-blockers alone, or about whether or not beta-blockers plus potassium channel openers are more effective than beta-blockers alone. There is consensus that it is reasonable to use combinations of classes of anti-anginal drug treatment for the treatment of anginal symptoms when symptoms persist despite the use of a single class of anti-anginal drug treatment.

For GRADE evaluation of interventions for angina (stable), see table, p 14 .

Benefits:

Beta-blockers plus calcium channel blockers versus beta-blockers alone:
One systematic review [22] identified one RCT [13] that met our inclusion criteria. This RCT (682 people with stable angina who were not immediately being considered for coronary revascularisation)

compared three treatments: atenolol (50 mg twice daily), nifedipine (20 or 40 mg twice daily as tolerated), and atenolol plus nifedipine. [13] It found no significant difference between the combination of atenolol plus nifedipine and atenolol alone in the combined outcome of mortality, MI, or unstable angina, after a mean follow-up of 2 years (AR for combined death, MI, or unstable angina: 19/224 [8%] for combination therapy *v* 29/226 [13%] with atenolol, log rank P = 0.32). The long-term effect on anginal symptoms, exercise capacity, and quality of life was not tested.

Beta-blockers plus nitrates versus beta-blockers alone:
We found no systematic review or RCTs.

Beta-blockers plus potassium channel openers versus beta-blockers alone:
We found no systematic review or RCTs.

Harms:

Beta-blockers plus calcium channel blockers versus beta-blockers alone:
The RCT (682 people) found similar rates of treatment discontinuation over an average of 2 years' follow-up between the combination treatment and the atenolol alone (AR 60/226 [27%] with atenolol *v* 64/226 [29%] with combination treatment; P value not reported). [13] This trial included a 2-week open label treatment period on combination treatment, so the rate of tolerance of the drug treatments tested in this trial may be an over-estimate.

Beta-blockers plus nitrates versus beta-blockers alone:
We found no RCTs.

Beta-blockers plus potassium channel openers versus beta-blockers alone:
We found no RCTs.

Comment:

Clinical guide:
There is consensus that it is reasonable to use combinations of classes of anti-anginal drug treatment for the treatment of anginal symptoms when symptoms persist despite the use of a single class of anti-anginal drug treatment. The RCT included in this section is insufficiently powered to detect a clinically important difference betweeen groups in the rate of major cardiovascular events. [13]

OPTION CALCIUM CHANNEL BLOCKERS PLUS OTHER ANTI-ANGINAL DRUG TREATMENTS VERSUS CALCIUM CHANNEL BLOCKERS ALONE New

Symptom improvement
Calcium channel blockers plus beta-blockers compared with calcium channel blockers alone We don't know whether nifedipine plus atenolol is more effective than nifedipine alone at improving a composite outcome (including unstable angina, MI, or mortality) at 2 years (low-quality evidence).

Note
We found no direct information about whether calcium channel blockers plus nitrates are more effective than calcium channel blockers alone, or about whether calcium channel blockers plus potassium channel openers are more effective than calcium channel blockers alone. There is consensus that it is reasonable to use combinations of classes of anti-anginal drug treatment for anginal symptoms when symptoms persist despite the use of a single class of anti-anginal drug treatment.

For GRADE evaluation of interventions for angina (stable), see table, p 14 .

Benefits:

Calcium channel blockers and beta-blockers versus calcium channel blockers alone: One systematic review [22] identified one RCT [13] that met our inclusion criteria. This RCT (682 people with stable angina who were not immediately being considered for coronary revascularisation) compared three treatments: nifedipine (20 or 40 mg twice daily as tolerated), atenolol (50 mg twice daily), and atenolol plus nifedipine. [13] It found no significant difference between the combination of nifedipine plus atenolol versus nifedipine alone in the combined outcome of mortality, MI, or unstable angina, after a mean follow-up of 2 years (AR for combined death, MI, or unstable angina: 19/224 [9%] for combination therapy *v* 25/232 [11%] with nifedipine; log rank P = 0.32). The long-term effect on anginal symptoms, exercise capacity, and quality of life was not tested.

Calcium channel blockers plus nitrates versus calcium channel blockers alone:
We found no systematic review or RCTs.

Calcium channel blockers plus potassium channel openers versus calcium channel blocker alone:
We found no systematic review or RCTs.

Harms:

Calcium channel blockers beta-blockers versus calcium channel blockers alone:
The RCT (682 people) found that, over an average of 2 years' follow-up, significantly fewer people discontinued treatment because of adverse effects in the combination therapy group than in the nifedipine alone group (AR 64/224 [29%] with combination therapy *v* 93/232 [40%] with nifedipine; log rank P = 0.001). [13] The reasons for drug discontinuation were not stated. This trial included a 2-week open label treatment period on combination therapy so the rate of tolerance of the drug therapies tested in this trial may be an over-estimate.

Calcium channel blockers and nitrates versus calcium channel blockers alone:
We found no systematic review or RCTs.

Calcium channel blockers and potassium channel openers versus calcium channel blockers alone:
We found no systematic review or RCTs.

Comment:

Clinical guide:
There is consensus that it is reasonable to use combinations of classes of anti-anginal drug therapy for the treatment of anginal symptoms when symptoms persist despite the use of a single class of anti-anginal drug therapy. The RCT included in this section is insufficiently powered to detect a clinically important difference in the rate of major cardiovascular events between groups.

OPTION NITRATES PLUS OTHER ANTI-ANGINAL DRUG TREATMENTS VERSUS NITRATES ALONE

New

We found no direct information about whether nitrates plus other anti-anginal drug treatments are more effective than nitrates alone in people with stable angina.

Note
There is consensus that it is reasonable to use combinations of classes of anti-anginal drug treatment for the treatment of anginal symptoms when symptoms persist despite the use of a single class of anti-anginal drug treatment.

For GRADE evaluation of interventions for angina (stable), see table, p 14 .

Benefits:

Nitrates plus beta-blockers versus nitrates alone:
We found no systematic review or RCTs.

Nitrates plus calcium channel blockers and versus nitrates alone:
We found no systematic review or RCTs.

Nitrates plus potassium channel openers versus nitrates alone:
We found no systematic review or RCTs.

Harms:

Nitrates plus beta-blockers versus nitrates alone:
We found no RCTs.

Nitrates plus calcium channel blockers and versus nitrates alone:
We found no RCTs.

Nitrates plus potassium channel openers versus nitrates alone:
We found no RCTs.

Comment:

Clinical guide:
There is consensus that it is reasonable to use combinations of classes of anti-anginal drug treatment for anginal symptoms when symptoms persist despite the use of a single class of anti-anginal drug treatment.

OPTION POTASSIUM CHANNEL OPENERS PLUS OTHER ANTI-ANGINAL DRUG TREATMENTS VERSUS POTASSIUM CHANNEL OPENERS ALONE

New

We found no direct information about whether potassium channel openers plus other anti-anginal drug treatments are more effective than potassium channel openers alone in people with stable angina.

Note
There is consensus that it is reasonable to use combinations of classes of anti-anginal drug treatment for anginal symptoms when symptoms persist despite the use of a single class of anti-anginal drug treatment.

For GRADE evaluation of interventions for angina (stable), see table, p 14 .

Benefits:

Potassium channel openers and beta-blockers versus potassium channel openers alone:
We found no systematic review or RCTs.

Potassium channel openers and calcium channel blockers and versus potassium channel openers alone:
We found no systematic review or RCTs.

Potassium channel openers and nitrates versus potassium channel openers alone:
We found no systematic review or RCTs.

Harms:

Potassium channel openers plus beta-blockers versus potassium channel openers alone:
We found no RCTs.

Potassium channel openers and calcium channel blockers and versus potassium channel openers alone:
We found no RCTs.

Potassium channel openers and nitrates versus potassium channel openers alone:
We found no RCTs.

Comment:

Clinical guide:
There is consensus that it is reasonable to use combinations of classes of anti-anginal drug treatment for anginal symptoms when symptoms persist despite the use of a single class of anti-anginal drug treatment.

QUESTION What are the effects of long-term adjunctive drug treatment in people with stable angina who are receiving anti-anginal treatment?

OPTION BETA-BLOCKERS IN ADDITION TO EXISTING ANTI-ANGINAL DRUG TREATMENT New

We found no direct information about beta-blockers in addition to existing anti-anginal drug treatments in people with stable angina.

For GRADE evaluation of interventions for angina (stable), see table, p 14 .

Benefits: **Beta-blockers in addition to existing anti-anginal drug treatment:** We found no systematic review or RCTs.

Harms: **Beta-blockers in addition to existing anti-anginal drug treatment:** We found no RCTs.

Comment: None.

OPTION CALCIUM CHANNEL BLOCKERS IN ADDITION TO EXISTING ANTI-ANGINAL DRUG TREATMENT New

Symptom improvement
Calcium channel blockers in addition to existing drug treatment compared with placebo in addition to existing drug treatment Adding nifedipine to existing anti-anginal drug treatment (beta-blocker, oral nitrate, or both) seems more effective at decreasing the proportion of people who need coronary angiography or who have coronary artery bypass surgery. Adding nifedipine to existing anti-anginal drug treatment seems no more effective at decreasing the proportion of people with a composite outcome (combined death, MI, refractory angina, new overt heart failure, debilitating stroke and peripheral revascularisation) at 4.9 years (moderate-quality evidence).

Mortality
Calcium channel blockers in addition to existing drug treatment compared with placebo in addition to existing drug treatment Adding nifedipine to existing anti-anginal drug treatment (beta-blocker, oral nitrate, or both) seems no more effective at decreasing the number of deaths at 4.9 years (high-quality evidence).

For GRADE evaluation of interventions for angina (stable), see table, p 14 .

Benefits:

Calcium channel blockers in addition to existing drug treatment:
We found one RCT (7665 people with treated stable angina already taking a beta-blocker or oral nitrate, or, in half of the people, both drugs) comparing additional treatment with slow-release nifedipine 60 mg daily versus placebo. [28] Over an average of 4.9 years' follow-up, the RCT found no significant difference in the primary end point (combined death, MI, refractory angina, new overt

heart failure, debilitating stroke and peripheral revascularisation: 804/3825 [21%] with nifedipine *v* 828/3840 [22%] with placebo; HR 0.97, 95% CI 0.88 to 1.07, P = 0.54) or in death alone (number of deaths: 310/3825 [8%] with nifedipine *v* 291/3840 [8%] with placebo; HR 1.07, 95% CI 0.91 to 1.25, P = 0.41). The RCT found a significant reduction in the need for coronary angiography (number of coronary angiograms: 1200/3825 [31%] with nifedipine *v* 1357/3840 [35%] with placebo; HR 0.82, 95% CI 0.75 to 0.90, P less than 0.0001) and a significant reduction in the proportion of people sent for coronary artery bypass surgery in the nifedipine group compared with placebo (number of coronary bypass operations: 299/3825 [8%] with nifedipine *v* 371/3840 [10%] with placebo; HR 0.79, 95% CI, 0.68 to 0.92, P = 0.002). [28]

Harms: **Calcium channel blockers in addition to existing drug treatment:**
The RCT (7665 people) found no significant harms. [28] A slightly higher proportion of people stopped slow-release nifedipine compared with placebo (1305/3825 [34%] with nifedipine *v* 1179/3840 [31%] with placebo) over an average of 4.9 years' follow-up. A higher proportion of people stopped nifedipine owing to an adverse event compared with placebo (drug discontinuation for adverse event: 389/3825 [10%] with nifedipine *v* 172/3840 [5%] with placebo; P not reported), with peripheral oedema (139 cases with nifedipine *v* 20 cases with placebo) and headache (43 cases with nifedipine *v* 20 cases with placebo) being the most common complaints. [28]

Comment: None.

OPTION NITRATES IN ADDITION TO EXISTING ANTI-ANGINAL DRUG TREATMENT New

We found no direct information about nitrates in addition to existing anti-anginal drug treatment in people with stable angina.

For GRADE evaluation of interventions for angina (stable), see table, p 14 .

Benefits: **Nitrates in addition to existing anti-anginal drug treatment:**
We found no systematic review or RCTs.

Harms: **Nitrates in addition to existing anti-anginal drug treatment:**
We found no RCTs.

Comment: None.

OPTION POTASSIUM CHANNEL OPENERS IN ADDITION TO EXISTING ANTI-ANGINAL DRUG TREATMENT New

Symptom improvement
Potassium channel openers in addition to existing anti-anginal drug treatment compared with placebo in addition to existing anti-anginal drug treatment Adding nicorandil to existing anti-anginal drug treatment (56% beta-blockade, 55% calcium channel blocker, 87% nitrates) may be more effective at decreasing the proportion of people with a composite outcome (CHD death, non-fatal MI, or unplanned hospital admission for cardiac chest pain) at 1.6 years. We don't know whether adding nicorandil to existing anti-anginal drug treatment is more effective at improving functional status distribution (Canadian Cardiovascular Society [CCS] angina class I, II, III, or IV), or at decreasing the proportion of people with worsening of angina (low-quality evidence).

Mortality
Potassium channel openers in addition to existing anti-anginal drug treatment compared with placebo in addition to existing anti-anginal drug treatment Adding nicorandil to existing anti-anginal drug treatment (56% beta-blockade, 55% calcium channel blocker, 87% nitrates) seems no more effective at reducing-all cause mortality (moderate-quality evidence).

For GRADE evaluation of interventions for angina (stable), see table, p 14 .

Benefits: **Potassium channel openers in addition to existing anti-anginal drug treatment:**
One RCT (5126 people with stable angina already on drug treatment [56% beta-blockade, 55% calcium channel blocker, 87% nitrates] compared nicorandil 20 mg twice daily versus placebo. [14] Over an average of 1.6 years' follow-up, fewer people attained the composite primary end point of CHD death, non-fatal MI, or unplanned hospital admission for cardiac chest pain with nicorandil than with placebo (composite primary end point: 337/2565 [13%] with nicorandil *v* 398/2561 [16%] with placebo: HR 0.83, 95% CI 0.72 to 0.97, P = 0.014), with broadly similar reductions in all components of this composite. All-cause mortality did not differ between groups (deaths: 111/2565 [4%] with nicorandil *v* 129/2561 [5%] with placebo; HR 0.85, 95% CI, 0.66 to 1.10, P = 0.222), but the trial was not powered for this outcome. Ischaemic thresholds were not tested, but patient-reported functional status distribution at the end of the study did not differ between the groups

(Canadian Cardiovascular Society [CCS] angina class I, II, III or IV: 985 [43%], 1159 [50%), 162 [7%], 9 [less than 1%] with nicorandil; and: 989 [43%], 1124 [49%], 163 [7%] and 15 [1%] with placebo; P value not reported), and the frequency of worsening of anginal status did not differ between the groups (worsening of angina: 569/2565 [22%] with nicorandil *v* 602/2561 [24%] with placebo; OR 0.93, 95% CI 0.81 to 1.06, P = 0.26).

Harms: **Potassium channel openers in addition to existing anti-anginal drug treatment:** A higher proportion of people in the RCT stopped treatment with nicorandil than with placebo (withdrawals at end of study: 1003/2565 [39%] with nicorandil *v* 809/2561 [32%] with placebo; P value not reported), with an absolute difference in withdrawal rates of 10%. [14] This difference was mainly due to an increased incidence headache in the nicorandil group (numbers not reported). The rate of serious adverse events was similar in both groups (numbers not reported), but the number of gastrointestinal events was greater in the nicorandil group (194/2565 [8%] with nicorandil *v* 132/2561 [5%] with placebo; P value not reported).

Comment: None.

GLOSSARY

Exercise stress testing is widely used in the evaluation of people with chest pain. The person walks on a treadmill, the speed and slope of which are varied according to protocol, while being monitored by ECG. Exercise-induced horizontal or down-sloping ST segment depression is strongly suggestive of myocardial ischaemia, particularly when associated with typical chest pain. ST segment depression at a low workload usually indicates severe coronary artery disease, as may exercise-induced ventricular arrhythmia or a fall in blood pressure.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence 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.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Beta-blockers plus other anti-anginal drug treatments *v* beta-blockers alone One systematic review added [22] which included one RCT that met inclusion criteria. [13] The RCT compared three treatments: atenolol (50 mg twice daily), nifedipine (20 or 40 mg twice daily as tolerated), and atenolol plus nifedipine. It found no difference between the combination of atenolol plus nifedipine and atenolol alone in the combined outcome of mortality, MI, or unstable angina, after a mean follow-up of 2 years. Categorisation based on consensus (Likely to be beneficial).

Calcium channel blockers plus other anti-anginal drug treatments *v* calcium channel blockers alone One systematic review added [22] which included one RCT that met *Clinical Evidence* inclusion criteria. [13] The RCT compared three treatments: nifedipine, atenolol, and atenolol plus nifedipine. It found no difference between the combination of nifedipine plus atenolol versus nifedipine alone in the combined outcome of mortality, MI, or unstable angina, after a mean follow-up of 2 years. Categorisation based on consensus (Likely to be beneficial).

Nitrates plus other anti-anginal drug treatments versus nitrates alone We found no systematic review or RCTs that met the inclusion criteria for this review. Categorisation based on consensus (Likely to be beneficial).

Potassium channel openers plus other anti-ischaemic drug versus potassium channel openers alone We found no systematic review or RCTs that met the inclusion criteria for this review. Categorisation based on consensus (Likely to be beneficial).

Beta-blockers in addition to existing anti-anginal drug treatment We found no systematic review of RCTs that met *Clinical Evidence* inclusion criteria. Categorised as Unknown effectiveness.

Calcium channel blockers in addition to exisiting anti-anginal drug treatment One large RCT identified comparing additional treatment with slow-release nifedipine versus placebo. [28] Over an average of 4.9 years' follow-up, the RCT found no significant difference between groups in the primary end point of combined death, MI, refractory angina, new overt heart failure, debilitating stroke and peripheral revascularisation. The RCT found that nifedipine reduced the need for coronary angiography and bypass surgery compared with placebo. [28] Categorised as Likely to be beneficial.

Nitrates in addition to existing anti-anginal drug treatment: We found no systematic review or RCTs that met the inclusion criteria for this revew. Categorisation (Unknown effectiveness).

Potassium channel openers in addition to existing anti-anginal drug treatments One large RCT identified comparing nicorandil versus placebo. [14] The RCT found nicorandil reduced the rate of the composite primary end point (CHD death, non-fatal MI, or unplanned hospital admission for cardiac chest pain) compared with placebo at an average 1.6 years' follow-up. [14] Categorised as Likely to be beneficial.

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Competing interests: LOT has attended international cardiological conferences as a guest of a number of pharmaceutical companies. He has been paid by Novartis and Pfizer for running eductational programmes and has received research funds from Sanofi-Synthelabo.

Disclaimer

TABLE **GRADE evaluation of interventions for angina (chronic stable)**

Important outcomes	Symptom improvement, mortality, quality of life								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of long-term single-drug treatment for stable angina?									
1 (112) [23]	Symptom improvement	Beta-blockers *v* placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for no statistical comparison between groups for one outcome
5 (1542) [23] [24] [26] [13] [25]	Symptom improvement	Beta-blockers *v* calcium channel blockers	4	–2	0	–1	0	Very low	Quality point deducted for incomplete reporting and high rate of withdrawals in 1 RCT. Directness point deducted for composite outcome in 2 RCTs
1 (809) [26]	Mortality	Beta-blockers *v* calcium channel blockers	4	0	0	0	0	High	
1 (809) [26]	Quality of life	Beta-blockers *v* calcium channel blockers	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (112) [23]	Symptom improvement	Calcium channel blockers *v* placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for no statistical comparison between groups for one outcome
1 (196) [27]	Symptom improvement	Calcium channel blockers *v* nitrates	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (196) [27]	Quality of life	Calcium channel blockers *v* nitrates	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
What are the effects of long-term combination drug treatment for stable angina?									
1 (450) [13]	Symptom improvement	Beta-blockers plus calcium channel blockers *v* beta-blockers alone	4	0	0	–2	0	Low	Directness points deducted for use of composite outcome and limited outcomes reported
1 (456) [13]	Symptom improvement	Calcium channel blockers plus beta-blockers *v* calcium channel blockers alone	4	0	0	–2	0	Low	Directness points deducted for use of composite outcome and limited outcomes reported
What are the effects of long-term adjunctive treatment in people with stable angina?									
1 (7665) [28]	Symptom improvement	Calcium channel blockers in addition to existing anti-anginal drug treatment *v* adding placebo to existing anti-anginal drug treatment	4	0	0	–1	0	Moderate	Directness point deducted for use of compositie outcome
1 (7665) [28]	Mortality	Calcium channel blockers in addition to existinganti-anginal drug treatment *v* adding placebo to existing anti-anginal drug treatment	4	0	0	0	0	High	

Important outcomes	**Symptom improvement, mortality, quality of life**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1(5126) [14]	Symptom improvement	Potassium channel openers in addition to existing anti-anginal drug treatment *v* adding placebo to existing anti-anginal drug treatment	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for composite outcome
1(5126) [14]	Mortality	Potassium channel openers in addition to existing anti-anginal drug treatment *v* adding placebo to existing anti-anginal drug treatment	4	–1	0	0	0	Moderate	Quality point deducted as trial not adequately powered for this outcome

Type of evidence: 4 = RCT; 2 = Observational. Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio